UNIVERSIDAD DE GRANADA

Departamento de Personalidad, Evaluación y Tratamiento Psicológico

---

TESIS DOCTORAL

DETERIOROS NEUROCOGNITIVOS Y EMOCIONALES EN CONSUMIDORES DE DROGAS: PREVALENCIA, SIGNIFICACIÓN CLÍNICA Y EFECTOS DIFERENCIALES

Doctoranda: María Josefa Fernández Serrano

Directores: Dr. Antonio Verdejo García y Dr. Miguel Pérez García

Editor: Editorial de la Universidad de Granada
Autor: María Josefa Fernández Serrano
D.L.: GR 3069-2010
ISBN: 978-84-693-3297-9

UNIVERSIDAD DE GRANADA

FACULTAD DE PSICOLOGÍA

Los directores Dr. Antonio Verdejo García y Dr. Miguel Pérez García autorizan la presentación de la tesis doctoral titulada: "Deterioros neurocognitivos y emocionales en consumidores de drogas: prevalencia, significación clínica y efectos diferenciales" presentada por Dña. María Josefa Fernández Serrano.

Fdo. Dr. Antonio Verdejo García

Fdo. Dr. Miguel Pérez García

Fdo. María Josefa Fernández Serrano

Esta Tesis Doctoral se ha realizado según la normativa reguladora de los estudios del tercer ciclo y del título de doctor de la Universidad de Granada aprobada por **Consejo de Gobierno 26 de Septiembre de 2005 (artículo nº 27)** referida a la modalidad de *Tesis Doctoral compuesta por el reagrupamiento de trabajos de investigación publicados por el doctorando.*

AGRADECIMIENTOS

Quiero aprovechar este espacio para expresar mi más sincero agradecimiento a todas aquellas personas que han hecho posible este trabajo.

Muy especialmente a Antonio Verdejo y Miguel Pérez por haberme permitido trabajar con ellos y por todo el conocimiento, tiempo, apoyo, ánimo y fuerza que me han regalado en estos cuatro años.

A todos los participantes voluntarios, a Yimi Molina, Belén, José Carlos, Vanesa, Miguel Ángel, Salva, Paco, María Dolores, Lola, José María Tortosa, Miguel Mingorance y el resto de terapeutas de Proyecto Hombre Granada.
A Isabel Peralta, José Cesar Perales, María Sánchez, Óscar Lozano, Hugh Garavan, Celia Morgan y Valerie Curran.

Finalmente, y en mayúsculas, a Mis Padres, a Mi Hermano y a Jairo por haber creído en mí y haberme permitido llegar hasta aquí.

ÍNDICE

Presentación

El informe mundial sobre drogas emitido por Naciones Unidas para 2009 (UNODC: United Nations Office of Drugs and Crime, 2009) señala que el 4.85 % de población mundial con edades comprendidas entre los 15 y los 64 años ha usado drogas al menos en una ocasión durante los últimos 12 meses, y entorno al 0.64 % de población mundial tiene problemas con el uso de drogas. A nivel europeo, los últimos datos ofrecidos por el Observatorio Europeo de las Drogas y las Toxicomanías (EMCDDA: European Monitoring Centre for Drugs and Drug Addiction, 2009) indican que nuestro país se encuentra a la cabeza en el consumo de cocaína en población entre 15 y 34 años con una prevalencia de consumo del 5.5 % llegando a situarse por delante de países como Reino Unido (4.5 %) y Dinamarca (3.4 %). Además, España sigue estando entre los países con mayor tasa de prevalencia de consumo de cannabis, y drogas de diseño como el éxtasis o las anfetaminas comienzan a adquirir cada vez más protagonismo. El consumo de opiáceos sigue siendo el motivo principal de demanda de tratamiento en régimen de ingreso. Asimismo el alcohol constituye un factor determinante en el problema del consumo de sustancias. Entre la población de consumo crónico de drogas la ingesta de alcohol es tan frecuente que en ocasiones ni se hace referencia al mismo, y la necesidad de abordar este co-abuso ha pasado a ser una cuestión cada vez más importante para los centros de tratamiento en consumidores de drogas (EMCDDA, 2009).

La relevancia de este fenómeno ha suscitado un creciente interés científico que ha dado lugar a importantes aportaciones derivadas de estudios en modelos animales (Robinson & Kolb, 2004), estudios farmacológicos (Everitt & Robbins, 2005) y estudios de neuroimagen (Garavan & Stout, 2005; Volkow, Fowler & Wang, 2004). Estas investigaciones han destacado de forma consistente la relevancia de las alteraciones neurocognitivas y emocionales entre los consumidores de distintas drogas.

En consonancia con estos hallazgos, la realización de esta tesis tiene por objetivo dilucidar la existencia de deterioros de carácter neurocognitivo y emocional en consumidores de drogas, tratando de arrojar más luz en este área con la aportación de datos de prevalencia de deterioro neuropsicológico, información sobre la relevancia clínica de estos deterioros y sobre la posibilidad de que existan efectos diferenciales en función de las sustancias consumidas.

Resumen

La tesis consta de un total de ocho capítulos que agrupamos en cuatro secciones: (i) introducción, (ii) justificación y objetivos, (iii) memoria de trabajos de investigación publicados, (iv) discusión general, conclusiones y perspectivas futuras.

La sección de introducción consta de dos capítulos. En el Capítulo 1 expondremos los principales modelos teóricos que han abordado el fenómeno de la adicción y que justifican el abordaje neuropsicológico del mismo. En el Capítulo 2 describiremos el proceso de evaluación neuropsicológica en consumidores de drogas, mostrando cuáles son los principales procesos abordados en este, así como las pruebas más frecuentemente empleadas.

La segunda sección contiene el Capítulo 3 en el que aportamos la justificación de la realización de este trabajo así como el objetivo principal y los objetivos específicos e hipótesis que se pretenden con el mismo.

La tercera sección consta de cuatro capítulos en el que se recogen un conjunto de cuatro trabajos de investigación, uno de ellos de revisión y otros tres de carácter empírico. El Capítulo 4 consiste en una revisión sistemática y cuantitativa de estudios realizados en la última década (1999-2009/2010) sobre los efectos neuropsicológicos del consumo de drogas. Globalmente los estudios revisados pusieron de manifiesto la existencia de deterioros comunes al consumo de diferentes tipos de drogas en procesos de memoria episódica, en el componente de actualización de las funciones ejecutivas, en la toma de decisiones y en el procesamiento emocional. Asimismo se observó que el consumo de alcohol y psicoestimulantes parece estar particularmente asociado a alteraciones en mecanismos de acción impulsiva y flexibilidad cognitiva; el consumo de alcohol y MDMA con alteraciones en la velocidad perceptiva, procesamiento espacial y procesos de atención selectiva; el consumo de cannabis y metanfetaminas con

alteraciones en la memoria prospectiva; y el consumo de cannabis y MDMA con alteraciones en la velocidad de procesamiento y procesos de planificación.

El Capítulo 5 consiste en un estudio empírico en el que analizamos las tasas de prevalencia del deterioro neuropsicológico en las funciones ejecutivas en una amplia muestra de consumidores de distintas drogas en proceso de rehabilitación a través de comunidades terapéuticas. Además en este estudio llevamos a cabo la estimación del tamaño del efecto de las diferencias en el rendimiento neuropsicológico entre consumidores y no consumidores a fin de conocer qué pruebas de evaluación neuropsicológica podrían resultar más útiles en la detección de deterioro en esta población. Los resultados del estudio pusieron de manifiesto la existencia de una alta prevalencia de deterioro en las funciones ejecutivas entre los consumidores de drogas. Asimismo el estudio puso de manifiesto que la tarea de Aritmética (Wechsler Adult Intelligence Scale, WAIS-III) era la prueba que resultaba más discriminante en la ejecución entre consumidores y controles. Las tareas FAS y el Test de Fluidez Figurativa Ruff eran las pruebas más recomendables para la evaluación de la fluidez, la prueba de Categorías para evaluar flexibilidad, la tarea Stroop Colores-Palabras para evaluar inhibición, la prueba del Mapa del Zoo (Behavioral Assessment of the Dysexecutive Syndrome, BADS) para planificación y la tarea de los Seis Elementos (BADS) para multi-tarea.

El Capítulo 6 consiste en un estudio sobre los efectos comunes y diferenciales producidos por el consumo de cannabis, cocaína, heroína y alcohol sobre el rendimiento neuropsicológico en una serie de pruebas de control ejecutivo. Asimismo este estudio analiza la contribución realizada por la severidad de consumo, incluyendo parámetros de cantidad y duración, sobre cada uno de los procesos analizados. Los resultados de

esta investigación mostraron que el abuso de alcohol se encuentra asociado con la presencia de déficits en mecanismos ejecutivos de fluidez y toma de decisiones, mientras que el cannabis, la cocaína y la heroína ejercen efectos tanto comunes como específicos en diferentes componentes ejecutivos. Concretamente observamos que (i) el consumo de alcohol, cannabis y cocaína produce efectos comunes sobre la fluidez verbal y la toma de decisiones, (ii) la cantidad de cannabis y la cantidad de cocaína produce efectos comunes sobre la memoria de trabajo de tipo verbal y el razonamiento analógico, (iii) la duración del consumo de cocaína y del consumo de heroína afectan de forma común a la flexibilidad cognitiva, y (iv) que la duración del consumo de cocaína tenía efectos específicos en el control inhibitorio.

El Capítulo 7 esta formado por un estudio sobre los efectos del consumo de distintas drogas sobre el procesamiento emocional, en concreto sobre el reconocimiento de expresiones faciales de las seis emociones básicas (felicidad, tristeza, sorpresa, miedo, asco e ira). Asimismo, estudiamos los efectos de la severidad de consumo (cantidad y duración) sobre el reconocimiento de cada una de estas emociones. Los resultados generales de esta investigación mostraron que los sujetos consumidores de drogas tenían peor reconocimiento emocional que los no consumidores en las expresiones emocionales de ira, asco, miedo y tristeza. De forma más específica, la severidad del consumo de cocaína predecía de forma significativa la eficacia en el reconocimiento, concretamente, observamos que la cantidad de cocaína predecía un pobre reconocimiento de la expresión de ira y la duración de cocaína un pobre reconocimiento de la ira y el miedo.

La cuarta y última sección contiene el Capítulo 8 en el llevamos a cabo una discusión conjunta de los hallazgos obtenidos a través de los distintos estudios haciendo

especial énfasis en sus implicaciones teóricas y clínicas. Asimismo presentamos un apartado de conclusiones y perspectivas futuras de investigación.

I. INTRODUCCIÓN

Capítulo 1

Neuropsicología de las adicciones: modelos teóricos

1. Modelos neuropsicológicos en adicción

La dependencia del consumo de drogas es definida por el DSM-IV como un trastorno crónico y recurrente caracterizado por un consumo abusivo y continuo de esas sustancias a pesar de las consecuencias negativas que esta conducta provoca en el individuo. A partir de la irrupción de las técnicas de neuroimagen, los estudios de tomografía por emisión de positrones (PET) demostraron que estas características clínicas están vinculadas a alteraciones persistentes del funcionamiento cerebral (Volkow et al., 1996, 1997, 2001a), sentando las bases de la necesidad de un abordaje neuropsicológico de las adicciones.

Los modelos neuropsicológicos contemporáneos de adicción han asociado el consumo de drogas con déficits neuropsicológicos en mecanismos relacionados con la emoción, la memoria, los procesos atencionales y las funciones ejecutivas, entendidas estas últimas como un grupo integrado de habilidades implicadas en la generación, supervisión y monitorización de conductas dirigidas hacia objetivos socialmente adaptativos (Roberts, Robbins & Weiskrantz, 1998; Stuss & Knight, 2002; Verdejo-García & Pérez-García, 2007a). Varios de estos modelos coinciden en conceptualizar la adicción como un desequilibro entre los sistemas de procesamiento y aprendizaje de reforzadores y los sistemas de control ejecutivo (Everitt et al., 2008; Goldstein & Volkow, 2002; Redish, Jensen & Johnson, 2008; Verdejo-García & Bechara, 2009).

1.1. Modelo impaired-salience attribution and response inhibition (Goldstein & Volkow, 2002)

El modelo I-RISA (Impaired-Salience Attribution and Response Inhibition) de Goldstein & Volkow (2002) propone que la adicción es el resultado de la alteración en

dos sistemas complementarios, un sistema motivacional y otro de inhibición de respuestas automatizadas o guiadas por la recompensa. Por un lado, el sistema encargado de evaluar la relevancia motivacional de los reforzadores realizaría una valoración exagerada de las propiedades reforzantes de las drogas, y a su vez, devaluaría el valor motivacional de otros reforzadores naturales (p.e., comida, sexo, relaciones sociales). Por otro lado, la alteración en el sistema de inhibición, encargado de cancelar conductas inadecuadas para las demandas del organismo, provocaría la imposibilidad de inhibir la conducta motivacionalmente marcada; en este caso, la del consumo de drogas. El daño en estos dos sistemas repercutiría de manera transversal en varios estadios de la adicción, incluyendo los consumos iniciales, la intoxicación y el consumo en forma de atracones, el craving, o la recaída incluso después de periodos de abstinencia prolongada. Asimismo, el modelo propone que el daño en estos dos sistemas se traduce en una disfunción de los circuitos cerebrales encargados de los procesos de memoria y condicionamiento (hipocampo y amígdala), la motivación y programación de respuestas motoras (ganglios basales), la inhibición de respuestas (cíngulo anterior) y la toma de decisiones (corteza orbitofrontal). De este modo, en el "cerebro adicto" los sistemas de condicionamiento, aprendizaje y procesamiento de reforzadores estarían sensibilizados hacia estímulos asociados al consumo, mientras que el sistema de inhibición sería menos eficiente, facilitando las decisiones relacionadas con el consumo (Figura 1).

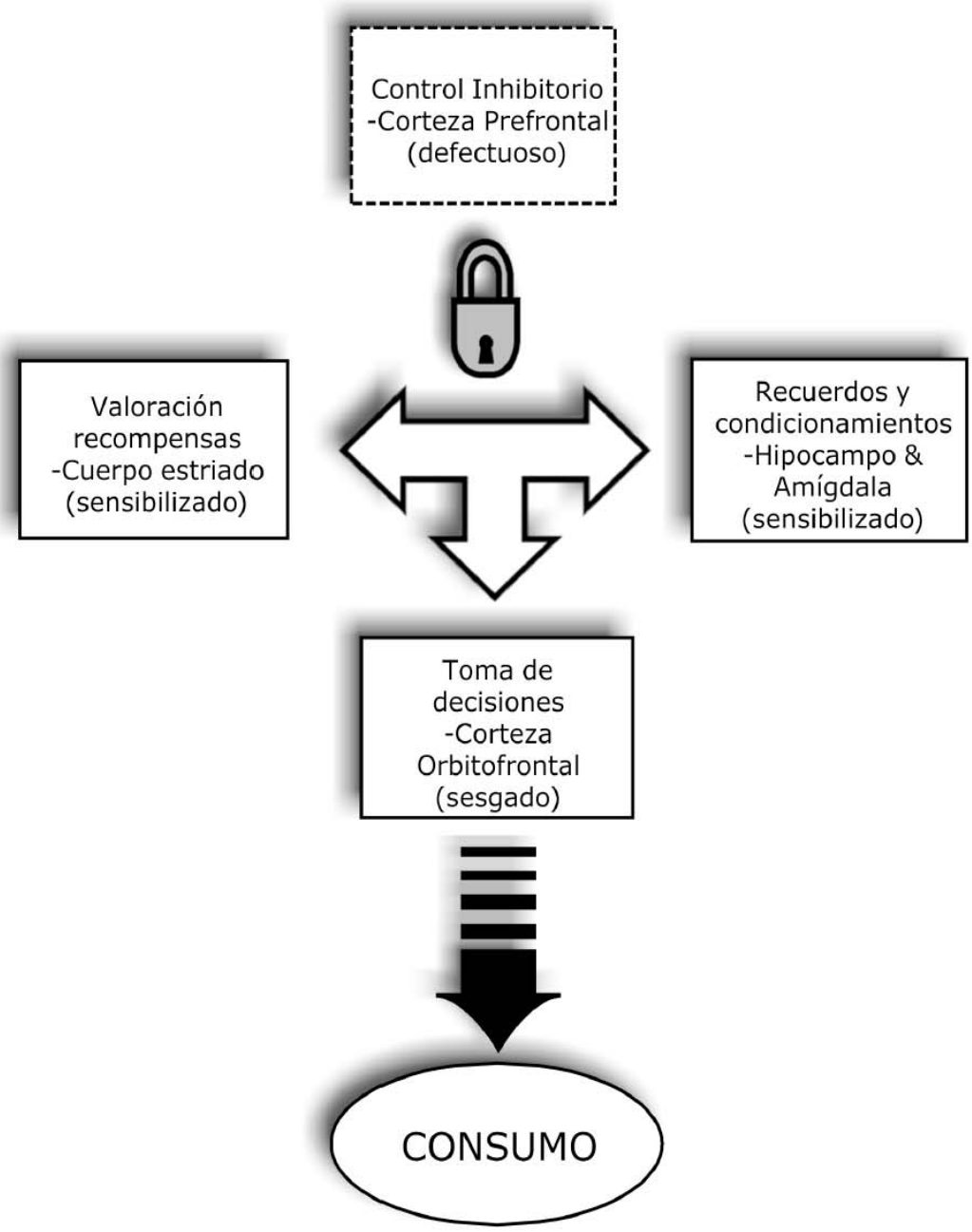


Figura1. Modelo I-RISA (Goldstein y Volkow, 2002).

- Los sistemas encargados de la atribución de relevancia a los estímulos (sistemas de recompensa, condicionamientos implícitos y memorias explícitas) están hipersensibilizados hacia estímulos relacionados con el consumo al tiempo que devalúan otros reforzadores naturales.
- Los sistemas encargados del control de respuestas impulsivas o guiadas por la recompensa inmediata están alterados, por lo que no pueden ejercer control sobre el resultado conductual.
- Los procesos de toma de decisiones están sesgados por la hiperactivación de los sistemas que señalan la necesidad de las drogas y la inoperancia de los sistemas de control, favoreciendo las conductas de consumo.

1. 2. Modelo del marcador somático (Verdejo-García & Bechara, 2009)

Otros modelos han tratado de explicar el proceso adictivo como resultado de la vulnerabilidad del sistema neuropsicológico de toma de decisiones. Uno de estos modelos basa sus propuestas en la hipótesis del marcador somático, propuesta originalmente por Damasio (1994; 2000). Esta hipótesis sostiene que la toma de decisiones es un proceso guiado por señales emocionales (marcadores somáticos) encargados de marcar afectivamente las consecuencias prospectivas de distintas opciones de elección siguiendo una lógica homeostática. La aplicación de esta noción al contexto de las adicciones explica el consumo repetido de drogas como el resultado de una disfunción de los sistemas neurobiológicos encargados de la generación y la adecuada "lectura" de los marcadores somáticos necesarios para la toma de decisiones adaptativa. Específicamente, esta disfunción resultaría en una mayor dificultad para asignar estados emocionales adecuados a los escenarios cognitivos de decisión, propiciando un proceso de decisión despojado del valor emocional asociado a las potenciales consecuencias de las distintas opciones de respuesta y, por tanto, sesgado hacia opciones de reforzamiento inmediato incluso cuando éstas conllevan importantes repercusiones negativas a medio y largo plazo. De este modo, cuando la persona adicta tiene disponibilidad de drogas en su entorno, o bien recuerda, imagina, o reexperimenta situaciones de consumo, los marcadores emocionales asociados con el consumo serían mucho más potentes que los marcadores adaptativos y sesgarían la toma de decisiones hacia el consumo en detrimento de otras posibilidades más adaptativas a largo plazo. El modelo especifica una serie de sistemas cerebrales que intervienen en (1) la generación de estos marcadores emocionales (corteza prefrontal ventromedial y amígdala), (2) la "lectura" que el cerebro hace de estos marcadores en áreas especializadas en mapeo

corporal (cortezas insulares y somatosensoriales), y (3) la selección final de la respuesta (núcleo estriado y corteza cingulada anterior). (Verdejo-García, Pérez-García & Bechara, 2006; Verdejo-García & Bechara, 2009) (Figura 2).

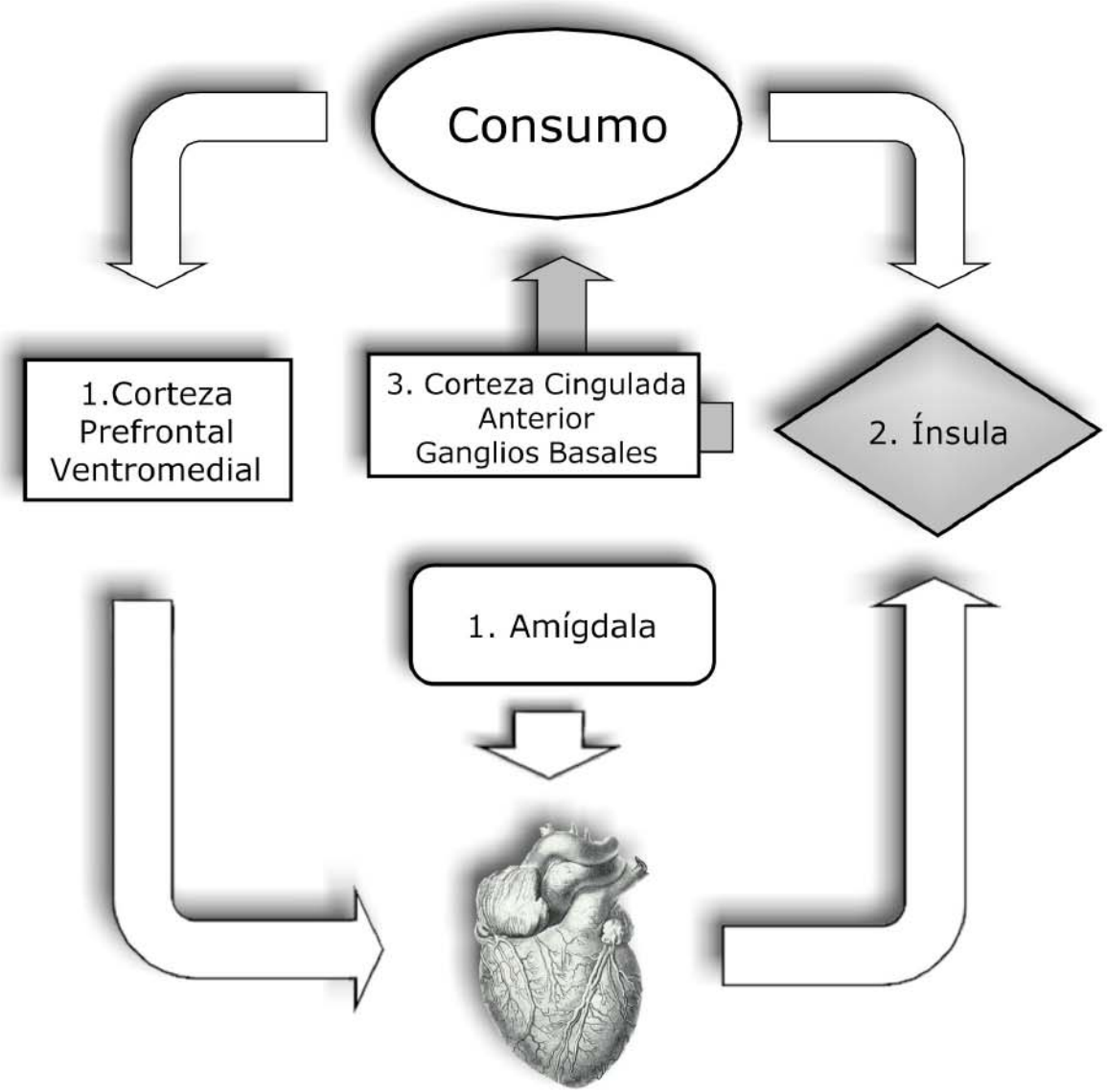


Figura 2. Modelo del marcador somático (Verdejo-García y Bechara, 2009).

- La Amígdala (en casos de exposición directa) o la Corteza Prefrontal Ventromedial (en procesos autoreflexivos) envían potentes señales relacionadas con la expectativa de consumo.
- Estas señales generan una intensa activación corporal, que devuelve señales interoceptivas procesadas por la Ínsula y traducidas en sensaciones de craving.
- Estas señales adquieren la capacidad de "secuestrar" los mecanismos motivacionales (Ganglios Basales) y de selección de respuesta (Corteza Cingulada Anterior), propiciando una toma de decisiones basada en la satisfacción de la necesidad inmediata.
- Las conductas de consumo retroalimentan este círculo vicioso.

1. 3. Modelo de vulnerabilidades (Redish, Jensen & Johnson, 2008)

En un modelo reciente con vocación integradora, Redish, Jensen & Johnson (2008) han postulado distintas vías de vulnerabilidad que pueden sesgar el sistema de toma de decisiones hacia la selección de hábitos inflexibles (p.e., las conductas de búsqueda y consumo de drogas) obviando la planificación de conductas dirigidas a objetivos más saludables. Por tanto, las múltiples fuentes de vulnerabilidad actuarían deshaciendo el equilibrio entre (i) el sistema de planificación (análogo del sistema ejecutivo, con bases cerebrales en la corteza prefrontal), (ii) el sistema de hábitos (relacionado con el funcionamiento de los ganglios basales) y (iii) el sistema de observación y categorización, que proporciona un marco contextual a la actividad de los dos anteriores. Las potenciales fuentes de vulnerabilidad que pueden desestabilizar el sistema incluyen: (i) desviaciones persistentes de la homeostasis y la alostasis relacionadas con la alteración del equilibrio hedónico (p.e., estados crónicos de anhedonia o estrés), (ii) aparición de potentes señales euforizantes de recompensa, (iii) incrementos desproporcionados del descuento de recompensas demoradas (el valor de los premios a largo plazo se devalúa exageradamente), (iv) sobrevaloración de los sistemas de planificación, habituación o desajuste entre ambos (estos sistemas pueden quedar persistentemente sensibilizados a la búsqueda y la obtención de drogas), (v) fallos del sistema de búsqueda e identificación de contextos relevantes (p.e., ilusiones de control o distorsiones de sobregeneralización o sobrecategorización) y (vi) alteraciones de los ratios de aprendizaje, que pueden llevar a despreciar asociaciones consistentes o a identificar asociaciones falsas o ilusorias entre estímulos (ver Figura 3). El modelo contempla diversas vías de actuación de estas vulnerabilidades, desde la

predisposición biológica a aprendizajes cognitivos y afectivos desadaptativos, así como la posibilidad de múltiples interacciones entre las distintas fuentes de vulnerabilidad.

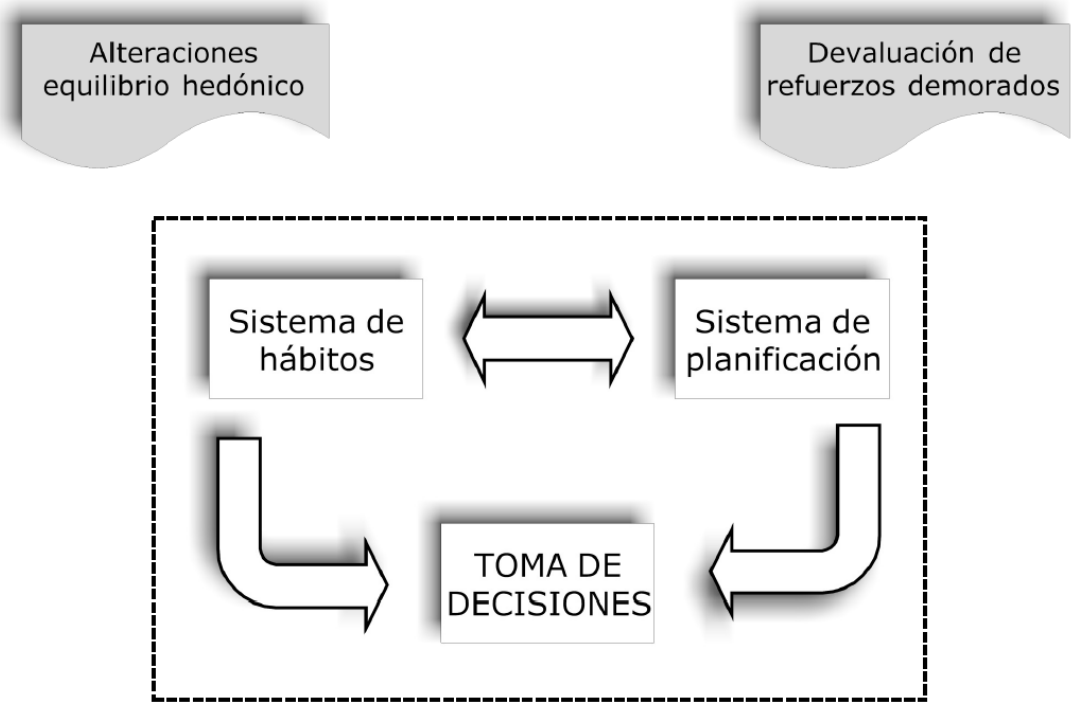


Figura 3. Modelo de vulnerabilidades de Redish et al., 2008

- El núcleo central de los cambios neuropsicológicos asociados con la adicción se produce en el equilibrio entre los sistemas de planificación y hábitos que hacen posible la toma de decisiones adaptativa.
- Este sistema es vulnerable a múltiples influencias que pueden sesgar la toma de decisiones hacia el consumo. De manera ilustrativa, se presentan dos ejemplos que pueden afectar más robustamente al sistema de hábitos (p.e., las alteraciones del equilibrio hedónico que hiperactivan los sistemas de estrés y reforzamiento negativo) o al sistema de planificación (p.e., la depreciación de reforzadores demorados sesga al sistema de planificación hacia reforzadores inmediatos).

1.4. Implicaciones sobre el abordaje del proceso adictivo

Actualmente, estos modelos neuropsicológicos que conciben la adicción como un desequilibrio progresivo entre un sistema de reforzamiento y estrés hipersensibilizados y un sistema ejecutivo deteriorado tienen un abundante apoyo empírico transversal a distintas metodologías, incluyendo estudios animales (Jentsch & Taylor, 1999), estudios de neuroimagen (Garavan & Stout, 2005) y estudios neuropsicológicos (Verdejo-García & Pérez-García, 2007a). Es fundamental hacer notar que estos modelos neuropsicológicos no sólo explican la adicción a un nivel "básico" sino que además tienen importantes repercusiones clínicas. De este modo por ejemplo, alteraciones en los mecanismos ejecutivos de los individuos consumidores de drogas podrían estar interfiriendo en su rendimiento cognitivo general y por ende repercutir en su calidad de vida, actividad y rendimiento laboral y/o académico o incluso en su estatus legal (véase Verdejo-García, Alcázar-Córcoles, Gómez-Jarabo & Pérez-García, 2004). Los déficits neuropsicológicos en los mecanismos inhibitorios de control de respuestas impulsivas podrían estar implicados en el consumo compulsivo y la perpetuación del trastorno (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999). Asimismo, estos déficits podrían limitar la posibilidad de beneficiarse de los programas de tratamiento de la adicción (Aharanovich et al., 2006; Fernández-Serrano, Pérez-García, Schmidt Río-Valle & Verdejo-García, 2010a; Teichner, Horner, Roitzsch, Herron & Thevos, 2002) y facilitar la ocurrencia de recaídas (Passetti, Clark, Mehta, Joyce & King, 2008; Paulus, Tapert & Schuckit, 2005; Streeter et al., 2008).

En conjunto, los hallazgos básicos sobre el impacto neuropsicológico del consumo crónico de drogas y sus implicaciones clínicas subrayan la necesidad de llevar a cabo un abordaje neuropsicológico del proceso adictivo.

Capítulo 2

Evaluación neuropsicológica en consumidores de drogas: procesos e instrumentos

1. Evalución neuropsicológica en drogodependencias

Los avances en la evaluación de las funciones neuropsicológicas, con el desarrollo de baterías clínicas y computarizadas que incluyen pruebas específicas de control ejecutivo y toma de decisiones sensibles a los déficits característicos de la adicción (Bechara, 2007; Clark, Robbins, Ersche & Sahakian, 2006), y la aplicación de nuevas pruebas con mayor validez ecológica, capaces de predecir con mayor precisión las consecuencias funcionales del deterioro neuropsicológico en la vida cotidiana (Verdejo-García & Pérez-García, 2007b), han contribuido notablemente a mejorar el conocimiento relativo a los efectos neuropsicológicos provocados por el abuso de drogas y el propio proceso adictivo. En conjunción con otras metodologías de exploración de las funciones cerebrales, como la neuroimagen funcional, la evaluación neuropsicológica sigue siendo una de las herramientas más empleadas para determinar la naturaleza y extensión de las posibles disfunciones del sistema nervioso central (SNC) asociadas al consumo de drogas, y sus repercusiones sobre la cognición, la emoción, la personalidad y la conducta.

La evaluación neuropsicológica se define como un proceso dinámico de generación y contraste de hipótesis que a través del uso de instrumentos sensibles a la captación del desempeño neuropsicológico, permite caracterizar posibles alteraciones del rendimiento del individuo asociadas con sistemas cerebrales específicos (Lezak, 2004; Pérez-García, 2009; Vanderploeg, 2000). En el campo de las drogodependencias la evaluación neuropsicológica ha abarcado tradicionalmente el estudio de procesos cognitivos como la atención, y la memoria, el estudio de las funciones ejecutivas, así como el estudio de los procesos emocionales. A continuación haremos una descripción de cada uno de estos procesos neuropsicológicos e indicaremos algunas de las pruebas y

tareas que con mayor frecuencia han sido empleadas para su evaluación en consumidores de drogas (ver Tabla 1 para una descripción de estos instrumentos).

DOMINIOS NEUROPSICOLÓGICOS		INSTRUMENTOS DE EVALUACIÓN
ATENCIÓN	Selectiva Sostenida	- *Stroop:* se requiere controlar una respuesta automatizada (leer la palabra) por una controlada (decir el color de la tinta con la que esta escrita) - *Test de atención numérica:* versión abreviada del *Digit Vigilance Test*, requiere identificar y señalar todos los "6" ó "9" de entre un conjunto de dígitos - *Test d2:* requiere identificar y señalar todos las "d" marcadas con dos guiones de entre un conjunto de ítems ("b" y "d") marcados con distinto número de guiones.
	Dividida	- *Trail making test:* requiere la conexión consecutiva de números (parte A) y de números y letras de forma alternante (parte B).
MEMORIA	Verbal	- *TAVEC:* requiere el aprendizaje de una lista de dieciséis palabras agrupadas en cuatro categorías semánticas (frutas, especias, herramientas y prendas de vestir) a lo largo de cinco intentos consecutivos
	Visual	- *Test de la figura compleja de Rey:* se requiere realizar la copia de una figura compleja, posteriormente, sin previo aviso y sin la ayuda del modelo, se requiere reproducir inmediatamente y a los 30 minutos de nuevo la misma figura
FUNCIONES EJECUTIVAS	Memoria de trabajo	- *Dígitos:* consta de dos partes: (i) "orden directo" requiere reproducir una secuencia de dígitos en el mismo orden en que se ha presentado, (ii) "orden inverso" requiere reproducir una secuencia de dígitos en orden inverso a cómo le ha sido presentada - *Aritmética:* se requiere resolver una serie de problemas aritméticos en un tiempo límite - *Letras y números:* se requiere reproducir de forma ordenada una secuencia de letras y números que se le ha proporcionado desordenada (primero los números en orden ascendente y luego las letras en orden alfabético) - *Span visual:* en una tabla formada por una serie de cubos se requiere (i) "orden directo" que el participante toque la misma secuencia de cubos que tocó el evaluador, en el mismo orden, (ii) "orden inverso" requiere reproducir la secuencia de cubos en orden inverso a como fue tocada por el evaluador. - *N-back:* ante una serie continua de estímulos se requiere responder cuando el estímulo objetivo se presenta después de uno (n = 1), dos (n = 2) o tres (n = 3) estímulos distractores
	Fluidez	- *FAS:* requieren la producción rápida y continua de palabras que empiezan por una determinada letra (F, A, S) evitando perseveraciones - *Animales, frutas, herramientas:* requieren la producción rápida y continua de palabras que empiezan por una determinada categoría semántica (animales, frutas, herramientas), evitando perseveraciones. - *RFFT:* requieren la producción rápida y continua de diseños o patrones en respuesta a instrucciones específicas, tratando de evitar perseveraciones
	Razonamiento	- *Semejanzas:* se enuncian parejas de palabras que representan objetos o conceptos comunes y se requiere que el participante indique en qué se parecen, qué tienen en común o qué son
	Control Inhibitorio	- *5DT:* consta de cuatro partes: (i) se requiere leer el dígito en cada casilla, (ii) se requiere contar el número de estrellas de cada casilla, (iii) se quiere contar el número de dígitos de cada casilla (condición de interferencia) y (iv) se requiere que en función del grosor que presenta el recuadro de la casilla el participante lea (como en condición i) o cuente (como en condición iii) - *Stop signal, Go/no go:* requiere responder de manera continua ante la presentación de la mayoría de estímulos (normalmente presionando teclas del ordenador), pero intentar suprimir esta respuesta motora ante la presentación de una minoría de estímulos. Por ejemplo, responder a todas las letras del alfabeto menos la "Y" - *Delay discounting:* se requiere elegir entre una opción que proporciona una recompensa inmediata de menor valor y otra opción que proporciona una recompensa demorada de mayor valor. Se pueden utilizar recompensas reales (normalmente monetarias) o hipotéticas, con resultados de ejecución similares - *MFFT-20:* Se presenta un dibujo modelo al participante y 6 posibles opciones de respuesta entre las que se requiere que elija aquella que es igual al modelo presentado - *R-SAT:* Consta de 6 bloques de hojas en las que aparecen elementos que varían en su tamaño (grandes-pequeños) y extensión (breves-largos) y que implican la realización de tres subtareas: (i) trazar figuras, (ii) copiar frases, (iii) numerar series de objetos. Estas tareas deben ser realizadas teniendo en cuenta una serie de reglas: los elementos pequeños valen 100 puntos y los grandes 0, objetivo es obtener el máximo de puntos posible, si se trabaja en hojas en las que aparezcan caras se pierden los puntos, deben trabajar en cada uno de los 6 bloques, límite temporal de 10 minutos, hacer una marca por cada minuto

Tabla 1 (continuación)

	Flexibilidad	- *Prueba de Categorías:* consta de 7 subtest en cada uno de los cuales aparecen una serie de estímulos que consisten en distintos tipos de diseños (cuadrados, círculos, letras, etc) en los que se requiere la inferencia de la regla o concepto que determina la adecuación de las respuestas en ese subtest - *Wisconsin:* se requiere emparejar una serie de tarjetas que contienen estímulos simples caracterizados por tres dimensiones relevantes (color, forma y número de elementos) con cuatro tarjetas de referencia en función de unas reglas que son conocidas sólo por el evaluador quien proporciona feedback sobre la corrección o incorrección de cada ensayo y que varían a lo largo de la tarea - *Reversal learning:* requieren la inversión de un aprendizaje que ha dejado de ser reforzado por otro que resulta reforzado en este momento (p.e. dejar de elegir un estímulo que antes conllevaba un sonido asociado a acierto pero que ahora conlleva un sonido asociado a error e invertirlo por la elección de otro estímulo diferente)
	Toma de decisiones	- *IGT:* se requiere elegir entre cuatro barajas de cartas que producen ganancias/pérdidas que varían en el valor de las recompensas inmediatas y los castigos demorados (por ejemplo, dos barajas producen altas recompensas y castigos desproporcionados y dos barajas producen bajas recompensas pero pequeños castigos) - *CGT, GDT:* se requiere elegir entre opciones de recompensa que producen un conflicto entre la probabilidad de ganar y la cantidad asociada (por ejemplo, elegir entre un 10% de posibilidades de ganar 100 euros ó un 90% de ganar 10 euros)
PROCESOS EMOCIONALES	Percepción	- *Ekman:* se presenta al participante 60 fotografías en las que se requiere que identifique la emoción que expresan los individuos allí expuestos a partir de sus expresiones faciales. Se emplean 6 emociones básicas: asco, miedo, ira, felicidad, sorpresa y tristeza
	Experiencia	- *ICERE:* se requiere la valoración de una serie de imágenes de diferente contenido emocional a partir de tres dimensiones: arousal (activación), valencia (agradabilidad) y dominancia.

Tabla 1. Descripción de algunos instrumentos empleados en la evaluación neuropsicológica de consumidores de drogas

1.1. Procesos cognitivos

1.1.1. Atención

Hace referencia a diferentes capacidades y procesos relacionados con el modo en que el organismo llega ser receptivo a ciertos estímulos siendo capaz de prescindir de los restantes (Lezak, 2004). Se trata de un proceso neuropsicológico multidimensional que requiere de instrumentos específicos capaces de captar sus diversos subprocesos. Con frecuencia se postula la existencia de tres tipos de atención: selectiva, dividida y sostenida. La atención selectiva es aquella que permite que en una situación o tarea la persona pueda seleccionar la información o el esquema de acción más relevante para la misma (García-Ogueta, 2001; Posner & Petersen, 1990). La atención sostenida ha sido definida como la capacidad de mantener la selectividad atencional durante un tiempo prolongado en la realización de una tarea (García-Ogueta, 2001; Posner & Petersen, 1990). Por ultimo, la atención dividida es aquella que permite al individuo seleccionar más de una información o esquema de acción a la vez, pudiendo atender las demandas de múltiples tareas de forma simultánea (García-Ogueta, 2001; Posner & Petersen, 1990).

Para la evaluación de la atención selectiva un instrumento frecuentemente empleado es la tarea de Stroop, que evalúa la capacidad de desplazar los recursos atencionales que se activan "por defecto" en la lectura de palabras para focalizar la atención en una respuesta más controlada (nombrar el color). Diversas investigaciones han desarrollado adaptaciones de esta tarea en la que se insertan palabras relacionadas con el consumo de drogas. Estos estudios han demostrado que los consumidores de drogas suelen tener dificultades para filtrar la información irrelevante o inadecuada cuando ésta tiene que ver con estímulos asociados al consumo; en este sentido, el sesgo

atencional ha sido propuesto como una de los principales factores implicados en los estados de "craving" (Field & Cox, 2008). Para la evaluación de la atención sostenida suele recurrirse al empleo de pruebas como el *Test de atención numérica,* que ha demostrado ser sensible a la detección de deterioros neuropsicológicos en atención sostenida en consumidores de psicoestimulantes (Jovanovski, Erb & Zakzanis, 2005; O'Malley, Adamse, Heaton & Gawin, 1992), o tests de cancelación como el *test d2.* Para evaluar la atención dividida tradicionalmente se ha empleado la prueba *Trail Making Test parte B*, una tarea que requiere la activación de habilidades viso-espaciales, viso-motoras, atencionales y de flexibilidad cognitiva y planificación de conducta (Spreen & Strauss, 1991).

1.1.2. Memoria

Definida como la capacidad para almacenar y recuperar conocimientos (Lezak, 2004), los modelos neuropsicológicos contemporáneos postulan que se organiza en dos sistemas principales, el de memoria declarativa y el de memoria procedimental (Squire & Knowlton, 2000). La memoria declarativa implica el recuerdo consciente de eventos o experiencias pasadas, mientras que la procedimental se relaciona con el aprendizaje de habilidades y rutinas. Ambos sistemas se han vinculado a las neuroadaptaciones que subyacen a la progresión del proceso adictivo (Robbins, Ersche & Everitt, 2008).

Entre las pruebas empleadas para la evaluación de las capacidades mnésicas podemos destacar la *Escala de Memoria Wechsler* (Wechsler, 1997a), que permite obtener información detallada sobre la memoria del individuo tanto a través de estímulos auditivos como de tipo visual, posee buenas propiedades psicométricas (validez y fiabilidad) y ha demostrado ser sensible a la detección de alteraciones en memoria entre consumidores de distintas drogas, incluyendo cannabis, cocaína y

MDMA (Bolla et al., 1998; Grant, Gonzalez, Carey, Natarajan & Wolfson, 2003; Halpern et al., 2004; Jovanovsky et al., 2005). Asimismo, pruebas de aprendizaje verbal, que han demostrado gran sensibilidad y especificidad en la detección de alteraciones de memoria declarativa en consumidores de distintos tipos de sustancias (Bolla, Brown, Eldreth, Tate & Cadet, 2002; Bondi, Drake & Grant, 1998; Halpern et al., 2004; Mittenberg & Motta, 1993). En esta categoría se encuadra el Test de Aprendizaje Verbal España-Complutense (Benedet & Alejandre, 1998) que presenta buenas propiedades psicométricas, una adecuada estructura interna y buenos índices de validez ecológica (Chirivella, Villodre, Sebastián & Ferri, 2003). El Test de la Figura Compleja de Rey es un instrumento frecuentemente empleado para la evaluación de la memoria visual y la organización perceptual y también ha demostrado buena sensibilidad y especificidad en la detección de alteraciones en consumidores de drogas (Bhattachary & Powell, 2001; Bolla et al., 2002; Medina et al., 2007).

1.2. Funciones ejecutivas

Han sido definidas como un grupo integrado de habilidades implicadas en la generación, supervisión y monitorización de conductas dirigidas hacia objetivos socialmente adaptativos (Roberts, Robbins & Weiskrantz, 1998; Stuss & Knight, 2002; Verdejo-García & Pérez-García, 2007a). Aunque tradicionalmente las funciones ejecutivas han sido consideradas como un dominio cognitivo general (Denckla & Reiss, 1997; Zelazo et al., 1997), estudios recientes han concordado en la existencia de diversos componentes o subfunciones relativamente independientes aunque interrelacionadas a la hora de dar respuesta a situaciones complejas y novedosas (Fisk & Sharp, 2004; Miyake, Friedman, Emerson, Witzky & Howerther, 2000; Verdejo-García

& Pérez-García, 2007a). Recientes estudios factoriales realizados a partir de múltiples índices neuropsicológicos han indicado la existencia de al menos cuatro componentes en las funciones ejecutivas: actualización, control inhibitorio, flexibilidad cognitiva y toma de decisiones (Verdejo-Garcia & Perez-Garcia, 2007a).

1.2.1. Actualización: memoria de trabajo, razonamiento y fluidez

El componente de actualización implica la monitorización, actualización y manipulación de información "on line" en la memoria operativa (Miyake et al., 2000). Estudios factoriales indican que dentro de este componente se incluyen los procesos de memoria de trabajo, fluidez y razonamiento (Verdejo-Garcia & Perez-Garcia, 2007a).

La memoria de trabajo es un sistema que permite el almacenamiento, manipulación y actualización temporal de la información en el cerebro (D'Esposito et al., 1995). Para evaluar este componente algunas investigaciones han recurrido a algunos subtests de la escala WAIS (Wechsler Adult Intelligence Scale, Wechsler, 1997b) incluyendo *Dígitos*, que permite evaluar la capacidad para mantener o almacenar la información temporalmente (y manipularla en la parte de dígitos en orden inverso), y *Artimética* y *Letras y Números* que además de evaluar el mantenimiento temporal de información permiten evaluar la capacidad de manipularla para generar nuevas secuencias. Otros instrumentos frecuentemente empleados en la literatura son la prueba de *Span visual* de la *Escala de memoria Wechsler*, o las tareas *n-back*. Estas tareas permiten evaluar, además de la capacidad para mantener y manipular temporalmente la información, la capacidad para actualizar esa información. Asimismo, han demostrado ser tareas eficaces en la detección de alteraciones en procesos de memoria de trabajo en consumidores de distintas sustancias (Gouzoulis-Mayfrank, Thimm, Rezk, Hensen & Daumann, 2003; Mintzer, Copersino & Stitzer, 2005, Pitel et

al., 2007). Además, en estas tareas los sesgos culturales, como el nivel socioeconómico o el nivel educativo, que parecen ejercer una influencia importante en las tareas verbales (Rice, 1997) ejercen una menor influencia, ya que su realización no depende de habilidades asociadas al desempeño académico (p.e. operaciones matemáticas, vocabulario específico). De este modo, estas tareas presentan la ventaja de poder ser empleadas con personas de diferentes niveles socioeconómicos o académicos. No obstante la inexistencia de baremos en el caso de las tareas *n-back*, que fueron concebidas como tareas experimentales de investigación, constituyen una limitación a tener en cuenta en posibles usos clínicos.

El razonamiento analógico consiste en obtener una conclusión a partir de premisas sobre las que se establece una comparación o analogía entre elementos o conjuntos de elementos distintos. Para la evaluación de este dominio tradicionalmente se ha recurrido, entre otras, al empleo del subtest de *Semejanzas* del *WAIS*. Esta tarea ha sido empleada con frecuencia en el estudio de consumidores de distintas sustancias (Fernández-Serrano et al., 2010a; Jovanovksky et al., 2005; Verdejo-García & Pérez-García, 2007a) y ha demostrado una importante capacidad discriminativa en la caracterización de los efectos neuropsicológicos diferenciales de los opiáceos o el alcohol (Verdejo-García, Toribio, Orozco, Puente & Pérez-García, 2005a).

Por último podemos definir la fluidez como la capacidad del individuo para iniciar su conducta de forma espontánea y creativa en respuesta a una orden novedosa. La evaluación de la fluidez ha sido abordada a través de dos tipos de instrumentos: los dirigidos a evaluar fluidez verbal y los dirigidos a la evaluación de la fluidez figurativa. Dentro de las primeras el instrumento más usado es el *Test de fluidez verbal FAS* (Lezak, 2004) que permite la evaluación de la fluidez fonológica y la tarea de generar

ejemplares de *Animales, Frutas* y *Herramientas* para evaluar la fluidez semántica. Para la evaluación de la fluidez figurativa se ha recurrido al uso del *Ruff Figural Fluency Test -RFFT* (Ruff, 1996). Sus limitaciones más importantes son la influencia de los años de escolaridad en el caso del *FAS* y la inexistencia de baremos para población española en el caso del *RFFT*.

1.2.2. Control inhibitorio

Este componente ha sido definido como la habilidad para inhibir o demorar de manera eficiente la producción de respuestas automáticas, impulsivas o guiadas por el reforzamiento inmediato. No obstante se trata de un constructo multidimensional asociado con distintos procesos neuropsicológicos con bases cerebrales relativamente independientes. Por tanto, existen diversos modelos neuropsicológicos de control inhibitorio (y distintas tareas para medirlos) incluyendo: (i) inhibición de respuesta, la habilidad para cancelar respuestas (habitualmente en referencia a respuestas motoras) que no son adecuadas para la situación actual, (ii) descuento asociado a la demora (delay discounting), la preferencia por refuerzos inmediatos incluso aunque sean de menor magnitud que otros refuerzos más demorados en el tiempo, (iii) reflexión-impulsividad, la tendencia a recopilar y evaluar mayor o menor cantidad de información antes de tomar una decisión y (iv) auto-regulación, la habilidad para regular la conducta con objeto de optimizar objetivos a largo plazo en ausencia de control externo (Verdejo, Lawrence & Clark, 2008).

Para la evaluación de la inhibición de respuesta suelen emplearse dos tipos de pruebas: aquellas que evalúan la inhibición atencional (la capacidad para sustituir una respuesta automatizada por otra que exige mayor control cognitivo) y las que evalúan la inhibición motora (la capacidad para retener respuestas motoras salientes ante la

presentación de estímulos sobreaprendidos o competitivos). Dentro de las que permiten evaluar inhibición atencional destacan el *Test de los Cinco Dígitos* (Sedó, 2005), que ofrece la ventaja de ser una prueba breve y de fácil aplicación, que puede ser empleada con personas de bajo nivel cultural e incluso no alfabetizadas, y el test de *Stroop*, mencionado anteriormente. El *Stroop* ha demostrado además ser un buen predictor de resultado del tratamiento del abuso de cocaína (Streeter et al., 2008). El *Test de los 5 Dígitos* ha demostrado ser una herramienta útil en la discriminación de los perfiles neuropsicológicos de consumidores de cocaína vs. opiáceos (Verdejo-García, Perales & Pérez-García, 2007a). Para evaluar la inhibición motora se utilizan las tareas *Stop-Signal* o *Go/No go*, que también presentan la ventaja de poder ser administradas en personas no alfabetizadas y que han sido empleadas consistentemente en investigaciones neuropsicológicas en consumidores de distintas drogas (Fillmore & Rush, 2002; Monterosso, Aron, Cordova, Xu & London, 2005). Para evaluar la tendencia a descontar el valor de una recompensa en función del tiempo es frecuente recurrir al empleo de cuestionarios de "descuento asociado a la demora" en los que se pide al individuo que seleccione sus preferencias a un nivel hipotético (Kirby et al., 2004) o las tareas "experienciales" de descuento, en las que hay dinero sobre la mesa y el individuo tiene que elegir entre pequeñas cantidades entregadas de inmediato (p.e., 20 céntimos ahora) o mayores cantidades entregadas en un tiempo medio (p.e., 2 euros dentro de 30 minutos) (Reynolds & Schiffbauer, 2004). Ambas han sido empleadas de forma recurrente en la literatura en consumidores de drogas (Heil, Johnson, Higgins & Bickel, 2006; Hoffman et al., 2006). Para medir el continuo reflexividad-impulsividad tradicionalmente se ha recurrido al empleo el *Test de Emparejamiento de Figuras Conocidas: MFFT-20* (Cairns & Cammock, 2002). Esta tarea presenta buenas

propiedades psicométricas (fiabilidad y validez) (Fernández-Martín & Hinojo-Lucena, 2006) y ha sido empleada en el contexto de la evaluación de la impulsividad en distintos perfiles de consumidores de drogas (Morgan, Impallomeni, Pirona & Rogers, 2006; Morgan et al., 1998). Asimismo, recientemente se desarrolló la Tarea de Recolección de Información (*Information Sampling Task*; Clark et al., 2006) que está dirigida a la evaluación específica de este componente intentando minimizar la influencia de otros procesos neuropsicológicos (p.e., procesamiento viso-espacial, atención, memoria de trabajo). Su aplicación al campo de las drogodependencias ha demostrado buenos niveles de sensibilidad y especificidad en la captación de distintos perfiles de consumo (Clark et al., 2006). Finalmente, para evaluar los procesos complejos de auto-regulación habitualmente se utiliza el Test de Aplicación de Estrategias (*Revised Strategy Aplications Test -R-SAT,* Levine, Dawson, Boutet, Schwartz, & Stuss, 2000). Éste es un test multi-tarea (con varias tareas paralelas que se deben resolver en un tiempo límite) que mide la capacidad del individuo para organizar y reajustar de manera dinámica su estrategia de respuesta en función de un objetivo a largo plazo, para lo que además debe controlar tendencias de respuesta automatizadas. Ha sido utilizada con buenos índices discriminativos en consumidores de distintos tipos de sustancias, como la MDMA y otros psicoestimulantes (Halpern et al., 2004; Verdejo-García, Rivas-Pérez, Vilar-López y Pérez-García, 2007b).

1.2.3. Flexibilidad cognitiva

La flexibilidad cognitiva es la capacidad de reestructurar el propio conocimiento de forma espontánea para dar una respuesta adaptada a las exigencias cambiantes del ambiente (Spiro & Jehng, 1990). Se trata también de un componente multidimensional que ha sido estudiado a través de distintos índices, incluyendo pruebas que miden la

respuesta del individuo ante el cambio en las reglas de la tarea, el criterio de respuesta o el set (esquema) atencional y tareas de aprendizaje reverso ("reversal learning") que miden la capacidad del individuo para cambiar su respuesta en función de cambios en los patrones de reforzamiento.

Para la evaluación de la respuesta del individuo ante el cambio de set se ha recurrido a tareas como la *Prueba de Categorías* o el *Test de Clasificación de Tarjetas de Wisconsin*. La *Prueba de Categorías* (De Filippis, 2002) es una tarea informatizada que presenta tamaños del efecto considerables en la discriminación del rendimiento de consumidores y controles (Verdejo-Garcia & Perez-Garcia, 2007a). El *Test de Winconsin* es una de las herramientas más empleadas para la detección de errores perseverativos en consumidores de drogas (Dafters, Hoshi & Talbot, 2004; Goldstein et al., 2004; Lyvers & Yakimoff, 2003; Ratti, Giardini & Soragna, 2002) y ha demostrado buenos valores de predicción del resultado del tratamiento en consumidores de cocaína (Turner, LaRowe, Horner, Herron & Malcolm, 2009). Entre las tareas de aprendizaje reverso destacan por su sensibilidad en población drogodependiente las tareas de refuerzo probabilístico que generan aprendizajes afectivos más potentes cuya reversión provoca niveles significativos de perseveración, especialmente en consumidores de psicoestimulantes (Ersche, Roiser, Robbins & Sahakian, 2008; Ornstein et al., 2000).

1.2.4. Toma de decisiones

La toma de decisiones es la habilidad para seleccionar de entre un conjunto de posibles alternativas existentes aquella que resulta más adaptativa para el individuo. Se postula la existencia de dos tipos de procesos de toma de decisiones que son relevantes en los trastornos adictivos: (i) aquellos que tienen lugar bajo condiciones de ambigüedad, es decir, en las que las consecuencias de las distintas opciones son inciertas, y (ii) aquellos

que tienen lugar en condiciones de riesgo, en las que las consecuencias de cada opción son conocidas por el individuo (Brand, Labudda & Markowitsch, 2006).

Para la evaluación de la toma de decisiones en condiciones de ambigüedad la prueba más utilizada es la *Iowa Gambling Task* (IGT) que ha demostrado una elevada validez ecológica ya que predice de forma significativa la gravedad de un amplio rango de problemas relacionados con la adicción, incluyendo problemas de empleo, socio-familiares o legales (Verdejo-García, Bechara, Recknor & Pérez-García, 2006). Además es una tarea sensible a la detección de alteraciones en la toma de decisiones entre consumidores de diversas drogas (Bolla et al., 2003; Bolla, Eldreth, Matochik & Cadet, 2005; Dom, D´haene, Hulstijn & Sabbe, 2006; González et al., 2007; Hanson, Luciana & Sullwold, 2008; Mintzer et al., 2005; Verdejo-García et al., 2007b, Verdejo-García, et al., 2007c). Como desventaja se puede mencionar la ausencia de baremos para población española aunque algunos estudios han evaluado el rendimiento a partir de puntos de corte obtenidos en poblaciones clínicas (Verdejo-García, Aguilar de Arcos & Pérez-García, 2004). No obstante, los estudios originales con la prueba mostraron que en torno al 15% de población no consumidora tiene una pobre ejecución es esta tarea (Bechara et al., 2001) por lo que sus resultados deben siempre interpretarse con cautela y deben ser contrastados con los resultados de otras pruebas e informes. Para la evaluación de la toma de decisiones en condiciones de riesgo algunas investigaciones han empleado las tareas del Juego de Dados (*Game of Dice Task*; GDT) o la tarea de Apuestas de Cambridge (*Cambridge Gamble Task;* CGT). Estas tareas implican situaciones de decisión en la que el individuo tiene información sobre las potenciales consecuencias y las probabilidades de obtención de refuerzo y castigo de cada opción, por lo que son teóricamente más cercanas a las decisiones de la vida diaria en las que el

individuo tiene conocimiento sobre las implicaciones de las mismas (Brand et al., 2006). La utilización combinada de diversos índices de toma de decisiones en condiciones ambiguas y de riesgo ha demostrado un excelente valor predictivo del resultado del tratamiento en consumidores de opiáceos: los resultados de un estudio prospectivo encontraron que 2/3 de los consumidores que rindieron adaptativamente en ambas tareas, permanecían abstinentes a los 3 meses, mientras que el 100% de los que rendían desadaptativamente habían recaído al cabo de estos tres meses (Passetti et al., 2008).

1.3. Procesos emocionales: percepción y experiencia emocional

Aunque la evaluación del área emocional ha sido tradicionalmente ignorada en el contexto de la evaluación neuropsicológica, como vimos anteriormente, algunos modelos contemporáneos de adicción asignan un papel fundamental a los déficits de procesamiento y regulación emocional (Verdejo-García, Pérez-García & Bechara, 2006; Verdejo-García & Bechara, 2009) por lo que debe ser un objetivo central en la evaluación en drogodependientes. La evaluación emocional se estructura habitualmente en dos constructos principales: (i) la capacidad del individuo para identificar emociones a partir de las expresiones faciales de otras personas y (ii) la experiencia emocional del individuo ante estímulos afectivos de distinta índole.

Para la evaluación de la percepción emocional el paradigma más usado es el *Ekman Faces Test*, que evalúa la capacidad del individuo para reconocer expresiones faciales representativas de las seis emociones básicas (felicidad, tristeza, miedo, asco, ira y sorpresa). Esta prueba ha sido ampliamente utilizada en la literatura y aunque carece de baremos para población española, algunos autores han recurrido al empleo de puntos de corte clínico para su evaluación (Verdejo-García et al., 2007c). Ha

demostrado su eficacia en la detección de alteraciones emocionales en consumidores de distintos tipos de sustancias incluyendo consumidores de cocaína y policonsumidores de sustancias psicoestimulantes (Kemmis, Hall, Kingston & Morgan, 2007; Verdejo-García et al., 2007b, c). Entre los instrumentos empleados para evaluar la experiencia emocional podemos destacar el *Instrumento Clínico de Evaluación de la Respuesta Emocional* (ICERE) (Aguilar de Arcos, Sánchez-Barrera & Pérez-García, 2003). Este instrumento fue desarrollado con población española por lo que a diferencia de la anterior carece de problemas relacionados con la baremación. Diversas investigaciones que han empleado este instrumento han obtenido buenos resultados en la detección de perfiles distintivos de alteración emocional en personas con diferentes perfiles de consumo (Aguilar de Arcos, Verdejo-García, Peralta, Sánchez-Barrera & Pérez-García, 2005; Aguilar de Arcos et al., 2008).

En resumen, la evaluación neuropsicológica es el proceso idóneo para la detección y caracterización de las posibles alteraciones neuropsicológicas asociadas al consumo de drogas. Este proceso se ve respaldado por el desarrollo de un importante número de pruebas y tareas que han demostrado su eficacia en la detección de déficits en el rendimiento neurocognitivo y emocional de consumidores de distintos tipos de drogas.

II. JUSTIFICACIÓN Y OBJETIVOS

Capítulo 3

Justificación y objetivos de la tesis

1. Justificación y objetivo principal

Los resultados de las investigaciones que se han realizado en el ámbito de las drogodependencias en los últimos años apuntan a la necesidad de un cambio en el paradigma desde el que deben ser abordados los trastornos adictivos. Los viejos dualismos genes/ambiente, cerebro/conducta o biológico/psicosocial desde los que se han abordado los procesos adictivos serían insuficientes para explicar estos procesos en su totalidad. En esta última década la investigación ha demostrado la estrecha vinculación existente entre la conducta adictiva y el funcionamiento cerebral como una unidad. Estos hallazgos justificarían el abordaje del fenómeno adictivo desde un paradigma neurocognitivo que permita explorar las relaciones etiológicas que subyacen a la adicción y al resto de fenómenos y procesos que se vinculan al mismo (Flores et al., 2010).

Diversos tipos de estudios (incluyendo estudios en animales, estudios farmacológicos y estudios de neuroimagen) han destacado la relevancia de las alteraciones neurocognitivas y emocionales asociadas al consumo de droga, con especial énfasis en aquellas habilidades encargadas de organizar y programar conductas dirigidas a objetivos (funciones ejecutivas). Es en este contexto dónde encuentra justificación la realización de la presente tesis doctoral. El estudio del funcionamiento de los mecanismos neuropsicólogicos (de control ejecutivo y emocionales) en los consumidores de drogas podría resultar de enorme utilidad en el ámbito de las drogodependencias, contribuyendo a un conocimiento más exhaustivo de los déficits asociados al uso de distintas drogas, y a partir del mismo, a la mejora o elaboración de nuevos programas de rehabilitación que sean realmente efectivos para los individuos consumidores y contribuyan a reducir la ocurrencia de recaídas en estos sujetos.

El **objetivo principal** de esta tesis consiste en estudiar los efectos de tipo neurocognitivo y de tipo emocional que están asociados al consumo y abuso de diferentes drogas, conociendo su prevalencia, significación clínica y la posible existencia de efectos diferenciales asociados al uso de distintas sustancias, incluyendo entre otras el cannabis, la cocaína, los opiáceos y el alcohol (ver Figura 4 para un resumen de los objetivos).

2. Objetivos específicos e hipótesis

Para la consecución de nuestro objetivo principal se llevaron a cabo diferentes estudios.

En primer lugar procedimos a realizar una revisión sistemática y cuantitativa de la literatura científica que ha sido publicada en la última década en relación a los efectos neuropsicológicos del consumo de drogas. En la literatura encontramos frecuentemente dos tipos de aproximaciones al estudio de los efectos neuropsicológicos producidos por las distintas drogas, de un lado aquella que trata de investigar estos efectos a partir del empleo de muestras de sujetos policonsumidores (la mayoría de estudios que encontramos en la literatura), y de otro lado aquella que recurre al estudio aislado de los efectos producidos por una única sustancia a través de distintos procedimientos (muestras de sujetos con un consumo relativamente puro de una única sustancia, muestras de sujetos que comparten el consumo de determinadas sustancias pero difieren en el consumo de la sustancia objeto de estudio [p.e. consumidores de MDMA+cannabis vs. consumidores de cannabis, para estudiar los efectos del MDMA], y muestras de sujetos policonsumidores con sustancias de consumo preferente diferentes). Por este motivo, este primer estudio de revisión persigue los siguientes **objetivos**:

1. Discutir de manera crítica estudios neuropsicológicos realizados en consumidores de drogas desde ambas aproximaciones
2. Determinar qué mecanismos neuropsicológicos están deteriorados de manera común por el consumo de distintas drogas, y qué deterioros son específicos de determinadas sustancias.

La **hipótesis** planteada en este estudio de revisión es que los individuos drogodependientes consumidores de diferentes tipos de drogas presentarán efectos neuropsicológicos comunes en dominios afectados de manera transversal por el proceso adictivo (p.e., procesamiento emocional, toma de decisiones), mientras que existirán efectos neuropsicológicos específicos en dominios relacionados con los efectos farmacológicos selectivos de determinadas sustancias (p.e., memoria en el caso del consumo de cannabis).

Este estudio ha sido enviado a la revista *Neuroscience and Biobehavioral Reviews* que ha mostrado su interés en el mismo por lo que en este momento se encuentra en segunda revisión. Se encuentra íntegramente en el Anexo I.

Tras este primer estudio de revisión y una vez constatado a través de la misma la existencia de numerosos estudios que han observado alteraciones neuropsicológicas relevantes entre los consumidores de distintas drogas, procedimos a realizar un segundo estudio para tratar de determinar la prevalencia y magnitud de estas alteraciones, en concreto las producidas en las funciones ejecutivas, entre un amplio grupo de sujetos consumidores usuarios de comunidades terapéuticas españolas. Más concretamente los **objetivos** perseguidos en este segundo estudio fueron:

1. Estimar las tasas de prevalencia de deterioro neuropsicológico de las funciones ejecutivas en sujetos policonsumidores usuarios de comunidades terapeúticas,

tomando como referencia el rendimiento obtenido por un numeroso grupo de no consumidores de drogas en las tareas empleadas.

2. Estimar las tasas de prevalencia de deterioro ejecutivo de distintos grupos de policonsumidores clasificados en función de su droga preferente de consumo.
3. Estimar la magnitud del tamaño del efecto de las diferencias en el rendimiento de las pruebas empleadas entre policonsumidores y no consumidores, y entre distintos grupos de policonsumidores, para detectar las pruebas de evaluación que resultan más adecuadas.

Las **hipótesis** planteadas para este estudio son: (i) los sujetos consumidores de drogas presentarán una tasas de prevalencia de deterioro ejecutivo superiores al 50 % adoptando un criterio moderado (1.5 S.D.) y superiores al 25 % adoptando un criterio severo (2 S.D.) con respecto a los sujetos no consumidores, (ii) los distintos grupos de sujetos consumidores presentarán tasas de prevalencia de deterioro similares, y (iii) la magnitud del tamaño del efecto de las diferencias en el rendimiento entre consumidores y controles será al menos de una magnitud media ($d \geq 0.5$) a diferencia del rendimiento entre grupos de consumidores (que esperamos sea inferior a 0.5).

Este estudio está publicado en la revista *European Journal of Pharmacology* (Fernández-Serrano, M.J., Pérez-García, M., Perales, J.C., Verdejo-García, A., 2010). Se encuentra íntegramente en el Anexo II.

Nuestro estudio de revisión constató asimismo que ninguna de las metodologías empleadas por los estudios revisados permitía determinar de forma clara qué efectos neuropsicológicos son comunes y cuáles son específicos del consumo de las distintas drogas, así como la existencia de una proporción notablemente menor de estudios realizados tras períodos de abstinencia media-prolongada, aquellos que

realmente nos permiten distinguir entre los efectos del consumo que son reversibles y aquellos que perduran en el tiempo. Estos resultados, junto con los derivados del estudio de prevalencia de deterioro ejecutivo en sujetos consumidores en comunidades terapéuticas, hacían necesaria la realización de un tercer estudio que, mediante el uso de modelos de regresión estadística en una muestra de sujetos policonsumidores en abstinencia prolongada, nos permitiera conocer los efectos diferenciales de cada una de las sustancias de abuso objeto de estudio. Concretamente los **objetivos** específicos de este tercer estudio fueron:

1. Analizar la contribución diferencial ejercida por las drogas de abuso que motivaron tratamiento en la muestra estudiada, en concreto el cannabis, la cocaína y la heroína, con respecto a la ejercida por el alcohol (sustancia de frecuente co-abuso en la mayoría de los sujetos consumidores de drogas) sobre los diferentes componentes de las funciones ejecutivas.
2. Analizar la contribución realizada por la cantidad y duración del consumo de las diferentes drogas analizadas sobre el rendimiento neuropsicológico en estas funciones ejecutivas.

Las **hipótesis** planteadas para este estudio son: (i) el alcohol y las otras drogas de abuso analizadas harán una contribución diferencial a cada uno de los componentes de las funciones ejecutivas analizados, y (ii) esperamos que exista una asociación entre la severidad del uso de las distintas drogas y el grado de deterioro encontrado en las funciones ejecutivas objeto de estudio.

Este estudio está publicado en la revista *Journal of Psychopharmacology* (Fernández-Serrano, M.J., Pérez-García, M., Schmidt Río-Valle, J., Verdejo-García, A., 2010). Se encuentra íntegramente en el Anexo III.

Por último los resultados de nuestro estudio de revisión indicaron la existencia de alteraciones en el procesamiento emocional que eran comunes a la mayor parte de las sustancias analizadas. No obstante nuestra revisión mostró que existe un número de estudios sobre procesamiento emocional en consumidores de drogas notablemente inferior al existente en otros procesos neuropsicológicos. Asimismo, observamos que estos estudios analizaban la relación entre el consumo de drogas y la percepción emocional como un constructo unitario, pero no la capacidad de percibir expresiones emocionales específicas, que parecen tener bases cerebrales diferenciadas (Calder, Lawrence & Young, 2001; Calder, Keane, Lawrence & Manes, 2004; Murphy, Nimmo-Smith & Lawrence, 2003). Por este motivo, llevamos a cabo un cuarto estudio a fin de conocer los efectos producidos por el consumo de distintas sustancias en el reconocimiento de expresiones faciales de contenido emocional. Más específicamente los **objetivos** de este estudio fueron:

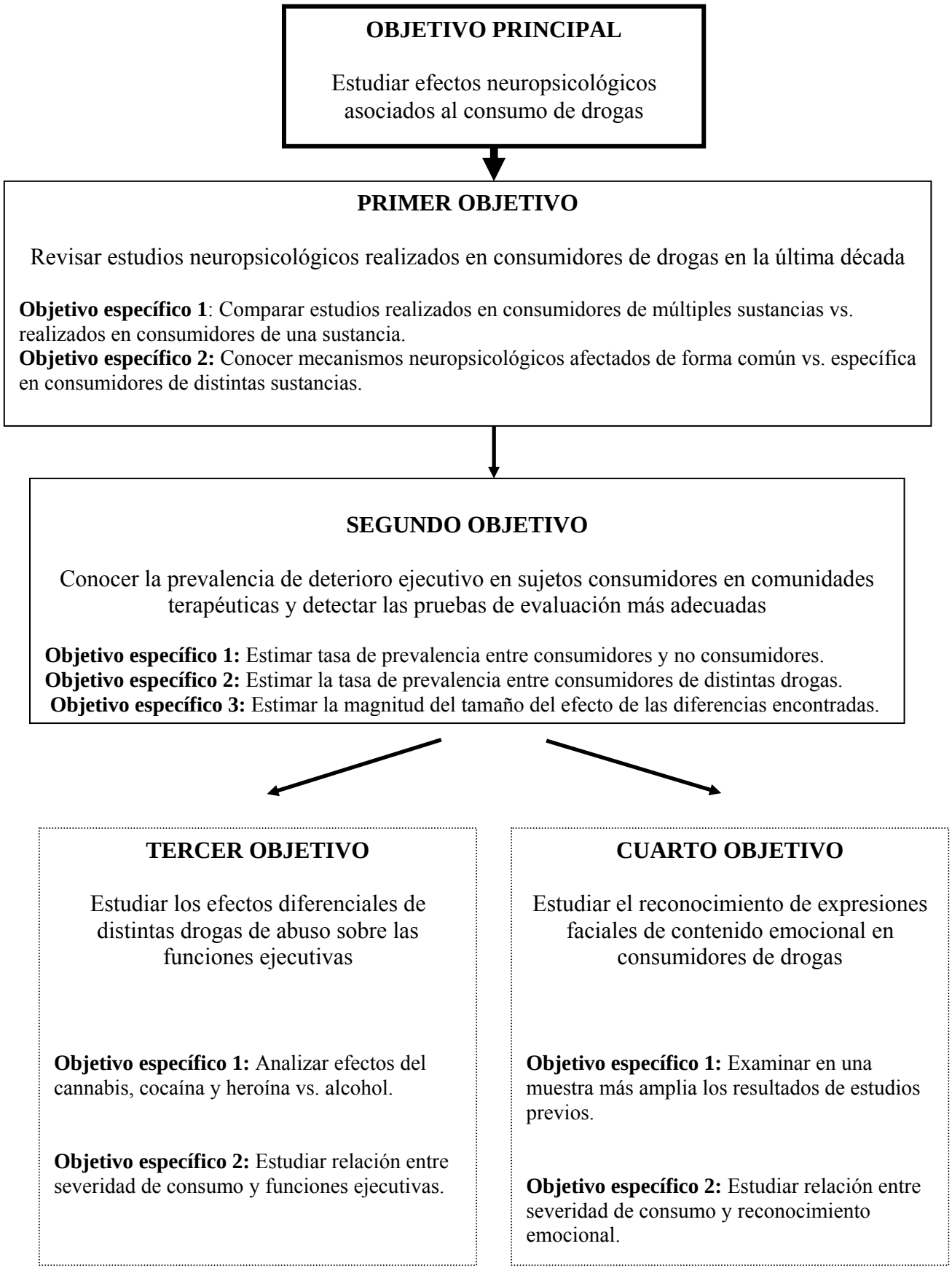
1. Examinar en una muestra más amplia los resultados de algunos estudios previos que han encontrado la existencia de dificultades en el reconocimiento de expresiones faciales emocionales en sujetos policonsumidores de distintas drogas.
2. Explorar la asociación existente entre los patrones de severidad de consumo (cantidad y duración) de distintas drogas, incluyendo alcohol, cannabis, cocaína, heroína y MDMA, y la habilidad para identificar expresiones faciales en sujetos policonsumidores.

Las **hipótesis** propuestas para este estudio son: (i) los individuos consumidores de drogas presentarán un reconocimiento emocional más deficiente que los sujetos no consumidores de drogas, y (ii) esperamos que la severidad de consumo de

las distintas drogas realicen una contribución diferencial a las alteraciones encontradas en el reconocimiento emocional de los sujetos consumidores.

Este estudio ha sido publicado en la revista *Drug and Alcohol Dependence* (Fernández-Serrano, M.J., Lozano, O., Pérez-García, M., Verdejo-García, A., 2010). Se encuentra íntegramente en el Anexo IV.

Figura 4. Esquema de los objetivos seguidos en el trabajo



III. MEMORIA DE TRABAJOS

Capítulo 4

What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance?

Fernández-Serrano, M.J., Pérez-García, M., Verdejo-García, A. What are the specific vs generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehaviural Reviews,* under review.

1. Introduction

The use of psychoactive substances is associated with neuropsychological deficits in mechanisms related to emotion, memory and executive functions. Impairment of these functions does not only interfere with the cognitive performance of drug users in a general manner (thus influencing their quality of life, their academic/work performance, or their ability to receive cognitive treatment), but they also affect the core aspect of addiction: the tendency to continue drug use despite its increasingly negative consequences. The interaction between: (1) motivational and memory mechanisms, which amplify the reinforcing value associated with the substance, and (2) poor performance of the executive control mechanisms, in charge of regulating automated behaviors, is at the root of the dependence on different drugs (Bechara, 2005; Garavan and Hester, 2007; Goldstein and Volkow, 2002; Verdejo-García and Bechara, 2009). Therefore, one possibility is that all drugs of abuse produce generalized impairments in these neuropsychological mechanisms. In this case, the specific neuropsychological effects of a substance (e.g., a stimulant) and those produced by another substance (e.g., an opioid) would overlap, even though their pharmacological effects are quite different. This possibility would reduce the scientific interest in studying a certain substance in isolation, and it would support the explanatory power of studies performed on polysubstance users (which are most of those found in the literature). The alternative possibility is that each substance, depending on its characteristic pharmacological effects, produces a specific neuropsychological profile differing from the neuropsychological profiles of other drugs. This hypothesis would reduce the explanatory value of the research on polysubstance use, as it would mask the characteristic effects of each drug on neuropsychological performance. Although studies

with animals have elegantly addressed this question, research with humans is clearly hindered by the difficulties to select 'pure' users of one drug only. In spite of this limitation, some studies have dealt with the problem by sampling populations with cultural peculiarities (Fishbein et al., 2007; Halpern et al., 2004), investigating substances with a relatively low co-abuse rate (e.g., alcohol or cannabis) (Fein et al., 2004; Fried et al., 2005), or controlling polysubstance use through methodological designs or statistical techniques (Bolla et al., 2000; Morgan et al., 1999, 2006). The objectives of this review are: (1) to critically examine neuropsychological studies carried out on drug users from both approaches and (2) to determine which neuropsychological mechanisms are impaired in the same manner by the use of different drugs, and which deficits are specific to certain substances. Given these fundamental objectives, this will be a systematic review analyzing both specific and general neuropsychological effects of the abuse of cannabis, stimulants (cocaine and methamphetamine), 3, 4-Methylenedioxymethamphetamine (MDMA; "Ecstasy"), opioids (heroin and methadone) and alcohol on mechanisms of emotion, memory and executive control. Due to the inherent diversity of the concept of "executive control", the review will be approached from a multi-component perspective, encompassing mechanisms of updating (including tests of working memory, controlled access and production of information and reasoning), inhibition (including tests of impulsive action –response inhibition and self-regulation, and impulsive choice –reflection-impulsivity, time estimation, delay discounting), flexibility (including attentional/set-shifting and reversal learning tests) and decision-making (including probabilistic choice and gambling decision tests) (Verdejo-García and Pérez-García, 2007). We present a brief definition of each of the neuropsychological domains addressed in the review, and a list

of the neuropsychological tests typically used to measure them, in Table 1. It is important to mention that dysfunctions in some of these neuropsychological domains (e.g., inhibition or decision-making) have been proposed to precede initial drug use and to predispose certain individuals to being attracted to different drugs (Dalley et al., 2007; Verdejo-García et al., 2008); therefore, although this review is focused on neuropsychological effects of drugs use, we prevent ourselves about providing strong causal assumptions throughout the text.

In the first part of the manuscript, we shall briefly present relevant evidence about specific effects of these substances based on animal and pharmacological studies using controlled drug administration in healthy individuals. In the second part of the manuscript, we perform a systematic review of neuropsychological studies investigating specific vs. generalized effects of these drugs through three different research approaches that can shed light on our objectives: (i) studies on selected samples of 'pure' users of certain substances, (ii) studies with methodological control of the effect of the co-abuse of drugs other than the one of interest, and (iii) studies on polysubstance users with different main drugs of choice. Finally, we will integrate the results, in order to provide insights about which skills are affected indistinctly by all drugs and which skills are differentially affected by specific substances taking into account the time line of drug effects (i.e., acute, short-term, mid-term and long-term).

DOMAINS	COMPONENTS	MEASURES[a]
MEMORY	Declarative memory (explicit): involves the conscious recollection of past events or experiences and is typically measured through recall or recognition. It includes semantic and episodic memory. -Episodic memory (EM): acquisition and retention of knowledge about personally experienced events and their temporal relations in subjective time and the ability to mentally "travel back" in time. -Semantic memory (SM): capability of internally representing states of the world that is not perceptually present. The memory of meanings of words, facts or rules.	EM: BSRT, RAVLT, RCFT, CAVLT, WMS (Logical memory, verbal paired association, visual reproduction, inmmediate memory, general memory), AFLT, CVLT, PAL, HRDT, MC: (story recall, wordlist2, address), WRMT, CLDL, FRT, RBMT, BVRT, SMT, FMT, HVLT-R, BVMT-R, VLMT, VIG, PSR, PRM PAL, IDPR, IFRT, DFRT, BCSR, LGT-3, AMIPB, FCSRT, ECM, DPT, ST, SpT, PMT, SDPALT SM: SPT, BNT, WAIS (Vocabulary), SILS-V, PPVT
	Prospective memory (PrM): capability to remember to do something in the future, or remembering to perform an intended action.	PrM: RBMT, Virtual week
	Non-declarative memory (implicit) (IM): capability to remember something without being aware that you are remembering it.	WSC
ATTENTION	-Divided attention (DAT): the ability to respond simultaneously to multiple tasks or multiple task demands -Selective attention (SAT): the capacity to maintain a behavioral or cognitive set in the face of distracting or competing stimuli. -Sustained attention (SUAT): the ability to maintain a consistent behavioral response during continuous and repetitive activity.	DAT: TAP (subtest 5), TMT, CTT. CalCap (RT2) SAT: TAP (subtest 6), FAT, SAT, CTT, RSCT, DCT, MC: alphabet, numbers forward, numbers reversed, wordlist1, SDMT, DVT, CPT, ACPT, RT, SSPT, ANT, Stroop SUAT: TEA, SSST, Stroop
EXECUTIVE FUNCTION	Updating: online monitoring and manipulation of different information modalities -Fluency (UP-Fl): capacity of the individual to initiate his/her behavior in a fluid way in response to a new order. -Analogical reasoning/abstraction/problem solving (UP-Rs): non deductive reasoning that consists of reaching a conclusion based on premises in which a comparison or analogy is established between elements or sets of different elements. -Working memory (UP-WM): a system for temporarily storing and managing the information required to carry out complex cognitive tasks, such as learning, reasoning and comprehension.	UP-FI: FAS, RFFT, VFT, WF, SFVF, D-KEFS (verbal fluency), COVF, CWF UP-Rs: Sim, CANTAB_SC, LPS-4, CT, ACatT, SOC ,BCT, MC (analogies), IT, SILS-A, CLAT UP-WM: FBDS, FDST, BDST, WMS (working memory), PASAT, DMS (Spatial span), WAIS (digit forwards, digit backward), CBTT, SWM, TileMT, SST, KTT, CS, VRT, 2-back, Tic tac
	Cognitive flexibility: ability to flexibly change forward and backward in relation to different tasks, mental operations, or schemas -Set shifting (CogFlx-SS): ability to switch between perceptive or attentional or perceptual sets or criteria. -Reversal learning (CogFlx-RL): ability to switch between reinforcement patterns.	CogFlx-SS: WCST, TMT, TEA, MC (object match), OT, ASST, TDIDED, AAT (alternate response),CTT CogFlx-RL: PRL
	Inhibition: ability to inhibit in a controlled way the production of prepotent, automatic, or impulsive responses when necessary Impulsive action (ImpAC): -Response Inhibition: the ability to inhibit inappropriate responses -Self regulation: the regulation of one's own behavior without external control or monitoring Impulsive choice (ImpCH): -Reflection-impulsivity: the tendency to gather and evaluate information before making a decision -Time estimation: the ability to estimate and pace the passage of time -Delay discounting: a greater preference for immediate rewards, even when they are less advantageous than other rewards	ImpAC: Go-No go, Stroop, R-SAT, SCT, IMT, DelayedMT, RLG, FDT, HSCT, PMQS, CRT ImpCH: TCDDT,DDT,MFFT,TEP, CARROT, IST, MCQ

Table 1 (continued)

EXECUTIVE FUNCTIONS	Decision-making: the ability to select the most adaptive course of action for the organism among a set of possible behavioral alternatives. Planning/Organization/Sequencing: the process of setting goals, developing strategies, and outlining tasks and schedules to accomplish goals	DMK: IGT, CDMT, RTT, SGT, The Bets 16, DMT, GDT, CBT PLAN: CANTAB_SC, TOL, TMT, WAIS (mosaic test, block design), TileMT, D-KEFS (towers), BADS, TOH
PSYCHOMOTOR FUNCTIONING	Psychomotor performance, encompasses motor strength, hand-eye coordination, balance, dexterity, tracking and other skills (MOT) -Manual dexterity: fine motor skills of hands (or fingers) -Psychomotor speed: the amount of time it takes a person to process a signal, prepare a response and execute that response	MOT: FOT, FTT, GPT, DSST, HRNTB, WAIS (digit symbol), SDMT, CalCAP, DVT, MC (timers), GSM, PRT, D-KEFS, SRTT, FAT, CST, Timed gait, TPT, FAB, HDT
SPATIAL PROCESSING	The ability to accurately judge the relationship between visual stimuli (SPA)	SPA: WAIS (block design, pictures, cubes, object assembling), MC : Tic Tac, clocks, SDMT, MRT, JoLO, OT, CCSE, VST
PROCESSING SPEED	The ability to process information automatically and therefore speedily, without intentional thinking through (Speed)	Speed: SDMT, FDT, SRT. CalCAP
EMOTION PROCESSING	The ability to recognize, experience, and express valence specific emotion (PrEMO)	PrEMO: FEEST, DERS, PFA, ME, BFRT, EFE, Eyes task, ICERE

Table 1. Definition of neuropsychological domains and list of neuropsychological instruments used to measure them in the field of neuropsychology and addiction.

Neuropsychological instruments are listed in alphabetical order.

[a] AAT: Attentional assessment test, ACatT: Adult category test; ACPT: Auditory Continuous Performance Test, AFLT: Aggie figures learning test; AMIPB: Adult memory and information processing battery; ANT: Attention network test, ASST:Attentional Set-Shifting task; BCSR: Babcock story recall, BCT: Booklet Categories Test, BD: Block design; BDST: Backward digit span test; BFRT: Benton facial recognition test, BNT, Boston naming test, BSRT: The Buschke Selective Reminding Task; BVMT-R: Brief visuospatial memory test, BVRT: Benton visual retention test, CalCAP: California computerized assessment package; CANTAB: DMS, Delayed Matching to Sample, CANTAB_SC: Stocking of Cambridge; CAVLT: Chinese auditory verbal learning test; CBT: Cognitive bias task, CBTT: Corsi block tapping test, CCSE: Cognitive capacity screening examination, CDMT: Cambridge decision making task; ; CLAT: Conceptual levels analogies; CLDL: Coughlan list and design learning; COVF: Controlled oral verbal fluency,COWAT: Controlled Oral Word Association Test, CPT: Continuous Performance Test; CRTT: Choice reaction time task (stop-signal), CS: computation span, CST: Categoric search task; CT: Category test; CTT: Colour trails test; CVLT: California verbal learning test, CWF: Chicago word fluency, DCT: Digit cancellation test, DDT: Delay discounting task; DelayedMT: Delayed memory task; DERS: Difficulties emotional regulation scale, DFRT: Delayed free recall task; D-KEFS: Delis-Kaplan Executive function system, DMT: Decision making task; DPT Doors and people test; DSST: Digit symbol substitution test; DVT: Digit vigilance test, ECM: Ecological contextual memory, EFE: Emotional facial expressions recognition task, FAB: Fregly Ataxia Battery; FAS: Oral word association test; FAT: Focused attention task, FBDS: Forward and backward digit span; FCSRT: Free and cued selective reminding test; FDST: Forward digit span test; FDT: Five digit test, FEEST: Facial expressions of emotions: stimuli and tests; FMT: Figure memory test, FOT: Finger oscillation test; FRT: Free recall test, FTT: Finger tapping test;GDT: Game of dice task, GSM: Gibson's spiral maze, GPT: Grooved pegboard test; HDT: Hand Dynamometer Test, HRDT: Hebbs recurring digits test, HRNTB: Halstead-Reitan Neuropsychological test battery; HSCT: Hayling sentence completion test,HVLT-R: Hopkins verbal learning test;ICERE: Clinical Instrument for Emotional Response Evaluation, IDPR: Immediate and delayed prose recall;IGT: Iowa gambling task; IFRT: Immediate free recall task; IMT: Immediate memory task; IST: Information sampling test, IT: Integration task; JoLO: Judgment of Line Orientation, KTT: Keep Track Task, LGT-3: Lern-und Gedachtnistest learning and memory test, LPS-4: Leistungsprüfsystem, abstract logical thinking; MC: MicroCog assessment of cognitive functioning; MCQ: Monetary choice questionnaire, ME: Mind in the Eyestest; MFFT: Matching familiar figures test; MRT: Mental rotation task, OT: Oral trails,PAL, Paired Associate learning, PASAT: Paced Auditory Serial Addition Test, PFA: Pictures of facial affect, PMQS: Porteus maze test; PMT: Pictorial associative memory task, PPVT: Peabody picture vocabulary test, PRL: Probabilistic reversal learning; PRM: Delayed pattern recognition memory; PRT: Pursuit rotor task, PSR: Pattern and spatial recognition; RAVLT: Rey Auditory Verbal Learning Test; RBMT: Rivermead behavioural memory test; RCFT: Rey-Osterrieth Complex Figure Test, RFFT: Ruff figural fluency test; RLG: Random letter generation, R-SAT: Revised strategy applications test; RSCT (BADS): Rule shift cards test (Behavioural assessment of the dysexecutive syndrome); RT: Rhytm test, RTT: Risk taking task; SAT: Visuo-auditory selective attention task, SCT: Stop Change Task, SDMT: Symbol Digit Modalities Test, SDPALT: Symbol digit paired associate learning test; SFVF: Semantic and phonemic verbal fluency SGT: Simulated gambling task, SILS-A: Abstraction scale, SILS-V: Vocabulary scale, Sim: Similarites subtest (WAIS), SMT: Story memory test, SN-SALT: Spatial and non-spatial associative learning test; SOC: Speed of Comprehension; SOT, Stocking of Cambridge, SpT: Spondee test, SPT: Semantic processing task; SRT: Simple reaction time; SSPT: Speech sounds perception test; SSST: Serial seven subtraction test, ST: shaped test; SWM: Spatial working memory,TAP: Test of attentional performance; TCDDT: Two choice delay discounting task; TDIDED: Three dimensional IDED; TEA: Test of everyday attention, TEP: Time estimation and production; TileMT: Tile manipulation test,TMT: Trail making test; TOH: Tower of Hanoi; TOL: Tower of London; TPT: Tactual performance test,VFT: Verbal fluency test; VIG: Visuospatial memory, VLMT: Verbal learning memory test, VRT: Verbal reasoning task; VST: Visuo-spatial strategy task; WCST: Wisconsin card sorting test; WF: Word fluency, WRMT: Warrington recognition memory tests for words and faces; WSC: Word stem completation

2. Methods.

First, in Section 3, we narratively review relevant findings from animal and human controlled drug-administration studies selected by the authors with the aim of providing a background about the selective pharmacological/ neuropsychological effects of each of the individual substances studied.

For Sections 4 to 6, we performed a systematic review of peer-reviewed studies tracked from the PubMed and PsycInfo databases. These studies stemmed from searches combining the following terms:

DRUG (OR SUBSTANCE) ABUSE,

DRUG (OR SUBSTANCE) DEPENDENCE,

DRUG (OR SUBSTANCE) ADDICTION,

CANNABIS (+ABUSE/DEPENDENCE/ADDICTION),

PSYCHOSTIMULANTS (+ABUSE/DEPENDENCE/ADDICTION),

COCAINE (+ABUSE/DEPENDENCE/ADDICTION),

AMPHETAMINE (+ABUSE/DEPENDENCE/ADDICTION),

METHAMPHETAMINE (+ABUSE/DEPENDENCE/ADDICTION),

MDMA (+ABUSE/DEPENDENCE/ADDICTION),

ECSTASY (+ABUSE/DEPENDENCE/ADDICTION),

OPIATES (+ABUSE/DEPENDENCE/ADDICTION),

OPIOIDS (+ABUSE/DEPENDENCE/ADDICTION),

HEROIN (+ABUSE/DEPENDENCE/ADDICTION),

METHADONE (+ABUSE/DEPENDENCE/ADDICTION),

ALCOHOL (+ABUSE/DEPENDENCE/ADDICTION).

AND

COGNITION, NEUROPSYCHOL*, MEMORY, ATTENTION, EXECUTIVE FUNCTIONS, WORKING MEMORY, FLUENCY, REASONING, FLEXIBILITY, IMPULSIVITY, (DIS)INHIBITION, DELAY DISCOUNTING, DECISION MAKING, EMOTION PERCEPTION, EMOTION EXPERIENCE, EMOTION PROCESSING, (PSYCHO)MOTOR PROCESSING, (VISUAL)SPATIAL PROCESSING.

Next, we reviewed the resulting papers according to the inclusion criteria detailed below and distributed them, based on their methodological approach, in one of the three main sections: studies in 'pure' users, studies with methodological control of polysubstance use, or studies in polysubstance users (these latter studies were subdivided in two subgroups: studies comparing polysubstance users with healthy controls, and studies comparing polysubstance users of one drug of choice with polysubstance users of another drug of choice). The inclusion/exclusion criteria for the systematic search were:

- Manuscripts published between 1999 and 2009 (including papers ahead of print available at databases before January 2010): this criteria was meant to review only those studies published during the last decade, encompassing the period after the surge of contemporary neuroscientific models of addiction (e.g., Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Koob and LeMoal, 2001) and filtering earlier studies, many of which had important methodological drawbacks (see Verdejo-García et al., 2004 for review).

- Studies conducted in individuals with substance use disorders with no psychiatric comorbidities.

- Studies in which the main aim was neuropsychological assessment (excluding neuroimaging studies in which neurocognitive paradigms are adapted to be

administered inside the scanner and studies using cognitive psychology tests not validated for use in neuropsychology).

- Studies including at least one psychometrically validated neuropsychological measure of the domains of interest (see Table 1 for a definition of the domains of interest).

- Participants had to have a minimum abstinence of 24 hours, since our main interest was to review non-acute neuropsychological effects of drugs of abuse and to rule out effects of drug-related intoxication.

- They had to include at least one comparison group of non-drug using individuals (with the exception of methodologically controlled subtraction studies –Section 5, where the control group of interest is, by definition, formed by other drug-using groups). These comparison groups had to be demographically matched to the drug using groups, or in case there were differences in demographic characteristics, they had to be statistically controlled.

We present the resulting selected studies organized according to the duration of abstinence in the drug user participants throughout the text; this is the key variable to differentiate between short-term (>48 hours<30 days of abstinence), mid-term (1 to 6 months of abstinence) and long-term (>6 months of abstinence) neuropsychological effects of drug use. In Tables (Tables 2 to 6) studies are organized in the same way. In these Tables we also provide, for each study, information about the number, main drug of choice and treatment status (i.e., non-treatment seekers, community treatment or residential treatment patients) of drug using participants, about the neuropsychological tests employed, and about which neuropsychological domains were found to be impaired vs. intact. With this information, readers can differentiate between domains that were assessed but found to be intact vs. domains that were not taxed by the

neuropsychological test batteries. We have marked **in bold** those domains that were found to be impaired by each study. Furthermore, we have marked *in italics* those domains that were found to be impaired by different studies on the same drug, and we have underlined those domains that were found to be impaired across different studies addressing the effects of different drugs. Therefore, in each Table, those domains that are marked **in bold and underlined** represent generalized effects of different drugs, whereas those domains marked ***in bold and italics*** (not underlined) are the ones that have been shown to be associated with one specific drug by two or more studies (an index of consistent exclusive effects). These marks have been included to provide readers with shortcuts and rules to interpret the often quite diverse research findings in the field.

Finally, in Section 7 we provide a quantitative estimation of the mean magnitude of the neuropsychological effects (specific vs. generalized) of different drugs on different domains by calculating mean effect sizes obtained by studies using each of the three methodologies reviewed. We also provide a quantitative estimation of the mean magnitude of the neuropsychological effects of different drugs according to abstinence duration (short-, mid- or long-term). These results are displayed in Tables 6 and 7. These results are also used to build up the *Summary* subsections placed at the end of each section, where we only comment on neuropsychological effects reaching at least an average medium effect size (mean Cohen´s $d \geq 0.5$). Finally, we integrate the overall results and provide quantitatively-lead insights about the specific vs. generalized neuropsychological effects of different drugs.

3. Specific action mechanisms of each drug: animal studies and studies of acute drug administration in humans.

3.1. Cannabis

Cannabis produces its psychoactive effects in the brain by acting on the CB1 receptors. Animal evidence showed that the cannabinoid receptors are distributed in the brain in a similar way to the dopaminergic receptors, with high concentrations in the basal ganglia and hippocampus, although the highest concentrations of cannabinoid receptors are found in the cerebellum (Herkenham, 1992). Human imaging techniques have shown that the human brain also contains high densities of cannabinoid CB1 receptors in the frontal cortical regions, including the posterior cingulate cortex, superior frontal gyrus and orbitofrontal cortex (Burns et al., 2007). Cannabis stimulates the production of dopamine (DA) in an indirect way through the action of the CB1 receptors on the neurons of the GABA neurotransmitters and glutamate in the ventral tegmental area and the striatum (Camí and Farré, 2003).

Studies performed on mice (Niyuhire et al., 2007) and rats (Deadwyler et al., 2007; Fadda et al., 2004; Jentsch et al., 1998; Nava et al., 2001) reveal that administration of cannabis produces important alterations in working memory when doing the delayed-non-match-to-sample, radial maze, T maze, delay and Morris swimming pool navigation tasks. In rhesus monkeys, exposure to cannabis produced chronic changes in brain structures related to memory and emotion (hippocampus and amygdala) (Heath et al. 1980), and in rats THC exposure induced selective and persistent reductions in medial prefrontal cortex dopamine turnover (a key system for reward learning and decision-making) (Vericco et al., 2003).

Regarding the effects of acute cannabis administration, a review by Ranganathan and D'Souza (2006) concluded that the most consistent impairments were found on measures of episodic memory, both immediate and delayed free recall. Regarding executive functions, several studies have shown that at the acute level cannabis produces alterations in working memory (Ilan et al., 2004), response inhibition (Ramaekers et al., 2006) and decision-making (Lane et al., 2005; Ramaekers et al., 2006) in healthy subjects.

3.2. Psychostimulants (cocaine and methamphetamine)

From a neurochemical point of view, cocaine's most important action is the blockage of the monoamine transporters, inhibiting the reuptake of dopamine (DA), serotonin (5HT) and norepinephrine (NE). In their acute stage, methamphetamine blocks the reuptake of DA, producing depletion of DA and, to a lesser extent, 5HT, in the long term. In addition, methamphetamine exposure is associated with lower levels of dopamine in the striatum and a tendency toward a decrease in this neurotransmitter in the prefrontal cortex (Clemens et al., 2005).

Animal models have shown that repeated administration of cocaine leads to impairment in cognitive flexibility, specifically in perseveration and reversal learning linked to orbitofrontal cortex functioning (Jentsch et al., 2002; Schoenbaum et al., 2004; Stalnaker et al., 2006, 2009). Other authors have observed the existence of impairments in short term and long term memory and an increase in impulsivity, specifically in the delayed reinforcement paradigm, in rats exposed to cocaine (Paine et al., 2003; Santucci et al., 2004; Simon et al., 2007). In rats, methamphetamine produce various types of alterations, including alterations in time perception, time-based prospective memory, reversal learning, and spatial working memory (Cheng et al., 2007; Nagai et al., 2007).

Acute cocaine administration produces functional magnetic resonance imaging (fMRI)-indexed alterations in brain regions involved in reward processing, executive functions and emotional regulation, including mesolimbic and mesocortical regions, prefrontal cortex, and orbitofrontal cortex (Kufahl et al., 2005). Contradictory results have been found regarding the effects of acute cocaine administration on response inhibition, with some studies showing detrimental effects (Fillmore et al., 2002), while others found paradoxical improvements (Fillmore et al., 2005), mainly as a function of the dose (Fillmore et al., 2006). A recent fMRI study showed that acute cocaine-induced performance improvements were associated with increases in activation in the medial and lateral prefrontal regions, which may be chronically dysregulated in chronic users (Garavan et al., 2008). Acute administration of methamphetamine has been associated with transient improvements in psychomotor functioning, attention and perceptual speed, as well as an increase in risky decision-making (Johnson et al., 2000; Silber et al., 2006).

3.3. MDMA ('Ecstasy')

The most relevant component of ecstasy, MDMA causes alterations in the serotonergic brain system. Neurochemical and anatomical studies carried out using Positron Emission Tomography (PET) in humans and animals, specifically monkeys and baboons, reveal that the use of MDMA produces significant reductions in the 5HT transporter in different cortical and subcortical brain regions (McCann et al., 2005; Ricaurte et al., 2002).

Studies performed on non-human primates exposed to repeated doses of MDMA showed the existence of major behavioral impairments related to the serotonergic system (Frederick et al. 1998; Taffe et al., 2002, 2003). Long-lasting impairments were

observed in the performance of MDMA-treated monkeys on impulsivity and memory domains measured with time estimation, learning and short-term memory tests (Frederick et al., 1995).

With regard to the acute effects of MDMA, various studies have shown that controlled low-dose administration of the drug produces acute alterations in selective attention, spatial memory, response inhibition and decision-making (Kuypers et al., 2007; Kuypers and Ramaekers, 2007; Ramaekers and Kuypers, 2006; Vollenweider et al., 2005). Other authors have also observed the existence of alterations in episodic memory as a result of co-administration of MDMA and alcohol (Dumont et al., 2008), and high motor activation as a result of the acute administration of MDMA alone (Dumont et al., 2007).

3.4. Opioids

Opioids produce their effects by stimulating the opioid receptor system (mu, delta and kappa). They also increase the levels of dopamine, but through an indirect route, by reducing the inhibitory activity of the GABA in the ventral tegmental area (Camí and Farré, 2003).

Studies performed on rats have shown that opioid exposure produces impairment in learning on the Morris swimming pool tasks and in performance across different spatial memory tasks (radial and Y maze) (Pu et al., 2002; Spain and Newsom, 1991).

Although difficult to perform for ethical reasons, studies on acute opioid administration in humans have observed impairments in working memory, episodic memory (Curran et al., 2001; Friswell et al., 2008) and emotional processing (Aguilar de Arcos et al., 2008).

3.5. Alcohol

Alcohol favors the synaptic inhibition produced by the GABA transmitter. The anesthetic effect occurs mainly through the inhibitory action it performs on the NMDA receptors of the glutamate neurotransmitter (see Sánchez-Tutret, 1997). Alcohol inhibits the release of oxytocin, vasopressin and possibly other hypothalamic peptides in a concentration within pharmacological limits. As for the stimulant effect of alcohol, at a neurochemical level it has been associated with increases in the release of dopamine in the ventral tegmental area and in the nucleus accumbens (Sánchez-Tutret, 1997).

Studies performed on animals have shown that postnatal exposure of rats to different doses of alcohol produces alterations in cerebral structures related to memory in the adult stage, specifically in hippocampal areas (Klintsova et al., 2007). Other studies performed on rats have shown that mice exposed to alcohol experienced difficulties in reversing previously acquired learning (reversal learning tasks, O'Leary-Moore et al., 2006).

Acute effects of alcohol exposure in adults include dissociated alterations in the memory systems. Alterations have been observed in the recognition of explicit, but not implicit, memory contents, in prospective memory and in response inhibition (Corbin and Cronce, 2007; Leitz et al., 2009; Ramaekers and Kuypers, 2006; Ray and Bates, 2006). Alcohol-exposed subjects also showed a slowing of the motor skills and alterations in emotional processing, specifically in the processing of unpleasant information (Franken et al, 2007).

4. Studies on samples of relatively 'pure' users.

In spite of the fact that they are quite difficult to conduct, since most drug users tend to use several substances simultaneously, studies on samples of mostly 'pure' users of one specific substance are ideally suited to reveal the neuropsychological effects of that particular substance.

4.1. Cannabis

Only one study of 'pure' cannabis users met criteria for inclusion. The study by Fried et al. (2005) used a non-treatment-seeker sample of 113 young probands: 19 current heavy users, 19 current light users, 16 former regular users and 59 controls. They were assessed yearly up to age 7 and once during each of the 9-12, 13-16 and 17-21 year intervals using neuropsychological tests measuring IQ, processing speed, memory and reasoning. This is a particularly strong design, since it allowed authors to disentangle current marijuana-related cognitive deficits from potential premorbid alterations. The period of abstinence of current users was 24 hours, whereas the abstinence duration of former users was of at least 3 months. The results of this study showed that, after controlling for premorbid cognitive function, current marijuana use produced alterations in episodic memory, both immediate and delayed, and in visual processing speed, with these subjects also showing a significantly lower IQ than the subjects who were not marijuana users. However, none of these deficits were observed in former users.

4.2. Psychostimulants

No studies of 'pure' cocaine users met criteria for inclusion. Two consecutive studies by Bolla et al. (2003) and Verdejo-García et al. (2007a) revealed decision-making deficits measured with the Iowa Gambling Task in the same sample of 'pure' cocaine users (with carefully monitored abstinence duration of 25 days). However, in both studies

behavioral performance was obtained while subjects performed the task inside the scanner, and therefore results are not entirely comparable to those obtained using standard neuropsychological measures outside the scanner.

With regard to methamphetamine, three studies taxing the neuropsychological effects of this drug in 'pure' users during mid- and long-term abstinence met criteria for inclusion. All these studies were conducted in individuals following residential treatment or on probation. Volkow et al. (2001) conducted a neuropsychological and dopamine-transporter-binding PET imaging study that retested five methamphetamine-abusing individuals after a 12- to 17-month period of abstinence. Their imaging results showed significant increases in basal ganglia dopamine transporters availability at follow-up. However, re-test of cognitive performance showed only mild (non-significant) improvements in gross motor skills and episodic memory, but persistent deficits on fine-grained psychomotor function and executive-based interference during memory encoding. Moon et al. (2007) studied verbal and visual episodic memory in 19 methamphetamine dependent subjects with a mean abstinence of 1.79 years (although with a high variability) and 18 non-drug users. The results showed that mid-term abstinent methamphetamine users had intact performance on verbal memory, but impaired performance on the visual memory task (an adaptation of the Rey Complex Figure Test), which involves visual memory as well as planning and organizational skills. More recently, Salo et al. (2009) evaluated performance differences on the Stroop test between methamphetamine users who recently initiated abstinence (n=38, average abstinence of 2.6 months), methamphetamine users who had a long-term abstinence duration (n=27, average abstinence of 31.5 months), and non-users (n=33). The results showed that methamphetamine users with mid-term abstinence exhibited greater deficits

in response inhibition compared to both the non-user group and methamphetamine users who had long-term abstinence; long-term abstinent methamphetamine users did not differ from controls. This finding may be interpreted as a sign of recovery of response inhibition skills with protracted methamphetamine abstinence.

4.3. MDMA ('Ecstasy')

Two recent studies that have managed to sample relatively 'pure' MDMA users met criteria for inclusion. Halpern et al., (2004) examined the effects of exclusive MDMA use on executive functions, specifically on working memory and response inhibition. The sample of non-treatment seeker exclusive MDMA users was recruited in a region of the United States where religious traditions strongly discouraged alcohol, tobacco, and any other illicit drug use. More specifically, the sample of users was made up of two subgroups: light MDMA users (n=12) who presented a lifetime consumption ranging from 22 to 50 pills, and heavy MDMA users (n=11) who presented a lifetime consumption of more than 50 pills. Both groups were evaluated after 10 days of abstinence. The results of the study showed the existence of statistically significant cognitive deficits only among users who consumed more than 50 pills. These users showed alterations on the Stroop test, where they performed more slowly on all parts of the task and had a greater number of interference errors, demonstrating alterations in cognitive processing speed and higher impairment in response inhibition. Moreover, they presented alterations in their performance on a multitasking self-regulation test, the Revised Strategy Application Task (R-SAT), as they used inappropriate strategies, in spite of beginning the task more quickly than the other groups. This response pattern in the R-SAT indicates poor inhibition, as well as alterations in the ability to self-regulate prepotent response, since MDMA users were unable to reverse a response pattern

yielding initial benefits that would progressively disappear. A second study on the effects of MDMA use after mid-term abstinence was conducted in Hong Kong by Yip and Lee (2005) in a sample of non-treatment seeker 'pure' users. These authors investigated the effects of MDMA on episodic memory and on the updating component of executive functions, specifically in tests of working memory, fluency and selective attention. They compared 100 controls to a sample of 100 regular ecstasy users who were not users of any other substance and had an average abstinence of 2.23 months. The results showed that ecstasy users presented alterations on both verbal and non-verbal tasks of episodic memory, selective attention, and on the updating component of executive functions, specifically for working memory and verbal fluency measures, but not figural fluency, where they performed better than controls.

4.4. Opioids

There has been little research on the neurocognitive effects produced by heroin in pure users of this substance, probably because heroin is a 'late-stage' drug that users get to after an extensive use of other substances. Nonetheless, one recent study, conducted in a selected sample of Russian heroin users following residential treatment, met the proposed criteria for inclusion. Fishbein et al. (2007) contrasted the cognitive performance of four groups of participants: pure users of heroin (n=100), co-users of heroin and alcohol (n=60), pure alcohol users (n=102), and non-users (n=160), on measures of episodic memory and different components of executive functions, including working memory, decision-making, planning/problem solving, response inhibition, and cognitive flexibility. Users were evaluated after 3 weeks of abstinence. The data showed that heroin users had impaired performance on decision-making (measured by the Cambridge Decision Making Task); as their decisions were riskier in

spite of taking more time to make them. However, performance of 'pure' heroin users on visual episodic memory and problem-solving tasks was better than that of the other two groups, heroin+alcohol and alcohol. It seems, therefore, that visual memory and reasoning/problem solving alterations would be more closely linked to alcohol rather than heroin use, whereas there is a significant association between heroin use and decision-making alterations.

4.5. Alcohol

Several studies have addressed the neuropsychological effects produced by exclusive alcohol use, most of them conducted in samples of alcohol-dependent individuals following residential-treatment. A first group of these studies investigated cognitive performance during short-term abstinence (<30 days). Bjork et al. (2004) found significant alterations in different forms of impulsivity (including response inhibition, delay discounting and risk-taking) in 130 alcohol dependent subjects who had been alcohol abstinent for 1 week. Interestingly, when alcohol users were subdivided according to age at onset of alcohol use and family history (Type I vs. Type II), early onset alcoholics (Type II) had poorer performance on response inhibition, but both groups performed similarly on delay discounting and risk taking measures. These results suggest that alcohol-related deleterious effects relate to impulsive choice and decision-making, whereas alterations in impulsive action might be premorbid. A study by Ratti et al. (2002) showed that a group of alcoholics (n=22 with 3 weeks of abstinence) who were not users of other substances presented impairments in abstraction, problem-solving, cognitive flexibility, attention and perceptual motor speed. They also had higher impulsivity levels than non-users in different dimensions, including motor inhibition alterations on reaction time tasks and a significant increase in

the preference for immediate reward options in a delay-discounting task. A study by Schottenbauer et al. (2007) evaluated memory alterations in a group of alcoholics (n=176) who had not used any other drugs for at least 6 months prior to the study and who had been alcohol abstinent for 3 weeks. The results showed that the alcohol-using subjects presented an altered performance on a word-learning memory task; they needed more time to learn the word list and had more difficulties to retrieve what they had learned.

When considering alcohol effects observed after a mid-term abstinence period, Errico et al. (2002) employed a comprehensive neuropsychological battery of memory and executive functions measures, but only found alterations in verbal episodic memory in alcoholic subjects abstinent for 32 days. When considering the effects of this substance at long-term, two consecutive studies from the same group have provided some keys to reveal potential recovery of cognitive functioning across abstinence. The first study by Fein et al. (2004) specifically assessed decision-making performance (measured by the Iowa Gambling Task). The sample was composed by 44 long-term abstinent alcoholics (average abstinence of 6.6 years), who were non-treatment seekers, and 58 healthy subjects. Results showed that, after this period of abstinence, alcoholic users had yet a poorer decision-making performance than controls. A later study by Fein et al. (2006), employing a much more comprehensive neuropsychological assessment to explore cognitive flexibility, attention, auditory working memory, immediate and delayed episodic memory, psychomotor function, reaction time, spatial processing and verbal skills, showed that long-term abstinent alcoholics (average abstinence of 6.7 years, n=48), non-treatment seekers and ex- residential treatment participants, performed similarly to non alcohol users (n=48) in all the domains assessed, except for

the spatial processing domain. These results show that protracted abstinence can resolve most of the neurocognitive deficits associated with alcoholism, except for persistent deficits in spatial processing and decision-making.

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
Cannabis	Fried et al., 2005 (SAC/MT)	NTxS: 19 current heavy users, 19 current light users, 16 former regular users; 59 controls	Current: 24 h Former: at least 3 months	Vocabulary, AcatT, WAIS (General IQ, Block design, Picture completion, Digit symbol), WMS (IMI, GMI)	IQ, SM, UP-Rs, **speed**, **EM**: 24 hours
Psychostimulants	Bolla et al., 2003 (ST)	NTxS: 13 cocaine users; 13 controls [#]	25 days	IGT	***DMK***
	Verdejo et al., 2007a (ST)	NTxS: 12 cocaine users; 13 controls [#]	25 days	IGT	***DMK***
	*Volkow et al., 2001 (MT/LT)	RESTx: 5 methamphetamine users; 11 controls	3 months 12-17 months	RAVLT, GPT	***EM***, **MOT**: After 3 months
	Salo et al., 2009 (MT/LT)	COMTx: 38 methamphetamine mid abstinence, 27 methamphetamine long abstinence; 33 non users [+]	78 days 31.5 months	Stroop Attention Task	**ImpAC**: After 2.6 months
	Moon et al., 2007 (LT)	19 methamphetamine users, 18 controls	1.79 years	RAVLT, RCFT	***EM***
MDMA	Halpern et al., 2004 (ST)	NTxS: 23 MDMA users (12 light users with consumption between 22-50 pills, 11 heavy users with more than 50 pills consumption); 16 controls	10 days	Vocabulary, Digit symbol, Digit span, Block design (WAIS-III), Stroop, RPM, Mental control, Logical memory, Verbal paired associates, Spatial span, Visual reproduction (WMS-II), COWAT, RCFT, WCST, TMT, CVLT-II, R-SAT	IQ, SUAT, SPA, MOT, SM, EM, UP-WM, UP-Fl, Cogflx-SS, **ImpAC**, **speed**
	Yip & Lee 2005 (MT)	NTxS: 100 MDMA users; 100 controls	67 days	FDST, BDST, CAVLT, Stroop, AFLT, CTT, SDMT, VFT, RFFT	SPA, Cogflx-SS, ImpAC, **EM**, **SAT**, **UP-WM**, **UP-Fl**
Opioids	Fishbein et al., 2007 (ST)	RESTx: 100 heroin users, 102 alcohol users, 60 alcohol and heroin users; 160 controls [+]	21 days	CANTAB test battery: DMS, PAL, SOC; E-Prime battery: Stroop, CDMT, SCT	UP-WM, ImpAC, ***EM*** (alcohol), ***UP-Rs*** (alcohol), **DMK** (heroin)
Alcohol	Bjork et al., 2004 (ST)	RESTx: 130 alcohol dependent patients; 41 controls [+]	7 days	IMT, DelayedMT, RTT, TTDDT	DMK, **ImpAC**, **ImpCH**
	Ratti et al., 2002 (ST)	RESTx: 22 alcohol users; 22 controls	21 days	Digit symbol, TMT, Stroop, Digit cancellation test, Choice Reaction time, WCST	SUAT, speed, ImpAC, **MOT**, **SAT**, ***UP-Rs***, **Cogflx-SS**
	Schottenbauer et al., 2007 (ST)	RESTx: 176 alcohol users; 35 controls [+]	Alcohol: 21 days Other substances: 6 months	The Buschke selective reminding task, WAIS: Vocabulary, Block design	IQ, ***EM***
	Errico et al., 2002 (MT)	RESTx: 48 alcohol users; 30 controls	32 days	WMS: Logical memory, Wechsler immediate and delayed visual reproduction subtests, RCFT, HRDT, CBTT WCST	CogFlx-SS, UP-WM, ***EM***
	Fein et al., 2004 (LT)	NTxS: 44 long term abstinent; 58 controls	6.6 years	SGT	**DMK**
	Fein et al., 2006 (LT)	NTxS and ex-RESTx: 48 long term abstinent; 48 controls	6.7 years	MicroCog, RCFT, TMT, Symbol Digit Modalities Test, AMNART, COWAT, PASAT, Block Design (WAIS-R), Stroop, FAB, SGT	IQ, MOT, SAT, EM, UP-WM, UP-Fl, Cogflx-SS, ImpAC, speed, **SPA**

Table 2. Neuropsychological studies on relatively 'pure' users of one substance (excluding nicotine and minimal alcohol use).

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] RPM: Raven's progressive matrices; AMNART: American version of the Nelson Adult Reading Test.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models;
[#] Comparison groups were not demographically matched but these variables were not correlated with neuropsychological measures and were no longer considered.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

4.6. Summary

According to the studies on samples of relatively 'pure' users of one particular drug, the most consistent generalized effects across substances are: episodic memory, showing large mean effect sizes for cannabis, methamphetamine and MDMA, and medium mean effect sizes for opioids and alcohol; and impulsive action, showing large mean effect sizes for methamphetamine and medium mean effect sizes for MDMA and alcohol. Interestingly, the effects of methamphetamine and alcohol on impulsive action covary with their effects on psychomotor functioning, possibly indicating generalized neural substrates of both substances. Recent imaging work indicates that these deficits are related to dysfunction of the brain system formed by the pre-supplementary motor area, the inferior frontal gyrus and the basal ganglia (Aron et al., 2007). With regard to episodic memory, although all drugs seem to impair this function, they could be tapping on different subprocesses. For example, the effects of methamphetamine on episodic memory appear to be related to altered executive monitoring of encoding strategies during verbal learning (Volkow et al., 2001) and to altered planning/organization skills during visual memory (Moon et al., 2007). Reasoning deficits are shared by pure users of heroin and alcohol, although mean effect sizes are larger for alcohol. Similarly, processing speed deficits are shared by alcohol and cannabis users, although they only seem to persist during mid-term abstinence in alcohol-using individuals. As for exclusive effects of different drugs, results from this methodology indicate robust exclusive effects of alcohol use on spatial processing and cognitive flexibility –set-shifting, and of MDMA use on verbal fluency. Nonetheless, these conclusions should be qualified by the fact that there are not available studies in 'pure' users' studies of drugs like cocaine, which is also significantly linked to updating and set-shifting

abnormalities. The same limitation (due to the lack of available studies) applies to the domain of decision-making, which has been only explored by studies in 'pure' users of alcohol and cocaine, preventing us from drawing strong conclusions about this ability. Future studies should aim to address these gaps in the literature. Finally, the most robust long-term effects (>6 months of abstinence) are visual-spatial and decision-making deficits in alcoholics, and episodic memory and psychomotor functioning deficits in methamphetamine abusers.

5. Methodologically controlled studies for studying specific effects

The obvious difficulties in recruiting samples of 'pure' users of any drug have favored the development of studies that attempt to control for polysubstance use through methodological strategies. One of the most commonly used designs for this purpose is that in which researchers compare one group of polysubstance users of the drug of interest with a comparison group of polysubstance users of the same drugs except for the drug under study. In this way, potential differences between the two groups can be attributed to the drug of interest, which is the only one that the two groups do not have in common. This strategy, which has been used by various studies, employs a subtraction rationale where the effects of the other drugs used are subtracted from those of the main drug by using matched polydrug control groups.

5.1. Psychostimulants:

- *Cocaine+Alcohol*

Cocaine and alcohol are a combination of substances frequently consumed by drug users. Numerous studies have tried to investigate the neuropsychological effects of each substance separately. However, given the high frequency of their combined

consumption, many authors have recently examined whether the concurrence of the two can produce combined effects on neuropsychological performance. Several studies have revealed that the combination of cocaine and alcohol produces a metabolite called cocaethylene that produces further deterioration than the use of each substance separately (Andrews, 1997; Carroll, 1993; Jatlow et al., 1996). Our systematic review identified two neuropsychological studies conducted in cocaine+alcohol users after short-term abstinence that yielded results consistent with this notion. Goldstein et al. (2004) contrasted the neuropsychological performance of three groups: a group of crack/cocaine users who also used alcohol (n=42; average abstinence of 22.9 days), a group of alcohol users (n=40; average abstinence of 16.9 days), and a group of non drug users (n=72). The cocaine/alcohol groups were formed by community and residential treatment participants. The results showed that the cocaine group had significantly generalized neuropsychological impairments, although of a moderate nature, in the neuropsychological domains studied: verbal knowledge, episodic memory, including visual and verbal memory, attention and executive functions, specifically on cognitive flexibility measures. The specific analysis of the performance associated with cocaine use (controlling the use of alcohol) showed an association of this substance with verbal memory impairments. In contrast, alcohol use was associated with a greater effect on attention and executive functions; cocaine users who also consumed alcohol performed worse on these measures than those who did not use alcohol. Bolla et al. (2000) used regression techniques in a non-treatment seeking sample including cocaine users who did not consume alcohol (n=29) and cocaine users who did (n=27), in order to dissociate the effects of the two substances on the different neuropsychological functions. Subjects were assessed twice, after 1-3 days of abstinence and after 28-29 days of abstinence.

After 1-3 days of abstinence, they found dose related associations between cocaine dose and alcohol dose and neuropsychological performance. Specifically, processing speed and executive function, including cognitive flexibility and planning, were affected by the use of alcohol, while episodic memory, verbal learning and attention were affected by cocaine. The authors observed that these alterations persisted after 4 weeks of abstinence, although with somewhat different results depending on the dose. Specifically, they found a decline in the Stroop test relative to baseline in participants who reported mid-range cocaine use together with mid-range alcohol use. This decline was not found in those who reported using small amounts of cocaine in conjunction with heavy drinking or those who used heavy amounts of cocaine together with light drinking. These results suggest that a moderate amount of both cocaine and alcohol is required to produce a maximum synergy that might exert more deleterious and persistent effects on the brain. Thus, the neuropsychological effects of the combined consumption of both substances would be additive.

A second group of studies have found evidence of the opposite notion, i.e. alcohol co-abuse may decrease cocaine-induced neuropsychological deficits. Two studies supporting this notion met criteria for inclusion, one conducted during short-term abstinence and one carried out during mid-term abstinence. Abi-Saab et al. (2005) investigated the effects of co-abuse during short-term abstinence. Participants were 22 cocaine users and 71 cocaine and alcohol users, both groups' non-treatment seekers, with an average abstinence of 4.82 days. These authors observed that the two groups presented alterations on measures of episodic memory, attention and manual dexterity. The magnitude of alterations in both groups was quite similar, although it was slightly higher in the cocaine group for all the measures and considerably higher on the memory

tests. When considering mid-term abstinence duration, Robinson et al. (1999) evaluated community and residential treatment groups of cocaine users (n=30) vs. users of cocaine and alcohol (n=30) with a mean cocaine abstinence of 95.8 days and a mean alcohol abstinence of 72.9 days. These authors observed that the individuals who consumed both substances performed better than those who only consumed cocaine on global neuropsychological functioning, including measures of psychomotor functioning and manual dexterity, where they found significant differences between the two groups. The authors suggested that this superior performance was due to the vasodilator effect produced by alcohol, which would counteract the vasoconstriction produced by cocaine. This effect would mean an improved functioning of the subject as a result of the combination of the two substances. One possible explanation for the discrepancy between the results of these studies and those mentioned previously can be the differences in parameters of severity (i.e., dose, frequency or duration) of the drugs used among these studies. When inspecting the duration of alcohol use, we observe that, while in the Bolla and Goldstein study the users of cocaine and alcohol presented duration of use ranging from 15 to 23 years, those in the Robinson and Abi-Saab study ranged between 5 and 17 years. Moreover, the period of abstinence in the studies by Bolla and Goldstein varied between 1 and 29 days, while in the Robinson and Abi-Saab study the period of abstinence ranged from 1 to 95 days. Therefore, the severity of alcohol and cocaine abuse and the duration of abstinence may modulate their relative contribution to neuropsychological deficits in mixed cocaine and alcohol users.

In spite of these findings, most of the studies that met inclusion criteria in our systematic review found that alcohol did not increase the cognitive performance decrements associated with cocaine, nor did it seem to attenuate its effects. The study by

Colzato et al. (2009) was conducted in cocaine+alcohol polysubstance users vs. non-cocaine polysubstance users during short-term abstinence. Participants were non-treatment seekers. This study was focused only in selective attention skills, and found that cocaine polysubstance users performed poorer than alcohol users on this domain. Addressing a longer mid-term abstinence, Fein et al. (2002) found that the two groups of drug users, cocaine (n=17) and cocaine+alcohol (n=29), both following residential treatment with an average abstinence of 6 weeks, did not differ from each other in the different domains; both showed alterations in episodic memory, reasoning, flexibility, selective attention, spatial processing and processing speed. Di Sclafani et al. (2002) found similar results when studying the neuropsychological performance of crack users (n=20) vs. crack and alcohol co-users (n=37) with different abstinence periods: 6 weeks and 6 months. The results showed that both groups had comparable alterations on episodic memory, specifically on measures of immediate and delayed recall, selective attention, spatial processing, reasoning and cognitive flexibility –set-shifting. The most robust effects were found on measures of spatial processing, and indices of the executive components of reasoning and cognitive flexibility. These effects were present at both 6 weeks and 6 months. On the other hand, some improvements were observed in immediate recall, possibly due to the effect of practice.

- *Methamphetamine+Cannabis*

Only one study meeting inclusion criteria used this type of subtraction design. González et al. (2004) carried out a study to test whether cannabis can produce an attenuation of the effects of methamphetamine during short-term abstinence. For this purpose, they compared two subgroups from a mixed sample of non-treatment seeker and residential treatment-enrolled methamphetamine users: methamphetamine+cannabis co-users

(n=27) and users of methamphetamine alone (n=26), both with an abstinence of 1 to 30 days. Although there were no significant differences between the groups, they found that methamphetamine users performed worse than methamphetamine and cannabis co-users, above all with regard to episodic memory, specifically on measures of delayed memory and learning. It seems, therefore, that while cannabis may not necessarily improve the neuropsychological effects caused by methamphetamine, at least it does not make them worse.

5.2. MDMA ('Ecstasy'):

- MDMA + cannabis

It is common for MDMA users to consume also other substances, the most frequent of which is cannabis (Wu et al., 2009). We found four studies that have tried to dissociate the neuropsychological effects stemming from the MDMA and cannabis co-use by means of subtraction techniques. Since MDMA use rarely generates addiction treatment demands, all of these studies are conducted in non-treatment seeking samples. The first of these studies investigated these effects during short-term abstinence. Gouzoulis-Mayfrank et al. (2000) compared a sample of ecstasy and cannabis co-users (n=28) to another group who used only cannabis (n=28) and a group of non-users (n=28). The average abstinence period was 41 days for the use of ecstasy and 4 days for the use of cannabis. The results of the study showed that the MDMA and cannabis co-user group was the most affected, especially on measures of episodic memory and learning, selective and divided attention, and executive functions such as fluency, working memory, reasoning, and problem solving. Importantly, the heavier the use of ecstasy (around 100 units) and cannabis, the worse the performance, with longer reaction times on verbal memory and divided attention, as well as poorer working memory. In

contrast, the groups that only used cannabis showed a very similar performance to that of the non drug using subjects. De Sola et al. (2008) investigated the effects of MDMA + cannabis use across a period of two years. They examined a group of polysubstance users with regular co-abuse of ecstasy and cannabis (n=37), another group of cannabis using subjects who were not polysubstance users (n=23), and a third group of non drug users (n=34). The results revealed that 72 hours after the last use, ecstasy and cannabis co-users showed specific impairments in semantic verbal fluency, and those who were heavier ecstasy users throughout their lifetime (more than 100 units) presented alterations in visual episodic memory, visual working memory and processing speed. Moreover, after six, 12 and 24 months, ecstasy users had persistently poorer performance than non-drug users on measures of word fluency, working memory and processing speed.

Although these studies clearly point to ecstasy use as being mainly responsible for the alterations found, other studies have obtained contradictory results. Two studies supporting this notion met criteria for inclusion, both conducted during short-term abstinence. Croft et al. (2001) compared the performance of a group of cannabis users (n=18), a second group who used cannabis and an average of less than 50 units of ecstasy (n= 11), and a third group of non drug users (n= 31). The users had at least 17 hours of cannabis abstinence and at least 1 week of MDMA abstinence. The results showed that both groups of drug users presented alterations in memory, verbal fluency, working memory, learning, processing speed and manual dexterity, with no significant differences between them. However, the covariate models that analyzed the isolated contribution of each substance indicated that MDMA contributed differentially to impairments in processing speed, whereas cannabis contributed to impairments in

fluency and verbal learning. Both substances were related to deficits in working memory and manual dexterity. Dafters et al. (2004) found similar results when using four groups, cannabis users (n=15), cannabis users who consumed less than 50 units of ecstasy (n=19), cannabis users who consumed more than 50 units of ecstasy (n=16) and non drug users (n=19). All the subjects stated that they had abstained from MDMA use for at least 7 days and from cannabis use for 48 hours prior to testing. The results showed that the groups that consumed cannabis, whether or not they used ecstasy, demonstrated impairments in episodic memory (free immediate, and delayed recall), which seems to indicate that the effects were due to the use of cannabis. In both the study by Dafters and the one by Croft, the authors observed that the subjects used other substances (cocaine, alcohol, amphetamines, etc.); thus, once again the problem of polysubstance use may be confusing the results obtained from various studies. Furthermore, the period of abstinence from using cannabis in these studies varied between 17 and 48 hours, whereas MDMA abstinence was about one week; therefore some of the specific effects observed for cannabis could be acute or sub-acute and transient.

- *MDMA + polysubstance use*

In trying to dissociate the effects of polysubstance use from those produced by the use of MDMA, several studies have contrasted performance of groups of polysubstance users who used MDMA with that of polysubstance users who did not use MDMA. Four of the studies selected were conducted during short-term abstinence. In a sample including 20 polysubstance users with MDMA use and at least 2 weeks of abstinence, 20 polysubstance non MDMA users, and 20 non-drug users, Fox et al. (2002) found that the ecstasy group presented impairments in verbal learning, visual memory, spatial

working memory and verbal fluency (but not on planning, impulsive action, cognitive flexibility or risky decision-making). Dafters et al. (2006) examined three groups: 18 MDMA + cannabis users, 18 cannabis users and 18 drug-free controls using tests of impulsive action and set-shifting. The duration of abstinence for cannabis was of 48 hours, whereas MDMA abstinence was of 5 days. The results showed that MDMA use was specifically associated with cognitive flexibility/set-shifting deficits. Morgan et al. (2006) found that after a mean abstinence of 23 days, MDMA users presented alterations on impulsive choice (measured by the Matching Familiar Figures Test) and risky decision-making (measured by the Risky Decision-Making task). There is a certain degree of discrepancy between the findings from these studies, especially with regard to the domains of cognitive flexibility and risky decision-making, which may be explained by the use of different assessment instruments (e.g., Stroop-shifting vs. CANTAB ID/ED or Cambridge Gamble vs. Risk tasks) with slightly different cognitive demands. A recent study by Schilt et al. (2008) as a part of the Netherlands XTC Toxicity (NeXT) study, the first large-scale ecstasy study which, through the use of imaging techniques and a combination of both cross-sectional and longitudinal approaches, constitutes the gold standard in ecstasy studies (de Win et al., 2005), have compared the performance of 31 polysubstance users who used MDMA to that of 36 polysubstance non MDMA users with a minimum drug abstinence of 2 weeks for MDMA and 1 week for alcohol. Using regression techniques to separate the ecstasy effects from the effects of other drugs, the results showed that ecstasy use had a specific significant dose-related negative effect on verbal delayed recall after adjusting for the use of other drugs.

When considering results obtained after mid-term abstinence we identified three different studies meeting inclusion criteria. Butler and Montgomery (2004) found that in a sample of recreational users with a mean abstinence of 5 weeks, the group of polysubstance users who consumed more than 20 pills of MDMA (n=18) presented a greater preference for risky options on a decision-making task than those polysubstance users who did not take MDMA (n=37) or those who did not use as much (n=28). A first study by Morgan (1998)* found that polysubstance users who had used MDMA had more prominent impairments in impulsivity than non-MDMA polysubstance users, especially on a measure of reflection-impulsivity (Matching familiar figures test, MFFT), and these impairments persisted after 65 days of abstinence (Morgan, 1998). In a subsequent study that tested part of the same sample, Morgan et al. (1999) compared a group of 25 polysubstance users who used MDMA with 22 polysubstance users who did not use it, both with an average MDMA abstinence period of from less than 1 month to 6 months. The results showed impairment in episodic memory in the group that used MDMA, both immediate and delayed recall, which was not observed in the other group. These memory impairments were also associated with the amount of ecstasy consumed per session and, in the case of immediate recall, with the number of years it was used as well. The study also reflected the persistence of the impairments produced by the MDMA up to 6 months after its use.

However, the studies conducted on MDMA polysubstance abusers presenting long-term abstinence duration have provided little evidence of the existence of durable neuropsychological effects associated with the use of MDMA (Hoshi et al., 2007; Roiser et al., 2007). Specifically, the study by Hoshi et al. (2007) found that current MDMA users (n=25; mean abstinence of 14 days) and polysubstance users (n=29)

presented alterations on verbal learning and episodic memory measures, as well as on impulsive action. However, these alterations were not observed among former users (n=28; mean abstinence of 2.78 years). Furthermore, there were no differences between the groups on measures of the executive component of updating, including attention, working memory and verbal fluency measures, or on cognitive flexibility. Using a similar methodological design, Roiser et al. (2007) compared the performance of a group of 30 current MDMA users (mean abstinence of 75 days), 20 ex-MDMA users (mean abstinence of 2.79 years), 30 polysubstance users who did not consume MDMA, and a group of 30 non users on a series of neuropsychological tests. The results only showed the existence of subtle differences on a spatial ability task between former users of MDMA and non users.

5.3. Opioids

Regarding opioid users, only one study corresponding to this methodology met our inclusion criteria. Verdejo-García et al. (2005a) carried out a study with two groups of opioid users, one group enrolled in methadone maintenance treatment (n=18) and another group of former heroin users (n=23), during a period of at least 15 days of abstinence. Given that the subjects had different histories of substance use, with the subjects in the methadone group having higher scores on both amount and duration of use of cannabis and heroin, the authors used multiple regression techniques to subtract the effects of the use of these substances from the scores obtained by the subjects on the neuropsychological measures employed. After controlling for the co-abuse of other drugs the results showed that, compared to the heroin group, subjects in the methadone group performed more slowly on measures of processing speed, visuospatial attention and cognitive flexibility, and they performed worse on measures of the executive

component of updating, including measures of working memory and analogical reasoning. Thus, the results showed that it was the use of methadone itself that was associated with the cognitive impairments found in these participants.

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
Psychostimulants	Bolla et al. 2000 (SAC/ST)	NTxS: 29 cocaine users, 27 cocaine and alcohol users	1-3 days 28 days	Shipley IQ, WAIS-R, RAVLT, Digit Symbol (WAIS-R), TMT Stroop, Block design (WAIS-R), CalCAP, GPT.	IQ, ***MOT*** (alcohol), ***SAT*** (cocaine), ***EM*** (cocaine), ***CogFlx-SS*** (alcohol), **PLAN** (alcohol)
	Abi-Saab et al. 2005 (ST)	NTxS and COMTx: 22 cocaine users, *71 cocaine and alcohol users; 16 controls [+]	Cocaine and alcohol: 5 days	Digit span, Digit symbol (WAIS-R), DVT, PASAT, TMT, FOT, GPT, RAVLT, COWAT.	UP-WM, CogFlx-SS, UP-Fl, Cocaine and alcohol: ***MOT, SAT, EM***
	Colzato et al., 2009 (ST)	NTxS: 18 polysubstance (non cocaine users), 18 polysubstance (cocaine users)	14 days	Raven's Progressive Matrices, Global local task	IQ, ***SAT***
	Goldstein et al, 2004 (ST)	RESTx and COMTx: 42 crack+alcohol users, 40 alcohol users; 72 controls [#]	Crack: 23 days Alcohol: 17 days	COWAT, BNT, Similarities (WAIS-R), CVLT, WMS, BVRT, DCT, SDMT, TMT, WCST, Stroop, BCT, WRAT, RPM	IQ, SM, MOT, UP-Rs, ImpAC*, ***SAT*** (alcohol), ***EM*** (crack), ***CogFlx-SS*** (alcohol)
	*Fein et al., 2002 (MT)	RESTx: 17 cocaine users, 29 cocaine and alcohol users; 20 controls	24 days	MC: numbers forward, numbers reversed, alphabet, word list, analogies, object match, tic tac, clock, story, word list, address, timers.	UP-WM, Cocaine and alcohol: ***MOT, SPA, SAT, EM, UP-Rs, CogFlx-SS***
	Di Sclafani et al., 2002 (MT)	RESTx: 20 crack users, 37 crack and alcohol users; 29 controls	24 days 6 months	MC, RCFT, TMT, SDMT, COWAT, GPT, SCT, Stroop.	MOT, UP-Fl, ImpAC*, Cocaine and alcohol: ***SPA, SAT*, EM, UP-Rs*, CogFlx-SS****
	Robinson et al. 1999 (MT)	RESTx and COMTx: 30 cocaine users, 30 cocaine and alcohol users; 30 controls	Cocaine: 96 days Alcohol: 73 days	HRNTB (CT, TMT, TPT,RT, SSPT, FTT), WAIS-R, GPT, SMT, FMT, HDT	SAT, CogFlx-SS Cocaine and alcohol: improve global neuropsychological, ***MOT*** (cocaine)
	González et al., 2004 (ST)	RESTx and NTxS: 26 methamphetamine users, 27 methamphetamine and cannabis users; 41 controls	1-30 days	FAS, CT, TMT, Letter and number (WAIS), PASAT, HVLT-R, BVMT-R, SMT, FMT, GPT	MOT, UP-WM, UP-Fl, Up-Rs, CogFlx-SS, ***EM***
MDMA	Dafters et al., 2006 (ST)	NTxS: 18 cannabis and MDMA users, 18 cannabis users; 18 non users	MDMA: 5 days Cannabis: 48 h	Stroop, Stroop (task switching version), Keep Track Task	SAT, ImpAC, CogFlx-SS, UP-WM **Cog-Flx-SS** (MDMA)
	Croft et al., 2001(Cannabis SAC, MDMA ST)	NTxS: 18 cannabis users, 11 cannabis and MDMA users; 31 controls	Cannabis: 17 h MDMA: 7 days	WRMT, GPT, SN-SALT, FBDS, VFT, Stroop, CLDL, NART.	SAT, SPA, ImpAC, ***speed*** (MDMA), **MOT** (MDMA and cannabis), ***UP-Fl*** (cannabis), ***UP-WM*** (MDMA and cannabis)
	Dafters et al., 2004 (ST)	NTxS: 19 cannabis and MDMA users (light), 16 cannabis and MDMA users (heavy), 15 cannabis users; 19 controls	Cannabis: 48 h MDMA: 7 days	FDST, FRT, RBMT (immediate and delayed), RSCT (BADS), TEA, MFFT.	SAT, CogFlx-SS, UP-WM, ImpCH, ***EM*** (cannabis)
	Morgan 2006 (ST)	NTxS: 12 polysubstance users (non MDMA users), 20 MDMA users; 20 controls	23 days	MFFT, CARROT, Risky decision making	***ImpCH, DMK***

Table 3 (continued)

MDMA	Schilt et al., 2008 (ST)	NTxS: 31 polysubstance users (MDMA users), 36 polysbustance users (non MDMA users)	Psychoactive drugs: 14 days Alcohol: 7 days	PASAT, Digit span, RAVLT, Memory for design test, Mental rotation task, Judgment of Line Orientation (JoLO)	SPA, UP-WM, ***EM*** (MDMA)
	Fox et al., 2002 (ST)	NTxS: 20 polysubstance users (non MDMA users), 20 polysubstance users (MDMA users)	14 days	VFT, SWM, 3-D IDED (CANTAB), PSR, PAL, Go-nogo, One touch TOL, DMT	Cog Flx-SS, ImpAC, DMK, PLAN, MDMA: ***EM***, ***UP-WM***, ***UP-Fl***
	Gouzoulis-Mayfrank, 2000 (MT MDMA, ST Cannabis)	NTxS: 28 cannabis users, 28 cannabis and MDMA users; 28 controls	MDMA: 41 days Cannabis: 4 days	TAP (1,6,5,8,12), Stroop, Digit span (WAIS), VLMT, VIG, WF, LPS-4, Mosaic test (WAIS), General knowledge (WAIS)	IQ, ImpAC, Cannabis and MDMA: **SAT**, ***EM***, ***UP-Fl***, ***UP-WM***, **UP-Rs**, **PLAN**, **DAT**
	Butler and Montgomery 2004 (MT)	NTxS: 37 polysubstance users, 28 polysubstance users (light MDMA users), 18 polysubstance users (heavy MDMA users), 55 cannabis users; 116 controls	35 days	The Bets16.	***DMK*** (MDMA)
	Morgan et al. 1999 (MT)	NTxS: 22 polysubstance users (non MDMA users), 25 polysubstance users (MDMA users); 19 controls	1-6 months	RBMT	***EM*** (MDMA)
	Morgan 1998 (MT)	NTxS: 12 polysubstance users (non MDMA users), 16 polysubstance users (MDMA users); 16 controls	65 days	TOL, MFFT	PLAN ***ImpCH***
	De Sola et al., 2008 (ST/LT)	NTxS: 37 polydrug users (MDMA and cannabis), 23 cannabis users; 34 non-users	72 h 24 months	Vocabulary (WAIS), CALCAP, TOL, WF, SDMT, CVLT, RCFT, CBT, Letter and number (WAIS)	SM, DAT, PLAN, 72 h cannabis and MDMA: ***speed***, ***EM***, ***UP-Fl***, ***UP-WM***, 24 months MDMA: ***speed***, ***UP-Fl***, ***UP-WM***
	Hoshi et al., 2007 (ST/LT)	NTxS: 25 current MDMA users, 28 ex MDMA users, 29 polydrug users; 27 non users	Current MDMA: 14 days Ex MDMA: 1017 days	IDPR, BSRT, Go/No go task, SST, SFVF, TMT, CANTAB spatial working memory, stockings of Cambridge, GSM	MOT*, UP-WM*, UP-Rs, CogFlx-SS*, Current MDMA and polydrug users: ***EM***, **ImpAC***
	Roiser et al., 2007 (MT/LT)	NTxS: 30 current MDMA users, 20 ex MDMA users, 30 polydrug users; 30 non users	Current MDMA: 75 days Ex MDMA: 2 years and 10 months	Tile manipulation test, Mental rotation task, DMT, Pattern recognition memory, DMS	EM, UP-WM, DKM, PLAN, **SPA** (MDMA)
Opioids	Verdejo et al., 2005a (ST)	RESTx: 23 heroin users, 18 methadone patients	Heroin: 15 days	FAS, Letter Number Sequencing (WAIS), Oral trails, Stroop, Similarities, FDT, WCST	UP-Fl, ImpAC, Methadone: **speed**, **UP-WM**, **UP-Rs**, **CogFlx-SS**,

Table 3. Neuropsychological studies implementing methodological control of co-abused drugs.

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] NART: National adult reading test; HRNTB: Halstead-Reitan Battery; SCT: Short category test (Booklet format); RPM: Raven´s progressive matrices.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models;
[#] Comparison groups were not demographically matched but these variables were not correlated with neuropsychological measures and were no longer considered.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

5.4. Summary

The bulk of evidence stemming from this research methodology focuses on the neuropsychological effects of psychostimulants (cocaine and MDMA) vs. alcohol, cannabis and polysubstance use. With regard to the direct comparison of alcohol and cocaine, the overall conclusion is that alcohol co-abuse is associated with increased motor and executive functions deficits (including fluency, selective attention and set-shifting), which reach medium effect sizes at mid-term abstinence. However most of the studies indicate that, during long-term abstinence, there are only mild persistent neuropsychological effects of cocaine and alcohol (small effect sized decrements in spatial processing, selective attention, episodic memory, reasoning and set-shifting), and that the relative contributions of each substance are indistinguishable. With regard to the generalized and specific effects of MDMA vs. cannabis and polysubstance abuse, results show that: (i) at short-term abstinence, MDMA is associated with medium sized effects indicating greater impairments in selective/divided attention, updating and response speed; (ii) at mid-term abstinence, MDMA is associated with low sized effects indicating mildly increased deficits in episodic memory and impulsive choice; and (iii) at long-term abstinence, the differential effects of MDMA are of low-to-medium size (*d* values of 0.3-0.5), and relate to deficits on response speed, spatial processing, episodic memory and motor/impulsive action. The lack of correspondence between results at the different time points is partly related to the fact that certain cognitive abilities (e.g., set-shifting, impulsive choice or decision-making) were measured by several studies during short- and mid-term but are not well-represented in studies addressing long-term abstinence. Finally, with regard to the specific effects of opioids, the results from the

only study that met inclusion criteria revealed medium-large additive specific effects of methadone on speed, working memory, reasoning and set-shifting skills.

The results provided by these studies must be interpreted with caution due to the inherent limitations of the type of designs used to subtract the neuropsychological effects of different drugs. We have repeatedly observed a lack of consensus among studies that use similar designs to study the effects of joint use of cocaine and alcohol, MDMA and cannabis, or MDMA and many other substances. This lack of consensus may be related to several factors, including the non-homogeneous assessment protocols, or the differences in the duration of abstinence of the main drugs contrasted (e.g., in MDMA vs. cannabis studies, cannabis abstinence is usually shorter than MDMA abstinence). In addition, the dose-related effects of the severity of drugs use on several of the neurocognitive decrements observed may also contribute to disparity of findings. Some of these dose-related effects have been well-documented; for example, there are significant detrimental effects of severity of MDMA used on episodic memory, processing speed and executive functions (De Sola et al., 2008), and detrimental effects of severity of alcohol and psychostimulants use on impulsive action and decision-making (Verdejo-García et al., 2005b; Verdejo-García et al., 2007a). Future studies using this methodology should assess to what extent the different degrees of drug exposure contribute to generalized vs. differential drug effects.

6. Neuropsychological studies in polysubstance users with different principal drugs of choice

Most drug users are frequently users of more than one substance and even take more than one substance in the same session (National Institute of Drug Abuse, 1998).

Regarding cocaine, Robinson et al. (1999) found that subjects who use this substance usually develop dependence on many other substances of a sedative nature, usually alcohol (Miller et al, 1990; Rounsaville et al, 1991). On the other hand, cocaine and heroin are often consumed together using freebase administration. Some studies suggest that the incidence of this type of polysubstance use is relatively high in the United States (Metzger et al., 1996; Schütz et al., 1994) and in the European Union (EMCDDA Annual Report, 2008). Similarly, a study by Butler et al. (2004) revealed that in a broad sample of ecstasy users, all of them had used other illegal substances, especially stimulants and hallucinogens. Hammersley et al. (1999) did not find even one subject who had consumed ecstasy and had not used other drugs.

Furthermore, we sometimes encounter studies in which there is little information about the possible polysubstance use of the samples under study. This lack of information may be due to the fact that the subjects' history of drug use was not thoroughly explored, or to the reliability of the data provided by the subjects about their drug use, or to the heterogeneous profile of the subjects found in treatment centers. For one reason or another, the reality is that most studies on drug dependence use samples of subjects who are 'main users' of one substance. Among them, we can distinguish between two types of studies. On the one hand, there are those that study the effects of the different abused drugs in polysubstance users who have a principal drug of choice, comparing their performance with that of healthy subjects. On the other hand, we have those studies that also seek to study the effects of the different drugs, but they do so by comparing the performance of two or more groups of polysubstance users who have different drugs of choice, also comparing their performance with that of healthy subjects. Although both types of studies are useful to contrast the neuropsychological

performance of drug users, the latter are better suited to address the question of which effects are specific and which effects are common to the use of the different drugs of choice compared in the study.

6.1. Studies comparing polysubstance users with a principal drug of choice and drug-free controls:

6.1.1. Cannabis

Five studies meeting inclusion criteria have contrasted the neuropsychological performance of individuals who use mainly cannabis and that of non drug users. Three of these studies were conducted during early/short-term abstinence (24h to 7 days) employing measures of psychomotor functioning, episodic memory and executive functions (McHale et al., 2008; Pope et al., 2001; Wadsworth et al., 2006). Their results showed that during the first day of abstinence, deficits are observed in psychomotor skills, episodic, prospective memory and the updating component of executive functions. However, after 7 days of abstinence, only fluency and episodic memory deficits are still observable. According to Pope et al. (2001), up to 28 days after cannabis use ceased, none of the significant differences between users and controls remain significant. This conclusion is at odds with the results from Medina et al. (2007) on mid-term cannabis effects in adolescent users (after 30 days of abstinence). These authors showed decreased performance of abstinent cannabis users on tests of spatial processing, speed, episodic memory, selective attention and planning. Their results also showed that the frequency of cannabis use was significantly associated with poorer performance on these tests (even after controlling for alcohol use). Therefore, potential differences on patterns of severity of cannabis use, or adolescence-related brain developments may contribute to explain the discrepancies between the findings of these

two studies, The only available study addressing long-term cognitive effects related to cannabis use was carried out with twins who were discordant for regular cannabis use; the twin-pair regular users group had been abstinent for almost 20 years (Lyons et al., 2004). These authors used a comprehensive neuropsychological test battery, and only found significant differences between cannabis users and their non-using co-twins on one measure of planning and perceptual organization (block design subtest, WAIS). These results indicate an absence of marked residual effects of cannabis use on cognitive abilities at the very long-term.

6.1.2. Psychostimulant:

- Cocaine

Ten studies contrasting neuropsychological performance between cocaine polysubstance users and drug-free controls met criteria for inclusion. Four of these studies investigated performance during short-term abstinence using non-treatment seeker participants. Two of these four focused specifically on impulsive action (measured with the Stop-signal task) (Colzato et al., 2007; Fillmore and Rush, 2002) and one of them focused specifically on decision-making (measured by the Iowa Gambling Task) (Tucker et al., 2004). All of them found significant differences between cocaine users and controls on these domains. The other study by Woicik et al. (2008) employed a more comprehensive neuropsychological battery and found significant deficits in episodic memory, selective attention and working memory, which were less prominent in cocaine users who had recently used the substance, consistent with neuroimaging data (Garavan et al., 2008).

A second group of five studies have assessed neuropsychological performance in cocaine polysubstance users during mid-term abstinence. Three of these studies focused

on specific domains and found significant decrements in cocaine users performing episodic memory (van Gorp et al., 1999), impulsive choice –measured with the delay-discounting task (Heil et al., 2006), and emotional decoding (i.e., recognition of facial emotional expressions). The other two employed more thorough neuropsychological assessments. Bolla et al. (1999) in a sample of non-treatment seeker cocaine abusers observed performance decrements in tests of speed, episodic memory, selective attention, psychomotor functioning, impulsive action and set-shifting. Similarly, Verdejo-García et al. (2007b) found significant decrements in cocaine users performing tests of impulsive action/set-shifting, decision-making and emotional decoding in residential treatment participants. In the only study addressing long-term effects of cocaine abuse (after 7 months of abstinence), Fernández-Serrano et al. (2010a) showed that deficits on emotional decoding remained significant during protracted abstinence. It is important to keep in mind that in all the studies mentioned, the experimental group used, in addition to cocaine, other addictive substances, usually alcohol, which may have significantly affected the results.

- *Methamphetamine*

Six studies contrasting neuropsychological performance between methamphetamine polysubstance users and drug-free controls met criteria for inclusion. Two of these studies investigated performance during short-term abstinence, both using non-treatment seeker participants. Monterosso et al. (2005) specifically focused on the domain of impulsive action (taxed by the Stop-signal task) and found that methamphetamine users display longer stop signal reaction time (i.e., the latency to inhibit an initiated motor response) after 5-7 days of abstinence. On the other hand, Kalechstein et al. (2003) administered a more comprehensive neuropsychological

battery including motor, attentional and executive measures and observed that methamphetamine users had decreased performance on tests of psychomotor functioning, episodic memory and verbal fluency.

Two other studies investigated neuropsychological performance during methamphetamine mid-term abstinence. Both of them used a mixed-sample of non-treatment seekers and in-treatment participants and both focused on specific cognitive domains: impulsive action (measured with the Stroop) (Salo et al., 2002) and verbal episodic memory (Woods et al., 2005). Both domains were significantly impaired in methamphetamine users after an abstinence interval ranging between two and four months.

Finally, three recent studies have examined neuropsychological performance in methamphetamine users during long-term abstinence (6 months) (Henry et al., 2009; Hoffman et al., 2006; Rendell et al., 2009). All of them examined community treatment participants and administered comprehensive protocols taxing memory and executive functions. However, the significant differences between groups were only found on certain cognitive/emotional functions that were assessed only by each of them: prospective memory (Rendell et al., 2009), emotional processing (Henry et al., 2009) and impulsive choice (measured by the delay-discounting task) (Hoffman et al., 2006). These studies indicate that gross deficits on memory and executive functions are not durable in methamphetamine users; however, specific deficits on some complex aspects of prospective memory/planning ahead, impulsive choice and emotion processing can be persistently altered in these individuals. Again, we have to take into account that these studies either did not exclude subjects with a history of co-abuse of other substances (Hoffman et al., 2006) or the subjects actually self-reported being co-users

of other substances (Henry et al., 2009; Monterosso et al., 2005; Rendell et al., 2009; Woods et al., 2005).

6.1.3. MDMA ('Ecstasy')

Eleven studies contrasting neuropsychological performance between MDMA polysubstance users and drug-free controls met criteria for inclusion; all of them were performed in non-treatment seeker individuals. Only one study addressed early residual MDMA effects during the first four days of abstinence (Hoshi et al., 2004). This study focused on emotional decoding, finding that MDMA users have residual alterations in the recognition of fear. Two studies investigated neuropsychological performance of MDMA users during the first month of abstinence (short-term). One of them specifically focused on memory assessments and found significant decrements in tests of semantic memory, prospective memory (Zakzanis et al., 2003). The second study, by Gouzoulis-Mayfrank et al. (2003) used a slightly more comprehensive assessment including measures of memory and executive functions. Results showed that the only domain significantly affected in MDMA users was episodic memory.

A second group of four studies have assessed neuropsychological performance in MDMA polysubstance users during mid-term abstinence. All of these studies administered short cognitive batteries focused on selective aspects of memory and executive functions (mainly related to the updating component). Two studies from the same group found convergent declines on working memory performance by using different probes assessing this domain (Fisk and Montgomery, 2009; Montgomery et al., 2005). On the other hand, Bhattachary and Powell (2001) found significant declines in episodic memory and fluency (but not in working memory, which was assessed using a task that only taxed the maintenance but not the manipulation component of this

domain). Finally, Zakzanis and Young (2001), using an ecologically-valid battery of complex executive functions (the Behavioural Assessment of the Dysexecutive Syndrome Battery; Wilson et al., 1996) found significant alterations of the planning skills of MDMA users. Although apparently disparate these results seem to point out that MDMA mid-term effects are related to the updating component of executive functions (Verdejo-García and Pérez-García 2007), which may underlie performance decrements in episodic memory, fluency, working memory and planning tests.

Finally, three studies have examined neuropsychological performance in MDMA polysubstance users during long-term abstinence. All of them focused on two aspects of memory/executive functions interplay: episodic and working memory. Results from two of the three studies, performed by the same group, observed significant working memory declines after six-months abstinence (Wareing et al., 2004, 2005). The third study only detected episodic memory alterations after 2 years of abstinence (Ward et al., 2006).

6.1.4. Opioids

Seven studies contrasting neuropsychological performance between opioid polysubstance users and drug-free controls met criteria for inclusion. In this case all the studies were conducted on residential treatment participants. Three of these studies explored cognition and emotion during the first days of abstinence, thus taxing residual or sub-acute effects. In heroin users, Aguilar et al. (2008) found that recent heroin consumption is associated with alterations of emotional experience, characterized by a flattening of the arousal response towards pleasant arousing stimuli and a hypersensitisation of the arousal response towards highly unpleasant stimuli. When assessing cognition in methadone-maintained patients (MMP), Mintzer et al. (2004)

demonstrated that methadone use is associated with greater declines in episodic memory, psychomotor functioning and set-shifting measures. Compared to MMP, former opioid abusers (abstinence duration between 6 weeks and 12 months) showed a performance level between that of MMP and non users, suggesting that cognitive functioning can be restored in heroin users during abstinence. Brand et al. (2008), who administered a remarkably comprehensive battery of attention and executive tests, demonstrated that 14-days abstinent heroin polysubstance users had significant performance decrements on tests of sustained attention (an exclusive heroin effect), reasoning, impulsive action, flexibility –set-shifting and risky decision-making.

Two selected studies have assessed cognitive performance in opioid users during mid-term abstinence. In a way similar to the Aguilar et al. (2008) study, Gerra et al. (2003) specifically focused on the domain of experienced emotion. Their results showed that 84-days abstinent heroin users also showed an altered pattern of emotional reactivity towards emotionally-laden stimuli: they displayed reduced reactivity to pleasant stimuli and increased reactivity to unpleasant stimuli. On the other hand, they showed intact performance on an abstract reasoning/rule shifting cognitive test (the Category Test). In the second study, aimed to assess cognitive functioning using a short battery of tests of visual memory, word fluency and response inhibition, Prosser et al. (2006) observed significant deficits of episodic memory and impulsive action in 3-months abstinent heroin users.

Finally, two selected studies have targeted neuropsychological performance in heroin users during long-term abstinence (around 1 year). Both of them used similarly-shaped cognitive batteries assessing attention and executive functions, but significant results were obtained on measures that did not overlap between studies: verbal fluency

(Davis et al., 2002) and impulsive action (Pau et al., 2002). More studies using comprehensive neuropsychological tests protocols are warranted to reveal which of the wide range of functions impaired in heroin users at short-term remain significantly impaired at the very long-term. So far, studies contrasting current MMP and former heroin users indicate some recovery of verbal fluency and cognitive flexibility impairments correlated with abstinence duration.

6.1.5. Alcohol

Three studies contrasting neuropsychological performance between alcohol polysubstance users and drug-free controls met criteria for inclusion. The first of them was conducted during short-term alcohol abstinence -11 days (Pitel et al., 2007). These authors employed a quite thorough assessment protocol aimed to measure different aspects of memory and executive functions. Results showed that alcohol abusers had significant declines on tests of episodic memory, working memory, reasoning, impulsive action and cognitive flexibility –set-shifting.

The other two studies were conducted during mid-term abstinence, but they used less comprehensive neuropsychological protocols. Beatty et al. (2000) found significant alterations in psychomotor functioning, semantic memory and reasoning. On the other hand, Foisy et al. (2007) were selectively focused on different aspects of facial perception (testing both visual-spatial and emotional skills related to the processing of faces). Their results showed specific effects on the emotional decoding of facial expressions in the alcoholic group.

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
Cannabis	*Wadsworth et al., 2006 (SAC)	NTxS: 34 cannabis users; 85 controls [+]	24 h	SRTT, FAT, CST, IFRT, DFRT, VRT, SPT	PLAN, **MOT**, ***EM***, **UP-WM**
	Mc Hale et al., 2008 (SAC/ST)	Study 1: NTxS, 12 cannabis acute abstinence, 25 cannabis short abstinence; 23 controls; Study 2 & 3: NTxS, 18 acute abstinence; 20 controls	24 h 7 days	Study 1: Verbal fluency, Phonemic verbal fluency task Study 2: Doors and People test, Shapes test Study 3: RBMT (belonging)	1 week abstinence: **UP-Fl** 1 day: ***EM*, PrM**
	Pope et al., 2001 (SAC/ST)	NTxS: 63 current heavy cannabis users, 45 former heavy cannabis users; 72 non users [+]	0, 1, 7, 28 days	WAIS, CPT, ACPT, BSRT, BVRT, WCST, WMS, block design (WAIS-R), COWAT, Stroop, RPM	IQ, AT, CogFlx-SS, SPA, UP-Fl, ImpAC, ***EM*** (after 7 days)
	Medina et al., 2007 (MT)	NTxS: 65 cannabis users; 65 controls	30 days	D-KEFS (verbal fluency, towers), TMT, WAIS (Letter and Lumber sequencing, digit symbol, arithmetic, digit span bakwards) CVLT-II, PASAT, WMS (verbal story, logical memory), RCFT, WASI (block design)	UP-Fl, UP-WM, **speed**, **SPA**, **SAT, *EM***, ***PLAN***,
	Lyons et al., 2004 (LT)	NTxS: 54 twin pairs, 54 former cannabis users, 54 non cannabis users	20 years	WAIS, RPM, WRAT, CT, CPT, TMT, WMS (logical memory, visual reproduction), CVLT, RCFT, WCST, Stroop, FTT, GP	IQ, SPA, SAT, DAT, EM, UP-Rs, UP-WM, CogFlx-SS, MOT, ***PLAN***
Psychostimulants	*Tucker et al., 2004 (ST)	NTxS: 17 cocaine users; 14 non users [+]	3 days	IGT	***DMK***
	Woicik et al., 2008 (ST)	NTxS: 64 cocaine users; 64 controls [+]	3-25 days	COWAT, Digit span, Letter and Sequencing (WAIS-III), SDMT, TMT, WCST, Stroop, ANT, IGT, CVLT-II, Ekman faces, BFRT, Timed gait, Finger Tapping, GP	MOT, PrEMO, UP-Fl, , CogFlx-SS, ImpAC, DMK, **UP-WM, *SAT*, *EM***
	Fillmore & Rush., 2002 (ST)	NTxS: 22 cocaine users; 22 controls	7 days	Choice reaction time task (stop-signal paradigm)	***ImpAC***
	Colzato et al., 2007 (ST)	NTxS: 13 recreational cocaine users; 13 controls	7 days	Stop-signal task	***ImpAC***
	Bolla et al., 1999 (MT)	NTxS: 21 cocaine; 20 control	30 days	Shipley-IQ, COVF, WMS (logical memory), RAVLT, RCFT, SDPAL, Cancellation test, WAIS (digit symbol, block design), TMT, Stroop, WCST, JoLO, CalCAP, FTT, GP	IQ, SPA, UP-Fl, **speed, *SAT*, MOT**, ***EM***, **CogFlx-SS**, ***ImpAC***,
	Heil et al., 2006 (MT)	COMTx: 21 abstinent cocaine users (30 days), 21 current cocaine users; 21 controls	30 days	Delay discounting task	***ImpCH***
	Van Gorp et al., 1999 (MT)	RESTx: 37 cocaine; 27 controls [++]	45 days	CAVLT, RCFT, Pursuit Rotor Task	MOT, ***EM***
	Kemmis et al., 2007 (ST/MT)	NTxS: 30 occasional cocaine, 48 regular recreational cocaine; 21cocaine naïve participants [+]	Ocassional: 6 months Regular: 4 days	EFE Recognition task, Eyes task	***PrEMO***

Table 4 (continued)

Psychostimulants	Verdejo et al., 2007b (MT)	RESTx: 30 poly-substance abusers; 35 controls	4 months	Ekman Faces Test, R-SAT, IGT	***ImpAC*, *DMK*, *PrEMO***
	Fernandez-Serrano et al., 2010b (LT)	RESTx: 65 polydrug users; 30 non-users +	7 months	Ekman Faces Test, FrsBe	***PrEMO***
	Monterosso et al., 2005 (ST)	NTxS: 11 methamphetamine users; 43 controls ++	5-7 days	Stop-signal task	***ImpAC***
	Kalechstein et al., 2003 (ST)	NTxS: 27 methamphetamine; 18 controls	5-14 days	COWAT, WAIS(Letter and number, VMS), RFFT, RAVLT, WMS (logical memory), RCFT, Stroop, SDMT, TMT	SUAT, UP-WM, CogFlx-SS, ImpAC, ***MOT***, ***EM***, **UP-Fl**
	Salo et al., 2002 (MT)	COMTx and NTxS: 8 methamphetamine; 12 controls +	56-112 days	Stroop	***ImpAC***
	Woods et al., 2005 (MT)	RESTx and NTxS: 87 methamphetamine users; 71 controls	4 months	HVLT-R	***EM***
	Rendell et al., 2009 (LT)	RESTx and COMTx: 20 methamphetamine; 20 controls	6 months	Visual week, FAS, HSCT, RAVLT, Digit forwards, digit bakwards	EM, UP-WM, UP-Fl, ImpAC, **PrM**
	Henry et al., 2009 (LT)	RESTx: 20 methamphetamine, 20 controls	6 months	PFA, ME, FAS, HSCT, RAVLT	EM, UP-Fl, ImpAC, ***PrEMO***
	Hoffman et al., 2006 (LT)	RESTx: 41 methamphetamine users, 41 controls +	6 months	Shipley-IQ, RCFT, Babcock story recall, RAVLT, TMT, GP, Stroop, WCST, Delay discounting task	IQ, SUAT, MOT, EM, SM, CogFlx-SS, ImpAC, ***ImpCH***
MDMA	Hoshi et al., 2004 (SAC/ST)	NTxS: 16 MDMA users; 21 controls +	0-4 days	FEEST	**PrEMO**
	Zakzanis et al., 2003 (ST)	NTxS: 15 MDMA users; 17 controls	14 days	RBMT, Vocabulary (WAIS), WSC.	EM, IM, **SM, PrM**
	Gouzoulis-Mayfrank et al., 2003 (ST)	NTxS: 30 MDMA users (heavy +80 pills), 30 MDMA (light -80); 30 controls	28 days	WAIS (General Knowledge) Go-no go, Visual scanning, Plan-A-Day, Digit span backwards, 2-back, LGT-3	IQ, UP-WM, ImpAC, PLAN, ***EM***
	Bhattachary and Powell, 2001 (MT)	NTxS: 18 new users MDMA, 26 regular users MDMA, 16 past users MDMA; 20 controls	60 days	Quick test, Prose recall test, RCFT, Reversed digit span, COWAT, Verbal Fluency test.	IQ, UP-WM, ***EM***, **UP-Fl**
	Montgomery et al., 2005 (MT)	NTxS: 27 MDMA users; 34 controls	35 days	Letter span, Consonant updating, Computation span, Semantic fluency, CWF	UP-Fl, ***UP-WM***
	Fisk & Montgomery, 2009 (AC/MT)	NTxS: 14 heavy MDMA, 39 light MDMA; 28 non users +	Heavy: 38 days Light: 28 days Others: 24 hours	Letter span, Digits span, Spatial span, Updating task, Computation span, Random Letter Generation	ImpAC, ***UP-WM*** (MDMA)
	Zakzanis and Young,2001(MT)	NTxS: 24 MDMA users; 24 controls +	4 months	BADS	SAT, **PLAN**

Table 4 (continued)

MDMA	Wareing et al., 2004 (AC/ST/LT)	NTxS: 42 current MDMA, 17 former MDMA; 31 controls +	Current: 7 days MDMA, 24 h other drugs, Former: 6 months MDMA, 24 h other	Reading span, Computation span, Raven's Progressive Matrices (word, digit span).	***UP-WM*** (current and former MDMA)
	Wareing et al., 2005 (ST/LT)	NTxS: 36 current MDMA, 12 former MDMA; 31 controls +	Current: 7 days Former: 6 months	SWM, Spatial span task, Computation task, Digit span	***UP-WM*** (current and former MDMA)
	Ward et al., 2006 (ST/LT)	NTxS: 31 current MDMA, 30 former MDMA; 30 controls +	Current: 7 days Former: 2 years	WMS	UP-WM, ***EM*** (current and former MDMA)
Opioids	Mintzer et al., 2005 (SAC)	RESTx: 20 former heroin users, 18 methadone patients; 21control	24 h	DSST, TMT, 2-back, Recognition memory, Free recall, IGT	UP-WM, DMK, **MOT**, ***EM***, ***CogFlx-SS***
	*Aguilar et al., 2008 (ST)	RESTx: 22 current opioid users, 41 abstinent opioid users ++	Current: 24 h Abstinent: 14 days	Clinical Instrument for Emotional Response Evaluation	***PrEMO*** current)
	Brand et al., 2008 (ST)	RESTx: 18 opiate dependence; 18 controls	14 days	Game of Dice Task, MCST, FAS, FWIT (Stroop), LPS (reasoniing subtest), Tower Hanoi, ME	PrEMO, UP-Fl, PLAN, **SUAT, UP-Rs**, ***CogFlx-SS, ImpAC,*** **DMK**
	Prosser et al., 2006 (MT)	RESTx: 29 former heroin actual methadone, 29 former heroin; 29 controls +	3 months	WAIS (Vocabulary), Stroop, COWAT, Benton visual retention test	SAT, SM, UP-Fl, ***ImpAC*** (former), ***EM*** (former and actual)
Opioids	*Gerra et al., 2003 (MT)	RESTx: 12 heroin users; 12 controls	84 days	Pictures from the International Affective System	***PrEMO***
	Davis et al., 2002 (MT/LT)	RESTx: 15 methadone patients, 16 former opiate users; 14 controls +	42 days-12 months	AMIPB, Test of everyday attention, WAIS (comprehension, similarities, block design, object assembly), COWAT	SPA*, EM*, UP-Rs*, **UP-Fl**
	Pau et al., 2002 (LT)	RESTx: 30 heroin users; 25 controls +	13 months	SSST, CTT, PMQS, WCST	DAT, SUAT, CogFlx-SS, ***ImpAC***
Alcohol	Pitel et al., 2007 (ST)	RESTx: 40 alcohol users; 55 controls	11 days	FCSRT, ECM, Integration task, Spondee test, Verbal fluency tasks, Stroop, Attentional assessment test, N-Back (N-2) paradigm	UP-Fl, **EM**, **UP-WM, CogFlx-SS**, **ImpAC**, ***UP-Rs***
	Beatty et al., 2000 (ST/MT)	RESTx and COMTx: 55 alcohol users (4 - 9 years), 107 alcohol users (more than 10 years); 165 controls +	14- 42 days	SILS-V, SILS-A, Digit symbol (WAIS), CLAT, Six verbal fluency test.	UP-Fl, **SM, MOT,** ***UP-Rs***
	Foisy et al., 2007 (ST/MT)	RESTx: 22 abstinent alcoholic, 27 dropping alcoholic; 22 controls	21-60 days	Emotional facial expression test, WAIS (picture completion, cubes, objects assembling), CCSE, Benton facial recognition test	SPA, **PrEMO**

Table 4. Neuropsychological studies on polysubstance users of the different drugs studied.

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] RPM: Raven's progressive matrices; WRAT: Wide range achievement test; BDI: Beck depression inventory; MCST: Modified card sorting test, FWIT: Farbe wort interferenz test, LPS: Leistungs Prüfsystem.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models;
[++] Comparison groups were not demographically matched and these variables were controlled through covariance models;
[#] Comparison groups were not demographically matched but these variables were not correlated with neuropsychological measures and were no longer considered.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

6.1.6. Summary

Results regarding generalized vs. specific effects stemming from this methodological approach indicate that most cognitive/emotional deficits are shared by a number of groups of polysubstance abusers differing on main drug of choice. Medium to large effect sized differences in episodic memory are shared by MDMA, heroin and alcohol users. Decrements on semantic memory are shared by MDMA (large effects) and alcohol (medium effects) users. Declines in verbal fluency are shared by cannabis, methamphetamine (large effects) and methadone (medium effects) users. Deficits in working memory are shared by cocaine, methamphetamine, MDMA and methadone users (all medium effect sizes). Decrements in impulsive action are shared by cocaine, methamphetamine, alcohol (all large effects) and heroin (medium effects) users, similar to deficits on psychomotor functioning (shared by the same type of drugs). Finally, deficits in emotional processing are shared by methamphetamine (large effects), cocaine and alcohol (medium effects) polysubstance users, and maintained throughout protracted abstinence.

More specifically, decrements in prospective memory are shared by cannabis and methamphetamine users; reasoning deficits are shared by heroin and alcohol users; and declines in cognitive flexibility –set-shifting are shared by heroin and alcohol users (medium effects).

As for exclusive effects, there is a small magnitude exclusive effect of cannabis use on planning function (maintained across long-term abstinence); there are significant medium magnitude exclusive effects of MDMA use on processing speed, and of methamphetamine use on cognitive flexibility –reversal learning; and there is a significant large magnitude exclusive effect of psychostimulants use (i.e., cocaine and

amphetamine) on impulsive choice, which is persistent across abstinence in the case of methamphetamine users.

6.2. Comparisons of polysubstance users with different principal drugs of choice

A number of studies have directly contrasted the neuropsychological performance of two groups of polysubstance users with different drugs of choice. Despite the limitations associated with the interpretation of the neuropsychological results obtained by polysubstance users, this type of studies provides indirect evidence about alterations that are more typical of using one main substance vs. others.

6.2.1. MDMA ('Ecstasy') vs. Cannabis

Three studies contrasting neuropsychological performance between MDMA and cannabis polysubstance users met criteria for inclusion. The first two studies (conducted by the same group in the same sample) were carried out during very short abstinence, thus measuring sub-acute or residual effects of these drugs. Quednow et al. (2006) carried out an analysis of cognitive subprocesses involved in a verbal memory test using a sample of polysubstance users whose preferred drug of choice was MDMA (n=19, average abstinence of 3 days), polysubstance users whose preferred drug of choice was cannabis (n=19, average abstinence of 3 days), and control subjects (n=19). The results showed that, while cannabis users performed similarly to controls, MDMA users presented alterations in general indices of learning, memory consolidation, recall and recognition, as well as alterations in sub-indices indicative of working memory deficits, organization of information during learning, and retroactive interference, which are linked to executive processes and prefrontal cortex functioning. Furthermore, they observed positive correlations between memory alterations and the amount of MDMA used. Using this same sample, Quednow et al. (2007) also showed that after 3 days of

abstinence, MDMA users presented selective alterations on impulsive choice (MFFT) and decision-making measures. In this case, the amount and duration of MDMA use was also significantly related to the performance on these measures. The third study (Clark et al., 2009) contrasted performance of one group of MDMA users with short-term abstinence (n=46, 21 days), one group of cannabis users with short-term abstinence (n=15, 21 days), a third group of former MDMA users with long-term abstinence (n=14, 12 months), and a drug-free control group (n=19). The cognitive assessment focused on one single measure of impulsive choice (the Information Sampling Task –Clark et al., 2006) and results showed that the only group showing abnormal performance, as compared to controls, was the short-term abstinent cannabis group. These findings stand in contrast with those of Quednow et al. (2007). This discrepancy might be explained by the different patterns of severity of MDMA use in both samples or by the additional cognitive demands of the MFFT, which requires working memory and attentional skills on top of the impulsive choice response tendencies.

6.2.2. Psychostimulants vs. Opioids

Six studies contrasting neuropsychological performance between psychostimulant and opioid polysubstance users met criteria for inclusion. Most of these studies were conducted with residential treatment participants. The first of them was conducted during very early abstinence, just after resolving withdrawal symptoms. Ornstein et al. (2000) compared the performance of two groups of drug users with different drugs of choice, 23 amphetamine vs. 22 heroin users, and a third group of non-drug users. Participants were assessed after resolving withdrawal symptoms by using memory and executive function tests. They observed an important dissociation on a test of reinforced

learning and flexibility (intra/extradimensional set-shifting), which consists of a first part in which the reinforcement contingencies are learned according to a criterion, and a second part in which the reinforcement criterion changes and it is necessary to use a flexible behavior. The results showed that subjects who used heroin presented alterations in the acquisition of the initial reinforcement contingencies, while amphetamine users showed alterations in the second part of the test only, when they had to adjust their response pattern to the new criterion. However, both groups presented impairments on a recognition memory test. Nevertheless, the authors mention that the experimental groups were also heavy polysubstance users, especially of cannabis, and within each group there were users of the principal drug of the other group; within the heroin group there were subjects who had used amphetamines and vice versa.

Two other studies (from the same group) examined neuropsychological performance in psychostimulants vs. opioids polysubstance users during mid-term abstinence (4-6 months) using comprehensive assessments of cognitive impulsivity and executive functions respectively. Verdejo-García et al. (2007c) contrasted the performance of three groups made up of polysubstance users of cocaine (n=34, average abstinence of 17.18 weeks), polysubstance users of opioids (n=25 average abstinence of 25.04 weeks) and controls (n=27) on tasks of cognitive impulsivity. In this case, the degree of polysubstance use in the opioid group was superior to that of the cocaine group. In contrast, the results showed that cocaine users performed significantly worse on tasks of selective attention and impulsive action. However, performance on decision-making (measured with the IGT) was equivalent in the two groups of users, but worse than that of the controls. In an extension of this study with the same design but a broader sample and a comprehensive executive functions assessment battery (Verdejo-

García and Pérez-García, 2007a), the results also showed that the cocaine group performed significantly worse than the opioid group on tests of response inhibition and cognitive flexibility. Nonetheless, both groups of polysubstance users performed worse than the controls on updating measures of fluency, working memory and reasoning, and on decision-making.

Finally, three other studies examined neuropsychological performance in psychostimulants vs. opioids polysubstance users during long-term abstinence (by including a mixed group of former polysubstance psychostimulant and opioid users abstinent for 8 years). Ersche et al. (2006) contrasted the neuropsychological performance of four groups: current amphetamine users (n=25), current opioid users (n=42), former amphetamine and/or opioid users (n=26, average abstinence=8.2 years), and non-drug users (n=27). All the drug-user groups had used drugs other than the main substance of choice. The results showed that the performance of former users was not significantly different from that of the current amphetamine users, as both groups showed more significant alterations than the opioid group on tests of spatial planning, pattern recognition memory and cognitive flexibility –set-shifting. In an extension of this study in which they included an additional group of current cocaine polysubstance users (n=27) and specifically analyzed the performance on a probabilistic task of reversal learning (i.e., flexibility is more related to a change in reinforcement pattern than to a change in external criterion), the results showed that polysubstance users of cocaine showed a significantly higher number of perseverations than the other consumer groups (amphetamines, opioids and ex-users) (Ersche et al., 2008). A related study in a similar sample, by Clark et al. (2006), contrasted the performance of similarly shaped four groups: current amphetamine users (n=24), current opioid users (n=40), former

amphetamine and/or opioid users (n=24, average abstinence=8 years), and non-drug users (n=26), in a specific probe of impulsive choice (Information Sampling Task). Results showed that both current and former amphetamine and opioid drug groups displayed more impulsive choice responses.

6.2.3. Psychostimulants vs. Opioids vs. Alcohol

Only one study met criteria for inclusion that corresponded to this subsection. Kirby and Petry (2004) contrasted the delay-discounting performance of three groups of current users and three groups of abstinent users of cocaine, heroin and alcohol respectively. Abstinence duration in the ex-users groups was of 14 days (short-term). Results showed that during current use both cocaine and heroin users have steeper delay-discounting compared to controls. However, after 14-days of abstinence, significant differences only remained for the cocaine group.

6.2.4. Psychostimulants vs. Alcohol

Two studies met criteria for inclusion that corresponded to this subsection. Both of them were conducted during short-term abstinence in samples of residential treatment participants. González et al. (2007) contrasted the performance of alcohol (n=17) and methamphetamine users (n=16), and drug-free controls, on typical measures of working memory (delayed-non-matched-to-sample) and decision-making (Iowa Gambling Task). Results showed that methamphetamine users, but not alcohol users had significantly decreased performance on both neuropsychological indices. More recently, van der Plas et al. (2009) contrasted the performance of alcohol users (n=33), cocaine users (n=38), methamphetamine users (n=27) and drug-free controls (n=36) on a selective neuropsychological battery assessing relevant aspects of executive functions. Results showed that both cocaine and methamphetamine users performed significantly poorer

than alcohol users and controls on measures of working memory, cognitive flexibility – set-shifting and decision-making.

6.2.5. Opioids vs. Alcohol

Only one study met criteria for inclusion that corresponded to this subsection. Kornreich et al., (2003) contrasted the performance of four drug using groups and drug-free controls on a measure of emotional processing (Decoding of facial emotional expressions). Groups were formed by alcohol users (n=30, 21 days of abstinence), opioid users following methadone treatment (n=30), opioid users not following methadone treatment (n=30, 3.8 months of abstinence), and former users of both alcohol and opioids (n=30, alcohol abstinence of 21 days and heroin abstinence of 11 months), as compared with healthy controls (n=30). Results showed that both shortly-abstinent alcohol users and current and former opioid users displayed poorer emotion recognition in the task.

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
MDMA & Cannabis	Quednow et al., 2006 (ST)	NTxS: 19 abstinent MDMA users, 19 abstinent cannabis users; 19 drug-naïve control	3 days	VMLT/RAVLT	MDMA: **EM, UP-WM***
	Quednow et al., 2007 (ST)	NTxS: 19 abstinent MDMA users, 19 abstinent cannabis users; 19 drug-naïve control	3 days	Go/no go task, Matching Familiar Figures Test, Decision making task	ImpAC, **DMK** (MDMA), **ImpCH** (MDMA)
	Clark et al., 2009 (ST/LT)	NTxS: 46 current MDMA users, 14 ex MDMA users, 15 current cannabis users; 19 controls	Current: 21 days Ex users: 1 year	IST, NART, IVE, BDI	IQ, **ImpCH** (cannabis)
Opioids & Psychostimulants & Alcohol	Kirby et al., 2004 (SAC/ST)	NTxS and COMTx: 14 current alcohol users, 19 ex alcohol users, 20 current cocaine users, 21 ex cocaine users, 7 current heroin users, 20 ex heroin users; 44 controls	Ex users: 14 days	MCQ, Shipley (vocabulary, abstract reasoning), IVE, ZSS, BIS	IQ, ***ImpCH*** (current cocaine, ex cocaine, current heroin)
Opioids & Alcohol	Kornreinch et al., 2003 (Alcohol ST, Opiate MT/LT)	RESTx: 30 alcohol users, 30 opiate users with methadone, 30 opiate abstinent users, 30 ex opiates and alcohol users; 30 controls [+]	Alcohol users: 21 days Opiate abstinents: 3.8 months Ex opiates and alcohol: 11 months for opiates, 21 days for alcohol	EFE	**PrEMO** (alcohol and opiates)
Psychostimulants & Alcohol	González et al., 2007 (ST)	RESTx: 17 alcohol users, 16 methamphetamine; 19 controls [+]	14 days	IGT, Delayed non match to sample task	***DMK, UP-WM*** (methamphetamines)
	Van der Plas et al., 2009 (ST)	RESTx: 33 alcohol users, 38 cocaine, 27 methamphetamine; 36 controls [+]	15 days	IGT, Tic Tac Toe, Cognitive flexibility, WCST, Response inhibition task	ImpAC, Cocaine and metham: ***UP-WM, CogFlx-SS, DMK***
Psychostimulants & Opioids	Ornstein et al., 2000 (SAC)	RESTx: 22 heroin users, 23 amphetamines users (9 heroin dependent); 3 control groups x 22)	After withdrawal symptoms	FAS, Category fluency (animals), Attentional Set-Shifting task, Spatial working memory task, O-TTOLT, Visuospatial strategy task.	SPA, UP-Fl, UP-WM, PLAN, Heroin: **EM** Amphetamines: ***EM, CogFlx-SS,***
	Verdejo-García y Pérez-García, 2007 (Cocaine MT, Heroin LT)	RESTx: 45 cocaine polysubstance abusers, 28 heroin polysubstance abusers, 8 alcohol polysubstance abusers; 37 controls	Cocaine: 4 months Heroin: 6 months	FAS, RFFT, WAIS (letter-number sequencing, arithmetic, digit, similarities, WMS (spatial span), Stroop, FDT, Go/no go task, Category test, WCST, CBT, IGT	Cocaine: ***CogFlx-SS, ImpAC*** Cocaine and Heroin: ***UP-WM, DMK*, UP-Rs, UP-Fl**
	Verdejo-García et al., 2007c (Cocaine MT, Heroin LT)	RESTx: 34 cocaine polysubstance abusers, 25 heroin polysubstance abusers; 27 controls	Cocaine: 4 months Heroin: 5.8 months	TWAT, Stroop, FDT, Go/no go task, IGT	IQ, Cocaine and Heroin: ***DMK*** Cocaine: ***ImpAC***
	Ersche et al., 2006 (LT)	COMTx and NTxS: 25 chronic amphetamine users, 42 chronic opiate users, 26 former drug users of psychostimulants and opiates; 27 controls	Former users: 8 years	O-TTOL, Three dimensional IDED, PAL, PRM	Former and current amphetamine users: **PLAN, *CogFlx-SS, EM***

Table 5 (continued)	Ersche et al., 2008 (LT)	COMTx and NTxS: 30 chronic amphetamine users, 27 chronic cocaine users, 42 chronic opiate, 26 former drug users of psychostimulants and opiates; 25 controls [+]	Former: 8 years	Probabilistic Reversal-Learning	Cocaine: **CogFlx-RL**
	Clark et al., 2006 (LT)	NTxS: 24 current amphetamines users, 40 current opiates users, 24 former users of amphetamines and opiates; 26 controls	Former: 8 years	NART, IST, BDI, BIS	IQ, ***ImpCH*** (current and former amphetamines users, current and former opiates users)

Table 5. Neuropsychological studies comparing performance of polysubstance users with different principal drug of choice.

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] VLMT/RAVLT: Verbaler Lern- und Merkfähigkeitstest; O-TTOLT: One-touch tower of London task; TWAT: Test word accentuation test; NART: National adult reading test; BDI: Beck depression inventory; BIS: Barratt Impulsivity Scale; IVE: Eysenck Impulsiveness Venturesomeness Empathy questionnaire; ZSS: Zuckerman sensation seeking scale.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

6.2.6. Summary

Results regarding generalized vs. specific effects stemming from this methodological approach indicate that some neuropsychological deficits can be dissociated between groups of polysubstance users with different main drug of choice. As for generalized effects, results indicate that deficits on episodic memory are shared by cannabis, MDMA and methamphetamine users (all medium effect sizes). Declines on the updating component of executive functions and on impulsive choice are both shared by cocaine and heroin polysubstance users, in contrast to less significant decrements in alcohol users.

As for relatively exclusive neuropsychological effects of different substances, results indicate that psychostimulants abuse is associated with selectively decreased performance on tests of planning, impulsive action and cognitive flexibility –both set-shifting and reversal learning (medium to large effect sizes), especially when compared to opioid users.

According to evidence from this methodological approach, psychostimulants-related deficits on episodic memory, planning and cognitive flexibility are the more persistent ones, remaining significant after several years of abstinence.

7. Correspondence between methodologies and quantitatively-derived estimations of neuropsychological effects of drug use: Insights on generalized vs. specific effects.

This final section provides an integration of the review's findings through the quantitative evaluation of the results obtained by the different research methodologies about the issues of (i) generalized vs. specific neuropsychological effects of different

drugs of abuse (see Table 6), and (ii) which of these neuropsychological effects are durable across abstinence (see Tables 7). In the text and tables of this section, we mainly highlight findings that achieved an average medium effect size (Cohen's $d \geq 0.5$).

	CANNABIS				COCAINE				METHAMPHETAMINES				MDMA				HEROIN				METHADONE				ALCOHOL			
	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP
EM	**2.21** (1)	0.33 (1)	0.36 (4)	0.42 (1)		0.36 (1)	0.27 (3)		**0.87** (1)		0.46 (5)	**0.51** (2)	**1.04** (2)	0.49 (8)	**0.52** (3)	**1.06** (1)	0.48 (1)		**0.52** (2)	0.12 (1)			0.16 (2)		0.35 (3)	0.28 (2)	**0.54** (1)	
SM	**3** (1)					0.16 (1)					0.27 (1)		**0.50** (2)	0.49 (1)	**0.94** (1)				0.32 (1)	0.28 (2)				0.23 (1)			**0.54** (1)	
PrM			**0.95** (1)								**1.25** (1)				0.43 (1)													
IM															0.41 (1)													
SAT			0.15 (2)			0.38 (2)	0.45 (2)						**1.40** (1)	**0.56** (4)	**0.53** (1)				**0.83** (1)				0.36 (1)		**0.83** (2)	**0.56** (4)		
DAT			0.05 (1)											**0.52** (2)					**0.53** (1)									
SUAT											0.43 (2)		**0.51** (1)						0.42 (2)						**1.03** (1)			
UP-Fl		0.17 (1)	**1.05** (3)			0.49 (2)	0.11 (2)	**0.83** (1)			**1.11** (3)	**0.68** (2)	**0.63** (2)	0.39 (4)	**0.76** (2)				**0.60** (3)	**0.78** (2)		0.16 (1)	**0.64** (2)		0.05 (1)	**0.52** (1)	0.35 (2)	
UP-Rs	0.39 (1)	0.40 (1)	0.16 (1)			0.13 (1)		**1.79** (1)						**0.60** (2)			**0.71** (1)		**1** (1)	**1.81** (1)		**0.89** (1)			0.10 (1)		**0.69** (2)	
UP-WM		0.15 (1)	0.14 (2)	0.44 (1)		**0.56** (1)	**0.79** (1)	**1.19** (2)			**0.71** (2)	**0.73** (3)	0.40 (2)	0.25 (8)	0.47 (7)	0.44 (1)	**0.53** (1)		0.17 (1)	**1.06** (2)		**0.63** (1)	**0.53** (1)		0.28 (2)	0.43 (1)	**0.56** (1)	
CogFlx-SS		0.47 (1)	0.38 (2)			0.20 (1)	0.26 (2)	0.30 (2)			0.36 (2)	0.33 (3)	0.35 (1)	**0.65** (3)					**0.62** (3)	0.36 (3)		**0.76** (1)	0.46 (1)	0.05 (1)	0.45 (3)	**0.55** (2)	**0.53** (1)	0.31 (1)
CogFlx-RL								0.43 (1)			**0.57** (1)	0.24 (1)							0.37 (1)	0.25 (1)				0.26 (1)				
ImpAC			0.28 (1)	0.10 (1)			**0.93** (5)	**0.55** (2)	**0.82** (1)		**1.12** (6)	0.37 (1)	**0.54** (1)	0.31 (5)	0.15 (2)	0.13 (1)	0.27 (1)		**0.84** (3)	0.24 (1)		0.40 (1)	**0.66** (1)		0.49 (3)		**0.87** (1)	0.37 (1)
ImpCH				0.39 (2)			**1.92** (1)	**0.90** (1)			**0.81** (1)	0.09 (1)		0.44 (3)		0.35 (2)				**0.60** (2)				0.03 (1)	0.17 (1)			0.22 (1)
DMK					**0.63** (2)		0.33 (2)	0.49 (2)				0.40 (1)		0.19 (4)		**0.69** (1)	0.38 (1)		0.29 (2)	0.46 (2)			**0.51** (1)		0.26 (2)			0.47 (2)
PLAN			0.37 (2)	0.06 (1)								**0.89** (2)		0.26 (5)	0.42 (2)				0.19 (1)	0.42 (2)				**0.92** (1)		**0.82** (1)		
MOT		0.20 (1)	0.22 (1)			0.49 (2)	0.25 (3)				**0.61** (2)		0.27 (1)	0.49 (2)					**0.51** (1)				**0.98** (1)		**0.74** (2)	0.47 (4)	**0.69** (1)	
SPA			0.12 (3)			**0.96** (1)	0.25 (1)			0.10 (1)		0.41 (1)	**0.96** (2)	0.28 (3)						0.34 (1)					0.33 (1)	0.19 (3)	**0.61** (1)	
Speed	**1.20** (1)		0.16 (1)				0.28 (1)						**0.58** (1)	**0.51** (2)								**0.65** (1)			**0.84** (1)			
PrEMO							**0.58** (4)				**2.03** (1)				0.45 (1)				0.41 (1)	0.45 (1)				**0.57** (1)			**0.59** (1)	**1.18** (1)

Table 6. Summary of mean effect sizes (Cohen´s *d*) of the neuropsychological deficits related to different drugs according to the three different methodological approaches reviewed. Numbers in parentheses represent the number of studies used to calculate the mean effect size for each drug/domain.

Notes.
PU, Pure Users, MC, Methodological Control, PS, Polysubstance, PP, Comparison of Polysubstance Users, EM, Episodic Memory, SM, Semantic Memory, PrM, Prospective Memory, IM, Implicit Memory, SAT, Selective Attention, DAT, Divided Attention, SUAT, Sustained Attention, UP-Fl, Updating Fluency, UP-Rs, Updating Reasoning, UP-WM, Updating Working Memory, CogFlx-SS, Cognitive Flexibility Self-shifting, CogFlx-RL, Cognitive Flexibility Reversal Learning, ImpAC, Impulsive Actions, ImpCH, Impulsive Choice, DMK, Decision Making, PLAN, Planning, MOT, Psychomotor Functioning, SPA, Spatial Processing, Speed, Processing Speed, PrEMO, Emotional Processing.
In bold: Mean effect sizes reaching at least a medium magnitude (mean Cohen´s $d \geq 0.5$) across studies. Significant mean effect sizes are reported regardless of the statistical significance (p value) of the results reported in the original studies.

	CANNABIS				COCAINE				METHAMPHETAMINES				MDMA				HEROIN				METHADONE				ALCOHOL			
	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT
EM	**1.1** (4)	0.31 (3)	0.23 (1)	0.14 (1)		0.38 (2)	0.34 (2)		**1** (1)	**0.85** (1)	0.41 (1)	**0.7** (5)		**0.55** (9)	**0.86** (5)	0.46 (3)	**0.51** (2)	0.48 (1)	**1.39** (1)	0.12 (1)	0.29 (1)					**0.53** (4)	0.3 (2)	0.27 (1)
SM	**3** (1)					0.16 (1)						0.27 (1)		**0.69** (3)		0.49 (1)			0.32 (1)								**0.54** (1)	
PrM	**0.95** (1)											**1.25** (1)		0.43 (1)														
IM														0.41 (1)														
SAT			0.19 (1)	0.08 (1)		**0.69** (3)	0.29 (1)							0.23 (3)	**1.08** (2)				**0.83** (1)							**0.99** (2)	**0.51** (1)	0.23 (1)
DAT				0.05 (1)										0.04 (1)	**1.01** (1)	0.06 (1)				**0.53** (1)								
SUAT										**0.62** (1)		0.34 (1)		0.49 (1)				**0.75** (1)		0.22 (1)						**1.03** (1)		
UP-Fl	**2.30** (2)	**1.01** (3)	0.22 (1)			0.10 (1)	0.44 (2)		**0.68** (1)	**0.77** (1)		**0.79** (2)		0.38 (4)	**0.82** (3)	0.24 (1)	0.49 (1)	**0.52** (1)	**0.61** (1)	**1.08** (1)		0.16 (1)	**1.09** (1)			**0.62** (1)	0.3 (2)	0.05 (1)
UP-Rs	0.39 (1)	0.40 (1)		0.16 (1)		0.13 (1)	**1.79** (1)							0.36 (1)	**0.84** (1)			**0.85** (2)		**1.81** (1)		**0.89** (1)				**0.53** (3)	0.48 (1)	
UP-WM		0.35 (2)	0.12 (1)	0.17 (1)		**0.79** (1)	**1.07** (1)		**0.53** (1)	**0.57** (3)		**0.84** (1)		0.41 (13)	0.35 (5)	0.4 (5)	0.35 (2)	**0.53** (1)		**1.19** (1)	0.47 (1)	**0.63** (1)				**0.52** (2)	0.37 (1)	0.19 (1)
CogFlx-SS	0.40 (1)	0.43 (2)		0.06 (1)		0.14 (2)	0.31 (2)		**0.53** (1)	0.38 (2)		0.22 (2)		**0.66** (4)	0.35 (1)		**0.57** (2)	**0.96** (1)		0.38 (3)	**0.64** (1)	**0.76** (1)				**0.7** (3)	0.38 (2)	0.12 (1)
CogFlx-RL								0.43 (1)												0.25 (1)								
ImpAC	0.16 (1)	0.17 (2)				**1.05** (3)	**0.82** (4)			**0.56** (3)	**0.94** (2)	**1.21** (3)		0.23 (7)	0.26 (3)			**0.79** (2)	**1.2** (1)	0.49 (2)		0.4 (1)				**0.65** (4)		0.18 (1)
ImpCH		0.39 (2)				**0.9** (1)	0.36 (1)					**0.81** (1)		0.36 (4)	**0.61** (1)			**1.1** (1)		0.11 (1)						0.19 (2)		
DMK						0.46 (3)	**0.51** (3)			0.47 (2)				0.41 (3)	0.24 (2)	0.12 (1)	0.23 (1)	**0.8** (1)		**0.85** (1)	**0.6** (1)				0.32 (2)		0.4 (1)
PLAN	0.35 (1)		**0.55** (1)	0.19 (1)					**0.85** (1)			0.15 (1)		0.31 (3)	**0.52** (3)	0.33 (2)	**1.21** (1)	0.19 (1)		0.1 (1)					**0.6** (1)		
MOT		0.20 (1)		0.22 (1)		0.13 (2)	0.37 (2)			**0.96** (1)		0.44 (1)		0.48 (2)			**0.51** (1)				**0.98** (1)				1 (2)	0.49 (3)	0.24 (1)
SPA	0.07 (1)	0.19 (1)	0.03 (1)	0.21 (1)			0.25 (1)		0.41 (1)					0.28 (3)	**0.81** (2)	0.17 (1)	0.34 (1)									0.39 (2)	0.33 (1)
Speed	**1.20** (1)		0.16 (1)				0.28 (1)							**0.58** (2)		0.46 (1)						**0.65** (1)			**0.84** (1)	**0.75** (1)	0.26 (1)
PrEMO						0.35 (2)	**0.66** (1)	0.45 (2)				**2.03** (1)	0.47 (1)					0.4 (2)					**0.57** (1)			**1.18** (1)	**0.59** (1)	

Table 7. Summary of mean effect sizes (Cohen´s *d*) of the neuropsychological deficits related to different drugs according to the time-line of abstinence duration.

Numbers in parentheses represent the number of studies used to calculate the mean effect size for each drug/domain.

Notes.
SAC, Sub-acute abstinence, ST: Short-term abstinence, MT, Mid-term abstinence, LT, Long-term abstinence , EM, Episodic Memory, SM, Semantic Memory, PrM, Prospective Memory, IM, Implicit Memory, SAT, Selective Attention, DAT, Divided Attention, SUAT, Sustained Attention, UP-Fl, Updating Fluency, UP-Rs, Updating Reasoning, UP-WM, Updating Working Memory, CogFlx-SS, Cognitive Flexibility Self-shifting, CogFlx-RL, Cognitive Flexibility Reversal Learning, ImpAC, Impulsive Actions, ImpCH, Impulsive Choice, DMK, Decision Making, PLAN, Planning, MOT, Psychomotor Functioning, SPA, Spatial Processing, Speed, Processing Speed, PrEMO, Emotional Processing.
In bold: Mean effect sizes reaching at least a medium magnitude (mean Cohen´s $d \geq 0.5$) across studies. Significant mean effect sizes are reported regardless of the statistical significance (p value) of the results reported in the original studies.

With regard to cannabis use, there is a relative lack of correspondence between results stemming from the different research methodologies; pure users' studies seem to be superior to reveal significant deficits on episodic memory and processing speed, but this data mainly stem from single-studies that need to be replicated. Only episodic memory and planning deficits seem to persist at mid-term in cannabis users. No effects are observable at long-term abstinence.

With regard to cocaine-related effects, there is consistency in the results from at least two of the different research methodologies with regard to significant declines in the domains of working memory, impulsive action, impulsive choice and decision-making. Some relevant domains, such as emotional processing, have been only examined by one particular methodology (polysubstance users, showing consistency across 4 different studies) and should be addressed by other methods in future studies. Significant deficits in the updating component of executive functions, impulsive action, decision-making and emotional processing persists at mid-term abstinence. At long-term abstinence, only mild deficits in reversal learning and emotional processing have been detected, but there is a lack of studies examining other skills.

For methamphetamine, there is consistency in the results from at least two of the different research methodologies with regard to significant decrements in episodic memory, fluency, working memory and impulsive action. Some relevant domains, such as planning, have only been studied by one particular methodology (comparison between groups of polysubstance users, showing consistency across 2 different studies) and should be addressed by other methods in future studies. Significant deficits in episodic memory, prospective memory, fluency, working memory, impulsive action and choice and emotional processing persist at long-term abstinence.

For MDMA, there is consistency in the results from at least two of the different research methodologies with regard to significant deficits in processing speed, episodic memory, fluency and selective attention. There is also consensus between the four methodologies for deficits in working memory, but these are of low-to-medium size (not reaching 0.5). Significant deficits in spatial processing, episodic memory, updating, planning, selective and divided attention and impulsive choice persist at mid-term abstinence. Only mild deficits in processing speed, working memory and episodic/semantic memory persist at long-term abstinence.

For opioids, there is consistency in the results from at least two of the different research methodologies with regard to significant deficits in fluency, working memory and reasoning. There is also consensus between the four methodologies for deficits in emotional processing, but these are of low-to-medium size (not reaching 0.5). Significant deficits in episodic memory, selective attention, impulsive action, fluency and emotional processing persist at mid-term abstinence. At long-term abstinence, the updating component of executive functions and decision-making seem to be pervasively altered.

For alcohol, there is consistency in the results from at least two of the different research methodologies with regard to significant deficits in selective attention, cognitive flexibility –set-shifting, psychomotor functioning/impulsive action, and emotional processing. Significant deficits in speed, semantic memory, selective attention and emotional processing seem to persist at mid-term. No deficits persist at long-term abstinence.

Overall, the studies discussed in this systematic quantitative review point to generalized effects of different types of drugs on episodic memory, the updating

component of executive functions, decision-making and emotional processing. On the other hand, alcohol and psychostimulants use seem to be particularly associated with deficits in impulsive action and cognitive flexibility; alcohol and MDMA use with perceptual speed, spatial processing and selective attention declines; cannabis and methamphetamine with prospective memory deficits; and cannabis and MDMA with alterations in processing speed and complex planning. The magnitude of both generalized and specific neuropsychological effects is generally attenuated in samples achieving long-term abstinence, but there are persistent psychostimulant-related effects on updating, inhibition, flexibility and emotional processing, and opioid-related persistent effects on updating and decision-making. Importantly, these specific effects are overall consistent with results from animal and controlled drug-administration studies.

A more detailed account of generalized vs. specific effects of different drugs, taking into account the time-line of these alterations across abstinence, is displayed in Figure 1. Similar to other findings summarized in this section, Figure 1 only depicts results with effect sizes ≥0.5. As the Figure displays, when we focus on mid-term abstinence –probably the most relevant interval for addiction treatment, there are generalized effects of different drugs on episodic memory, selective attention, selective components of updating (fluency and reasoning), planning, impulsive action and emotional processing. On the other hand, there are relatively specific effects of psychostimulants on impulsive choice/decision-making (but these domains have not been tested in cannabis, opioid or alcohol users during this period), of cocaine use on working memory, of MDMA use on spatial processing and divided attention, and of alcohol use on processing speed and semantic memory. Nonetheless, it is important to

take into account that evidence about specific effects at mid-term abstinence mostly stems from single studies that need to be replicated. Moreover, when we focus on long-term abstinence –the most relevant interval to understand long-term recovery of neuropsychological functioning, there are generalized effects of different drugs on the updating component of executive functions. On the other hand, there are specific effects of methamphetamine on episodic and prospective memory and impulsive action and choice, and of heroin use on divided attention, reasoning and decision-making. However, these specific effects should be interpreted with particular caution because most of them stem from single studies (with the exception of memory and impulsive action findings on methamphetamine users), and because some of the domains (e.g., prospective memory) have not been properly tested in users of other substances. The obvious implication of these observations is that, in spite of the abundant literature on the topic, there is a selective scarcity of studies on the neuropsychological effects of different drugs during mid-term and long-term abstinence. More studies are warranted to gain insights about the generalized vs. specific effects of different drugs during these periods that are critical for addiction treatment and recovery.

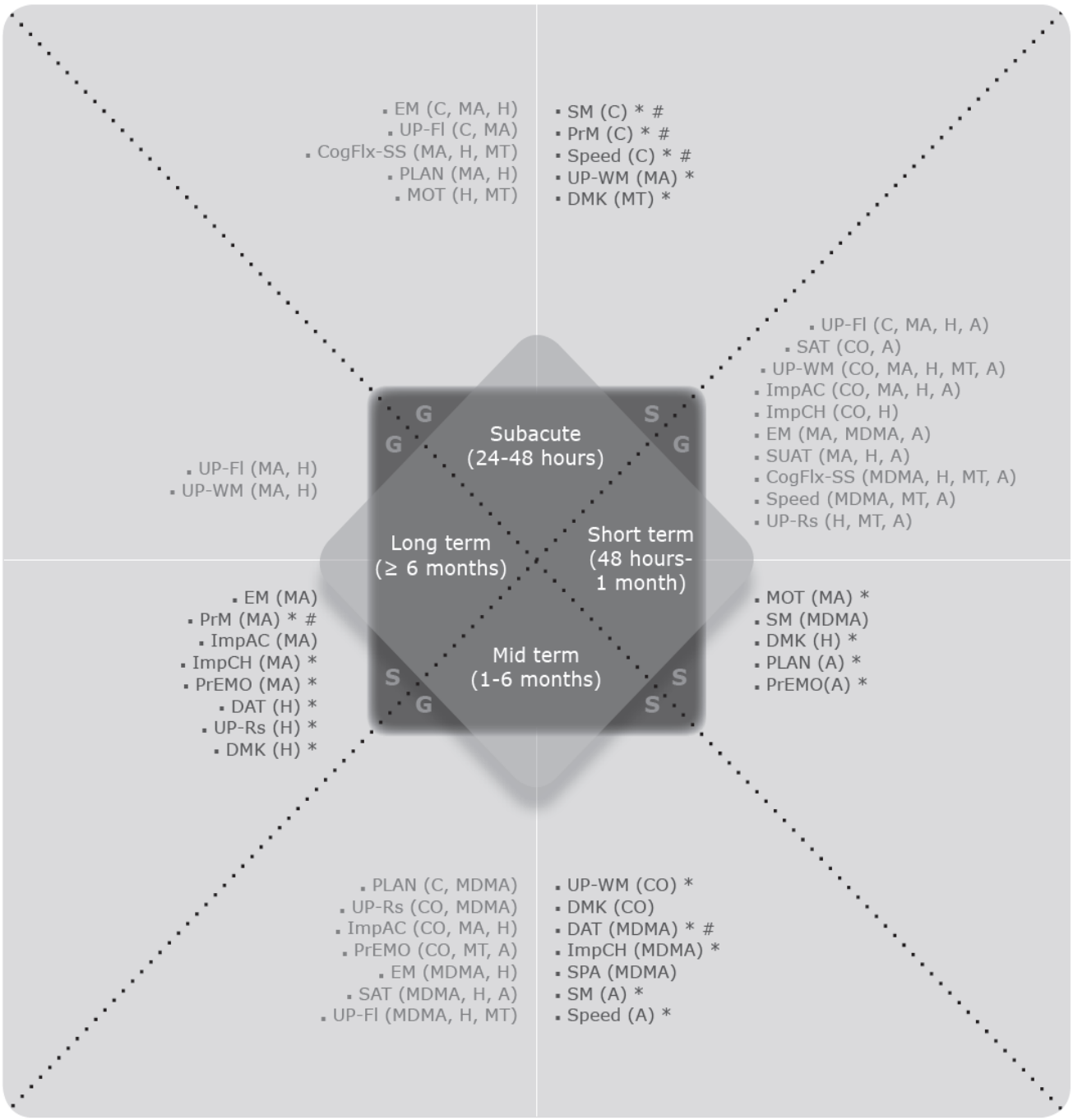


Figure 1. Time-line of specific vs. generalized neuropsychological effects associated with cannabis, cocaine, methamphetamines, MDMA, heroin, methadone and alcohol abuse.

Note. G: generalized, S: specific, C: cannabis, CO: cocaine, MA: methamphetamines, MDMA: ecstasy, H: heroin, MT: methadone, A: alcohol, EM, Episodic Memory, SM, Semantic Memory, PrM, Prospective Memory, IM, Implicit Memory, SAT, Selective Attention, DAT, Divided Attention, SUAT, Sustained Attention, UP-Fl, Updating Fluency, UP-Rs, Updating Reasoning, UP-WM, Updating Working Memory, CogFlx-SS, Cognitive Flexibility Self-shifting, CogFlx-RL, Cognitive Flexibility Reversal Learning, ImpAC, Impulsive Actions, ImpCH, Impulsive Choice, DMK, Decision Making, PLAN, Planning, MOT, Psychomotor Functioning, SPA, Spatial Processing, Speed, Processing Speed, PrEMO, Emotional Processing.

* Results obtained from a single study. # Neuropsychological domain tested only for this substance

Even though there is a reasonable degree of correspondence between the three different methodologies discussed, especially when considering only robust medium-to-large effect sizes, none of them is completely satisfactory to unravel the specific vs. generalized effects associated with the use of different drugs. Studies with 'pure' users can provide more direct evidence, but their samples introduce important biases (e.g., cultural, socio-demographic), and therefore the possibility of generalizing results to the entire population of drug users is hindered. Furthermore, studies of this nature are quite difficult to implement in users of substances like cocaine or opioids (i.e., it is virtually impossible to find users of these substances who have not previously consumed alcohol or cannabis), although epidemiological changes in drug use patterns could increase their significance in the future. In contrast, subtraction studies are useful in cases of substances with frequent patterns of co-abuse (cocaine vs. alcohol, MDMA vs. cannabis), but they are difficult to apply in some substances (e.g., cannabis vs. other substances). Furthermore, results stemming from these studies have provided very contradictory findings (Bolla et al., 2000; Robinson et al., 1999), and they often vary depending on the plan of analysis (De Sola et al., 2008; Croft et al., 2001). Future studies using this methodology should attempt to match relevant variables (e.g., severity of use or duration of abstinence) with regard to the main drugs of interest. As for the studies with polysubstance users, paradoxically, we found that some of these studies have produced more indicative evidence of specific effects of certain substances than the 'pure' user models have. In this regard, various studies of polysubstance users with different drugs of choice indicate that the use of psychostimulants is related to especially robust alterations in impulsive action and choice and cognitive/affective

flexibility. However, these models present obvious limitations when interpreting potential selective effects. A related limitation of these designs is that they might obscure the neuropsychological correlates of other earlier-stage drugs co-abused (e.g., alcohol or cannabis). Therefore, they are not appropriate to draw conclusions about these quite commonly abused drugs.

Several other factors should also be taken into account when interpreting these findings. Among the studies reviewed, we observed a great variability of results that may be related to key factors that vary between studies, including the demographic and clinical background of participants, the type of neuropsychological measures selected, the amount and duration of use of the different drugs studied, and the ranges of the periods of abstinence. These differences make it difficult to neatly determine the specific and generalized effects produced by the different drugs. For example, we found a remarkably high number of studies with non-demographically matched comparison groups (see Tables 2 to 6). Although most of these studies used covariance models to control the potential influence of these variables, there is increasing evidence indicating that this method is not ideally suited to address mismatch of demographics or IQ variables in neuropsychological research (Adams et al., 1985; Krull et al., 1997). This is especially true in the case of substance addiction, which might be viewed as a marker for a whole cluster of educational, occupational and health-related factors (e.g., accelerated aging) that negatively impact neuropsychological performance. In addition, a clearly noticeable bias related to demographic background is the preponderance of studies conducted in men vs. women. Although this is partly due to the greated prevalence of substance use disorders among males, more studies are warranted to

understand the nature and relevance of neuropsychological effects of drug use in women, especially in light of increasing evidence of gender differences in the brain correlates of drug use (see Medina et al., 2008, 2009). A related issue is that of heterogeneity in the clinical background of participants, with marked differences concerning the treatment status of participants across different drugs (e.g., MDMA or cannabis participants are rarely treatment seekers) and across studies. There is evidence that indicates that the brain substrates of certain addiction-related symptoms, such as craving, sharply differ as a function of treatment status (see Wilson et al., 2004); thus this variable might also contribute to explain the diversity of results across neuropsychological studies.

With regard to the neuropsychological tests used, as Table 1 illustrates, there is a great degree of variability in the type of instruments used in the field. This is especially relevant because there is evidence to reckon that certain tests are more sensitive than others to detect particular deficits in this population (see Fernández-Serrano et al., 2010c). The development of evidence-based consensus on the best-suited neuropsychological instruments for this population could importantly optimize research headways on the field. There is also a bias to perform studies on particular neuropsychological domains (e.g., inhibition or decision-making) while neglecting others in spite of the fact that comprehensive neuropsychological test batteries assessing all relevant domains are much more informative. Moreover, we observed that several of the studies reviewed employed tests that tap into various neurocognitive domains simultaneously (i.e. IGT, R-SAT, BADS). This approach complicates the possibility of providing a straightforward link between impaired task performance and dysfunction of

any specific domain. However, these tests usually have greater ecological validity (Verdejo-García et al., 2006; Verdejo-García and Pérez-García, 2007a), which makes them quite useful for measuring and predicting the problems that can arise in the daily functioning of drug users. On the other hand, it should be noted that some studies that have adapted classical neuropsychological tests to incorporate drug-related context (e.g., drug Stroop-like tasks, drug verbal fluency or episodic memory tasks) have shown improvements in the performance of addicted individuals on this kind of tests (Beatty and Borrell, 2000; Goldstein et al., 2007a,b). This effect may indicate that drug abusers become more cognitively active when drug-related information is pertinent, and maybe more cognitive dysfunctional in neutral conditions because drug contents overload their memory, attentional or executive resources (see Field and Cox, 2008 for a discussion on the attentional bias effect). This possibility should be further explored in order to better characterize the neuropsychological deficits more prominent in drug users when they find themselves in drug-related contexts. Nonetheless, we should take into account that the exposure degree to drug-related contexts rapidly decrease during drug abstinence, and therefore findings on neutral conditions are equally important to predict off-drug clinical and everyday functioning in drug users.

Parameters of amount and duration of drug use must also be considered. In this paper we have observed associations between the severity of cannabis use and memory, learning and decision-making deficits, and between the severity of MDMA use and memory, processing speed, impulsive action and choice, and decision-making deficits. Alongside these lines, several studies have shown consistent associations between patterns of severity of use of a number of substances and neuropsychological deficits;

for example, between the severity of cocaine use and alterations in response inhibition, working memory, reasoning and set-shifting measures (Bolla et al., 2000; Fernández-Serrano et al., 2010b; Fillmore and Rush, 2002; Roselli and Ardila, 1996; Verdejo-García et al., 2005b), and between the severity of opioid consumption and cognitive flexibility and impulsive choice (Fernández-Serrano et al., 2010b; Lyvers and Yakimoff, 2003). Future studies could contribute to an improved delimitation of the alterations associated with similar parameters of use among the users of different drugs.

Additionally to these limitations we must refer one that is inherent to research on the neurocognitive effects of substance misuse. Most of the data reviewed here stem from cross-sectional designs, and therefore do not allow us to determine whether these alterations precede drug use, or if they occur as a consequence of the effects of continued substance use. A growing line of evidence from animal and human studies indicates that pre-existing executive dysfunctions may predate the onset of drug use and constitute vulnerability markers for liability to addiction (see Verdejo-García et al., 2008 for review). In fact, neurobehavioral disinhibition (a latent construct including neuropsychological and self-report indices of neurocognitive inhibition and trait impulsivity) during childhood is associated with earlier age of onset and rapid progression of substance user disorders across a variety of drugs (Clark, D.B., et al., 2005; Kirisci et al., 2005, 2006; Tarter et al., 2004). Of all the studies reviewed, only those included in NeXT, the study by Fried et al. (2005) and the one by Lyons et al. (2004), use longitudinal designs that allow to control this variable, which in the case of the Lyons study is also controlled by the use of a sample composed of twins.

Overall, the results obtained indicate that the objective of determining specific vs. generalized neuropsychological effects of different drugs requires the integration of data emerging from the different methodologies reviewed. Moreover, a very useful contribution comes from meta-analysis techniques on the effects of specific substances, and the use of regression models in sufficiently large samples to obtain conclusive results. As for the use of meta-analysis, we must highlight that the conclusions of our review are coherent with several meta-analyses describing medium/large effects of the learning/memory impairments in cannabis users (Grant et al., 2003; Solowij and Battisti, 2008), and memory and executive function in psychostimulant users (Jovanovski et al., 2005; Zakzanis et al., 2007). As for regression models, efforts to increase sample sizes or use neuropsychological measures in epidemiological studies can yield important advances on this issue.

Nota: las referencias citadas en este capítulo pueden consultarse en el Anexo I

Capítulo 5

Prevalence of executive dysfunction in cocaine, heroin and alcohol users enrolled in therapeutic communities

Fernández-Serrano, M.J., Pérez-García, M., Perales, J.C., & Verdejo-García. A. (2010). Prevalence of executive dysfunction in cocaine, heroin and alcohol users enrolled in therapeutic communities. *European Journal of Pharmacology, 646,* 104-112.

1. Introduction

The progressive increase of drug consumption-related problems has yielded an important number of research projects aimed at detecting neuropsychological alterations in drug-users' executive functions. Executive functions are an integrated group of abilities involved in the generation, supervision and monitoring of behaviours directed towards goals (Roberts et al., 1998; Stuss and Knight, 2002; Verdejo-García and Perez-Garcia, 2007a). Several research papers agree in the existence of alterations in different components of these executive functions in polysubstance users with a main consumption of cocaine (Fillmore et al., 2002; Bolla et al., 2003; Kubler et al., 2005; Verdejo-Garcia and Perez- Garcia, 2007a), heroin (Lee and Pau, 2002; Pau et al., 2002; Verdejo-García et al., 2005b; Fishbein et al., 2007; Brand et al., 2008) or alcohol (Ratti et al., 2002; Bjork et al., 2004). Moreover, these alterations negatively affect the users' family and social relations as well as their occupational status (Bechara et al., 2001; Moriyama et al., 2002). In addition, executive functions are also essential for the success of interventional programs that are carried out with substance users. Treatment of addiction-related disorders requires many intervention types some of which imply cognitive requirements, such as working memory, problem solving and abstract reasoning (Teichner et al., 2002). Other executive processes, such as inhibition and decision-making, have been associated with relapse occurrence in substance-dependent individuals (Franken, 2003; Tapert et al., 2004; Paulus et al., 2005). A number of studies agree that the existence of executive function alterations in users may interfere in the success of interventional programs undertaken within therapeutic communities (Fals-Stewart and Schafer, 1992; Bowden-Jones et al., 2005; Passetti et al., 2008).

These findings reveal the necessity to design and implement programs tailored to the individuals' executive function limitations, since these may influence and condition the rehabilitation process itself.

Despite the fact that many studies have observed relevant executive alterations in terms of extension (number of affected regions) and magnitude (effect size) in drug-users vs. non-users, no data have been generated to date in terms of prevalence of these alterations among users using several therapeutic contexts, including therapeutic communities. Studies on the prevalence of neuropsychological impairment have been undertaken for other disorders, such as Parkinson disease (Kulisevsky et al., 2008), multiple sclerosis (Massman et al., 1996; Karlinska et al., 2008), lupus (Carbotte et al., 1986; Monastero et al., 2001) and HIV (Cysique et al., 2004). These have proved useful in the design and implementation of interventional programs for the relevant patient populations. In the same fashion, studies on the prevalence of neuropsychological impairment in drug-users using therapeutic communities could be very useful and constitute the foundations for political actions aiming at supporting suitable programs according to the neuropsychological profile of the consuming population. Furthermore, it would be interesting to learn which tools have a higher discriminating potential in detecting alterations in the executive functions of substance-dependent individuals, since this could make both clinical assessment and research in the drug-dependence field easier.

Previous studies in our laboratory have shown alterations in several components of executive functions in polysubstance users under treatment (Verdejo-Garcia et al., 2005a,b; Verdejo-Garcia et al., 2006; Verdejo-Garcia et al., 2007a,b; Verdejo-Garcia

and Perez-Garcia, 2007a,b; Verdejo-Garcia and Perez-Garcia, 2008). In this paper we will use data from these studies and successive samples to establish the prevalence of executive impairment in polysubstance-dependent individuals as a reference for the potential application of specific interventions in order to address these impairments in the treatment setting. The specific goals of this paper are: (i) estimate the prevalence of the neuropsychological impairment in executive functions in polysubstance users enrolled in therapeutic community, taking as a reference the performance in the tests of a large group of non-drug users; (ii) estimate the prevalence of executive impairment in several groups of polysubstance users classified according to their main drug consumed, and (iii) estimate the extent of the effect size of the differences in the executive performance of polysubstance users vs. non-users, and between the several groups of polysubstance users.

2. Method and materials

2.1. Participants

One hundred twenty-three poly-substance-dependent individuals (thirteen women), aged 18–58 years, and 67 healthy control individuals (eight women), aged 18–50 years, participated in this study. Poly-substance-dependent individuals and control participants were matched on variables of age, educational level and gender (see Table 1). Poly-substance-dependent individuals were recruited during their treatment at the therapeutic communities “Proyecto Hombre” and “Cortijo Buenos Aires”, in Granada-Spain. Both centers are residential therapeutic communities that provide psychological treatment and educational/occupational counseling in a controlled environment during an extended period of time. The dependent individuals sample was principally

composed of polysubstance users who requested treatment for: cocaine, heroin, heroin + cocaine or alcohol use. According to the main substance leading to treatment, within the dependent individuals sample we can distinguish 4 groups of polysubstance users: cocaine poly-substance-dependents (CPSD; n=74), heroin poly-substance-dependents (HPSD; n=34) and alcohol dependents (n=15). In the HPSD sub-group we can distinguish in turn two sub-groups of users: heroin dependents (n=17), composed by those individuals who were users mainly of heroin, and heroin+cocaine dependents (n=17) composed by those individuals who were initially users mainly of heroin but at some point started to consume it along with cocaine, which made polyconsumption of both substances the reason for demanding treatment.

Table 1. Descriptive scores for the sociodemographic characteristics of poly-substance-dependent individuals (PSD) and controls (CON).

Socio-demographic variables		PSD		CON		*t/chi square* [a]	*p*
		Mean	S.D.	Mean	S.D.		
Age		31.05	7.73	30.11	8.48	.77*	.442
Educational level (%)	Primary	7.8		1.5			
	Secondary	74.2		76.1		3.57**	.167
	Superior	18		22.4			
Gender (%)	Men	89.4		88.05		.08**	.811
	Women	10.6		11.95			

[a] * value of *Student's t*

** value of *Chi-square* χ^2

All of the polysubstance users had a minimum abstinence duration of 15 days before testing, although the mean duration of abstinence in the group was 23.79 (S.D.=18.19) weeks, so that it was possible to rule out the presence of alterations associated with the acute or short term effects of the drugs. None of them were following methadone maintenance treatment or any other pharmacological substitution treatment during the course of the neuropsychological testing. Urine analyses for cannabis, benzodiazepines, cocaine, and heroin metabolites were conducted to confirm abstinence. Potential participants who had previously been diagnosed with any disorder from DSM-IV Axes I and II (other than substance dependence) were not included in the target sample. Those potential participants who had been previously diagnosed with traumatic brain injury, neurological disorders or HIV were also excluded.

Control participants were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these control participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than ten drinks per week), (ii) absence of documented major psychiatric disorders, (iii) absence of documented head injury or neurological disorder, and (iv) not being on any medication affecting Central Nervous System. The mean amount of alcohol use in control participants was 35.91units/month (S.D.=71.82) and the mean of alcohol duration consumption was 7.79 years (S.D.=7.63).

2.2. Instruments and assessment procedures

2.2.1. Background information

Data regarding lifetime amount and duration of use of the different drugs was self-reported by participants and collected using the Interview for Research on Addictive

Behavior (IRAB; Verdejo-García et al., 2005a). This interview provides an estimation of monthly use of each substance (amount per month) and total duration of use of each substance (in years). The descriptive scores for these variables in the present sample are presented in Table 2.

Table 2. Descriptive scores for patterns of quantity and duration of drug use in the group of cocaine poly-substance dependents (CPSD), heroin poly-substance dependents (HPSD) and alcohol dependents (ALCO).

Substances	Variables	CPSD		HPSD		ALCO	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Cannabis	Joints/month	161.35	203.67	200.22	204.77	38.53	86.18
	Duration	5.58	5.97	11.35	6.94	4.86	8.78
Cocaine	Grams/month	61.01	46.41	37.58	43.58	6.33	15.75
	Duration	7.41	4.49	9.26	5.90	4.93	7.75
Heroin	Grams/month	5.82	22.78	51.63	46.05	2.00	7.74
	Duration	0.72	2.27	9.16	6.10	0.20	0.77
Methadone	Mililiters/month	12.16	104.62	676.82	1111.74	0.00	0.00
	Duration	0.013	0.11	1.35	2.99	0.00	0.00
MDMA	Units/month	13.70	24.87	16.82	35.78	2.60	7.06
	Duration	1.64	2.56	2.26	4.24	0.20	0.56
Alcohol	Units/month	385.40	415.72	269.23	331.34	944.00	452.72
	Duration	7.84	5.92	10.77	8.11	15.26	7.42
Amphetamines	Units/month	2.79	8.95	4.67	17.46	3.06	10.33
	Duration	0.70	1.71	0.411	1.04	1.06	2.84
Benzodiazepines	Units/month	5.48	19.12	20.00	39.68	34.28	90.71
	Duration	0.20	0.65	0.24	0.66	2.85	7.55
Abstinence (weeks)		22.50	14.69	26.53	26.31	23.85	10.39

2.2.2. Neuropsychological tests

We initially designed a battery of neuropsychological tests aimed to assess a number of aspects associated with executive functioning, including fluency, working memory, inhibition, shifting, and decision making. After evaluating our preliminary results, we decided to add to this battery a number of tests originally designed to enhance the ecological validity of executive functions assessment, including complex planning and multi-tasking tasks (e.g., the BADS and the Revised Strategy Application Test). In this report we include results from both the initial and the extended battery; therefore, the number of participants vary across tests and will be stated in each case. We have not included results from the decision-making test (the Iowa Gambling Task); previous studies have shown that this test is poorly performed by roughly 15% of the healthy population (Bechara et al., 2001), and therefore is inadequate to estimate prevalence of neuropsychological impairment based on a comparison group. Previous reports have provided a detailed description of the instruments used (Verdejo-Garcia et al., 2005a; Verdejo-Garcia et al., 2007b; Verdejo-Garcia and Perez-Garcia, 2007a,b); here we provide a summarized description.

2.2.2.1. Fluency tests

– FAS, Animals and Fruits: for semantic and phonological fluency assessment. We used the number of animals, the number of fruits and the sum of the number of words beginning with F, A, and S produced in a 60-s period as the primary dependent measures from this test. All participants (n=190) were assessed with these tasks.

– Ruff Figural Fluency Test (RFFT) (Ruff, 1996): for figural fluency assessment. The dependent variable used in this test was the total number of original figures produced. All participants (n=190) were assessed with this task.

2.2.2.2. Working memory

– Letter Number Sequencing (LNS) (WAIS-III, Wechsler, 1997a): the dependent variable used on this test was the number of correct answers. All participants (n=190) were assessed with this task.

– Arithmetic (WAIS-III, Wechsler 1997a): the dependent measure was the number of correct answers. All participants (n=190) were assessed with this task.

– Digits (WAIS-III, Wechsler 1997a): the dependent measure was the total number of correct answers on "digit forward" and "digit backward". All participants (n=190) were assessed with this task.

– Spatial Span (Wechsler Memory Scale—WMS-III, Wechsler, 1997b): for visuo-spatial working memory assessment. We used the total number of correct responses as the primary dependent measures from this test. One hundred nineteen poly-substance dependent individuals and the entire control sample (n=67) were assessed with this task.

– Rule Shift Cards (Behavioural Assessment of the Dysexecutive Syndrome—BADS, Wilson et al., 1996): the performance index on this task was the profile score from the test which is obtained according to the number of errors made (with a range between 0 and 4). Seventy-six poly-substance-dependent individuals and the entire control sample (n=67) were assessed with this task.

2.2.2.3. Shifting

– Wisconsin Card Sorting Test (WCST): for cognitive flexibility assessment. We used the percentage of perseverative errors as primary dependent measure. One hundred and twenty two polysubstance-dependent individuals and the entire control sample (n=67) were assessed with this task.

– Category Test (DeFilippis, 2002): for cognitive flexibility assessment. A computerized version of this test was administered. The main index of performance on the test was the total number of errors on the seven subtests. One hundred nineteen polysubstance-dependent individuals and the entire control sample (n=67) were assessed with this task.

– Five Digit Test (Sedó, 2005): for cognitive flexibility assessment. We used the differential "shifting" score (time on part 4 minus mean time on parts 1 and 2) as the primary dependent measure from this test. All participants (n=190) were assessed with this task.

– Oral Trail Making (Sedó et al., 1995): for cognitive flexibility assessment. The dependent measure was the shifting score obtained by subtracting time in part 1 from time in part 2 (OT 2−1). One hundred twenty two poly-substance-dependent individuals and sixty six controls were assessed with this task.

2.2.2.4. Interference

– Stroop Colour–Word Interference Test (Golden, 1978): for selective attention/interference assessment. The main dependent variable used in this test was the interference score (Golden, 1978). One hundred twenty one poly-substance-dependent individuals and the entire control sample were assessed with this task.

– Five Digit Test (Sedó, 2005): for interference assessment. We used the differential "interference" score (time on part 3 minus mean time on parts 1 and 2) as the primary dependent measure from this test.

– Go/no go task: for motor response inhibition assessment. The main dependent variable used in this test was the total number of commission errors made. One hundred eleven poly-substance-dependent individuals and sixty six controls were assessed with this task.

2.2.2.5. Planning

– Key Search (BADS, Wilson et al., 1996): application of strategies to solve a problem. The performance index on this task was the raw score from the test, which is obtained according to the appropriateness and efficacy of the strategy developed (with a range from 0 to 16). Seventy-six poly-substance-dependent individuals and the entire control sample (n=67) were assessed with this task.

– Zoo Map (BADS, Wilson et al., 1996): planning. The performance index on the test was the raw score (sum of parts 1 and 2, based on the efficacy of the plan designed, with a range from 0 to 16). Seventy-six poly-substance-dependent individuals and the entire control sample (n=67) were assessed with this task.

2.2.2.6. Multi-tasking

– Six Elements (BADS, Wilson et al., 1996): the performance index on this test was the raw score, which was obtained based on the number of tasks attempted minus the number of rule violations committed (with a range from 0 to 6). Seventy-six poly-substance dependent individuals and the entire control sample (n=67) were assessed with this task.

– Revised Strategy Application Test (Levine et al., 2000): self regulation in a multi-tasking task. The dependent variable from the R-SAT was the proportion of brief items completed (not including the first page of each stack) with regard to the total number of items attempted. Sixty-five poly-substance-dependent individuals and sixty six controls were assessed with this task.

2.3. Procedure

Participants were assessed individually between March 2003 and December 2007 in a single session that lasted approximately 3 h and 45 min (including breaks) or on two consecutive days, depending on the rehabilitation center availability. Test administration was arranged to alternate between verbal and non-verbal tasks and between more and less demanding tasks. All of the participants in the study were informed about the objectives, benefits, and possible inconveniences associated with the research protocol. Likewise, all the participants signed an informed consent form certifying their voluntary participation. The poly-substance-dependents and the control participants who requested it received a neuropsychological report about their performance on the tests. In addition, the control participants were paid €18 for their collaboration to ensure motivation.

2.4. Data analysis

To calculate the prevalence of impairment, scores directly obtained by polysubstance users in each of the neuropsychological tests were transformed into a Z-score, taking as a reference the mean and standard deviation (S.D.) obtained by the non-user group in each test. We then codified Z-scores according to two levels of neuropsychological impairment based on the criteria of Heaton et al. (1991): (i) mild impairment: if the

scores were 1.5 S.D. below those of the normative group, and (ii) moderate to severe impairment: if the scores were 2 S.D. below those of the normative group. Next, we classified the individuals according to the existence of impairment of each of the analyzed components in only one test, or in two or more tests. To do so, we followed the criteria of both mild and moderate–severe impairment. A series of $\chi 2$ analyses were undertaken to find out whether there were differences in the impairment proportions of each of the groups according to the adopted criteria.

Also, a global executive impairment index was calculated by adopting the criterion of (mild or moderate–severe) impairment in at least 3 of the 6 executive components assessed.

Finally we calculated the effect size in each of the neuropsychological tests by using Cohen's δ, following the formulae by Zakzanis (2001). The effect size of each task was obtained for the comparisons between differents analyzed groups, comparing effect sizes between poly-substance-dependent individuals and controls, and between the different groups of substance users: (i) between the CPSD and HPSD groups, and (ii) between the CPSD, heroin, heroin + cocaine and alcohol dependents groups. Overlap proportions between the compared groups for the dependent variables in each of the tests were obtained from the δ values.

3. Results

3.1. Poly-substance-dependents vs. controls

The results obtained from the comparison between poly-substance dependent individuals vs. healthy controls individuals in terms of prevalence of mild and

moderate–severe neuropsychological impairment, global impairment index and Cohen's Deltas obtained for each of the neuropsychological are detailed in Table 3.

3.1.1. Prevalences

Results obtained from the application of the mild impairment criterion (1.5 S.D.) revealed that it was working memory the component where a higher poly-substance-dependents proportion (62%) showed impairment in the performance of 2 or more tests. The moderate–severe criterion (2 S.D.) also showed that working memory was the component with the most poly-substance-dependents (48.4%) with impairment in the performance of at least 1 test. As for the global impairment index, results revealed that, under the mild impairment criterion, 68.8% of poly-substance-dependents showed global impairment in executive functions. Under the moderate–severe criterion, it was 32.8% of poly-substance-dependents that showed a global impairment of their executive functions.

Table 3. Prevalence of neuropsychological impairment, global impairment index and effect size in the neuropsychological tests in poly-substance dependents (PSD) and controls (CON).

		1. 5 S.D.[a]		2 S.D.		Cohen's $d^{b,c,d}$	
		PSD	CON	PSD	CON		
Fluency	1 task	**57**	**19.4**	**34.4**	**10.4**	anim fas	.65 (CON)*
						phono fas	-1.07 (PSD)**
	2 task	**33.6**	**7.5**	7.8	1.5	fruits fas	-.96 (PSD)**
						rfft	-1.07 (PSD)**
Working memory	1 task	**84.4**	**22.4**	**48.4**	**4.5**	lns	-1.51 (PSD)**
						arithm	-1.69 (PSD)**
						digit	-1.27 (PSD)**
	2 task	**62.2**	**7.5**	**19.7**	**3.0**	span	-1.03 (PSD)**
						rule	-.81 (PSD)**
Shifting	1 task	**64.8**	**22.4**	**43**	**14.9**	wcst	.57 (PSD)*
						category	1.17 (PSD)**
	2 task	**27.3**	**4.5**	**13.4**	**4.5**	5dt shift	.49 (PSD)*
						otm	.38 (PSD)
Interference	1 task	**38.3**	**19.4**	**20.3**	**9**	stroop	-.75 (PSD)*
						5dt interf	.42 (PSD)*
	2 task	**8.6**	**1.5**	3.9	0		.48 (PSD)*

Table 3 (continued)

Planning	1 task	**56.8**	**23.9**	**29**	**6**	key	-.093 (PSD)
	2 task	**16**	**0**	**7.4**	**0**	zoo	-.63 (PSD)*
Multitasking	1 task	**66.3**	**22.4**	**40.3**	**6**	six	-.69 (PSD)*
	2 task	11.3	6	1.5	0	r-sat	-.66 (PSD)*
% Global impairment		**68.8**	**19.4**	**32.8**	**4.5**		

[a] In bold significative differences between groups. [b] Between parentheses groups with the worse execution in that task. [c] anim fas: animals FAS; phono fas: phonological FAS; rfft: Ruff figural fluency task; lns: Letter and numbers (WAIS-III); arithm: Arithmetic (WAIS-III); digit: Digits (WAIS-III); span: Spatial span (WMS-III); rule: Rule shift cards (BADS); wcst: Wisconsin card sorting test; category: Category test; 5dt shift: Five digit test shifting score; otm: Oral trail making; stroop: Stroop colour-word interference test; 5dt interf: Five digit test interference score; key: Key search (BADS); zoo: Zoo map (BADS); six: Six elements (BADS); r-sat: Revised strategy application test.

[d] * effect size ≥0.4

** effect size ≥0.8

3.1.2. Effect size (Cohen's Delta)

When comparing performance of poly-substance-dependent individuals vs. controls in the different tests, we observed that effect size (Cohen's δ) was over 0.8, which indicates a high effect size (Cohen, 1988) in 45% of the tests, including fluency process, working memory and shifting measures. Specifically for fluency components, δ values ranged from 1.07 to 0.65. The most discriminating tasks were phonologic FAS and RFFT (41.1% of overlap between groups). As for working memory component, δ ranged from 1.69 to 0.81. For this component, the arithmetic test was the most discriminating (24.6% of overlap). For the shifting component, values ranged from 1.17 to 0.38. Category Test was the most discriminating (37.8% of overlap). For the interference component, values ranged from 0.75 to 0.42, Stroop being the most discriminating test (57% of overlap). For the planning component, values ranged from 0.63 to 0.093. Zoo Map was the most discriminating task for this component (61.8% of overlap). Finally, values for multi-tasking ranged from 0.69 to 0.66, Six Elements being the task with a higher discrimination (57% of overlap).

3.2. Cocaine poly-substance-dependents vs. heroin poly-substance dependents

The results obtained from the comparison between CPSD vs. HPSD in terms of prevalence of mild and moderate–severe neuropsychological impairment, global impairment index and Cohen's Deltas obtained for each of the tasks are detailed in Table 4.

Table 4. Prevalence of neuropsychological impairment, global impairment index and effect size in the neuropsychological tests in cocaine poly-substance dependents (CPSD) and heroin poly-substance dependents (HPSD)

		1. 5 S.D.[a]		2 S.D.		Cohen's $d^{b,c,d}$	
		CPSD	HPSD	CPSD	HPSD		
Fluency	1 task	56.8	64.7	31.1	41.2	anim fas	.-11 (CPSD)
						phono fas	.07 (HPSD)
	2 task	31.1	41.2	6.8	11.8	fruits fas	-.00 (CPSD)
						rfft	.36 (HPSD)
Working memory	1 task	**89.2**	**73.5**	45.9	52.9	lns	.23 (HPSD)
						arithm	.25 (HPSD)
						digit	.05 (HPSD)
	2 task	64.4	58.8	17.8	26.5	span	-.18 (CPSD)
						rule	-.16 (CPSD)
Shifting	1 task	63.5	61.8	47.3	41.2	wcst	-.35 (HPSD)
						category	.25 (CPSD)
	2 task	29.7	26.5	13.5	15.2	5dt shift	.10 (CPSD)
						otm	.03 (CPSD)
Interference	1 task	36.5	41.2	21.6	23.5	stroop	-.00 (CPSD)
						5dt interf	.40 (CPSD)*
	2 task	12.2	2.9	6.8	0		.14 (CPSD)

Table 4 (continued)

Planning	1 task	**45.8**	**85.7**	34.7	57.1	key	-.00 (CPSD)
	2 task	12.5	21.4	6.1	7.1	zoo	.54 (HPSD)*
Multitasking	1 task	60.9	80	44.2	36.4	six	.10 (HPSD)
	2 task	10.9	6.7	2.5	0	r-sat	.09 (HPSD)
% Global impairment		66.2	67.6	33.8	29.4		

[a] In bold significative differences between groups. [b] Between parentheses groups with the worse execution in that task.[c] anim fas: animals FAS; phono fas: phonological FAS; rfft: Ruff figural fluency task; lns: Letter and numbers (WAIS-III); arithm: Arithmetic (WAIS-III); digit: Digits (WAIS-III); span: Spatial span (WMS-III); rule: Rule shift cards (BADS); wcst: Wisconsin card sorting test; category: Category test; 5dt shift: Five digit test shifting score; otm: Oral trail making; stroop: Stroop colour-word interference test; 5dt interf: Five digit test interference score; key: Key search (BADS); zoo: Zoo map (BADS); six: Six elements (BADS); r-sat: Revised strategy application test.

[d] *effect size ≥0.4.

3.2.1. Prevalences

Results obtained from the application of the mild impairment criterion (1.5 S.D.) revealed that it was working memory the component where a higher CPSD proportion (64.4%) showed impairment in the performance of 2 or more tests. Among HPSD individuals it was working memory the component with a greater number of individuals with impairment (58.8%). Results obtained from the application of the moderate–severe (2 S.D.) criterion revealed that shifting was the component with the more CPSD (47.3%) with impairment in at least 1 task. As for the HPSD group, planning was the component with more impaired individuals (57.1%). As for the global impairment index, results obtained from the application of the mild impairment criterion revealed that 66.2% of CPSD showed global impairment in executive functions vs. 67.6% of HPSD. Results obtained from the application of the moderate–severe impairment showed that 33.8% of CPSD showed global impairment vs. 29.4% of HPSD.

3.2.2. Effect size (Cohen's Delta)

Comparison of performance in neuropsychological tests obtained by sub-groups CPSD and HPSD cast Cohen's Deltas below 0.4 (with an overlap range between groups ranging from 100% to 72.6%) in all tasks involving fluency, working memory, shifting and multi-tasking components. For the interference component, we observed that δ values ranged from 0.40 to 0.00. Five Digit Test was the most discriminating task (72.6% of overlap between groups) where the CPSD group showed the poorest performance. For the planning component, δ values ranged from 0.54 to 0.00. In this case, Zoo Map was the most discriminating task (66.6% of overlap) where HPSD group showed a poorer performance.

3.3. Cocaine poly-substance vs. heroin vs. heroin + cocaine vs. alcohol dependents.

Results obtained from comparing CPSD vs. heroin vs. heroin + cocaine vs. alcohol dependents in terms of prevalence of mild and severe–moderate neuropsychological impairment and global impairment index are detailed in Table 5 below. Table 6 shows Cohen's Deltas obtained from comparing performance of different groups in the used tasks.

Table 5. Prevalence of neuropsychological impairment and global impairment index in cocaine poly-substance dependents (CPSD), heroin dependents (HERO), heroin+cocaine dependents (HERO+COCA) and alcohol dependents (ALCO)

		1. 5 S.D.				2 S.D.			
		CPSD	HERO	HERO+COCA	ALCO	CPSD	HERO	HERO+COCA	ALCO
Fluency	1 task	56.8	58.8	70.6	40	31.1	41.2	41.2	33.3
	2 task	31.1	47.1	35.3	26.7	6.8	17.6	5.9	6.7
Working memory	1 task	89.2	64.7	82.4	80	45.9	41.2	64.7	53.3
	2 task	64.4	47.1	70.6	66.7	17.8	23.5	29.4	13.3
Shifting	1 task	63.5	64.7	58.8	73.3	47.3	52.9	29.4	26.7
	2 task	29.7	29.4	23.5	26.7	13.5	12.5	17.6	13.3
Interference	1 task	36.5	47.1	35.3	46.7	21.6	35.3	11.8	13.3
	2 task	12.2	0	5.9	6.7	6.8	0	0	0
Planning	1 task	45.8	90	75	71.4	34.7	60	50	42.9
	2 task	12.5	10	50	28.6	6.1	10	0	14.3
Multitasking	1 task	60.9	90	60	64.3	44.2	28.6	50	30.8
	2 task	10.9	0	20	14.3	2.5	0	0	0
% Global impairment		66.2	70.6	64.7	80	33.8	35.3	23.5	40

Table 6. Effect size in the neuropsychological tests in cocaine poly-substance dependents, heroin dependents, heroin+cocaine dependents and alcohol dependents

	Cohen's $d^{a,b,c}$	CPSD vs HERO	CPSD vs HERO+COCA	CPSD vs ALCO	HERO vs HERO+COCA	HERO vs ALCO	HERO+COCA vs ALCO
Fluency	anim fas	-.17 (CPSD)	-.05 (CPSD)	-.58 (CPSD)*	.12 (HERO+COCA)	-.32 (HERO)	-.05 (HERO+COCA)
	phono fas	.17 (HERO)	-.02 (CPSD)	-.21 (CPSD)	-.20 (HERO)	-.34 (HERO)	-.18 (HERO+COCA)
	fruits fas	-.26 (CPSD)	.26 (HERO+COCA)	-.19 (CPSD)	.48 (HERO+COCA)*	.05 (ALCO)	-.40 (HERO+COCA)*
	rfft	.09 (HERO)	.63 (HERO+COCA)*	-.10 (CPSD)	.67 (HERO+COCA)*	-.19 (HERO)	-.85 (HERO+COCA)*
WM	lns	.06 (HERO)	.38 (HERO+COCA)	-.47(CPSD)*	.34 (HERO+COCA)	-.47 (HERO)*	-.69 (HERO+COCA)*
	arithm	.13 (HERO)	.37 (HERO+COCA)	-.41(CPSD)*	.24 (HERO+COCA)	-.48 (HERO)*	-.76 (HERO+COCA)*
	digit	.00 (HERO)	.10 (HERO+COCA)	-.06(CPSD)	.09 (HERO+COCA)	-.07 (HERO)	-.16 (HERO+COCA)
	span	-.10 (CPSD)	-.24 (CPSD)	.24 (ALCO)	-.15 (HERO)	.34 (ALCO)	.41 (ALCO)*
	rule	-.15 (CPSD)	-.20 (CPSD)	-.25 (CPSD)	-.04 (HERO)	-.08 (HERO)	-.03 (HERO+COCA)
Shifting	wcst	-.20 (HERO)	-.49 (HERO+COCA)*	-.10 (ALCO)	-.29 (HERO+COCA)	.08 (HERO)	.36 (HERO+COCA)
	category	.29 (CPSD)	.21 (CPSD)	-.28 (ALCO)	-.06 (HERO+COCA)	-.64 (ALCO)*	-.52 (ALCO)*
	5dt shift	.06 (CPSD)	.14 (CPSD)	.08 (CPSD)	.07 (HERO)	.01 (HERO)	-.07 (ALCO)
	otm	.01 (CPSD)	.05 (CPSD)	.03 (CPSD)	.05 (HERO)	.01 (HERO)	-.04 (ALCO)
Interference	stroop	-.08 (CPSD)	.06 (HERO+COCA)	.46 (ALCO)*	.15 (HERO+COCA)	.54 (ALCO)*	.42 (ALCO)*
	5dt interf	.42 (CPSD)*	.36 (CPSD)	.03 (CPSD)	-.06 (HERO+COCA)	-.55 (ALCO)*	-.40 (ALCO)*
	go/no go	.11 (CPSD)	.16 (CPSD)	.11 (CPSD)	.05 (HERO)	-.00 (ALCO)	-.08 (ALCO)
Planning	key	-.13 (CPSD)	.31 (HERO+COCA)	.18 (ALCO)	.45 (HERO+COCA)*	.30 (ALCO)	-.11 (HERO+COCA)
	zoo	.51 (HERO)*	.59 (HERO+COCA)*	.44 (ALCO)*	.04 (HERO+COCA)	-.10 (HERO)	-.19 (HERO+COCA)
Multitasking	six	.20 (HERO)	.08 (HERO+COCA)	.10 (ALCO)	-.49 (HERO)*	-.10 (HERO)	.25 (ALCO)
	r-sat	-.52 (CPSD)*	1.04 (HERO+COCA)**	-.21 (CPSD)	1.09 (HERO+COCA)**	.35 (ALCO)	-1.07 (HERO+COCA)**

CPSD: cocaine poly-substance dependents, HERO: heroin dependents, HERO+COCA: heroin+cocaine dependents, ALCO: alcohol dependents.

[a] Between parentheses groups with the worse execution in that task. [b] anim fas: animals FAS; phono fas: phonological FAS; rfft: Ruff figural fluency task; lns: Letter and numbers (WAIS-III); arithm: Arithmetic (WAIS-III); digit: Digits (WAIS-III); span: Spatial span (WMS-III); rule: Rule shift cards (BADS); wcst: Wisconsin card sorting test; category: Category test; 5dt shift: Five digit test shifting score; otm: Oral trail making; stroop: Stroop colour-word interference test; 5dt interf: Five digit test interference score; key: Key search (BADS); zoo: Zoo map (BADS); six: Six elements (BADS); r-sat: Revised strategy application test.

[c] *effect size ≥0.4.

**effect size≥0.8.

3.3.1. Prevalences

Results obtained from the application of the mild impairment criterion (1.5 S.D.) revealed that fluency and working memory were the components where a higher heroin dependents proportion (47.1%) showed impairment in the performance of 2 or more tests. Both for heroin + cocaine dependents and alcohol dependents, working memory was the component with a higher number of impaired individuals (heroin + cocaine=70.6%; alcohol=66.7%). Results obtained from the application of the moderate–severe impairment criterion (2 S.D.) revealed that it was planning the component where a higher heroin dependents proportion (60%) showed impairment in the performance of 1 or more tests. Both for heroin + cocaine dependents and alcohol dependents, working memory was the component with a higher number of impaired individuals (heroin + cocaine=64.7%; alcohol=53.3%). As for the global impairment index, results obtained from the application of the mild impairment criterion revealed that 70.6% of heroin dependents showed global impairment vs. 64.7% of heroin + cocaine dependents and 80% of alcohol dependents. However, when applying the moderate–severe criterion, 35.3% of heroin dependents showed global impairment vs. 23.5% of heroin + cocaine dependents and 40% of alcohol dependents.

3.3.2. Effect size (Cohen's Delta)

Comparison of CPSD vs. heroin dependents sub-group showed Cohen's Deltas below 0.4 (with an overlap ranging from 100% and 78.7%) in all fluency, working memory and shifting component measures. For the interference component, δ values ranged from 0.42 to 0.08. Five Digit Test was the most discriminating task (72.6% of overlap) where the CPSD group showed the poorest performance. For the planning component, values

ranged from 0.51 to 0.13. Zoo Map was the most discriminating task (66.6% of overlap) where the heroin dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 0.52 to 0.20, R-SAT being the task with a higher discrimination (66.6% of overlap). For this test, CPSD was the group with the poorest performance.

Comparison of CPSD vs. heroin + cocaine dependents sub-groups showed Cohen's Deltas below 0.4 (with an overlap ranging from 92.3% and 72.6%) in all fluency, working memory and interference component measures. For the fluency component, Cohen's Deltas ranged from 0.63 to 0.02. RFFT was the most discriminating task (61.8% of overlap) where the heroin + cocaine dependents group showed the poorest performance. For the shifting component, δ values ranged from 0.49 to 0.05. WCST was the most discriminating task (66.6% of overlap) where the heroin+cocaine dependents group showed the poorest performance. For the planning component, values ranged from 0.59 to 0.31. Zoo Map was the most discriminating task (61.8% of overlap) where the heroin + cocaine dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 1.04 to 0.08. R-SAT was the most discriminating task (44.6% of overlap) where the heroin + cocaine dependents group showed the poorest performance.

Comparison of heroin dependents vs. heroin + cocaine dependents sub-groups showed Cohen's Deltas below 0.4 (with an overlap ranging from 100% to 72.6%) in all fluency, working memory and interference component measures. For the fluency component Cohen's Deltas ranged from 0.67 to 0.12. RFFT was the most discriminating task (57% of overlap) where the heroin + cocaine dependents group showed the poorest

performance. For the planning component, values ranged from 0.45 to 0.04. Key Search was the most discriminating task (72.6% of overlap) where the heroin + cocaine dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 1.09 to 0.49, R-SAT being the task with a higher discrimination (41.1% of overlap). For this test, heroin + cocaine dependents was the group with the poorest performance.

Comparison of CPSD vs. alcohol dependent sub-groups showed Cohen's Deltas below 0.4 (with an overlap ranging from 100% to 78.7%) in all shifting andmulti-tasking component measures. For the fluency component, Cohen's Deltas ranged from 0.58 to 0.10. FAS test for animals was the most discriminating task (61.8% of overlap) where the CPSD group showed the poorest performance. As for working memory component, Cohen's Deltas ranged from 0.47 to 0.06. Letter Number Sequencing was the most discriminating test (66.6% of overlap) where the CPSD group showed the poorest performance. For the interference component, δ values ranged from 0.46 to 0.03. Stroop was the most discriminating task (66.6% of overlap) where the alcohol dependents group showed the poorest performance. Finally, for the planning component, values ranged from 0.44 to 0.18. Zoo Map was the most discriminating task (72.6% of overlap) where the alcohol dependents group showed the poorest performance.

Comparison of heroin vs. alcohol dependents yielded Cohen's Deltas below 0.4 (with an overlap range from 100% to 78.7%) in all fluency, planning and multi-tasking measures. As for working memory component, Cohen's Deltas ranged from 0.48 to 0.07. Arithmetic was the most discriminating task (66.6% of overlap) where the heroin

dependents group showed the poorest performance. For the shifting component, δ values ranged from 0.64 to 0.01. Category Test was the most discriminating task (61.8% of overlap) where the alcohol dependents group showed the poorest performance. Finally, for the planning component, values ranged from 0.54 to 0.00. Five Digit Test was the most discriminating task (66.6% of overlap) where the alcohol dependents group showed the poorest performance.

Finally, when comparing heroin + cocaine vs. alcohol dependents, Cohen's Delta values were below 0.4 (with an overlap range from 92.3% to 85.3%) in all tests of the planning component. For the fluency component, Cohen's Deltas ranged from0.85 to 0.05. RFTT was the most discriminating test (52.6% of overlap) where heroin + cocaine dependents showed the poorest performance. As for working memory component, Cohen's Deltas ranged from 0.76 to 0.03. Arithmetic was the most discriminating test (52.6% of overlap) where heroin + cocaine dependents showed the poorest performance. For the shifting component, values ranged from 0.52 to 0.04. Category Test was the most discriminating task (66.6% of overlap) where the alcohol dependents group showed the poorest performance. For the interference component, δ values ranged from 0.42 to 0.08. Stroop was the most discriminating task (72.6% of overlap) where the alcohol dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 1.07 and 0.25, R-SAT being the most discriminating task (41.1% of overlap) where the heroin + cocaine dependents group showed the worst performance.

4. Discussion

Study results showed a high prevalence of executive function impairment in polysubstance users vs. non substance users. Working memory was the component with the highest impairment proportion, followed by fluency, shifting, planning, multi-tasking and interference. Comparisons between user groups showed very similar executive impairment prevalence for all the analyzed components. Nonetheless, higher impairment prevalence was observed in shifting for CPSD and planning for HPSD when applying a moderate–severe impairment criterion. Arithmetic was the best discriminating index between users and controls; Zoo Map for CPSD vs. HSPD, where the latter had a more impaired performance; and R-SAT for the several user sub-groups, allowing us to discriminate performance of the heroin + cocaine group from that of the rest of users.

As for the first goal of our study, estimation of prevalence of executive function impairment in polysubstance users, results revealed that about 70% of the individuals showed global impairment in executive functions when applying a mild impairment criterion (1.5 S.D. below the normative group) and about 35% when applying the moderate–severe impairment criterion (2 S.D.). Working memory was the component where a higher number of poly-substance-dependent individuals showed impairment in the performance or 2 or more tasks (about 60% when applying the mild impairment criterion, and 20% when applying the moderate–severe), followed by fluency (35% mild, and 8% moderate–severe), shifting (30% mild, and 15% moderate– severe), planning (15% mild, and 10% moderate–severe), multi-tasking (10% mild, and 1% moderate–severe), and interference (10% mild, and 5% moderate–severe). These

findings are coherent with previous research having proved impairment in many executive function components among users of several substances, including impairment in working memory (Beatty et al., 2000; Mintzer et al., 2005; Kubler et al., 2005), fluency (Noel et al., 2001; Davis et al., 2002; Verdejo-Garcia and Perez-Garcia, 2007a), shifting (Ratti et al., 2002; Fishbein et al., 2007; Ersche et al., 2008), planning (Pau et al., 2002; Verdejo-Garcia and Perez-Garcia, 2007b), and multi-tasking (Verdejo-Garcia et al., 2007b; Verdejo-Garcia and Perez-Garcia, 2007b). Alterations in each of these components could have important effects in the compliance and success of therapeutic programs addressed at drug-dependent individuals. Deficits in working memory may be associated with difficulties in retaining complex instructions, selecting relevant information in clinical sessions or group interactions, as well as generalizing specific learning to other familiar and social interactive activities (Verdejo-García et al., 2005a). Alterations in fluency and planning skills may be limiting the users' effectiveness to motivate in attaining the program's goals, and to start and plan new activities to help them rehabilitate. Also, for a good compliance of interventional programs the individual must be able to inhibit a previously-accustomed and reinforced response pattern, such as consumption, and modify it for another pattern that would in turn allow them reach the intervention's goals. Interference and self regulation components could therefore have an essential role in treatment. Some of these deficits have collectively been associated with inferior clinical progression levels (Leber et al., 1985), a lower level of participation and implication in the treatment (Fals-Stewart and Lucente, 1994) and a higher discontinuation rate in this programs (Aharonovich et al., 2003, 2006; Teichner et al., 2002). For this reason, one of the most relevant implications

of our study lies in the fact that it shows the need to design and implement treatment programs considering executive function impairments of polysubstance users using therapeutic communities. Programs adapted to these impairments will contribute to users' maximal benefit of the intervention (Teichner et al., 2002). This would facilitate their rehabilitation process and avoid potential relapses (Franken, 2003; Tapert et al., 2004; Paulus et al., 2005).

The second goal of our study was to estimate the executive impairment prevalence rates in different groups of polysubstance users. When comparing these, we observed that CPSD individuals had a global executive impairment very similar to that of HPSD individuals (70% under the mild impairment criterion, and 30% under the moderate–severe impairment criterion). When comparing the several user sub-groups, results showed very similar impairment proportions, around 65–80% under the mild impairment criterion and 25–40 under the moderate–severe impairment criterion. If we consider the executive components analyzed, we observe that working memory was the component with the highest impairment prevalence in all user groups. When applying a moderate–severe impairment criterion, we observed that shifting was the component with the highest impairment prevalence for the CPSD group, whereas for HPSD and the heroin dependents sub-group that was the planning component. These results are coherent with those of other studies having found the highest impairment in the shifting component for polysubstance users of cocaine and heroin (Ersche et al., 2008; Ornstein et al., 2000; Verdejo-Garcia and Perez-Garcia, 2007a). In the same fashion, other studies have related consumption of heroin with the occurrence of difficulties in planning (Pau et al., 2002). Our results are also in line with the clinics of these patients,

characterized by the persistence of answers that are no longer adaptive in cocaine users (Ersche et al., 2008) and by the slowness in the onset of response (motor sluggishness) in heroin users (Fishbein et al., 2007). However, a global vision of the results allows us to see a great similitude among user groups, which may indicate that the different analyzed drugs produce common impairments in the neuropsychological mechanisms under study. Recent data from regression studies with polysubstance users have found common effects of substances such as cocaine and alcohol on verbal fluency and decision-making executive processes (Fernandez-Serrano et al., in press).

The third and last goal of this study was to detect the most discriminating instruments for performance among the groups. In this sense, Arithmetic was the most discriminating task as to performance of users vs. control individuals. The best discriminators for performance in the remaining components were phonologic FAS and RFFT for fluency, Category Test for shifting, Stroop for interference, Zoo Map for planning, and Six Elements for multi-tasking. These tests may be proposed as an abbreviated clinical batch for reference to clinical assessment and research in the field of drug-dependency. When comparing CPSD vs. HPSD, Zoo Map was the most discriminating task, where HPSD group showed the poorest performance, in line with the highest impairment for planning observed in heroin users. In the several comparisons among the user sub-groups, we can observe that R-SAT was the test that most often allowed differentiate performance among groups, specifically for the heroin + cocaine dependents groups, where performance was more impaired compared with the rest of sub-groups (CPSD, heroine users, alcohol users). This result may show the existence of an addictive effect of heroin + cocaine consumption, which would become

evident in the behaviour self-regulation processes implied in the performance of this test. Studies with polysubstance users, with a relevant proportion of heroin + cocaine users, have yielded similar results for performance in R-SAT, which is coherent with this finding (Verdejo-Garcia et al., 2007b).

As limitations of our study we could elicit the lack of data of some individuals in BADS and R-SAT, due to the late incorporation of these tests to the evaluation protocol, along with small sample size for the heroin, heroin + cocaine and alcohol sub-groups. These circumstances may influence the impairment prevalence obtained. In addition, considering that the sample of participants in our study had very specific characteristics regarding treatment, since they were users of therapeutic communities, future research could study the prevalence of executive impairment in samples of polysubstance users involved in different treatment programs. Research undertaken with users under out-patient treatment programs has shown association between these individuals' executive functions and discontinuation of treatment (Aharonovich et al., 2003, 2006; Teichner et al., 2002). Therefore, it would be interesting to study the executive function prevalence grade in polysubstance users receiving this sort of treatments. It would also be interesting to extend these studies to polysubstance users with different socio-cultural characteristics to those of the sample, since some studies suggest that these characteristics may influence the success of treatment programs (Rounsaville et al., 1982; McCaul et al., 2001; Bernstein et al., 2006).

5. Conclusions

The study showed the existence of significant prevalence of executive impairment in polysubstance users using therapeutic communities. This reveals the need to redirect the actuation policies in the field of drug-dependency towards the creation of treatments addressed at the executive deficits of the participants, which in turn would facilitate the individuals' compliance and final rehabilitation.

Nota: las referencias citadas en este capítulo pueden consultarse en el Anexo II

Capítulo 6

Neuropsychological consequences of alcohol and drug abuse on different components of executive funtions

Fernández-Serrano, M.J., Pérez-García, M., Schmidt Río-Valle, J., Verdejo-García, A. (2010). Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. *Journal of Psychopharmacology, in press.*

1. Introduction

Drug use has increased notably among the world population, according to the United Nations World Drug Report 2008 (from the United Nations Office of Drugs and Crime, UNODC, 2008). It has been estimated that 4.9% of the world's population aged 15–64 have used drugs at least once over 2007–2008, and 0.6% of the world's population have drug-related problems, poly-consumption of diverse substances, such as heroin, cocaine, cannabis, amphetamines and ecstasy (MDMA), being the predominant abuse pattern (UNODC, 2008) especially in those individuals that demand treatment (European Monitoring Centre for Drugs and Drug Addiction, EMCDDA, 2008). In parallel with the increase of drug-related problems, there is increasing consensus on the notion of addiction as a brain disorder characterized by longstanding changes in cognitive functioning, especially in so-called executive functions (i.e. higher-order skills responsible for selection, monitoring and fine-tuning of goal-directed behaviour) (Goldstein and Volkow, 2002; Lubman et al., 2004). Recent evidence from animal and human studies indicate that specific components of executive functions, including dysfunctional impulsivity and decision-making, may predate initiation of drug use and mediate the transition between drug use and drug dependence (Belin et al., 2008; Dalley et al., 2007; Tarter et al., 2003). Accordingly, human studies have shown mild executive deficits in recreational users of cannabis and psychostimulants (De Win et al., 2007; Leland and Paulus, 2005). On the other hand, there is evidence that intensive exposure leading to dependence to different drugs, including cannabis, psychostimulants and opioids, dose-dependently impair several domains of executive functions (i.e. selective attention, inhibition, flexibility) and prefrontal cortex structure and function in animals

(Jentsch et al., 2002; Stalnaker et al., 2009; Verrico et al., 2004; Yanget al., 2007) and humans (Bolla et al., 2003, 2004, 2005; Verdejo-García et al., 2004; Whitlow et al., 2004). As compared with recreational users, executive deficits in individuals with substance dependence are more generalized (i.e. affecting mechanisms of access, working memory, inhibition, planning, flexibility and decision-making) and greater in magnitude (i.e. effect sizes ranging 0.5–2.2) (Verdejo-García and Pérez- García, 2007). Executive dysfunction is especially relevant in the context of substance dependence treatment, since performance on indices of executive functioning has been strongly associated with treatment retention and drug relapse (Aharonovich et al., 2006, 2008; Passetti et al., 2008; Streeter et al., 2008). Currently, cannabis, heroin and cocaine are the illegal drugs that generate more treatment demands in the European Union (EMCDDA 2008), and therefore there is a need to better understand the selective effects of these drugs on executive functions among substance dependents.

Despite being traditionally considered as a general cognitive domain (Denckla and Reiss, 1997; Zelazo et al., 1997), the literature agrees on the existence of a number of executive components or sub-functions (such as access, working memory, inhibition, flexibility or decision-making) (Fisk and Sharp, 2004; Miyake et al., 2000; Verdejo-García and Pérez-García, 2007). Evidence from lesion research and functional neuroimaging studies has supported this view by showing that discrete executive mechanisms are endorsed by differentiated neural systems. Hence, there is evidence of the prominent roles of the dorsolateral prefrontal cortex in working memory (D'Esposito et al., 1999), the inferior frontal gyrus and supplementary motor area in response inhibition (Aron et al., 2003; Picton et al., 2007), the lateral orbitofrontal

cortex in cognitive flexibility (Cools et al., 2002), the frontal pole (Area 10) in multitasking (Dreher et al., 2008; Gilbert et al., 2006) and the medial orbitofrontal cortex in decision-making (Bechara et al., 1994). Although distinct, these processes are flexibly assembled in response to complex task demands (Collette et al., 2005). Therefore, the abuse of different drugs may both selectively and commonly impair these separate but interrelated executive components. In the last few years, several studies have shown decrements in differentiated components of executive functioning in cannabis, cocaine and heroin abusers/dependents, the type of addicted individuals forming our sample. Studies have found impairments in working memory, decision-making, attention and planning in cannabis abusers/dependents (Bolla et al., 2005; Medina et al., 2007; Verdejo-García et al., 2007a; Wadsworth et al., 2006), impairments in decision making, working memory and inhibition in cocaine abusers/dependents (Bolla et al., 2003; Fillmore et al., 2002; Kübler et al., 2005; Verdejo-García et al., 2007a) and impairments in decision-making, inhibition and flexibility in heroin abusers/dependents (Brand et al., 2008; Fishbein et al., 2007; Lee and Pau, 2002; Pau et al., 2002; Verdejo-García et al., 2005a). However, it is difficult to establish a selective association between decrements in separate executive tasks and the abuse/dependence of any given drug, since virtually all of these studies have been conducted in polysubstance using groups. Along with the potential detrimental effects of aging and lower education on executive decline (Van der Elst et al., 2006; Verhaeghen and Cerella, 2002), one of the main confusing variables in most of these studies is co-abuse of alcohol, which is ubiquitous among polysubstance abusers. Alcohol abuse and dependence are related to long-lasting executive impairments affecting fluency, working

memory, inhibition, flexibility and decision-making, and decreases in prefrontal cortex structure (Chanraud et al., 2007; Loeber et al., 2009; Pitel et al., 2009). Furthermore, there is evidence of dose-dependent effects of severity of alcohol use on executive performance decrements (Glass et al., 2009). More importantly, there is some evidence that alcohol abuse may be more strongly associated with certain aspects of executive dysfunction (i.e. sustained attention, planning or flexibility) than the co-abuse of other drugs, such as cocaine (Bolla et al., 2000; Goldstein et al., 2004) or heroin (Fishbein et al, 2007). Therefore, alcohol co-abuse is a relevant confounding variable that complicates the interpretation of previously observed associations between cannabis, cocaine or heroin abuse and impairment of separate executive processes (Abi-Saab et al., 2005; Di Sclafani et al., 2002; Fishbein et al., 2007; Robinson et al., 1999). Nicotine is also a relevant confounding variable, but its neurocognitive effects appear to be more related to processing speed and memory functioning, with less deleterious effects on executive functions (Swan and Lessov-Schlaggar, 2007). On the other hand, in order to examine the association between abuse/dependence of different drugs and executive functioning, the patterns of quantity and duration of use of these drugs must be considered. As we explained earlier, there is a strong association between the intensity of drug use (in terms of both quantity and duration of use) and the degree of executive functions impairment and frontal cortex dysfunction (see Beveridge et al., 2008). In this regard, several studies have shown consistent associations between the severity of cannabis use and alterations in inhibition, flexibility and decision-making (Bolla et al., 2002, 2005; Verdejo-García et al., 2005b), between the severity of cocaine use and inhibition impairments (Bolla et al., 2000; Fillmore and Rush, 2002; Roselli and Ardila,

1996; Verdejo-García et al., 2005b) and between the severity of opioid consumption and cognitive flexibility decrements (Lyvers and Yakimoff, 2003).

Therefore, based on the multicomponent approach to executive functions, this study is aimed at: (i) analysing the independent impact of the three main drugs motivating treatment demand (cocaine, heroin and cannabis) versus the impact of alcohol co-abuse on polysubstance dependents' executive functions performance, and (ii) analysing the contribution made by the quantity and duration of consumption of the different drugs analysed on executive functions performance. We expect that alcohol and other drugs of abuse have a differential contribution in the separate components of the executive functions analysed. To reach both aims, we chose to make a three-stage multiple regression approach aimed to differentiate between detrimental effects due to the effects of demographic variables (age and education), those related to the effects of alcohol, and those related to the effects of the main drugs of choice motivating treatment (especially after discounting demographic and alcohol effects).

2. Method and materials

2.1. Participants

Sixty substance-dependent individuals (SDIs) (eight female), aged 21–49 years, and 30 healthy control individuals (HCIs) (six female), aged 18–49 years, participated in this study. All participants were Spaniards (European background) and spoke Spanish as their native language. SDIs and HCIs participants were matched for gender, but not for age or education level, which were used as independent variables in regression analyses. In Table 1, we present the main sociodemographic characteristics of both groups. SDIs were selected during their treatment at the 'Proyecto Hombre' rehabilitation centre, an

intreatment therapeutic community in Granada, Spain. This centre provides a controlled environment for dishabituation and treatment of drug abuse. SDIs were in a situation of controlled abstinence and urine toxicology screening (One Step Syva rapid tests for alcohol, cannabis-THC, amphetamines, benzodiazepines, cocaine and opiates) was conducted on these individuals weekly, allowing us to rule out drug use throughout the entire period of abstinence. Selection criteria for participants in the SDIs group were: (i) meeting the DSM-IV criteria for substance dependence; (ii) absence of documented comorbid mood or personality disorders as assessed by clinical reports; (iii) absence of documented head injury or neurological disorders; (iv) not being enrolled in opioid substitution treatment; and (v) minimum abstinence duration of 15 days before testing, although the median duration of abstinence for any drug in the group was of 32 weeks, so that it was possible to rule out the presence of alterations associated with the acute or short-term effects of the drugs. The SDIs sample was principally composed of polysubstance abusers who requested treatment for cocaine, heroin or cannabis use. Although five SDIs showed high level of MDMA use (a lifetime consumption of more than 50 pills), none of them requested treatment for this MDMA consumption. In Table 2, we present the consumption characteristics of the SDIs group.

Control participants were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these control participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than six units of alcohol per week); (ii) absence of documented major psychiatric disorders; (iii) absence of documented head injury or neurological disorder; and (iv) not being on any medication affecting the central

nervous system (CNS), including antidepressants, mood stabilizers, anxiolytics, antiepileptics or antipsychotics. The mean amount of alcohol use in male HCIs was 5.43 units/month (SD=5.24) and the mean of alcohol duration consumption was 6.12 years (SD=6.06). In female HCIs the mean amount of alcohol use was 5.33 units/month (SD=8.35) and the mean of alcohol duration consumption was 9.00 years (SD=11.45).

Table 1. Descriptive scores for the sociodemographic characteristics of substance dependent individuals (SDI) and healthy control individuals (HCI)

Socio-demographic variables	SDI		HCI		*t/chi square*	*p*
	Mean	S.D.	Mean	S.D.		
Age	30.58	7.08	26.40	8.03	2.52*	.013
Years of education	9.88	2.48	11.63	2.04	-3.33*	.001
Gender (%)					.677**	.538
Men	86.7		80			
Women	13.3		20			

* value of *Student's t*

** value of *Chi-square* χ^2

Table 2. Descriptive scores for patterns of quantity and duration of drug use in the group of substance dependent individuals (SDI).

Substances	Variables	SDI	
		Mean	S.D.
Cocaine	Grams/month	49.53	42.22
	Duration (years)	8.07	5.57
Cannabis	Joints/month	148.65	179.87
	Duration (years)	8.27	7.63
Heroin	Grams/month	10.90	24.05
	Duration (years)	1.90	4.14
Alcohol	Units/month	506.98	445.58
	Duration (years)	10.40	7.17
	Abstinence (weeks)	33.28	Md=32.00

Note: Md, median.

2.2. Instruments and assessment procedures

2.2.1. Background information

In order to examine the lifetime use of different substances, we used the Interview for Research on Addictive Behaviour (IRAB) (López-Torrecillas et al., 2001). This instrument evaluates the dosing, frequency (consumption episodes per month) and duration of use of a number of substances. For every substance the subject had actually consumed, including cannabis, alcohol, cocaine, heroin, amphetamines, benzodiazepines and MDMA, the following information was requested:

(1) The average amount of each target drug taken in each episode of use (number of joints for cannabis; number of grams for cocaine and heroin; and number of units for alcohol, considering that a glass of Scotch whisky equals one unit, while a glass of wine or beer equals 0.5 units), and the frequency of these consumption episodes per month (daily, between one and three times per week, once a week, between one and three times per month or once a month).

(2) The number of years elapsed since the onset of use.

From these data, two independent measures of quantity (average amount taken in each episode of use x monthly frequency) and duration (years) of consumption were calculated for each drug abused by the participants.

2.2.2. Neuropsychological tests

We used a selective battery of neuropsychological tests designed to assess several components of executive functions, including fluency, working memory, analogical reasoning, interference and cognitive flexibility (which have been associated with the functioning of different sections of the lateral prefrontal cortex) (Koechlin and

Summerfield, 2007), and decision-making and self regulation during multitasking (which are proposed to relate to more medial and rostral sections of the prefrontal cortex) (Bechara et al., 2000; Levine et al., 2000). Below we describe the tasks used grouped by executive components.

Fluency tests:

- FAS (verbal fluency) (Lezak, 2004): participants were asked to produce in 1 min the greatest possible number of words that start first with the letter "F", next with the letter "A" and finally with the letter ''S''. The main dependent variable was the sum of the words produced with these three letters.

- Ruff figural fluency test (RFFT) (Ruff, 1996): consists of five parts that present a similar structure, made up of 35 boxes with five dots in each. Participants were required to draw as many different figures as possible joining with straight lines at least two of the five dots each box contains. The main dependent variable used in this test was the total number of original figures produced.

Working memory tests:

- Letter number sequencing (LNS) (Wechsler adult intelligence scale, WAIS-III) (Wechsler, 1997a): the participant is read a sequence in which letters and numbers are combined, and they are asked to reproduce the sequence heard, first placing the numbers in ascending order and then the letters in alphabetical order. The test consists of seven elements, and each element consists of three tries. In each element, the sequence is read at one letter or number per second. The administration is stopped when the participant misses three tries in the same element. The main dependent variable used on this test was the number of correct answers.

- Spatial span (Wechsler memory scale, WMS-III) (Wechsler, 1997b): this task consists of a platform on which a series of 10 three-dimensional cubes are placed and organized according to a pre-determined pattern. The test consists of two parts: forward and backward span. In both cases the evaluator touches a series of cubes (whose number increases in successive trials) with his finger, and the participant must touch the same cubes as the evaluator (1) in the same order (forward span) or (2) in inverse order (backward span). The main dependent variable used in these tests was the total number of correct responses.

Analogical reasoning tests:

- Similarities (WAIS-III) (Wechsler, 1997a): pairs of words that represent common objects or concepts are read, and participants have to indicate how these objects/concepts are similar. This task consists of 19 pairs of words. The administration is stopped when the participant misses four consecutive elements. The main dependent variable analysed in this test was the number of correct answers.

- Category test (DeFilippis, 2002): a computerized version of this test was administered. The task consists of 208 stimuli that have different types of designs (squares, triangles, circles, letters, etc.) grouped in seven subtests with different rules. For all of the stimuli included in the same subtest, there is an underlying rule that determines the appropriateness of the responses throughout this subtest. However, this rule changes in the next subtest, so that the participant's performance on the test depends on the ability to infer these rules, and modify them when they are no longer valid. Test instructions are intentionally ambiguous: we explained to the participant that different types of designs will appear consecutively on the screen, and that each design is associated with

one of the first four numbers: 1, 2, 3 or 4. For each stimulus the participant must press the key with the number they think is associated with that design, and the computer provides auditory feedback related to the correctness or incorrectness of the response provided. The main index of performance on the test was the total number of errors on the seven subtests.

Tests of interference and shifting:

- Stroop: this test consists of three forms, each of which contains 100 elements distributed in five columns of 20 elements each. The first form (WORDS condition) is made up of the words 'RED', 'GREEN' and 'BLUE' ordered randomly and printed in black ink. In this condition the participant is asked to read aloud, as quickly as possible, the words written on this page in a time set at 45 s. The second form consists of strings of 'XXXX' (COLORS condition) printed in red, blue or green ink. In this condition, the participant is asked to read aloud as quickly as possible the colour of these elements with a time limit of 45 s. The third form (COLOR-WORD condition) introduces the condition of interference, and it consists of the words from the first form printed in the colours of the second. In this condition, the subject is asked to name the colour of the ink the word is written in, ignoring the word, also in 45 s. The main dependent variable used in this test was the interference score, obtained by subtracting subjects' response latency to WORDS and COLOR (using the formula: WORDS*COLORS/WORDS+COLORS) from their response latency to the COLOR-WORD condition (Golden, 1978).

- Five digit test (5DT) (Sedó, 2005): this consists of four parts of independent application, in which a series of 50 boxes are presented, each of which contains one to

five digits (parts 1, 3 and 4) or stars (part 2), organized in patterns similar to those on domino pieces or playing cards. In part 1 (reading), the participant is asked to read as quickly as possible the digit each box contains. In part 2 (counting), they are asked to count how many stars each box contains. In part 3 (interference), they are asked to count the number of digits each box contains, producing an effect of interference as the boxes present groups of digits that do not correspond to their arithmetic value (e.g. in a box with five twos, the correct response would be five and not two). Finally, in part 4 (shifting), the participant is asked to count, just as in part 3, or read, as in part 1, depending on whether the outline of the box is normal (count, 80% of the stimuli) or of double thickness (read, 20% of the stimuli). Parts 1 and 2 constitute basic measures of attention and processing speed. In contrast, parts 3 and 4 are sensitive to executive processes of inhibition. Therefore, the main dependent variables used in this test were the difference between the performance time on part 3 and the mean of parts 1 and 2 (differential 'interference' score), and the difference between the performance time on part 4 and the means of parts 1 and 2 (differential 'shifting' score).

- Oral Trail Making (OTM) (Sedó et al., 1995): this test includes two independent parts. The first part (OT 1) assesses visuo-spatial and naming abilities. It contains 20 items consisting of numbers (1–20) paired with four familiar fruit images (apple, banana, grapes and orange). The items (containing the number and the paired fruit represented together in 20 little boxes) are spread all over the test form. Participants are asked to visually search for the items by number, and to name the fruit paired with each item (one apple, two orange and so forth). The second part (OT 2) assesses visuo-spatial and cognitive flexibility skills. This portion of the test uses a presentation identical to that in

the first part, except that the fruits paired with the numbers are printed in different non-natural colours, in such a way that the shape and the colour of the fruit are always incongruent (e.g. red banana). Participants are asked to visually search for each item by number and to name the fruit paired according to the colour and not the shape (thus, a red banana should be named as 'apple'). The dependent measure was the interference score obtained by subtracting time in part 1 from time in part 2 (OT 2-1).

Decision making:

- Iowa gambling task (IGT) (Bechara et al., 1994): this is a computerized task that factors several aspects of decision-making including uncertainty, risk, and evaluation of reward and punishing events. The IGT involves four decks or cards, decks A', B', C' and D'. Participants were instructed to win as much money as possible by picking one card at a time from each of the four decks in any order until the computer instructed them to stop (after the selection of the 100th card). Each time a participant selects a card, a specified amount of play money is awarded. However, interspersed among these rewards, there are probabilistic punishments (monetary losses with different amounts). Two of the decks of cards, decks A' and B', produce high immediate gains; however, in the long run, these two decks will take more money than they give, and are therefore considered to be the disadvantageous decks. The other two decks, decks C' and D', are considered advantageous, as they result in small, immediate gains, but will yield more money than they take in the long run. The main dependent variable used on this task was the difference between the number of advantageous and disadvantageous choices [(C+D)-(A+B)] on each of the five blocks of 20 trials of the task.

Self-regulation:

- Revised Strategy Application Test (R-SAT) (Levine et al., 2000; Spanish adaptation by Verdejo-García et al., 2007b): this is an unstructured paper-and-pencil multitasking test sensitive to disturbed self-regulation. It consists of three simple activities: figure tracing, sentence copying and object numbering. Each activity has to be performed in two different stacks (A and B), each containing 10 pages with approximately 12 items each. The items differed in two dimensions: size (they can be large or small) and time required to complete them (they can be brief, taking a couple of seconds, medium or long, taking more than one minute). The different types of stimuli are intermixed within each page, but the number of brief items decreases progressively within each stack. The main goal of the task was to win as many points as possible, considering that large items scored 0 points and small items scored 100 points each. Nonetheless, points were used in the instructions only to see whether participants would respond accordingly, but the dependent variable in this task is the number of items and not points. In order to complete more items, given the limited time, the most efficient strategy (which the participant must discover as they perform the task) is to complete brief items to the exclusion of lengthy items. This requires the inhibition of a tendency to complete all of the items in sequence, which is established on the early pages of each stack, where all of the items are brief. Therefore, the main dependent variable from the R-SAT was the proportion of brief items completed (not including the first page of each stack) with regards to the total number of items attempted.

2.3. Procedure

Participants were assessed individually between April 2003 and November 2007 in a single session that lasted approximately 3 h and 45 min (including breaks) or on two consecutive days, depending on the rehabilitation centre availability. Participants did not consume food, caffeine or nicotine during tests administration, although smoking (a maximum of one cigarette) was allowed during the breaks to avoid nicotine withdrawal effects. SDIs and HCIs were not tested at a fixed time of the day, but to the best of the authors' knowledge there is no consistent evidence of biasing effects of this variable on neuropsychological performance in this population. The tests included in the study were part of a more comprehensive battery aimed at examining neuropsychological functions in SDIs. Test administration was blocked for all participants and arranged to alternate between verbal and non-verbal tasks and between more- and less demanding tasks. The order of administration was: FAS, RFFT, LNS, Stroop, Similarities, Category Test, R-SAT, OTM, Spatial Span, 5DT and IGT.

All of the participants in the study were informed about the objectives, benefits and possible inconveniences associated with the research protocol. Likewise, all of the participants signed an informed consent form certifying their voluntary participation. The SDIs and HCIs participants who requested it received a neuropsychological report about their performance on the tests. In addition, the control participants were paid €18 for their participation to ensure motivation.

2.4. Data analysis

First, in order to characterize neuropsychological performance differences between SDIs and HCIs, we conducted independent-samples t-tests (for those dependent

variables unrelated to age and education: 5DT shifting score, 5DT interference score and R-SAT) or univariate analyses of covariance (ANCOVAs; for those dependent variables significantly associated with age, education or both: FAS, RFFT, LNS, Spatial span, Similarities, Category test total errors, OTM shifting score, Stroop interference score and IGT) using group (SDIs versus HCIs) as a between-subjects factor and age and education as covariates. Next, we explored dependent variables to examine the possible presence of outliers (defined as atypical values by the Explore command of SPSS v.15). Two outliers were detected in the R-SAT proportion of brief items distribution, two outliers were detected in the 5DT–interference score distribution, and three outliers were detected in the 5DT–shifting score distribution. These subjects were removed from further analyses with the corresponding dependent variables; therefore SDIs sample size for R-SAT analyses, N=58, for 5DT interference, N=58 and for 5DT shifting, N=57. Next, we performed a series of multiple regression models to examine the impact of demographic variables, alcohol use and illegal drugs use on executive performance. Since the three illegal drugs motivating treatment demand in this sample were the main focus of the study, we first conducted multiple regression models including only cannabis, cocaine and heroin (both quantity and duration) as predictor variables; these analyses were included to assess the variance attributable to drug use before inclusion of demographics and alcohol. Next, to test the main aim of the study (i.e. to disentangle specific effects of alcohol versus illegal drugs on different executive components and determine the impact of cannabis, cocaine and heroin after discounting the effect of demographics and alcohol abuse), we conducted hierarchical multiple regression analyses. These models were set on three stages: (i) demographic variables

associated with executive performance (age and years of education); (ii) total consumption of alcohol, which is the main substance of co-abuse; and (iii) quantity and duration of consumption of cannabis, cocaine and heroin. We developed independent regression model series for the variables quantity and duration of consumption of the different substances, to determine the specific effects of both parameters and avoid collinearity effects. These separate models also allowed us to adjust the number of predictors as a function of sample size: we used a maximum of five predictor variables for a sample size of 90; ratio of 15 cases by predictor variable (a ratio of at least 10 cases by predictor is considered appropriate) (Hair et al., 2000). Therefore, for each analysis we introduced three differentiated blocks of predictor variables in a sequential manner: the first block included the variables of age and years of education, the second block included the total alcohol consumption (i.e. a combined quantity x duration measurement was calculated to avoid that alcohol consumption of healthy control individuals, similar to that of SDIs in duration, yet of quite lower intensity, could slant the contribution of this factor), and finally, the third block included the quantity or duration of consumption of cannabis, cocaine and heroin. The different performance indices of the executive function neuropsychological tests were included as dependent variables. For each new block of variables entered in the regression model, we estimated the R^2 of the prediction change associated with that block and its statistical significance, with the aim of determining the differential contribution of each of the blocks to the regression model. To facilitate reading, in text we only present results from hierarchical models showing significant effects of alcohol or drug use after discounting the effects of demographic variables. Data from regression models

including only drug use variables are presented in Tables (two first columns), along with hierarchical models.

3. Results

3.1. Group differences

SDIs performed significantly poorer than controls on all of the executive indices assessed, with effect sizes ranging from 0.6 (e.g. shifting) to 2.3 (analogical reasoning); see Table 3. All executive indices (with the exception of OTM shifting) yielded effect sizes circa or superior to 0.8 for differences between SDIs and HCIs, which are considered large effects according to Cohen (Zakzanis, 2001).

3.2. Regression models

The coefficients obtained with the hierarchical regression analyses are represented in Table 4, for the models including quantity of consumption, and in Table 5, for the models including duration of consumption. The impact of the entry of each block in each of the steps of the regression model is represented by means of the determination coefficient values (R^2). The results of multiple regressions including only drug measures (quantity or duration) are also included in the first two columns of Tables 4 and 5, respectively.

3.3. Quantity of consumption

Fluency: In the FAS test, after controlling for the effects of demographics, the block of total alcohol consumption was a significant predictor of performance. However, the entry of the block of quantity of consumption of other drugs significantly increased the predictive value of demographics and alcohol. The global model revealed that the quantity of cannabis was the most predictive variable of performance on this

test. In the RFFT, neither the block of total alcohol consumption nor the block of illegal drugs consumption were predictors of performance on this task.

Working memory: In the LNS test, the block of total alcohol consumption showed a trend to significant effects (p=0.057), but the entry of the block of quantity of consumption of drugs significantly improved the prediction of the former blocks. In the global model we observed that the quantity of cocaine and cannabis use had the highest predictive value of performance. In the Spatial Span task, we observed that the block of total alcohol consumption failed to predict performance on this task. Nevertheless, inclusion of the quantity of consumption of other drugs significantly improved the prediction of demographics and alcohol. The analysis of the global model coefficients showed that the quantity of cocaine use had the highest predictive value of performance on this task.

Reasoning: In the Similarities test, we observed that, after controlling for demographics and alcohol, the block of quantity of consumption of drugs was a significant predictor of performance. The analysis of the global model coefficients showed that the quantity of consumption of cannabis and cocaine were the variables with the highest predictive value of performance on this task. Similarly, in the Category test, the block of quantity of consumption of drugs showed a trend to significantly increase prediction of performance (p=0.062), and the analysis of global model coefficients revealed that the quantity of cocaine was the most predictive variable of performance on this task.

Interference and shifting: In the 5DT (both interference and shifting scores) and the Stroop tests, neither the block of total alcohol consumption nor the block of other

drugs had predictive capability of performance on these measures. In the OTM test, the entry of the block of quantity of consumption of drugs improved the prediction of previous blocks significantly, and quantity of heroin consumption was the most predictive variable.

Decision-making: In the IGT we observed that both the block of total alcohol consumption and the block of other drugs significantly predicted performance on this task. When analysing the global model, we observed that total alcohol consumption, quantity of cannabis and quantity of cocaine were the most predictive variables of performance on this task.

Self-regulation: In the R-SAT we observed that only the block of total alcohol consumption showed a trend to significantly predict performance on this task ($p=0.077$). The inclusion of the block of drug measures failed to increase the prediction of the global model significantly.

3.4. Duration of consumption

In this section we only refer to the predictive value of the variables of cannabis, cocaine and heroin consumption, since the predictive value of the blocks of total alcohol consumption variable is the same as that of the previously described models.

Fluency: In the FAS test we observed that the block of consumption of drugs (cannabis, cocaine and heroin) improved the predictive value of demographics and alcohol significantly, with duration of cocaine consumption being the variable with the highest predictive value. In the RFFT the block of duration of drug consumption improved prediction of previous blocks significantly, and duration of cocaine consumption was the variable with the highest predictive value.

Working memory: In the LNS test, the block of duration of drug consumption improved the predictive value of demographics and alcohol significantly. Duration of cocaine consumption was the best predictor variable of performance on this task. In the Spatial span task, the block of duration of drug consumption improved prediction of demographics and alcohol significantly, but in this case the variable with the highest predictive value was duration of cannabis consumption.

Reasoning: In the Similarities task, the block of duration of drug consumption improved the predictive value of demographics and alcohol significantly, and duration of cocaine consumption was the best predictor of performance on this task. In the Category test, we observed that the block of durations of drugs consumption failed to significantly predict performance on this measure.

Interference and shifting: In the Stroop test, the block of duration of drug consumption was only marginally significant for prediction of performance on this task, and none of the individual drug variables (cannabis, cocaine or heroin) showed significant β-coefficients. In the 5DT, we observed that, for the interference score, the block of duration of drugs consumption produced a significant improvement in prediction, being the duration of cocaine consumption the best predictor of performance. As for the shifting score, the block of duration of drugs use failed to significantly predict performance, and only duration of cocaine use had a marginally significant effect ($p=0.074$). In the OTM test, we observed that the block of drugs produced a significant improvement in prediction, with duration of heroin and cocaine being the variables with the highest prediction of performance.

Decision-making: In the IGT, we observed that the block of duration of drug consumption did not improve prediction of performance on this task, as compared with the block of alcohol consumption.

Self-regulation: In the R-SAT, we observed that the block of duration of drug consumption did not improve prediction of performance on this task, as compared with the block of alcohol consumption.

3.5. Summary

Group comparisons showed that SDIs performed significantly poorer than controls on all of the executive indices assessed, showing large effect sizes for differences on tests of fluency, working memory, reasoning, inhibition and decision making. The hierarchical regression models showed a significant contribution of total alcohol consumption on verbal fluency and decision-making. As for quantity of consumption of the drugs that motivated treatment, we observed that: (i) the quantity of cannabis consumption predicts performance on verbal working memory, verbal reasoning, verbal fluency and decision-making; (ii) the quantity of cocaine consumption predicts performance on verbal and visual–spatial working memory, verbal and visual reasoning, and decision making; and (iii) the quantity of heroin consumption predicts performance on visual–spatial shifting. As for duration, we observed that: (i) the duration of cannabis consumption predicts performance on visual working memory only; (ii) the duration of cocaine consumption predicts performance on verbal working memory and reasoning, both verbal and non-verbal fluency and shifting, and interference-based inhibition; and (iii) the duration of heroin consumption predicts performance on visual-spatial shifting (Table 6).

Table 3. Descriptive scores, independent group t-tests/univariate analyses of covariance –ANCOVAs, and effect sizes on the neuropsychological measures for substance dependent individuals (SDI) and healthy control individuals (HCI)

Domain	Task	SDI		HCI		*F/t*	p	Cohen's delta
		Mean	S.D.	Mean	S.D.			
Fluency	FAS	33.81	10.55	51.43	9.80	46.52[a]	.000	-1.71
	RFFT	82.86	23.72	110.33	19.94	20.11[a]	.000	-1.21
Working Memory	LNS	9.33	2.40	15.13	2.33	93.50[a]	.000	-1.57
	Spatial Span	14.89	3.36	19.90	4.35	24.55[a]	.000	-1.35
Reasoning	Similarities	18.11	4.51	27.76	3.01	90.55[a]	.000	-2.37
	CT_tot_errors	66.89	24.01	31.80	25.32	30.86[a]	.000	1.41
Shifting	5DT_shift	25.47	9.38	20.10	5.45	2.89[b]	.005	0.64
	OTM_shift	21.89	15.32	14.13	7.57	2.18[a]	.143	0.58
Interference	5DT_interf	15.74	6.46	11.10	3.77	4.28[b]	.000	0.81
	Strp_interf	-1.67	6.07	4.15	7.24	9.63[a]	.003	-0.89
Decision Making	IGT	-2.21	22.60	37.20	26.15	47.84[a]	.000	-1.65
Self-Regulation	R-SAT	82.95	16.46	93.98	5.70	-3.55[b]	.001	-0.79

[a] value of *F*

[b] value of *Student's t*

FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test.

Table 4. Multiple hierarchical regression models of the association between demographic variables, alcohol total consumption and quantity of cannabis, cocaine and heroin use and neuropsychological performance

Domain	Test	Model including only cannabis, cocaine and heroin		Hierarchical three-stage model including demographics, alcohol and drugs use				
		R^2 adjusted (*p*)	Significant contributors	Demographics R^2 change (*p*)	Alcohol R^2 change (*p*)	Cannabis/Cocaine/Heroin QUANTITY R^2 change (*p*)	Full Model R^2 adj (*p*)	Significant contributors
Fluency	FAS	.297 (.000)	Cann Quant (.000); Coc Quant (.027); Heroin Quant (.039)	.096 (.013)	.086 (.003)	.177 (.000)	.313 (.000)	Cann Quant (.001)
	RFFT	.061 (.038)	Cann Quant (.066)	.133 (.002)	.017 (.199)	.034 (.399)	.124 (.009)	Educ (.005)
WM	LNS	.286 (.000)	Cann Quant (.035); Coc Quant (.000)	.171 (.000)	.034 (.057)	.180 (.000)	.341 (.000)	Educ (.014); Cann Quant (.032); Coc Quant (.001)
	Spatial Span	.096 (.009)	Coc Quant (.015)	.109 (.007)	.006 (.443)	.081 (.049)	.137 (.006)	Coc Quant(.032)
Reasoning	Similarities	.207 (.000)	Cann Quant (.022); Coc Quant (.004)	.173 (.000)	.030 (.075)	.118 (.004)	.272 (.000)	Educ (.005); Cann Quant (.026); Coc Quant (.032)
	CT_tot_errors	.085 (.016)	Coc Quant (.027)	.074 (.039)	.012 (.308)	.079 (.062)	.103 (.022)	Coc Quant (.047)
Shifting	5DT_shift	.058 (.047)		.014 (.556)	.004 (.558)	.079 (.080)	.029 (.213)	
	OTM_shift	.130 (.002)	Coc Quant (.037); Heroin Quant (.018)	.105 (.008)	.008 (.375)	.092 (.028)	.148 (.004)	Heroin Quant (.047)
Interference	5DT_interf	.058 (.046)		.005(.814)	.011(.330)	.078(.081)	.027(.225)	
	Strp_interf	.021 (.191)		.087(.020)	.002(.667)	.036(347)	.061(.083)	Age (.073)
DM	IGT	.260 (.000)	Cann Quant (.003); Coc Quant (.011)	.049 (.111)	.127 (.000)	.160 (.000)	.288 (.000)	Alcoh tot cons (.037); Cann Quant (.004); Coc Quant (.067)
Self-Regulation	R-SAT	.030 (.136)	Cann Quant (.084)	.011 (.619)	.036 (.077)	.057 (.168)	.038 (.164)	

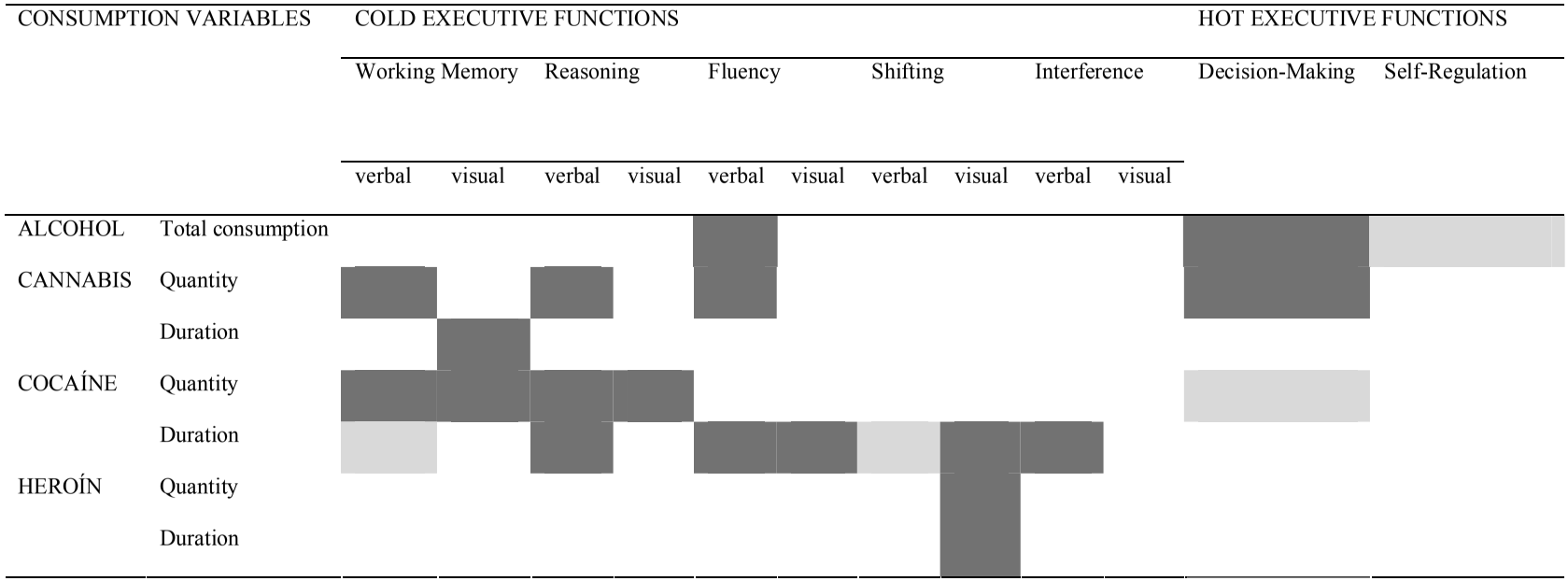
Note: R^2 adj: R^2 adjusted ; WM, Working Memory; DM, Decision Making; FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test; Cann, Cannabis; Quant, Quantity; Educ, Years of education; Coc, Cocaine; Alcoh tot cons, Alcohol total consumption.

Table 5. Multiple hierarchical regression models of the association between demographic variables, alcohol total consumption and duration of cannabis, cocaine and heroin use and neuropsychological performance

Domain	Test	Model including only cannabis, cocaine and heroin		Hierarchical three-stage model including demographics, alcohol and drugs use				
		R^2 adjusted (*p*)	Significant contributors	Demographics R^2 change (*p*)	Alcohol R^2 change (*p*)	Cannabis/ Cocaine/Heroin DURATION R^2 change (*p*)	Full Model R^2 adj. (*p*)	Significant contributors
Fluency	FAS	.160 (.000)	Coc Durat (.012)	.096 (.013)	.086 (.003)	.130 (.002)	.262 (.000)	Age (.002); Educ (.026); Coc Durat (.012)
	RFFT	.093 (.010)	Coc Durat (.007)	.133 (.002)	.017 (.199)	.179 (.033)	.179 (.001)	Educ (.003); Coc Durat (.015)
WM	LNS	.179 (.000)	Coc Durat (.020)	.171 (.000)	.034 (.057)	.113 (.005)	.269 (.000)	Educ (.001); Coc Durat (.069)
	Spatial Span	.098 (.008)	Cann Durat (.025)	.109 (.007)	.006 (.443)	.080 (.050)	.137 (.006)	Educ (.012); Cann Durat (.014)
Reasoning	Similarities	.193 (.000)	Coc Durat (.004)	.173 (.000)	.030 (.075)	.144 (.001)	.300 (.000)	Educ (.000); Coc Durat (.009)
	CT_tot_errors	.106 (.006)	Cann Durat (.090)	.074 (.039)	.012 (.308)	.073 (.084)	.096 (.028)	
Shifting	5DT_shift	-.003 (.432)		.014 (.556)	.004 (.558)	.052 (.224)	.000 (.430)	Coc Durat (.074)
	OTM_shift	.223 (.000)	Coc Durat (.002); Heroin Durat (.002)	.105 (.008)	.008 (.375)	.167 (.001)	.228 (.000)	Educ (.062); Coc Durat (.016); Heroin Durat (.003)
Interference	5DT_interf	.064 (.035)	Coc Durat (.066)	.005(.814)	.011(.330)	.098(.036)	.048(.124)	Coc Durat (.036)
	Strp_interf	.102 (.007)	Coc Durat (.089)	.087(.020)	.002(.667)	.076(.065)	.104(.019)	Educ (.065)
DM	IGT	.125 (.002)	Coc Durat (.076)	.049 (.111)	.127 (.000)	.060 (.099)	.181 (.001)	Alcoh tot cons (.013)
Self-Regulation	R-SAT	-.019 (710)		.011 (.619)	.036 (.077)	.006 (.916)	-.017 (.602)	

Note: R^2 adj: R^2 adjusted; WM, Working Memory; DM, Decision Making; FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test; Cann, Cannabis; Durat, Duration; Educ, Years of education; Coc, Cocaine; Alcoh tot cons, Alcohol total consumption.

Table 6. Summary of significant associations between the different substances analyzed and the different components of cold and hot executive functions



Consumption parameter that significantly predicted this process.

Consumption parameter showing a trend to significant prediction on this process.

4. Discussion

Results showed that SDIs have a broad range of executive impairments, including fluency, working memory, reasoning, inhibition, shifting and decision-making deficits, of moderate to large magnitude according to effect sizes (Cohen's d range: 0.6–2.4). Importantly, these decrements are observed in SDIs with a median abstinence duration of 8 months, and therefore they should be regarded as long-term effects with relevant implications for the notion of addiction as a chronic brain disorder associated with frontal systems dysfunction (Goldstein and Volkow, 2002). Previous studies had obtained similar results (see the review by Verdejo-García et al., 2004), but the fact that virtually all SDIs are polysubstance abusers complicates the attribution of specific or generalized executive deficits to the effects of alcohol or any given drug. In this respect, the results from regression models revealed that severity of alcohol use is robustly associated with verbal fluency and decision-making decrements. As for the main drugs motivating treatment (cannabis, cocaine and heroin), results showed that quantity of cannabis and cocaine use have common detrimental effects on verbal working memory, analogical reasoning and decision-making measures, and that duration of cocaine and heroin use have common detrimental effects of visual–spatial shifting measures. On the other hand, we found specific effects of duration of cannabis use on visual–spatial working memory, and of duration of cocaine use on response inhibition.

Our first aim was to separate the effects of alcohol versus drugs use on different components of executive functions. Severity of alcohol use showed significant detrimental effects on verbal fluency and decision-making (on the IGT), and a trend to significant effects on working memory, but not on other executive components.

Previous studies had proposed that severity of alcohol abuse was significantly associated with decrements on executive components of planning and flexibility in psychostimulants and heroin abusers coabusing alcohol (Bolla et al., 2000; Fishbein et al., 2007; Goldstein et al., 2004). However, these studies were conducted in short-term abstinent SDIs (range of 2–4 weeks), whereas one of the few studies available in long-term abstinent alcoholics found that decision-making performance (measured with the IGT) was impaired pervasively in these individuals even after six years of sobriety; being the magnitude of disadvantageous decision-making associated with the duration of peak alcohol use (Fein et al., 2004). Moreover, the alcoholic individuals who had impaired IGT performance had significant grey matter reductions in the amygdala, a key region for the operation of decision-making processes (Bechara et al., 2003). A recent structural magnetic resonance study have also provided evidence of significant structural reductions of grey matter (up to 20% lower) in the bilateral dorsolateral prefrontal cortex of alcoholics (Chanraud et al., 2007). This region has been proposed to be involved in verbal fluency and other executive operations associated with the updating of information in working memory (D'Esposito and Postle, 2002; Gauthier et al., 2009). Functional imaging studies have also demonstrated dysfunctional frontotemporal activation during verbal fluency performance using functional spectroscopy (Schecklmann et al., 2007), and significant correlations between PET-indexed left dorsolateral prefrontal hypometabolism and reduced verbal fluency performance in abstinent alcoholics (Dao-Castellana et al., 1998). There is also evidence that acute ethanol administration decreases left dorsolateral prefrontal cortex activation and impairs verbal fluency performance in healthy individuals (Wendt and Risberg,

2001). Overall, these studies support our results showing a prominent association between severity of alcohol use and poorer fluency and decision-making skills. Although fluency and decision-making are independent executive components (Verdejo-García and Pérez-García, 2007) they have in common being complex multifaceted operations encompassing access to long-term memory, clustering, monitoring and switching of information (in the case of fluency) (Fisk and Sharp, 2004; Troyer et al., 1998), and episodic/working memory, motivation and feedback processing and reversal learning (in the case of decision-making) (Bechara et al., 2005; Busemeyer and Stout, 2002; Gupta et al., 2009). Therefore, we may speculate that alcohol severity specifically affects some of the component operations of fluency and/or decision-making (e.g. working memory updating), or alternatively affects in a broad sense to multi-component executive processes.

Our second aim was to determine the contribution of quantity and duration of consumption of the main drugs that motivated treatment to decrements on executive components functioning. In this regard, we found common detrimental effects of quantity of cannabis use and cocaine use on measures of verbal updating of working memory, analogical reasoning and decision-making. A principal component analysis performed on a comprehensive battery of executive functions tests concluded that measures of working memory and analogical reasoning (along with fluency measures) load together on a factor that we and others have labelled 'updating' (Verdejo-García and Pérez-García, 2007); which consists of continuous refreshing/updating of working memory contents in order to set task demands and optimize performance (Miyake et al., 2000; Stuss and Alexander, 2007; Verdejo-García and Pérez-García, 2007). These

results are consistent with several sources of evidence, including animal studies showing cocaine and cannabinoid dose-related modulation of working memory performance (Deadwyler et al., 2007; Egerton et al., 2006; George et al., 2008), human studies showing dose-related negative effects of severity of cannabis and cocaine use on updating measures in polydrug abusers (Medina et al., 2007; Verdejo-García et al., 2007a), and the conclusions of a recent meta-analysis of neuropsychological studies in cocaine abusers showing moderate effect sizes for updating indices, which are durable across abstinence (Jovanovski et al., 2005). Functional imaging studies have linked these updating deficits to prefrontal cortex, cingulate cortex and superior parietal cortex dysfunctions (Jager et al., 2006; Kübler et al., 2005). Nonetheless, there is also intriguing evidence showing that cannabis users have abnormally increased hippocampal activation in response to executive tasks demands (Eldreth et al., 2004; Nestor et al., 2008). Moreover, a recent structural magnetic resonance imaging study has revealed significant volumetric reductions (circa 12%) in the hippocampus of long-term cannabis users (Yücel et al., 2008). Therefore, hippocampal dysfunction may also play a prominent role on cannabis-induced updating deficits. In fact, duration of cannabis was also linked to poorer spatial working memory, a process that has been associated with the hippocampal endocannabinoid system activation in animal models (Deadwyler et al., 2007). Similarly, for decision-making, very recent studies have shown that both cannabis and cocaine abuse have dose-related detrimental effects on IGT performance (Bolla et al., 2003, 2005; Verdejo-García et al., 2007a). However, results from functional imaging and cognitive models studies suggest that both groups may fail to make advantageous decisions for different reasons: cannabis abusers display

PET-indexed prominent activation in non-specialized areas (e.g. cerebellum and occipital cortex) during IGT performance (Bolla et al., 2005), whereas cocaine abusers exposed to the same paradigm show dysfunctional activation of regions typically involved in reward processing and decision-making (e.g. striatum and orbitofrontal cortex) (Bolla et al., 2003). Moreover, cognitive decision models of the IGT have shown that cannabis abusers fail the task because they place more attention on recent than distal outcomes, whereas cocaine abusers fail because they place more attention on gains than on losses (Busemeyer and Stout, 2002).

Regression models have also shown common effects of cocaine and heroin duration of use on cognitive shifting. Animal models have shown that repeated administration of cocaine produces impairments in cognitive flexibility, specifically in perseveration and reversal learning linked to orbitofrontal cortex functioning (Jentsch et al., 2002; Schoenbaum et al., 2004; Stalnaker et al., 2006, 2009). These findings have been nicely translated to humans by several studies showing relatively specific effects of cocaine abuse on cognitive shifting (Ersche et al., 2008; Verdejo-García and Pérez-García, 2007) and electrophysiological indices of decreased error-related processing and impaired behavioural correction of errors in cocaine abusers (Franken et al., 2007). Although there is no equivalent body of animal research on the opioid modulation of cognitive shifting, a number of human neuropsychological studies have shown that heroin abusers have significant impairments in intradimensional set-shifting, perseveration, risk-taking and decision-making tasks (Fishbein et al., 2007; Lyvers and Yakimoff, 2003; Ornstein et al., 2000; Verdejo-García et al., 2005a; see also the review by Gruber et al., 2007), which have been attributed to grey matter decrements in the

medial and inferior prefrontal cortex, insula and temporal cortex (Lyoo et al., 2006) and dysfunctional activation of the rostral anterior cingulate cortex in response to error feedback (Forman et al., 2004). Therefore, abnormal error processing and subsequent failure of 'quality control' executive mechanisms may underlie flexibility deficits in both cocaine and heroin abusers.

Finally, we found specific effects of duration of cocaine abuse on one inhibition measure, the 5DT interference index. Previous results from our lab and others have supported relatively specific deleterious effects of psychostimulants on a number of neuropsychological indices of response inhibition, including the Stroop test, the Go–No Go, the Continuous Performance test or the Stop-Signal task (Bolla et al., 2004; Colzato et al., 2007; Li et al., 2008; Verdejo-García et al., 2007c). Furthermore, these deficits have been linked to patterns of severity of drug use (Bolla et al., 2004; Verdejo-García et al., 2005b) and to brain measures of reduced activation of the anterior cingulate and lateral prefrontal cortices during inhibition trials (using PET or fMRI) (Bolla et al., 2004; Li et al., 2008), and white matter decrements in the genu of the corpus callosum (using diffusion tensor imaging) (Moeller et al., 2005). These effects may be explained by a more intense neuromodulatory effect of psychostimulants on the cingulate cortex-striatal system (Bolla et al., 2003; Paulus et al., 2002, 2003, 2005; see also the review by Li and Sinha, 2008). However, this result may be interpreted with caution for several reasons. First, there is growing evidence that disinhibition deficits may predate initiation of drug use and constitute a liability marker for substance use disorders (see Dalley et al., 2007 and Belin et al., 2008 for animal evidence; see Verdejo-García et al., 2008 for a review of human evidence); therefore, we cannot draw conclusions on the causality of

inhibition deficits. Second, there is no consistency between our findings on the 5DT and the results of other inhibition tests, such as the Stroop. We think this may be due to the fact that Stroop performance is more influenced by age and educational factors (Kaplan et al., 2009), making it harder to establish a drug-related effect. However, more research is warranted to investigate the specific effects of cocaine and other psychostimulants on inhibitory control processes.

Overall, these results obtained in mid-term abstinent substance abusers may have important implications for their quality of life and their ability to take advantage of cognitive behavioural therapy-based treatment programs. Deficits in working memory, reasoning, fluency and cognitive flexibility may be associated with difficulties in retaining complex instructions, selecting relevant information from clinical sessions or group interactions, and generalizing specific learning to other familiar and social interactive activities. On the other hand, treatment headways require that addicted individuals reverse strong habits and over-rehearsed decision patterns. Cognitive deficits have been associated with poorer clinical progression levels (Leber et al., 1985), a lower level of participation and implication in the treatment (Fals-Stewart and Lucente, 1994) and higher rates of treatment dropout and drug relapse (Aharonovich et al., 2003, 2006, 2008; Passetti et al., 2008; Streeter et al., 2008; Teichner et al., 2002). In this respect, our results stress the need to promote rehabilitation programs targeted to restore or compensate executive dysfunction in SDIs.

Finally, several limitations of this study should be mentioned. First, there is evidence of age-related cognitive decline from the thirties onwards (Herndon et al., 1997; Salthouse, 2009), and therefore some of the executive declines in our sample may

be related to normal aging. However, our regression models adequately controlled for the effects of age and education, and all of the drug effects reported were obtained after removing the effect of these variables. Second, due to a lower prevalence of female inpatients during recruitment, our sample was predominantly composed of males. Future studies should investigate how these findings may or may not generalize to a female population of SDI. Third, some executive indices that were impaired in SDI failed to show any association with alcohol or drug use (e.g. the R-SAT). It is possible that in these cases the relatively medium sample size (further limited after outliers exclusion) may have contributed to type II error or, alternatively, that these deficits relate to different aspects of the addiction phenomenon (e.g. age of first use, personality patterns). Furthermore, there is an inherent limitation linked to the reliability of self-reports of drug use; nonetheless, when considering the limitations of other methods, such as toxicological analyses or structured interviews categorical approaches, to catch the time line, peak effects and dimensional aspects of drug history, self-reports end up as the approach with highest face validity (see Verdejo-García et al., 2004 for a discussion of this methodological challenge of drug abuse cognitive studies). Finally, as mentioned above, the current cross-sectional data do not allow us to determine whether these alterations preceded drug use and contributed to higher severity patterns, or if they occur as a consequence of persistent drug use. Longitudinal studies are warranted to address this relevant question.

Nota: las referencias citadas en este capítulo pueden consultarse en el Anexo III

Capítulo 7

Impact of severity of drug use on discrete emotions recognition in polysubstance abusers

Fernández-Serrano, M.J., Lozano, O., Perez-Garcia, M., Verdejo-Garcia, A. (2010b) Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. *Drug and Alcohol Dependence, in press.*

1. Introduction

Addiction is a chronic relapsing disorder characterized by persistent brain alterations associated with cognitive, motivational and emotional alterations (Goldstein and Volkow, 2002; Verdejo-García and Bechara, 2009). Neuropsychological studies have demonstrated extensive mid- and long-term cognitive alterations in individuals with substance use disorders (see Ersche and Sahakian, 2007; Verdejo-García et al., 2004 for reviews), but there is disproportionately less research on the neuropsychology of emotional alterations associated with addiction. One of the key aspects of adaptive emotional functioning is the ability to decode emotional cues and recognize emotions in the faces of others, especially in relation to the six basic emotions: anger, disgust, fear, happiness, sadness and surprise (Adolphs, 2002). Emotion recognition is relevant to addiction in several regards. On the one hand, emotion recognition is fundamental for prosocial behavior, normal socialization and interaction (Blair, 2003), which is typically impaired in addiction (Reay et al., 2006; Roselli and Ardila, 1996; Homer et al., 2008). Moreover, simulation theories argue that the emotional states of others are understood and recognized by generating similar states in oneself (Goldman and Sripada, 2005), and evidence supports the link between altered emotion recognition and parallel alterations in emotion experience and behavioral manifestations (Calder and Young, 2005). These notions are particularly relevant to addiction according to the somatic marker theory, which posits that substance addiction is associated with abnormal activation and integration of emotional states involved in the experience of subjective urges (e.g., craving) and in the guidance of decision-making (Verdejo-García and Bechara, 2009). Furthermore, the neural substrates of emotion recognition overlap with neural systems strongly involved in the escalation and maintenance of addiction,

including the orbitofrontal cortex, the cingulate gyrus, the insula, and the ventral striatum (Verdejo-García and Bechara, 2009); and there is evidence of relative specificity in the neural systems supporting recognition of discrete emotions, with reliable and specific association between fear and the amygdala, disgust and the insula/ basal ganglia, and anger and the lateral orbitofrontal cortex and the ventral striatum (Calder et al., 2001, 2004; Murphy et al., 2003). Therefore, it is reasonable to assume that drug use can be selectively associated with poorer recognition of discrete emotions as much as it is selectively associated with decreased functioning of particular cognitive and neural systems.

Available studies about the chronic (non-acute) deficits of discrete emotions recognition in addiction have mainly focused on alcohol dependence, and most studies have chosen to index the ability to estimate the intensity of the emotions displayed (but not accuracy of recognition). Studies on alcohol have shown that alcoholics tend to overestimate the intensity of the emotion displayed by facial expressions of happiness, anger and disgust (Foisy et al., 2007a; Kornreich et al., 2001; Townshend and Duka, 2003). Studies measuring recognition accuracy have shown that alcoholics have poorer recognition of expressions of sadness (Frigerio et al., 2002) and difficulties to discriminate anger and disgust (Townshend and Duka, 2003); although other studies have failed to find differences in emotion recognition accuracy between alcoholics and non-drug comparison individuals (Foisy et al., 2007b; Salloum et al., 2007). A comparison between alcohol and opiate dependents showed that alcoholics had overall poorer emotion recognition (across several emotions) than abstinent and methadone maintained opiate dependents (Kornreich et al., 2003). A recent study comparing abstinent vs. methadone-maintained opiate users showed that methadone patients were

overall slower but more accurate in the recognition of expressions of disgust; being accuracy positively correlated with lifetime use of methadone (Martin et al., 2006). Studies on cocaine and polysubstance psycho-stimulants abusers have shown relatively specific alterations in the recognition of expressions of fear (Kemmis et al., 2007; Verdejo-García et al., 2007); however, the psycho-stimulant groups from both studies markedly differed on severity of drug exposure and patterns of other drugs co-abuse. Moreover, a more recent study did not find significant differences on emotion recognition between cocaine abusers and controls (Woicik et al., 2009). To our knowledge, no studies have been performed about the chronic effects of MDMA or cannabis use on emotion recognition, although there is suggestive evidence of acute and sub-acute effects of these drugs on facial emotional processing (Fusar-Poli et al., 2009; Hoshi et al., 2004). Overall, the evidence on chronic deficits of emotion recognition in addiction is scarce and has yielded considerably mixed results.

In addition, most studies have neglected the potential relevance of patterns of quantity and duration of drug use in relation to chronic emotion recognition deficits in the context of polysubstance abuse. Cognitive neuropsychological studies have successfully established an association between estimates of amount and duration of drug use and alterations in specific cognitive domains and neural systems (see Bolla et al., 1999, 2000, 2002, 2004; Fernández-Serrano et al., 2009; Goldstein et al., 2004; Verdejo-García et al., 2005). Similarly, we expect that severity of use of different drugs can contribute to explain differential alterations in discrete emotions recognition, since all the brain areas involved in emotion recognition are related to the motivational brain circuitry implicated in addiction. Therefore, the aims of this study are: (i) to replicate previous findings showing poorer facial emotion recognition in polysubstance abusers

(Verdejo-García et al., 2007) using a larger sample, and (ii) to explore the association between patterns of quantity and duration of use of several drugs co-abused (including alcohol, cannabis, cocaine, heroin and MDMA) and the ability to identify discrete facial emotional expressions portraying basic emotions in polysubstance abusers.

2. Methods

2.1. Participants

Sixty-five polysubstance abusers (PSA) aged 21-53 years (10 women), and 30 non-drug using comparison individuals (NDCI) aged 18-49 years (6 women), participated in this study; socio-demographic characteristics from both groups are displayed in Table 1. PSA and NDCI groups had similar distributions for gender and educational level but differed significantly on age; all these variables were explored in subsequent analyses. PSA were recruited during residential treatment at one therapeutic community ("Proyecto Hombre") in the city of Granada, Spain. This center provides psychological treatment and educational/occupational counseling in a controlled environment during an extended period of time. The PSA sample was composed of polysubstance users of several drugs, including cannabis, cocaine, heroin, alcohol, ecstasy (MDMA), amphetamines and benzodiazepines. Selection criteria for participants in the PSA group were: (i) meeting the DSM-IV criteria for substance dependence, (ii) absence of documented comorbid mood or personality disorders as assessed by clinical reports, (iii) absence of documented head injury or neurological disorders, (iv) not being currently enrolled in opioid substitution treatment or taking prescription drugs affecting Central Nervous System (CNS), and (v) minimum abstinence duration of 15 days before testing, although the mean duration of abstinence in the group was 33.10 weeks (SD=12.38, range 12-80 weeks), so that it was possible to rule out alterations related to the acute or

short term effects of the drugs used. Urine analyses for cannabis, benzodiazepines, cocaine, amphetamines, and heroin metabolites were conducted routinely at the treatment setting to confirm abstinence. NDCI were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these comparison participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than ten drinks per week), (ii) absence of documented major psychiatric disorders, (iii) absence of documented head injury or neurological disorder, and (iv) not being on any medication affecting CNS. The mean amount of alcohol use in control participants was 8.85 units/month (SD=20.66) and the mean duration of alcohol consumption was 6.70 years (SD=7.29).

Table 1. Descriptive scores for the socio-demographic characteristics of polysubstance abusers (PSA) and non-drug using comparison individuals (NDCI)

Socio-demographic variables		PSA	NDCI		
		Mean (SD)/frequency	Mean (SD)/frequency	t/χ^2	*p* vaule
Age		31.78 (8.05)	26.40 (8.03)	3.03 [a]	.003
Educational level (%)	Primary	6.2	3.3		
	Secondary	76.9	56.7	6.02 [b]	.05
	Superior	16.9	40		
Gender (%)	Men	84.6	80	.312 [b]	.58
	Women	15.4	20		

[a] Value of *Student's t*

[b] Value of *Chi-square* χ^2

2.2. Instruments

2.2.1. Information on patterns of quantity and duration of drug use

Data regarding lifetime amount and duration of use of the different drugs was self-reported by participants and collected using the Interview for Research on Addictive Behavior (IRAB; Verdejo-García et al., 2005). This interview provides an estimation of: (i) average lifetime monthly use of each substance (quantity per month), and (ii) total duration of use of each substance (duration in years). Descriptive scores for these variables in the present sample are presented in Table 2.

Table 2. Descriptive scores for patterns of quantity and duration of drug use in the group of polysubstance dependent abusers (PSA).

Substances used	Percentage users	Drug use variables	Mean	S.D.
Cannabis	53.1	Quantity (joints/month)	141.90	175.88
		Duration (years)	7.89	7.86
Cocaine	63.5	Quantity (grams/month)	45.95	42.54
		Duration (years)	7.36	5.83
Heroin	24	Quantity (grams/month)	9.60	23.17
		Duration (years)	1.67	3.95
Methadone	7.3	Quantity (mg/month)	112.64	557.47
		Duration (years)	0.17	0.80
Ecstasy	31.2	Quantity (pills/month)	11.76	22.63
		Duration (years)	1.70	3.92
Alcohol	87.5	Quantity (units/moth)	552.21	473.31
		Duration (years)	11.06	7.48
Amphetamines	13.5	Quantity (grams/month)	1.69	5.24
		Duration (years)	0.83	2.06
Benzodiazepines	9.8	Quantity (units/month)	13.07	40.80
		Duration (years)	0.66	2.90

2.2.2. Test of emotion recognition: Ekman Faces Test (EFT)

The Ekman Faces Test (EFT) is a computer task that assesses recognition of facial emotional expressions. The task uses stimuli from the Facial Expressions of Emotion: Stimuli and Tests (FEEST; Young et al., 2002). A series of 60 stimuli featuring faces portraying basic emotions were presented. Faces depicted expressions of anger, disgust, fear, happiness, sadness and surprise (6 emotions, 10 faces each). Photographs were posed by each of 10 models (six female, four male). Each face was presented on a computer monitor for a maximum of 5 s and individuals were asked to select one of the six expression labels (listed above) that best described the emotion expressed. The labels were visible throughout testing, thus minimizing working memory demands, and individuals were given as much time as they required to respond. No feedback was given regarding the appropriateness of their responses. For this study we were especially interested in measures of number of correct identifications for each of the six emotions displayed (discrete emotions recognition scores, ranging 0-10). We also obtained the sum score of total correct identifications (total recognition, ranging 0-60).

2.2.3. Apathy subscale from the Frontal Systems Behavioral Scale (Grace and Malloy, 2001)

The full scale contains 46 items that assess behavioral problems linked to prefrontal systems dysfunction. The instrument is divided in three independent subscales: apathy (linked to anterior cingulate and medial frontal dysfunctions), disinhibition (linked to orbitofrontal dysfunction), and executive dysfunction (linked to dorsolateral prefrontal cortex dysfunction). For this study we only used the scores from the apathy subscale in order to control for possible effects of blunted affect and lack of initiative on emotion recognition. Factor analyses of the FrSBe in several neurological populations have

supported the validity of these subscales (Stout et al., 2003). Furthermore, there is evidence in support of the reliability and utility of the FrSBe subscales in the detection of frontal behavioral symptoms in neuropsychiatric populations such as schizophrenia (Velligan et al., 2002), and substance use disorders (Verdejo-García et al., 2006).

2.3. Procedure

Participants were assessed individually as part of a 3h session aimed to thoroughly examine neuropsychological functioning in PSA. The duration of the EFT was on average approximately 10 minutes. All of the participants in the study were informed about the objectives, benefits, and possible inconveniences associated with the research protocol. Likewise, all the participants signed an informed consent form certifying their voluntary participation. The NDCI participants were paid €18 for their collaboration to ensure motivation; PSA were not compensated due to internal rules of the treatment program.

2.4. Data analysis

The main dependent variables (e.g., discrete emotions recognition) were not normally distributed; therefore, we conducted non-parametric analyses (Mann-Whitney *U* tests) to examine differences between PSA and NDCI on emotion recognition performance.

To address the main aim of the study, we first conducted non-parametric Spearman correlations between measures of quantity and duration of use of the different drugs (cannabis, cocaine, heroin, alcohol, ecstasy, amphetamines and benzodiazepines) and the discrete emotions recognition scores (anger, disgust, fear, happiness, sadness and surprise) in order to select relevant drug use variables to include in multivariate analyses (we selected those variables that were significantly correlated with emotion recognition). We also explored the correlations between other potentially confounding

variables (i.e., sex, age, education, apathy) and the dependent variables. Next, we included the selected drug measures and confounding variables (all variables with significant correlations) as independent variables using Tobit regression models (Tobit. 1958); the dependent variables were the six discrete emotions recognition scales. Therefore, correlation analyses were conducted for exploratory purposes and thus non corrected for multiple comparisons. On the other hand, we used Bonferroni adjustements to correct for multiple comparisons in multivariate Tobit regression models. The Tobit regression technique allowed us to counteract the influence of the non-normal distribution of the dependent variables that exhibited a ceiling effect. With this technique, the maximum score on the discrete emotions recognition scales can be handled as censored data (between 10.5% and 21% of data were right censured observations). Independent variables (quantity and duration of the different drugs) were categorized as dummy variables. Each of the independent variables was categorized into two sets of two variables. In the first set the first variable took a "1" value when participants had used the drug, and a "0" value when they had not used the drug. In the second set the first variable took a "1" value when participants had scores equal to or superior to the mean of the sample (indicating heavy quantity or duration of use), whereas the remaining scores took a "0" value. This approach allowed us to independently examine the influence of any use of each of the drugs, and of heavy (above the mean) use of each of the drugs. These four dummy coded variables were entered as predictors in the regression models conducted for each of the discrete emotion recognition scores and for the total recognition score. We conducted two separate models, one for quantity and one for duration of use of the different drugs. Model coefficients were estimated using maximum-likelihood methods. Variables with

p-values greater 0.05 were then progressively eliminated, in a backward-step process. Nonetheless, because there were significant correlations between the drug use predictor variables to be included in the model we conducted a multicollinearity test using the analysis of variance inflation factors (VIF) for the independent variables. In all the models subsequently reported the predictor variables yielded VIF values lower to 10 (the threshold for detection of multicollinearity); the higher values were obtained in the regression model of duration of drugs used on anger recognition (values ranging 4,46-4,27). Therefore, we can rule out that multicollinearity problems are biasing the results obtained in the regression models.

3. Results

3.1. Comparisons between PSA and NDCI

Table 3 shows comparisons between discrete emotions recognition scores of PSA and NDCI. PSA showed significantly poorer recognition of expressions of anger (U=585; p<0.01), disgust (U=610; p<0.01), fear (U=591; p<0.01), sadness (U=645; p<0.01), and total recognition score (U=403; p<0.01). We found no significant differences for recognition of expressions of happiness and surprise.

Table 3. Comparison between polysubstance abusers (PSA) and non-drug using comparison individuals (NDCI) on emotion recognition performance

Discrete emotions recognition scores	PSA mean (SD)	NDCI mean (SD)	Cohen's *d*
Anger	7.77 (1.69)	8.83 (1.44)	0.66*
Disgust	7.68 (1.70)	8.73 (1.36)	0.66*
Fear	6.37 (2.15)	7.80 (2.06)	0.67*
Happiness	9.86 (0.43)	9.87 (0.43)	0.023
Sadness	7.61 (1.83)	8.60 (1.38)	0.58*
Surprise	8.46 (1.66)	9.17 (1.02)	0.48
Total recognition score	47.75 (4.46)	53.00 (4.61)	1.16*

* Cohen's $d \geq 0.5$ indicating greater than medium effect sizes.

3.2. Correlations

Table 4 shows the correlations between measures of quantity and duration of the drugs used and discrete emotions and total recognition scores. Cocaine was the substance used that showed a greater number of significant correlations with emotion recognition scores. Duration of alcohol and amphetamines use, and measures of quantity and duration of benzodiazepines use failed to show significant correlations with the emotions recognition scores. None of the drugs measures was significantly correlated with recognition of expressions of happiness. Those drug measures that showed significant correlations with the dependent variables were selected and included in subsequent multivariate regression models.

Table 4. . Spearman's correlations between drug use parameters (quantity and duration) and recognition of discrete emotions and total emotion recognition.

	Anger	Disgust	Fear	Happiness	Sadness	Surprise	Total
Cannabis quantity	-0.351**	-0.125	-0.229*	0.059	-0.207	-0.151	-0.341**
Cannabis duration	-0.246*	-0.170	-0.249*	0.099	-0.175	-0.156	-0.334**
Cocaine quantity	-0.319**	-0.224*	-0.268*	0.106	-0.334**	-0.079	-0.389**
Cocaine duration	-0.335**	-0.242*	-0.339**	0.111	-0.301**	-0.125	-0.461**
Heroin quantity	-0.239*	-0.116	-0.269*	0.166	-0.114	-0.189	-0.3**
Heroin duration	-0.229*	-0.123	-0.273*	0.155	-0.106	-0.131	-0.279*
Methadone quantity	-0.197	-0.161	-0.239*	0.093	-0.147	-0.246*	-0.316**
Methadone duration	-0.275*	-0.113	-0.206	0.086	-0.108	-0.186	-0.276*
Ecstasy quantity	-0.195	-0.125	-0.143	0.017	-0.197	-0.152	-0.219*
Ecstasy duration	-0.257*	-0.039	-0.058	-0.089	-0.099	-0.085	-0.123
Alcohol quantity	-0.248*	-0.245*	-0.344**	0.038	-0.211	-0.102	-0.414**
Alcohol duration	0.021	-0.127	-0.081	-0.053	-0.008	-0.084	-0.124
Amph quantity	-0.054	-0.043	-0.222*	-0.039	-0.009	0.009	-0.146
Amph duration	-0.062	-0.035	-0.182	-0.052	-0.031	0.014	-0.125
Bzd quantity	-0.103	0.009	-0.052	0.100	-0.119	-0.054	-0.099
Bzd duration	-0.101	-0.006	-0.056	0.100	-0.121	-0.046	-0.010

Note: Amph, amphetamines, Bzd, benzodiazepines

*p<0.05; **p<0.01

For potentially confounding variables, results showed that sex and age had non-significant correlations with the dependent variables. On the other hand, years of education were significantly associated with recognition scores for anger (r=0.247; p<0.05), disgust (r=0.256; p<0.05), fear (r=0.415; p<0.01), and total emotion recognition (r=0.378; p<0.01) when using the whole sample, and only with recognition scores for fear within the PSA group. In addition, apathy scores were not significantly correlated with the dependent variables when using the whole sample, but they were significantly correlated with recognition scores for fear (r=-0.420; p<0.05), sadness (r=-0.623; p<0.01) and total emotion recognition (r=-0.465; p<0.05) within the PSA group. Therefore, we included years of education and apathy (but not sex or age) on subsequent regression models.

3.3. Tobit regression models

Tables 5 and 6 show the results of Tobit regression models. For quantity measures, regression models showed that quantity of cocaine use significantly predicted poorer recognition of expressions of anger; heavy (above the mean) quantity of alcohol use significantly predicted poorer recognition of expressions of fear although its effect turned non-significant after multiple testing corrections (Table 5). For duration measures, regression models showed that duration of cocaine use significantly predicted poorer recognition of expressions of anger and fear. Apathy scores and duration of ecstasy use were also significant predictors of the recognition of expressions of fear, although they did not survive Bonferroni adjustements for multiple comparisons (Table 6).

The results from the global model using total recognition as the dependent variable indicated that quantity and duration of cocaine use, apathy scores and years of

education were the variables that impacted more significantly negatively on emotion recognition. However, cocaine use parameters were the only significant predictor variables after Bonferroni adjustements for multiple comparisons.

Table 5. Tobit regression models using parameters of quantity of the different drugs used and confounding variables as independent variables and recognition of discrete emotions as dependent variables.

Emotions	Quantity of use	Coef	95% Coef Interval	*p* value
Anger	Cocaine quantity	-1.555	(-2.557, -0.553)	0.003
	Cons	9.324	(8.515, 10.133)	0.000
Fear	Alcohol quantity> Avg	-1.255	(-2.342, -0.167)	0.024
	Years of education	0.277	(0.075, 0.479)	0.08
	Cons	4.493	(2.193, 6.793)	0.000
Sadness	Years of education	0.245	(0.067, 0.422)	0.007
	Cons	5.545	(3.652, 7.439)	0.000
Total	Cocaine quantity	-4.04	(-6.213, -1.864)	0.000
	Years of education	0.484	(0.079, 0.889)	0.020
	Apathy	-0.159	(-0.277, -0.041)	0.009
	Cons	51.356	(44.727, 57.986)	0.000

Note: Avg, average, Coef, coefficients, Cons, constant.

*Significant results after correction for multiple testing, resulting in a significance levels of p=0.05/14=0.0035

Table 6. Tobit regression models using parameters of duration (years) of the different drugs used and confounding variables as independent variables and recognition of discrete emotions as dependent variables.

Emotions	Duration of use	Coef	95% Coef Interval	*p* value
Anger	Cocaine duration	-1.563	(-2.587, -0.539)	0.003
	Cons	9.321	(8.513, 10.129)	0.000
Fear	Cocaine duration	-2.159	(-3.252, -1.066)	0.000
	Ecstasy duration	-2.04	(-0.086, -3.994)	0.041
	Apathy	-0.075	(-0.135, -0.015)	0.015
	Cons	10.169	(8.162, 12.176)	0.000
Sadness	Years of education	0.245	(0.067, 0.422)	0.007
	Cons	5.545	(3.652, 7.439)	0.000
Total	Cocaine duration	-4.841	(-6.874, -2.808)	0.000
	Apathy	-0.160	(-0.280, -0.039)	0.010
	Cons	56.984	(52.997, 60.969)	0.000

Note. Avg, average, Coef, coefficients, Cons, constant.

*Significant results after correction for multiple testing, resulting in a significance levels of p=0.05/14=0.0035

4. Discussion

The principal novel findings from this study are: (i) that mid- to long-term abstinent polysubstance abusers have poorer recognition of facial expressions portraying negative emotions, including anger, disgust, fear and sadness, but not positive or neutral emotions (e.g., happiness and surprise); (ii) that patterns of quantity and duration of use of certain drugs are able to predict emotion recognition performance in polysubstance abusers. Specifically, quantity of cocaine use was associated with poorer recognition of anger, and duration of cocaine use predicted poorer recognition of both anger and fear. Overall, lifetime quantity and duration of cocaine use were the variables that best predicted total emotion recognition.

The results of comparing emotion recognition performance between polysubstance abusers and controls were consistent with previous results showing altered recognition of negative emotions in abusers of different substances, including alcohol (Frigerio et al., 2002; Townshend and Duka, 2003), opiates (Kornreich et al., 2003), cocaine (Kemmis et al., 2007) and polysubstance users with a predominant history of alcohol (Foisy et al., 2005) or psycho-stimulants use (Verdejo-García et al., 2007). With regard to our previous study, which showed that psycho-stimulants polysubstance abusers had prominent deficits in the recognition of fear, these results in a larger sample of similar clinical characteristics extend the range of discrete emotions affected by revealing additional deficits in anger, disgust and sadness recognition. However, our results stand in contrast with recent findings from Woicik et al. (2009), who did not find differences in emotion recognition between cocaine abusers and nondrug comparison individuals. As we show in our regression models, differences

related to lifetime quantity or duration of cocaine and co-abused drugs usage (e.g., alcohol) may account for discrepancies between studies. Furthermore, the main thesis of the Woicik paper (i.e., that recent cocaine use could mask neuropsychological impairment) applies to their results on emotion recognition, since cocaine users with positive urine tests outperformed recently abstinent cocaine users with negative urine screens (75% vs. 59% of hits in the EFT, respectively). Moreover, our study provides additional evidence on the stability of emotion recognition deficits, which are still observable after an abstinence period ranging between 3 and 20 months, extending results from previous studies that described persistent emotion recognition deficits during mid-term abstinence (circa 3 months) in alcoholics (Foisy et al., 2007a). Interestingly, correlation analyses failed to detect a significant association between duration of abstinence and emotion recognition (data not shown), suggesting there is not straightforward improvement of emotion recognition across time of abstinence. This is particularly relevant because emotion recognition deficits are associated with the number of previous detoxifications (a proxy of previous treatment failures) (Townshend and Duka, 2003) and severity of interpersonal problems (Kornreich et al., 2002) in alcoholics, what may similarly apply to other substance use disorders groups. Therefore, emotion recognition deficits may constitute a risk factor for poorer treatment outcome and social readjustment in addiction.

The patterns of quantity and duration of use of the different drugs are able to significantly predict selective alterations in the recognition of discrete emotions, similar to previous findings on cognitive neuropsychological domains (Bolla et al., 1999, 2000, 2002, 2004; Fernández-Serrano et al., 2009; Goldstein et al., 2004; Verdejo-García et

al., 2005). Our results showed that lifetime quantity of cocaine use was negatively associated with recognition of facial expressions of anger. Converging evidence from neuropsychological and neuroimaging studies indicates that anger recognition relies importantly on the functioning of the lateral orbitofrontal cortex and the ventral striatum (Calder et al., 2004; Murphy et al., 2003). Anger recognition is also selectively modulated by dopamine functioning; disruption of the recognition of anger expressions has been observed after acute administration of a D2 receptor antagonist (Lawrence et al., 2002), and during withdrawal from dopamine replacement therapy in Parkinson disease patients (Lawrence et al., 2007). In view of this evidence, it has been proposed that anger recognition is encompassed within a broader neural system mainly involved in incentive motivation and reward pursuit (Lawrence et al., 2007). Accordingly, the neural and pharmacological systems that support anger recognition overlap with the persistent neuroadaptations that characterize psycho-stimulant addiction (Fuchs et al., 2004; Jentsch and Taylor, 1999; Robinson and Berridge, 2003). Furthermore, the association between cocaine use and anger recognition is clinically relevant in light of comparative research showing that the same systems involved in coding discrete emotions are implicated in the experience and behavioral responses related to these emotions (Calder and Young, 2005). Accordingly, a previous study in cocaine abusers found significant associations between self-reported symptoms of anger and decreased lateral orbitofrontal cortex metabolism (Goldstein et al., 2005). Furthermore, both cue and stress-induced craving can specifically increase symptoms of anger and sadness in abstinent cocaine abusers but not social drinkers (Fox et al., 2008).

In addition, duration of cocaine use significantly predicted poorer fear recognition. These results partly replicate our previous finding of defective fear recognition in psycho-stimulant polysubstance users (Verdejo-García et al., 2007), and the results of a previous study showing that regular cocaine use was specifically associated with poorer fear recognition (Kemmis et al., 2007). Nonetheless, it is worth noting that regression models also showed a trend to significant prediction of heavy quantity of use of alcohol and duration of ecstasy use on fear recognition. The ability to recognize fear has been selectively associated with the amygdala, and previous studies have revealed decreased amygdala volumes in both cocaine users (Makris et al., 2004) and alcohol users (Fein et al., 2006); in fact, a recent study showed that decreased amygdala volumes are related to greater subjective craving and higher risk of relapse in alcoholics (Wrase et al., 2008). Moreover, alcoholic individuals have a selectively blunted startle response to negatively but not positively valenced stimuli (Miranda et al., 2003), similar to amygdala lesioned patients (Angrilli et al., 1996), and reflecting insensitivity to threatening stimuli and impaired fear conditioning. Less specific startle reflex alterations have also been observed in abstinent cocaine users (Efferen et al., 2000), but animal studies have demonstrated that cocaine administration can impair amygdala-dependent fear conditioning (Burke et al., 2006; Wood et al., 2007).

It is worth noting that other socio-demographic and affect-related variables were also relevant predictors of both specific and global indices of emotion recognition although neither of them survived multiple testing corrections. More years of education were correlated with better recognition of expressions of sadness and overall better emotion recognition accuracy. Correlation analyses indicated that this pattern was

mainly driven by the scores of the control group, and therefore this effect should be further explored in future research with clinical populations. In addition, apathy scores showed a trend to predict poorer recognition of fear and total emotion recognition. Although regression models showed that only cocaine use parameters were significantly associated with emotion recognition, the non-significant trends suggest that blunted affect and lack of initiative (proposed to relate to anterior cingulate cortex functioning) may also play a role in explaining the poorer ability of PSA to decode and recognize basic emotions in others´ faces. It is also reasonable to expect that other affect-related variables (e.g., depression, irritability or alexythimia) can importantly modulate emotion recognition in substance abusers but we could not test this effect in the present study because we did not included specific measures of these constructs. Nonetheless, the potential contribution of depression could work to increase (but not to decrease) recognition of negative emotions; studies in clinical and high risk depression groups have revealed that these individuals display increased sensitivity to negative emotions measured by behavioral and electrophysiological indices, coupled with increased negative emotion-induced activation of the amygdala (Leppanen, 2006). Similarly, previous studies have failed to detect a significant influence of alexythimia on emotion recognition in substance abusers (Mann et al., 1995) although it has a significant effect on emotion recognition in healthy controls (Lane et al., 2000). The differential and combined contribution of these affect-related variables should be further explored by future studies.

We should note that our study have worth mentioning limitations, including the mixed pattern of polysubstance use that characterized the sample, the fact that we used a

very selective, perhaps not entirely "normal" drug-free comparison group (with absence of drug use and minimal alcohol exposure–less than 9 units per month), and the use of only one index of emotion processing. The first limitation just reflects the typical pattern of use of individuals that demand and enter addiction treatment. Furthermore, we have attempted to address this polysubstance use pattern by means of regression models that targeted the selective influence of different substances while controlling for collinearity effects. A related issue is that some drugs were rather infrequently used (methadone, amphetamine, benzodiazepines) and that subsequently the power of the analyses for the different drugs of abuse might be rather different and, therefore, these differences in frequency might be partly responsible for the differences in significant association between the various drug variables and emotional face recognition variables. Although this issue may have impacted the explanatory power of infrequently used variables it did not seem to affect the main results obtained for relatively frequently used drugs; for example, cannabis was the one of the most ubiquitously used drug but failed to predict emotion recognition, whereas MDMA, comparatively less frequently used, showed a trend to significantly predict fear recognition. With respect to the composition of the control group, our aim was to minimize any effect of drug exposure on emotion recognition in our comparison probands. However, we acknowledge the need to extend these findings by using other clinical comparison groups with mild patterns of alcohol and drug use or with emotion-related alterations (e.g., depression, dysthimia). These other comparison groups could improve our knowledge on the specificity of emotion recognition alterations in clinical groups of PSA. The latter limitation should be addressed in future studies using more comprehensive assessment

of different emotion perception and experience modalities. In this regard, a key unresolved issue is that of if these deficits on emotion recognition have a neat parallel on emotion experience and behavioral symptoms. With regard to emotional experience, previous results from our lab indicate that polysubstance abusers have significant difficulties to experience arousal in response to negatively valenced images (Aguilar de Arcos et al., 2005). For behavioral responses, Lawrence et al. (2007) found that disruption of anger processing in Parkinson disease patients was linked to reduced levels of exploratory excitability, and in accordance, correlation and regression tests in our sample showed that both anger and fear recognition scores were linked to apathy symptoms measured by the Frontal Systems Behavioral Scale.

In spite of the above mentioned limitations these results have both important theoretical and clinical implications. The alterations of emotion perception in polysubstance abusers fit in with the formulations of the somatic marker theory (Verdejo-García and Bechara, 2009), which posits a key role of emotion regulation in addiction. Furthermore, deficits of emotion recognition can be tightly linked to the clinical functioning and risk of relapse of substance abusers. Alterations in the recognition of anger and sadness are related to clinical symptoms of apathy, depression, aggression and hostility, which are enhanced during craving and serve as a proxy of relapse (Dodge et al., 2005). Similarly, alterations of fear processing can impair adequate categorization and recognition of risky scenarios (Redish et al., 2008), one of the main targets of relapse prevention treatment (Marlatt and Gordon, 1985). Moreover, alterations in disgust recognition can strongly bias interpretation of interoceptive signals of anxiety and discomfort (Calder et al., 2001), thus promoting automatic behaviors

aimed to achieve immediate relieve, a mechanism that has been implicated in the everity of obsessive-compulsive disorder (Sprengelmeyer, 2007). Finally, overall defective emotion recognition has been proposed to affect adaptive decision-making (Verdejo-García et al., 2007), a reliable marker of drug relapse (Passetti et al., 2008; Paulus et al., 2005).

Nota: las referencias citadas en este capítulo pueden consultarse en el Anexo IV

IV. DISCUSIÓN GENERAL, CONCLUSIONES Y PERSPECTIVAS FUTURAS

Capítulo 8

Discusión general, conclusiones y perspectivas futuras

1. Discusión general

El objetivo principal de esta tesis consistió en estudiar los efectos neuropsicológicos asociados al consumo y abuso de diferentes drogas para conocer la prevalencia de estos efectos en la población consumidora, su significación clínica y posibles efectos diferenciales entre sustancias. La revisión de la literatura realizada al inicio de nuestra investigación nos permitió comprobar la existencia de deterioros comunes al consumo de diferentes tipos de drogas en diversos procesos neuropsicológicos, concretamente en procesos de memoria episódica, en el componente de actualización de las funciones ejecutivas, en la toma de decisiones y en el procesamiento emocional. Observamos sin embargo que ninguno de los estudios analizados aportaba datos relativos a la prevalencia de los deterioros neuropsicológicos estudiados entre la población consumidora y que ninguna de las metodologías empleadas por estos estudios permitía determinar de forma clara qué efectos son comunes y cuáles son específicos del consumo de las distintas drogas estudiadas. Además observamos la existencia de una proporción notablemente menor de estudios sobre el procesamiento emocional de los sujetos consumidores, y de estudios realizados tras períodos de abstinencia entre media-prolongada, aquellos que realmente nos permiten distinguir entre los efectos del consumo que son reversibles y aquellos que perduran en el tiempo. A partir de estos resultados dirigimos nuestra investigación a una serie de objetivos que pueden resumirse en tres fundamentalmente: (i) conocer la prevalencia de deterioro ejecutivo en sujetos consumidores y las pruebas más adecuadas para su evaluación, (ii) estudiar los efectos diferenciales de distintas drogas de abuso sobre las funciones ejecutivas tras un periodo de abstinencia prolongada y (iii) estudiar el reconocimiento de expresiones

faciales de contenido emocional de consumidores de drogas tras una abstinencia prolongada.

Respecto a la prevalencia de deterioro los resultados obtenidos mostraron que entre los sujetos policonsumidores existía una alta prevalencia de deterioro en las funciones ejecutivas (alrededor del 70 % de los individuos presentaba alteraciones al adoptar un criterio medio), siendo muy similar entre los distintos grupos de consumidores analizados. La memoria de trabajo era el componente con mayor porcentaje de deterioro seguido de la fluidez, la flexibilidad, la planificación, multi-tarea e interferencia.

El estudio de los efectos del consumo de diversas sustancias sobre las funciones ejecutivas reveló la existencia de efectos comunes del uso de alcohol, cannabis y cocaína sobre la toma de decisiones y la fluidez, de la cantidad de cocaína y cannabis sobre la memoria de trabajo y el razonamiento y de la duración del uso de la cocaína y la heroína sobre la flexibilidad. Respecto a los efectos específicos los resultados mostraron la asociación entre la duración del uso de la cocaína y la existencia de alteraciones en procesos de inhibición cognitiva.

Finalmente, el estudio del procesamiento emocional de los sujetos policonsumidores reflejó que estos tenían un pobre reconocimiento de emociones de contenido negativo (tristeza, asco, ira y miedo) al ser comparados con los sujetos no consumidores. Los resultados mostraron que eran los patrones de severidad de consumo de la cocaína los que mejor predecían el reconocimiento emocional de estos sujetos, estando asociada la cantidad de cocaína a un pobre reconocimiento de la ira y la duración del consumo de cocaína a un pobre reconocimiento de la ira y el miedo.

En su conjunto, estos resultados tienen una serie de implicaciones tanto teóricas como clínicas que abordamos a continuación.

1.1. Implicaciones teóricas

Las implicaciones teóricas de nuestros resultados pueden ser abordadas desde dos perspectivas: (i) la contribución que realizan al avance en el estudio de los procesos adictivos y (ii) la relación que guardan con los modelos teóricos que han estudiado el fenómeno de la adicción.

En relación a la aportación que realizan los resultados de nuestros estudios, observamos que realizan una contribución importante entorno al debate relativo a la existencia de efectos neuropsicológicos específicos vs. generalizados consecuencia del consumo de drogas. Los análisis de regresión estadística que utilizamos en nuestra muestra de sujetos policonsumidores nos permitieron estudiar la contribución diferencial de cada una de las sustancias sobre los procesos analizados. Los resultados mostraron la existencia de un importante solapamiento entre las sustancias y los procesos neuropsicológicos. Así observamos efectos comunes del consumo de alcohol, cocaína y cannabis sobre los procesos de toma de decisiones y fluidez, del consumo de cannabis y cocaína sobre procesos de actualización (memoria de trabajo y razonamiento), del consumo de heroína y cocaína sobre procesos de flexibilidad cognitiva, y del consumo de cocaína, alcohol y éxtasis sobre el procesamiento de la emoción de miedo. El solapamiento observado entre los efectos neuropsicológicos de distintas sustancias puede ser explicado por la existencia de mecanismos de acción comunes de distintas drogas sobre un conjunto de sistemas neuroquímicos y estructuras cerebrales que intervienen transversalmente en el desarrollo de cualquier proceso adictivo.

Respecto a los sistemas neuroquímicos, los estudios centrados en los efectos farmacológicos del consumo de drogas indican que los circuitos dopaminérgicos tienen un papel protagonista en el consumo de la mayoría de las drogas. Ya sea directa o indirectamente la dopamina se ve envuelta en el consumo de distintas drogas incluyendo alcohol (Camí & Farré, 2003; Sánchez-Tutret, 1997), psicoestimulantes (Clemens, Cornish, Kong, Kunt & McGregor, 2005; Gruber & Yurgelun-Todd, 2001), cannabis (Camí & Farré, 2003; Markianos & Stefanis, 1982) y opiáceos (Camí & Farré, 2003). Los cuerpos celulares del neurotransmisor dopamina están ubicados en el tronco cerebral, y sus terminales axonales se proyectan sobre múltiples regiones cerebrales, incluyendo regiones límbicas (Verdejo-García & Bechara, 2009) como la amígdala. Esta estructura ha sido asociada de forma consistente con el procesamiento emocional y más concretamente con la habilidad para reconocer el miedo. En consonancia con ello, algunos estudios han revelado alteraciones en esta estructura tanto en consumidores de cocaína (Makris et al., 2004) como en consumidores de alcohol (Fein, Torres, Price & Di Sclafani, 2006). Por otra parte, las proyecciones dopaminérgicas se extienden también hasta regiones corticales (Blessing, 1997), como el cortex orbitofrontal (Volkow et al., 2001 a, b; Wang et al., 2004) habitualmente relacionado con la toma de decisiones (Bechara, Tranel & Damasio, 2000). En relación a esto, distintos estudios han demostrado disminuciones en los niveles de dopamina de regiones prefrontales en consumidores de psicoestimulantes y opiáceos (Verdejo-García & Bechara, 2009). Además del cortex orbitofrontal, distintos estudios de neuroimagen estructural y funcional han demostrado de forma consistente la existencia de alteraciones en el cortex prefrontal dorsolateral en consumidores de distintas sustancias incluyendo alcohol (Dao-Castellana et al., 1998; Ende et al., 2005), cannabis (Eldreth, Matochik, Cadet &

Bolla, 2004), psicoestimulantes (Goldstein et al., 2004; Hester & Garavan, 2004) y opiáceos (Gerra et al., 1998). Esta región cortical está implicada en múltiples procesos ejecutivos que se ven afectados comúnmente en consumidores de distintas sustancias (Fein, Di Sclafani & Meyerhoff, 2002; Goldstein et al., 2004; Pfefferbaum et al., 2001; Yurgelun-Todd et al., 1999) lo que podría explicar el solapamiento entre sustancias y déficits observado en nuestros resultados.

Nuestros datos también reflejaron algunos efectos específicos del consumo. Concretamente observamos efectos específicos del consumo de cocaína sobre procesos de inhibición de respuesta o acción impulsiva y sobre el procesamiento de la emoción de ira y una mayor prevalencia de deterioro en procesos de planificación en consumidores de heroína. Estudios realizados en animales y en humanos indican que el consumo de psicoestimulantes produce una degeneración progresiva en el cerebro. En concreto, distintos estudios muestran que los consumos iniciales de cocaína producen deterioro en el cuerpo estriado ventral, sin embargo, en fases posteriores cuando el consumo se cronifica, el deterioro se extiende al estriado dorsal (Everitt & Robbins, 2005; Porrino, Lyons, Smith, Daunais & Nader, 2004; Volkow et al., 2006). El área ventral del estriado está asociada al procesamiento afectivo-motivacional (Risinger et al., 2005) y al reconocimiento de la emoción de ira (Calder, Keane, Lawrence & Manes, 2004; Murphy, Smith, Cowen, Robbins & Sahakian, 2003). En cambio, el estriado dorsal juega un papel crítico en la supresión de respuestas que son incorrectas o no relevantes, y el efecto de la cocaína sobre esta estructura ha sido asociado alteraciones en procesos de control motor y procesos de inhibición (Aron & Poldrak, 2006; Colzato, van Wildenberg & Hommel, 2007; Hanlon, Wesley & Porrino, 2009). Por otra parte, los estudios de neuroimagen en consumidores de opiáceos indican que el consumo de estas

sustancias se asocia a deterioros en áreas fronto-mediales (Danos et al., 1998; Lyoo et al., 2006; Rose et al., 1996) y en el cortex cingulado (área perigenual) (Galynker et al., 2007) que han sido relacionados con estados disfóricos-apáticos en distintas poblaciones, incluyendo consumidores de opiáceos (Drevets, 2000; Drevets & Raichle, 1998; Galynker et al., 2007) por lo que podría explicar la mayor prevalencia de déficits en planificación en consumidores de opiáceos. En cambio, los estudios realizados en consumidores de psicoestimulantes tienen a detectar alteraciones en la corteza obitofrontal medial-lateral (Goldstein et al., 2007; Volkow et al., 2001 a, b; Volkow et al., 2009), más relacionada con el control inhitorio. En conjunto, estos hallazgos podrían servir de explicación a la especificidad de efectos encontrada en nuestros resultados.

Por otra parte, nuestros datos contribuyen a determinar la influencia de distintos patrones de severidad de consumo de las drogas estudiadas, incluyendo índices de cantidad y duración, sobre el deterioro de los procesos neuropsicológicos. Estos datos reflejan la necesidad de tener en cuenta los patrones de severidad en el estudio de los efectos producidos por el consumo de drogas.

Finalmente, y a diferencia de gran parte de los estudios que encontramos en la literatura, nuestros datos aportan información sobre los efectos del consumo de sustancias tras un período de abstinencia entorno a los 8 meses contribuyendo de este modo a un mayor conocimiento sobre las repercusiones del consumo a largo plazo. Asimismo contribuyen a conocer las repercusiones del consumo de drogas sobre el procesamiento emocional, un dominio neuropsicológico que cada vez comienza a adquirir mayor importancia para la comprensión de los procesos adictivos pero que ha sido poco abordado en los estudios sobre los efectos del consumo de drogas.

Por otra parte nuestros resultados se encuentran claramente relacionados con los modelos teóricos que explican el proceso adictivo que mostrábamos al inicio de nuestro trabajo. Respecto a las alteraciones encontradas en las funciones ejecutivas nuestros resultados indican que el consumo de drogas, específicamente el consumo de cocaína, altera los mecanismos de inhibición de respuesta de los individuos consumidores a pesar de presentar una abstinencia prolongada. Además, la severidad del consumo se relacionaba con los déficits encontrados en estos sujetos. Estos hallazgos se encuentran en clara conexión con el modelo I-RISA de Goldstein & Volkow (2002) que conciben la adicción como un proceso de carácter crónico caracterizado por la alteración en un sistema motivacional y otro de inhibición de las respuestas que resultan inadecuadas para las demandas del organismo. Nuestros resultados también indican la existencia de alteraciones en la toma de decisiones en los consumidores de drogas. Este resultado puede ser explicado desde los tres modelos teóricos expuestos. Así, tomando como base el modelo I-RISA estas alteraciones en la toma de decisiones podrían ser explicadas como el resultado del sesgo producido por la hiperactivación de los sistemas que señalan la necesidad de las drogas y la inoperancia de los sistemas que se encargan de inhibir las conductas desadaptativas. El modelo del marcador somático (Verdejo-García & Bechara, 2009) explicaría estas alteraciones en la toma de decisiones como resultado de una disfunción en los sistemas neurobiológicos encargados de generar y dar una adecuada lectura a las señales emocionales o marcadores somáticos que indican las consecuencias de las distintas opciones de elección. El modelo de vulnerabilidades propuesto por Redish et al. (2008) explica las alteraciones en la toma de decisiones como resultado de la influencia de distintas fuentes de vulnerabilidad que provocan la desestabilización de los sistemas de planificación, hábitos y observación-categorización.

Nuestros resultados reflejaban la existencia de una elevada prevalencia de deterioro en los procesos de planificación que podrían explicar los déficits en la toma de decisiones observados en los sujetos consumidores.

De la misma manera estos modelos teóricos permiten explicar las alteraciones encontradas en el procesamiento emocional de los sujetos consumidores. Como mencionamos anteriormente el modelo I-RISA explica la adicción a partir de las alteraciones en un sistema de inhibición de respuestas pero también en un sistema de atribución de relevancia encargado de evaluar la relevancia motivacional-afectiva de los reforzadores. El modelo explica que el fallo en este sistema motivacional conllevaría una valoración exagerada de las propiedades reforzantes de las drogas, y a su vez, una devaluación del valor motivacional de otros reforzadores naturales (p.e., relaciones sociales, sexo, comida). Los déficits en el reconocimiento emocional encontrados en los sujetos consumidores podrían ser el resultado de un fallo en este sistema motivacional-afectivo que se vería reflejado en la incapacidad de estos sujetos para reconocer las emociones expresadas por otras personas a través de sus rostros. Las alteraciones encontradas en la percepción emocional encuentran asimismo su explicación en las formulaciones del modelo del marcador somático que señala la regulación emocional como la clave en el proceso adictivo. Finalmente estas alteraciones emocionales también pueden ser explicadas desde los postulados del modelo de vulnerabilidades. En la misma línea que el modelo I-RISA, Redish et al. proponen que una de las vulnerabilidades que pueden desestabilizar los sistemas de los que depende la toma de decisiones son las potentes señales euforizantes de recompensa asociadas al uso de drogas que dejarían en un segundo plano las generadas por estímulos naturales (p.e. las relaciones sociales). Esta vulnerabilidad podría explicar por qué los individuos

consumidores de nuestra muestra tenían dificultades en la detección de emociones de otros individuos. No obstante otra de las vulnerabilidades propuestas por estos autores eran las desviaciones de la alostasis relacionadas con la alteración del equilibrio hedónico de los sujetos consumidores. Nuestros datos también reflejaron que la apatía de los sujetos consumidores tendía a predecir el reconocimiento emocional de estos sujetos, por lo que nuevas investigaciones que permitan controlar esta variable podrían ser de utilidad para una mejor explicación de estos resultados.

1.2. Implicaciones clínicas

Las implicaciones clínicas de nuestros resultados pueden ser abordadas desde dos perspectivas: (i) la contribución que realizan al proceso de evaluación neuropsicológica, y (ii) las aportaciones que realizan a la mejora de la rehabilitación de los sujetos consumidores de drogas.

Los resultados de nuestros trabajos contribuyen a mejorar el proceso de evaluación neuropsicólogica indicando las tareas que resultan más recomendables para la evaluación de las funciones ejecutivas en sujetos consumidores de drogas. Los resultados mostraron que las tareas más adecuadas eran la tarea de Aritmética para la evaluación de la memoria de trabajo, las tareas FAS y RFFT para la evaluación de la fluidez verbal y figurativa, la tarea de Categorías para la evaluación de la flexibilidad cognitiva, la tarea de Stroop para la evaluación de la inhibición, la del Mapa de Zoo para la evaluación de los procesos de planificación, y la tarea de los Seis Elementos para la evaluación de multi-tarea. Estas tareas podrían formar parte de una batería breve para la evaluación de las funciones ejecutivas que podría resultar de enorme utilidad para clínicos e investigadores que trabajan en el campo de las drogodependencias.

La influencia diferencial de los parámetros de severidad de consumo sobre los distintos procesos neuropsicológicos indica la necesidad de tener muy en cuenta esta información en la evaluación neuropsicológica del sujeto consumidor. En este sentido sería oportuno hacer una exploración exhaustiva de parámetros como la cantidad habitual de consumo, la duración del mismo, las cantidades máximas consumidas, la continuidad del proceso (p.e., si ha habido períodos sin consumo, la duración de los mismos, etc.), el tiempo de abstinencia para cada sustancia, etc. Asimismo algunas investigaciones han mostrado que las personas que inician el consumo de drogas en periodos madurativos (cuando el SNC se encuentra aun en fase de desarrollo) pueden sufrir efectos más acusados como consecuencia del consumo de drogas en esta fase del desarrollo (Chambers, Taylor & Potenza, 2003; Jacobus, Bava, Cohen-Zion, Mahmood & Tapert, 2009; Schweinsburg et al., 2008), por lo que también sería interesante explorar el consumo de drogas existente en estos períodos madurativos.

Por otra parte, la elevada prevalencia de deterioro ejecutivo que muestran nuestros datos en los sujetos policonsumidores en proceso de rehabilitación indica la necesidad de que los centros terapéuticos tengan en cuenta estos procesos en la evaluación previa al inicio de tratamiento que realizan con estos sujetos. Los centros de rehabilitación suelen llevar a cabo una exhaustiva evaluación de los sujetos consumidores a su llegada al centro, incluyendo una evaluación psicopatológica del individuo y médica que será de utilidad para determinar los objetivos terapéuticos a seguir con cada paciente. Nuestros datos indican que también sería necesario incluir en este proceso de evaluación medidas sobre procesos neuropsicológicos que con frecuencia suelen verse afectados en los sujetos consumidores. Esta evaluación

neuropsicológica contribuirá a una mayor especificidad en los objetivos a tratar con cada paciente.

Finalmente los resultados que hemos obtenido también pueden hacer una contribución muy significativa al proceso de rehabilitación de los individuos consumidores de drogas. Nuestros datos proceden de sujetos consumidores en proceso de rehabilitación a través de comunidades terapéuticas con una media de permanencia en el programa de 8 meses de duración. A pesar de ello, los resultados reflejaron la existencia de alteraciones en múltiples procesos tanto de funciones ejecutivas como de tipo emocional. Los programas de rehabilitación utilizados en población drogodependiente requieren por lo general un buen funcionamiento de un amplio rango de procesos neuropsicológicos: del componente de actualización (memoria de trabajo, razonamiento, fluidez) y flexibilidad cognitiva, a fin de poder retener instrucciones complejas, seleccionar información relevante de las sesiones clínicas o generalizar lo aprendido a otros contextos; de inhibición, para poder controlar el patrón de respuestas reforzado previamente, como era el del consumo, por otro que le asegure su permanencia en el programa; de planificación y toma de decisiones, a fin de poder iniciar y elegir nuevas actividades que ayuden a su rehabilitación; y del reconocimiento de sus propias emociones y las de otros a fin de garantizar su ajuste social en el programa. Esta importante implicación de los procesos neuropsicológicos en los programas de rehabilitación indica la necesidad de que todos estos procesos sean trabajados en estos programas de tratamiento dirigidos a los sujetos consumidores. Asimismo, el hecho de que los déficits observados en nuestro estudio procedan de una muestra de sujetos consumidores que se encontraban en una fase avanzada del tratamiento (una media de 8 meses) subraya la necesidad de tener en cuenta y abordar

estos procesos neuropsicológicos desde el mismo inicio del tratamiento a fin de garantizar la obtención del máximo beneficio posible del programa de rehabilitación. Este abordaje podría hacerse a través de la adaptación de las terapias tradicionales a partir de los déficits de los usuarios, e incluso mediante la introducción de nuevos módulos en los programas que trabajen la rehabilitación de estos procesos.

Una forma de adaptar las terapias tradicionales teniendo en cuenta los déficits en mecanismos de actualización, por ejemplo en memoria de trabajo y razonamiento, podría consistir en hacer las sesiones terapéuticas más breves y frecuentes, o presentar el material dentro de las sesiones de una forma multimodal, esto es, empleando distintos materiales y formas de exposición, y procurar la obtención de feedback de parte del paciente (Aharonovich et al., 2006). Asimismo los déficits encontrados en mecanismos de flexibilidad podrían ser abordados adaptando los programas de rehabilitación para que sean más realistas y personalizados permitiendo de este modo incrementar la capacidad para generalizar o flexibilizar los aprendizajes a otros contextos.

También podrían trabajarse directamente algunos de estos déficits mediante la inclusión de nuevos módulos o formas de terapia. Por ejemplo una forma de mejorar los déficits que presentan estos sujetos en el control inhibitorio y la toma de decisiones podría consistir en la introducción de módulos que enseñen a estos sujetos distintas habilidades de afrontamiento y solución de problemas (Secades-Villa, García Rodríguez, Fernández Hermida & Carballo, 2007). Las alteraciones encontradas en el reconocimiento emocional podrían trabajarse por ejemplo a través de la inclusión de actividades que fomenten la percepción emocional ante distintos tipos de estímulos, así como la experiencia de distintos tipos de emociones. El empleo de las nuevas terapias denominadas de tercera generación que enfatizan elementos como la aceptación, la

conciencia plena, la desactivación cognitiva, la dialéctica, los valores, la espiritualidad y las relaciones (Hayes, 2004) también podría resultar de utilidad para abordar algunos de estos procesos neuropsicológicos. Una de estas terapias es la terapia cognitiva basada en la técnica de Mindfulness. Esta técnica enseña al individuo a prestar atención de forma deliberada al momento actual, procurando no juzgar, a aceptar el estado en que se encuentra tal y como es y a mirar a las emociones de cara aunque sean desagradables, en vez de intentar evitarlas o controlarlas (Appel & Kim-Appel, 2009). Los defensores de esta técnica proponen que la práctica de estas habilidades permite al individuo escoger con destreza aquellas respuestas/elecciones que realmente le resulten beneficiosas en lugar de aquellas que elegiría de forma automática e inconsciente (Teasdale et al., 2000). De este modo, la aplicación de esta técnica en los sujetos consumidores podría ayudarles a mejorar los déficits que presentan para inhibir la respuesta automática de consumo y la toma de decisiones inadecuada contribuyendo de este modo a una mejor rehabilitación. Recientes investigaciones han mostrado los beneficios de esta técnica en población consumidora de distintas sustancias (Bowen et al., 2006; Bowen, Witkiewitz, Dillworth & Marlatt, 2007; Davis, J.M., Fleming, Bonus & Baker, 2007; Hoppes, 2006; Marlatt, 2002; Marlatt et al., 2004; Zgierska et al., 2008) e incluso un reciente estudio piloto ha mostrado la superioridad de esta técnica con respecto a las tradicionales técnicas cognitivas-conductuales para el control de la activación psicológica y fisiológica de los sujetos consumidores en situaciones estresantes (Brewer et al., 2009).

Más investigaciones en el estudio neuropsicológico de la adicción podrán contribuir a la mejora de este tipo de intervenciones e incluso al desarrollo de nuevas y mejores técnicas de intervención.

2. Conclusiones

A partir de los resultados obtenidos, de esta tesis se derivan las siguientes conclusiones:

1. Existe una alta prevalencia de deterioro neuropsicológico (entre 35 y 70 %) en sujetos policonsumidores en situación de abstinencia que se encuentran recibiendo tratamiento en comunidades terapéuticas. El proceso cognitivo con mayor prevalencia de deterioro entre los sujetos policonsumidores es el de memoria de trabajo, seguido de los procesos de fluidez, flexibilidad cognitiva, planificación, multi-tarea e interferencia. Existen tasas de prevalencia de deterioro ejecutivo muy similares entre distintos grupos de consumidores. Entre los sujetos con consumo preferente de cocaína la tasa de prevalencia de deterioro más elevada se observa en los procesos de flexibilidad cognitiva, mientras que en aquellos que tenían un consumo preferente de heroína se observa en los procesos de planificación.
2. Entre las pruebas de evaluación estudiadas, las más recomendables para la evaluación de las funciones ejecutivas en sujetos consumidores de drogas son: Aritmética (para la evaluación de la memoria de trabajo), FAS y RFFT (para evaluación de fluidez), Categorías (para flexibilidad cognitiva), Stroop (para interferencia), Mapa del Zoo (para planificación) y Seis elementos (para multi-tarea).
3. Los individuos policonsumidores de drogas en situación de abstinencia prolongada presentan alteraciones significativas en procesos de fluidez, razonamiento, memoria de trabajo, inhibición, flexibilidad y toma de decisiones.
4. El consumo de alcohol, cannabis y cocaína produce efectos comunes sobre procesos de fluidez verbal y toma de decisiones, la cantidad de cannabis y

cocaína sobre procesos de memoria de trabajo y razonamiento, y la duración del consumo de cocaína y heroína sobre procesos de flexibilidad cognitiva. La duración del consumo de cocaína produce efectos específicos sobre procesos de inhibición cognitiva.

5. Los sujetos policonsumidores de drogas tienen un pobre reconocimiento de las expresiones faciales que reflejan emociones negativas (miedo, asco, ira y tristeza) tras períodos de abstinencia prolongados.
6. Los patrones de severidad de consumo de cocaína son aquellos que mejor predicen el reconocimiento emocional. La cantidad de cocaína y alcohol y la duración del uso de cocaína y éxtasis producen efectos comunes sobre el reconocimiento de la emoción de miedo. La cantidad y duración del uso de cocaína producen efectos específicos sobre el reconocimiento de la emoción de ira.

3. Perspectivas futuras

Algunas de las perspectivas de investigación futura derivadas de esta tesis son las siguientes:

1. Examinar la dirección de causalidad de las alteraciones sobre funcionamiento ejecutivo y emocional observadas en los sujetos policonsumidores. Para ello podría recurrirse a estudios longitudinales en población con alto de riesgo de iniciarse en el consumo (p.e. adolescentes, niños y adolescentes con problemas de conducta, etc.). Podría explorarse la relación entre mecanismos de vulnerabilidad genética y alteraciones neuropsicológicas en individuos drogodependientes.

2. Examinar la modulación ejercida por los estados emocionales sobre los procesos de toma de decisiones. Sería recomendable el empleo de medidas psicofisiológicas que permitan examinar los mecanismos emocionales (marcadores somáticos) implicados en los procesos de toma de decisiones.
3. Estudiar las consecuencias de los deterioros emocionales y en las funciones ejecutivas sobre el funcionamiento clínico de los sujetos policonsumidores.
4. Estudiar las áreas cerebrales implicadas en el funcionamiento de los procesos ejecutivos y emocionales en los sujetos policonsumidores. Para ello sería recomendable el empleo de técnicas de neuroimagen estructural (como el tensor de difusión) y funcional (tomografía por emisión de positrones-PET, o resonancia magnética funcional-fMRI). En particular, sería interesante investigar mediante paradigmas de neuroimagen funcional en condiciones de activación (fMRI) la interacción de los mecanismos de modulación emocional y de toma de decisiones.

Summary, conclusions and future perspectives

1. Summary

This thesis consists of eight chapters that are grouped in four main sections: (i) Introduction, (ii) Rationale and Aims, (iii) Published empirical studies, and, (iv) General Discussion, Conclusions and Future Perspectives.

The Introduction section consists of two chapters. In Chapter 1 we show the most important neuroscientific models that have been proposed to explain the addiction phenomenon and which justified the neuropsychological approach to it. In Chapter 2 we describe the neuropsychological assessment process in drug users and we show which are the most important neuropsychological domains studied in the field and the most frequent tasks used to measure them.

The second section consists of Chapter 3 in which we provide the rationale supporting this work, its main objective and the specific aims and hypothesis.

The third section consists of four chapters that included four studies: one review study, and three empirical studies. Chapter 4 is a systematic and quantitative review of those studies published during the last decade (between 1999 and 2009/2010) about the neuropsychological effects of drug use and abuse. Overall, the reviewed studies showed that users of different drugs have generalized effects on episodic memory, the updating component of executive functions, decision making and emotional processing. They also showed that alcohol and psychostimulants use seem to be particularly associated with deficits in impulsive action and cognitive flexibility; alcohol and MDMA use with perceptual speed, spatial processing and selective attention declines; cannabis and methamphetamine with prospective memory deficits; and cannabis and MDMA with alterations in processing speed and complex planning.

Chapter 5 consists of an empirical study in which we estimated the prevalence of neuropsychological impairment in different components of executive functions in polysubstance users enrolled in therapeutic communities. Moreover, we estimated the effect size of executive performance differences between polysubstance users and non substance users in order to know which neuropsychological tasks can be more discriminative to detect alterations in the executive functions in addicted populations. Study results showed a high prevalence of executive functions impairment in polysubstance users. The tests that better discriminated between drug users and controls were: Arithmetic (Wechsler Adult Intelligence Scale, WAIS-III) for working memory, FAS and Ruff Figural Fluency Test for fluency, Category Test for reasoning/flexibility, Stroop Colour-Word Interference Test for inhibition, Zoo Map (Behavioural Assessment of the Dysexecutive Syndrome, BADS) for planning, and Six Elements (BADS) for multi-tasking.

Chapter 6 consists of an empirical study about the specific and common neuropsychological effects caused by the use of cannabis, cocaine, heroin and alcohol on different tasks of executive functions. Moreover, it examines the association between the severity of consumption of different drugs –including quantity and duration patterns and the competence of executive functions. Results showed that the abuse of alcohol is associated with specific effects in fluency and decision making, whereas cannabis, cocaine and heroin are associated with both specific and generalized effects in different components of executive functions. Specifically results showed: (i) common correlates of the use of alcohol, cannabis and cocaine on verbal fluency and decision-making; (ii) common correlates of quantity of cannabis and cocaine use on verbal working memory

and analogical reasoning; (iii) common correlates of duration of cocaine and heroin use on shifting; and (iv) specific effects of duration of cocaine use on inhibition measures.

Chapter 7 consists of a study on the association between the use of different drugs and emotional processing, specifically with the ability to recognize basic emotions (happiness, sadness, surprise, fear, disgust and anger) in the faces of others. Also, we study the association between patters of severity (quantity and duration) of use of several drugs and the ability to identify facial expressions portraying particular emotions. Overall, results showed that drug users had poorer recognitions than non-users for facial expressions of anger, disgust, fear and sadness. More specifically, severity of cocaine use significantly predicted overall recognition accuracy. Quantity of cocaine use predicted poorer anger recognition, and duration of cocaine use predicted both poorer anger and fear recognition.

The fourth and last section consists of Chapter 8 in which we discuss the results obtained through the four studies highlighting the most important theoretical and clinical implications of these results. Moreover we have included the main conclusions and future perspectives which can be derived from our results.

2. Conclusions

Based on the results obtained, from this thesis, the following conclusions are reached:

1. There is a high prevalence of neuropsychological impairment (between 35 and 70%) in abstinent polysubstance users enrolled in therapeutic communities. Working memory was the component with the highest prevalence of impairment, followed by fluency, shifting, planning, multi-tasking and interference. Users of different drugs have very similar prevalence indices of

executive impairment. Cocaine users have a higher prevalence of impairment in shifting, while heroin users have a higher prevalence in planning processes.

2. Among the tasks used, the best tasks for the executive functions assessment of drug users are: Arithmetic (for working memory assessment), FAS and RFFT (for fluency), Category Test (for reasoning/flexibility), Stroop (for inhibition), Zoo Map (for planning) and Six Elements (for multi-tasking).
3. Polysubstance users with long-term abstinence have significant impairments in fluency, reasoning, working memory, inhibition, shifting and decision-making processes.
4. The use of alcohol, cannabis and cocaine produce common effects on verbal fluency and decision-making. The quantity of cannabis and cocaine use produce common effects on working memory and reasoning. Duration of cocaine and heroin use produce common effects on shifting. Duration of cocaine use produce specific effects on cognitive inhibition processes.
5. Polysubstance users have poorer recognition of facial expressions of negative emotions (fear, disgust, anger and sadness) even after protracted abstinence.
6. Patterns of severity of cocaine use predict overall emotional recognition accuracy. Quantity of cocaine and alcohol use and duration of cocaine and ecstasy use produce common effects on fear recognition. Quantity and duration of cocaine use produce specific effects on anger recognition.

3. Future perspectives

From the results obtained, important perspectives for future research can be derived, which we describe below:

1. To examine the direction of causality of the executive and emotional deficits of polysubstance dependent individuals. One possible approach to this issue is to perform longitudinal studies able to examine possible executive alterations in populations at high risk of initiating drug use (for example: adolescents, children and adolescents with conduct disorder, etc.). Another possible approach is to explore the relationship between mechanisms of genetic vulnerability and neuropsychological alterations in substance dependent individuals.
2. To study the modulation produced by different affective states on the decision-making processes. It would be interesting to use psychophysiological measures that could examine the emotional mechanisms (somatic markers) that are proposed to be involved in the abnormal decision-making processes of substance abusers.
3. To study the specific impact of executive functions and emotional processing impairments on different indices of clinical functioning.
4. To examine the specific brain systems that involved in the abnormal functioning of executive and emotional processes in addiction. To address this objective, it would be interesting to use novel structural neuroimaging techniques (for example Diffusion Tensor Imaging) and fuctional techniques (for example Positron Emission Tomography-PET, Fuctional Magnetic Resonance Imaging-fMRI). In particular, it would be interesting to study the interaction between mechanisms of emotional modulation and decision-making processes by using paradigms of fuctional neuroimaging in conditions of activation.

Referencias

Abi-Saab, D., Beauvais, J., Mehm, J., Brody, M., Gottschalk, C. & Kosten, T.R. (2005). The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. *The American Journal on Addictions 14*, 166-178

Adams, K.M., Brown, G.G. & Grant, I. (1985). Analysis of covariance as a remedy for demographic mismatch of research subject groups: some sobering simulations. *Journal of clinical and experimental neuropsychology, 7,* 445-462

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion in Neurobiology, 12*, 169-177.

Aguilar de Arcos, F., Pérez-García, M., & Sánchez-Barrera, M. B. (2003). Evaluación emocional en drogodependientes. Junta de Andalucía. Conserjería de asuntos sociales. Comisionado para las drogodependencias.

Aguilar de Arcos, F., Verdejo-García, A., Ceverino, A., Montañez-Pareja, M., López-Juárez, E., Sánchez-Barrera, M., López-Jiménez, A. & Pérez-García, M. (2008). Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. *Psychopharmacology, 198,* 159, 166.

Aguilar de Arcos, F., Verdejo-García, A., Peralta-Ramírez, M.I., Sánchez-Barrera, M., & Pérez-García, M. (2005). Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. *Drug and Alcohol Dependence, 78,* 159-167.

Aharonovich, E., Brooks, A.C., Nunes, E.V. & Hasin, D.S. (2008) Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioral therapy treatment outcome. *Drug and Alcohol Dependence, 95,* 279-283.

Aharonovich, E., Hasin, D.S., Brooks, A.C., Liu, X., Bisaga, A., & Nunes, E.V. (2006) Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug and Alcohol Dependence*, *81*, 313-322

Aharonovich, E., Nunes, E., & Hasin, D. (2003) Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug and Alcohol Dependence, 71*, 207-211.

Andrews, P. (1997). Cocaethylene toxicity. *Journal of Addictive Diseases, 16*, 75-84.

Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G. & di Paola, F. (1996). Startle reflex and emotion modulation impairment after a right amygdala lesion. *Brain: a journal of neurology, 119*, 1991-2000.

Appel, J. & Kim-Appel, D. (2009) Mindfulness: implications for substance abuse and addiction. *International Journal of Mental Health and Addiction, 7*, 506-512

Aron, A.R., Fletcher, P.C., Bullmore, E.T., Sahakian, B.J. & Robbins, T.W. (2003) Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience, 6,* 115-116.

Aron, A.R. & Poldrack, R.A. (2006). Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *Journal of Neuroscience, 26,* 2424-2433.

Beatty, W.W. & Borrel, G.K. (2000). Forms of knowledge, cognitive impairment and drug abuse: a demonstration. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 24,* 17-22.

Beatty, W.W., Tivis, R., Stott, H.D., Nixon, S.J. & Parsons, O.A. (2000). Neuropsychological deficits in sober alcoholics: influences of chronicity and

recent alcohol consumption. *Alcoholism, Clinical and Experimental Research, 24,* 149-154.

Bechara, A. (2005) Decision-making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nature Neuroscience, 8,* 1458-1463.

Bechara, A., Damasio, H. & Damasio, A.R. (2000) Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex, 10,* 295-307.

Bechara, A., Damasio, A.R., Damasio, H., & Anderson, S.W. (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50,* 7-15

Bechara, A., Damasio, H., Tranel, D. & Damasio, A.R. (2005) The Iowa Gambling Task and the somatic marker hypothesis: Some questions and answers. *Trends in Cognitive Sciences, 9*, 159-162.

Bechara, A., Dolan S., Denburg, N., Hindes, A., Anderson, S.W. & Nathan, E. (2001) Decision-making deficits linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. *Neuropsychologia, 39,* 376-389.

Bechara, A., Tranel, D., & Damasio, H. (2000). Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain, 123,* 2189-2202.

Belin, D., Mar, A.C., Dalley, J.W., Robbins, T.W. & Everitt, B.J. (2008) High impulsivity predicts the switch to compulsive cocaine taking. *Science 320*, 1352-1355.

Benedet, M.J., & Alejandre, M.A. (1998) TAVEC: test de aprendizaje verbal España-Complutense, *TEA Ediciones*.

Bernstein, J., Bernstein, E., Shepard, D.S., Valentine, A., Heeren, T., Winter, M., Levenson, S., Beaston-Blaakman, A., Tassiopoulos, K. & Hingson, R. (2006).

Racial and ethnic differences in health and health care: lessons from an inner-city patient population actively using heroin and cocaine. *Journal of Ethnicity in Substance Abuse, 5,* 35-50.

Beveridge, T.J.R., Gill, K.E., Hanlon, C.A. & Porrino, L.J. (2008) Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 363,* 3257-3266.

Bhattachary, S. & Powell, J. H. (2001). Recreational use of 3-4-methyledioxymethanphetamine (MDMA) or "ecstasy": evidence for cognitive impairment. *Psychological Medicine, 31,* 647-658.

Bjork, J.M., Hommer, D.W., Grant, S.J. & Danube, C. (2004). Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. *Alcohol, 34,* 133-150.

Blair, R.J. (2003). Facial expressions, their communicatory functions and neuro-cognitive substrates. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 358,* 561-572.

Blessing, W.W. (1997). Anatomy of the lower brainstem. In: *The Lower Brainstem and Bodily Homeostasis.* New York: Oxford University Press.

Bolla, K.I., Brown, K., Eldreth, B.A., Tate, K., Cadet, B.A. & Cadet, J.L. (2002) Dose-related neurocognitive effects of marijuana use. *Neurology, 59*, 1337-1343.

Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouraditis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Fundeburk, F.R., & Ernst, M. (2003) Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *Neuroimage, 19*, 1085-1094.

Bolla, K.I., Eldreth, D.A., Matochik, J.A. & Cadet, J.L. (2005) Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage*, *26,* 480- 492.

Bolla, K.I., Ernst, M., Kiehl, K., Mouratidis, M., Eldreth, D., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J-L., Kimes, A., Fundeburk, F., & London, E. (2004) Prefrontal cortical dysfunction in abstinent cocaine abusers. *The Journal of Neuropsychiatry and Clinical Neurosciences 16,* 456-464.

Bolla, K.I., Funderburk, F.R. & Cadet, J. (2000) Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology*, *54*, 2285-2292

Bolla, K.I., McCann, U.D., & Ricaurte, G.A. (1998). Memory impairment in abstinent MDMA (‘‘ecstasy’’) users. *Neurology, 51,* 1532-1537.

Bolla, K.I., Rothman, R. & Cadet, J.L. (1999). Dose-related neurobehavioral effects of chronic cocaine use. *The Journal of Neuropsychiatry and Clinical Neurosciences, 11,* 361-369.

Bondi, M.W., Drake, A.I., & Grant, I. (1998). Verbal learning and memory in alcohol abusers and polysubstance abusers with concurrent alcohol abuse. *Journal of the International Neuropsychological Society, 4,* 319-328.

Bowden-Jones, H., McPhillips, M., Rogers, R., Hutton, S. & Joyce, E. (2005). Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*, 417-420.

Bowen, S., Witkiewitz, K., Dillworth, T.M. & Marlatt, G.A. (2007) The role of thought suppression in the relationship between mindfulness meditation and alcohol use. *Addictive Behaviors, 32,* 2324-2328.

Bowen, S., Witkiewitz, K., Dillworth, T.M., Chawla, N., Simpson, T.L., Ostafin, B.D., Larimer, M.E., Blume, A.W., Parks, G.A. & Marlatt, G.A. (2006) Mindfulness meditation and substance use in an incarcerated population. *Psychology and Addictive Behaviors, 20,* 343-347

Brand, M., Labudda, K., & Markowitsch, H.J. (2006). Neuropsychological correlates of decision-making in ambiguous and risky situations. *Neural Networks, 19*, 1266-1276.

Brand, M., Roth-Bauer, M., Driessen, M. & Markowitsch, H.J. (2008) Executive functions and risky decision-making in patients with opiate dependence. *Drug and Alcohol Dependence, 7,* 64-72

Brewer, J.A., Sinha, R., Chen, J.A., Michalsen, R.N., Babuscio, T.A., Nich, C., Grier, A., Bergquist, K.L., Reis, D.L., Potenza, M.N., Carroll, K.M. & Rounsaville, B.J. (2009) Mindfulness training and stress reactivity in substance abuse: results from a randomized, controlled stage I pilot study. *Substance Abuse, 30,* 306-317

Burke, K.A., Franz, T.M., Gugsa, N. & Schoenbaum, G. (2006). Prior cocaine exposure disrupts extinction of fear conditioning. *Learning & Memory, 13,* 416-421.

Burns, H.D., Van, L.K., Sanabria-Bohorquez, S., Hamill, T.G., Bormans, G., Eng, W.S., Gibson, R., Ryan, C., Connolly, B., Patel, S., Krause, S., Vanko, A., Van, H.A., Dupont, P., De I, L., Rothenberg, P., Stoch, S.A., Cote, J., Hagmann,W.K., Jewell, J.P., Lin, L.S., Liu, P., Goulet, M.T., Gottesdiener, K., Wagner, J.A., de, H.J., Mortelmans, L., Fong, T.M. & Hargreaves, R.J. (2007). [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. *Proceedings of the National Academy of Sciences of the United States of America, 104,* 9800, 9805.

Busemeyer, J.R., & Stout, J.C. (2002) A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychological Assessment, 14*, 253-262

Butler, G.K. & Montgomery, A.M. (2004). Impulsivity, risk taking and recreational "ecstasy" (MDMA) use. *Drug and Alcohol Dependence, 76*, 55, 62.

Cairns, E. D., & Cammock, J. (2002) Test de emparejamiento de figuras conocidas: MFF-20. *TEA Ediciones*, Madrid.

Calder, A.J. & Young, A.W. (2005). Understanding the recognition of facial identity and facial expression. *Nature Reviews. Neuroscience, 6,* 641-651.

Calder, A.J., Keane, J., Lawrence, A.D. & Manes, F. (2004). Impaired recognition of anger following damage to the ventral striatum. *Brain, 127,* 1958-1969.

Calder, A.J., Lawrence, A.D. & Young, A.W. (2001). Neuropsychology of fear and loathing. *Nature Reviews. Neuroscience, 2,* 352-363.

Camí, J. & Farré, M. (2003). Drug addiction. *The New England Journal of Medicine*, *349,* 975-986.

Carbotte, R.M., Denburg, S.D. & Denburg, J.A. (1986). Prevalence of cognitive impairment in systemic lupus erythematosus. *The Journal of Nervous and Mental Disease, 174,* 357-364.

Carroll, K., Ziedonis, D., O'Malley, S., McCance-Katz, E., Gordon, L. & Rounsaville, A. (1993). Pharmacologic Interventions for Alcohol- and Cocaine-Abusing Individuals: A Pilot Study of Disulfiram vs. Naltrexone. *The American Journal on Addictions, 2,* 77-79.

Chambers, R.A., Taylor, J.R., & Potenza, M.N. (2003). Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *American Journal of Psychiatry, 160,* 1041-1052.

Chanraud, S., Martelli, C., Delain, F., Kostogianni, N., Douaud, G, Aubin, H.J., Reynaud, M. & Martinot, J.L. (2007) Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology, 32,* 429-438.

Cheng, R.K., Etchegaray, M. & Meck, W.H. (2007). Impairments in timing, temporal memory, and reversal learning linked to neurotoxic regimens of methamphetamine intoxication. *Brain Research, 1186,* 255, 266.

Chirivella, J., Villodre, R., Sebastián, E.N., & Ferri, J. (2003). Test de Aprendizaje Verbal Complutense frente a Escala de Memoria de Wechsler-Revisada. *Neurología: publicación oficial de la Sociedad Española de Neurología, 18,* 132-138.

Clark, D.B., Cornelius, J.R., Kirisci, L. & Tarter, R.E. (2005). Childhood risk categories for adolescent substance involvement: a general liability typology. *Drug and Alcohol Dependence, 77,* 13-21.

Clark, L., Robbins, T.W., Ersche, K.D., & Sahakian, B.J. (2006). Reflection impulsivity in current and former substance users. *Biological Psychiatry, 60*, 515-522.

Clark, L., Roiser, J.P., Robbins, T.W. & Sahakian, B.J. (2009). Disrupted 'reflection' impulsivity in cannabis users but not current or former ecstasy users. *Journal of Psychopharmacology, 23,* 14-22.

Clemens, K.J., Cornish, J.L., Kong, M.L., Kunt, G.E. & McGregor, I.S. (2005). MDMA ('Ecstasy') and methamphetamine combined: Order of administration influences

hyperthermic and long-term adverse effects in female rats. *Neuropharmacology, 49*, 195, 207.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). New York: Lawrence Erbaum Association Publishers.

Collette, F., Olivier, L., Van der Linden, M., Laureys, S., Delfiore, G., Luxen, A. & Salmon, E. (2005) Involvement of both prefrontal and inferior parietal cortex in dual-task performance. *Cognitive Brain Research, 24,* 237-251.

Colzato, L.S., van den Wildenberg, W.P.M. & Hommel, B. (2007) Impaired inhibitory control in recreational cocaine users. *PLoS ONE, 2*, 1143.

Colzato, L.S., van den Wildenberg, W.P.M. & Hommel, B. (2009). Reduced attentional scope in cocaine polydrug users. *PLoS ONE, 4,* 6043.

Cools, R., Clark, L., Owen, A.M. & Robbins, T.W. (2002) Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 22,* 4563-4567.

Corbin, W.R. & Cronce, J.M. (2007). Alcohol Effects on Behavioral Control: The Impact of Likelihood and Magnitude of Negative Consequences. *Alcoholism, Clinical and Experimental Research, 31,* 955,964.

Croft, R.J., Mackay, A.J., Mills, A.T.D. & Gruzelier, J.G.H. (2001). The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology, 153,* 373-379.

Curran, H.V., Kleckham, J., Bearn, J., Strang, J. & Wanigaratne, S. (2001). Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose response study. *Psychopharmacology, 154,* 153,160.

Cysique, L.A., Maruff, P. & Brew, B.J. (2004). Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. *Journal of Neurovirology, 10,* 350-357.

D'Esposito, M., & Postle, B. (2002) The organization of working memory function in lateral prefrontal cortex: evidence from event-related functional MRI. In: Stuss, D.T., Knight, R.T. (eds) *Principles of Frontal Lobe Functioning*. New York: Oxford University Press.

D'Esposito, M., Detre, J.A., Alsop, D.C, Shin, R.K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature, 378,* 279-281

D'Esposito, M., Postle, B.R., Ballard, D. & Lease, J. (1999) Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain and Cognition, 41,* 66-86.

Dafters, R.I. (2006). Chronic ecstasy (MDMA) use is associated with deficits in task-switching but not inhibition or memory updating executive functions. *Drug and Alcohol Dependence, 83,* 181-184.

Dafters, R.I., Hoshi, R., & Talbot, A.C. (2004). Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. *Psychopharmacology, 173*, 405-410.

Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Laane, K., Pena, Y., Murphy, E.R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F.I., Richards, H.K., Hong, Y., Baron, J.C., Everitt, B.J. & Robbins, T.W., 2007. Nucleus

accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science, 315,* 1267-1270.

Damasio, A.R. (1994). *Descartes´ error: Emotion, Reason, and the Human Brain*. New York: Grosset/Putnam.

Damasio, A.R. (2000). A neural basis for sociopathy. *Archives of General Psychiatry, 57,* 128-129.

Danos, P., Kasper, S., Grunwald, F., Klemm, E., Krappel, C., Broich, K., Hoflich, G., Overbeck, B., Biersack, H.J., & Moller, H.J. (1998). Pathological regional cerebral blood flow in opiate-dependent patients during withdrawal: a HMPAO-SPECT study. *Neuropsychobiology, 37,* 194-199.

Dao-Castella, M.H., Samson, Y., Legault, F., Martinot, J.L., Aubin, H.J., Crouzel, C., Feldman, L., Barrucand, D., Rancurel, G., Féline, A. & Syrota, A. (1998) Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. *Psychological Medicine, 28,* 1039-1048.

Davis, J.M., Fleming, M.F., Bonus, K.A. & Baker, T.B (2007) A pilot study on mindfulness based stress reduction for smokers. *BMC Complementary and Alternative Medicine, 7,* 2.

Davis, P.E., Liddiard, H. & McMillan, T.M. (2002). Neuropsychological deficits and opiate abuse. *Drug and Alcohol Dependence, 67,* 105-108.

De Sola, S., Miguelez-Pan, M., Peña-Casanova, J., Poudevida, S., Farré, M., Pacifini, R., Böhm, P., Abanades, S. Verdejo-Garcia, A., Zuccaro, P. & De la Torre, R. (2008). Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study. *Journal of Psychopharmacology, 200,* 425-437.

de Win, M.M.L., Jager, G., Verkaeke, H.K.E., Schilt, T., Reneman, L., Booij, J., Verhulst, F.C., Den Heeten, G.J., Ramsey, N.F., Korf, D.J. & van den Brink, W. (2005). The Netherlands XTC Toxicity (NeXT) study: objectives and methods of a study investigating causality, course, and clinical relevance. *International Journal of Methods in Psychiatric Research, 14,* 167, 185.

de Win, M.M.L., Reneman, L., Jager, G., Vlieger, E.J., Olabarriaga, S.D., Lavini, C., Bisschops, I., Majoie, C.B., Booij, J., den Heeten, G.J. & van den Brink, W. (2007) A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. *Neuropsychopharmacology, 32,* 458-470.

Deadwyler, S.A., Goonawardena, A.V. & Hampson, R.E. (2007) Short-term memory is modulated by the spontaneous release of endocannabinoids: evidence from hippocampal population codes. *Behavioural Pharmacology, 18,* 571-580.

DeFilippis, N.A. (2002) Category Test: Computer Version Research Edition. Lutz, FL: Psychological Assessment Resources.

Denckla, M.B., & Reiss, A.L. (1997) Prefrontal-subcortical circuits in developmental disorders In Krasnegor, N.A., Lyon, G.R., Goldman-Rakic, P.S. (eds), *Development of the prefrontal cortex: Evolution, neurobiology, and behaviour.* Baltimore: Brookes.

Di Sclafani, V., Tolou-Shams, M., Price, L.J. & Fein, G. (2002) Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug and Alcohol Dependence, 66,* 161-171.

Dodge, R., Sindelar, J. & Sinha, R. (2005). The role of depression symptoms in predicting drug abstinence in outpatient substance abuse treatment. *Journal of Substance Abuse Treatment, 28,* 189-196.

Dom, G., D´haene, P., Hulstijn, W., & Sabbe, B. (2006). Impulsivity in abstinent early- and late-onset alcoholics: Differences in self-report measures and a discounting task. *Addiction, 101,* 50-59.

Dreher, J.C., Koechlin, E., Tierney, M., & Grafman, J. (2008) Damage to the fronto-polar cortex is associated with impaired multitasking. *PLoS ONE, 3,* e3227.

Drevets, W.C. & Raichle, M.E. (1998) Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: implications for interactions between emotion and cognition. *Cognition Emotion, 12,* 353-385.

Drevets, W.C. (2000) Neuroimaging studies of mood disorders. *Biological Psychiatry, 48,* 813-829.

Dumont, G.J.H., Valkenberg, M.M., Schoemaker, R., Buitelaar, J.K., van Gerven, J.M.A, & Verkes, R.J. (2007). Acute MDMA and ethanol interaction effects on psychomotor performance. *British Journal of Clinical Pharmacology, 63,* 503.

Dumont, G.J.H., Wezenberg, E., Valkenberg, M.M., de Jong C.A.J., Buitelaar, J.K., van Gerven, J.M.A., & Verkes, R.J. (2008). Acute neuropsychological effects of MDMA and etanol (co-) administration in healthy volunteers. *Psychopharmacology, 197,* 465-474.

Efferen, T.R., Duncan, E.J., Szilagyi, S., Chakravorty, S., Adams, J.U., Gonzenbach, S., Angrist, B., Butler, P.D., & Rotrosen, J. (2000). Diminished acoustic startle in chronic cocaine users. *Neuropsychopharmacology, 22,* 89-96.

Egerton, A., Allison, C., Brett, R.R., & Pratt, J.A, (2006) Cannabinoids and prefrontal cortical function: insights from preclinical studies. *Neuroscience and Biobehavioural Reviews, 30,* 680-695.

Eldreth, D.A., Matochik, J.A., Cadet, J.L., & Bolla, K.I. (2004). Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *Neuroimage, 23,* 914-920.

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction (2008). *Annual Report 2008: the state of the drugs problem in the European Union.* Retrieved from http://www.emcdda.europa.eu/publications/annual-report/2008

EMCDDA: European Monitoring Centre for Drugs and Drug Addiction. (2009). *Annual Report 2009: the state of the drugs problem in the European Union.* Retrieved from http://www.emcdda.europa.eu/publications/annual-report/2009

Ende, G., Wetzel, H., Walter, S., Weber-Fahr, W., Diehl, A., Hermann, D., Heinz, A., & Mann, K. (2005). Monitoring the effects of chronic alcohol consumption and abstinence on brain metabolism: a longitudinal proton magnetic resonance spectroscopy study. *Biological Psychiatry, 58,* 974-980.

Errico, A.L., King, A.C., Lovallo, W.R., & Parsons, O.A. (2002). Cortisol dysregulation and cognitive impairment in abstinent male alcoholics. *Alcoholism, Clinical and Experimental Research, 26,* 1198-1204.

Ersche, K.D., Clark, L., London, M., Robbins, T.W., & Sahakian, B.J. (2006). Profile of executive and memory function associated with amphetamine and opiate dependence. *Neuropsychopharmacology, 31*, 1036-1047.

Ersche, K.D., & Sahakian, B.J. (2007). The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychology Review, 17,* 317-336.

Ersche, K.D., Roiser, J.P., Robbins, T.W., & Sahakian, B.J. (2008) Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans. *Psychopharmacology, 197*, 421-431.

Everitt, B.J., Belin, D., Economidou, D., Pelloux, Y, Dallew, J.W., & Robbins, T.W. (2008). Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philosophical Transactions of the Royal Society B: Biological Sciences, 363,* 3125-3135.

Everitt, B.J. & Robbins, T.W. (2005). Neural systems of reinforcement of drug addiction: from actions to habits to compulsion. *Nature Neuroscience, 8,* 1481-1489.

Fadda, P., Robinson, L., Fratta, W., Pertwee, R.G., & Riedel, G. (2004). Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. *Neuropharmacology, 47,* 1170-1179.

Fals-Stewart, W., & Lucente, S. (1994) The effect of neurocognitive status and personality functioning on length of stay in residential substance abuse treatment: An integrative study. *Psychology of Addictive Behaviors, 8,* 1-12.

Fals-Stewart, W., & Schafer, J. (1992). The relationship between length of stay in drug-free therapeutic communities and neurocognitive functioning. *Journal of Clinical Psychology, 48,* 539-543.

Fein, G., Di Sclafani, V., & Meyerhoff, D. J. (2002). Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. *Drug and Alcohol Dependence, 68*, 87- 93.

Fein, G., Klein, L., & Finn, P. (2004) Impairment on a simulated gambling task in long-term abstinent alcoholics. *Alcoholism, Clinical and Experimental Research, 28*, 1487-1491.

Fein, G., & McGillivray, S. (2007). Cognitive performance in long-term abstinent elderly alcoholics. *Alcoholism, Clinical and Experimental Research, 31,* 1788-1799.

Fein, G., Torres, J., Price, L.J., & Di Sclafani, V. (2006). Cognitive performance in long-term abstinent alcoholics. *Alcoholism, Clinical and Experimental Research, 30,* 1538-1544.

Fernández-Martín, F.D., & Hinojo-Lucena, F.J. (2006). El estilo cognitivo reflexividad-impulsividad (R-I) en el segundo ciclo de educación primaria: Diferencias entre los sistemas de clasificación e implicaciones educativas. *Enseñanza, 24,* 117-130.

Fernández-Serrano, M.J., Lozano, O., Perez-Garcia, M., & Verdejo-Garcia, A. (2010c) Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. *Drug and Alcohol Dependence, in press.*

Fernández-Serrano, M.J., Pérez-García, M., Perales, J.C., & Verdejo-García. A. (2010b). Prevalence of executive dysfunction in cocaine, heroin and alcohol users enrolled in therapeutic communities. *European Journal of Pharmacology, 646,* 104-112.

Fernández-Serrano, M.J., Pérez-García, M., Schmidt Río-Valle, J., & Verdejo-García, A. (2010a). Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. *Journal of Psychopharmacology, in press.*

Field, M., & Cox, W.M. (2008). Attentional bias in addictive behaviors: a review of its development, causes, and consequences. *Drug Alcohol Dependence, 97,* 1-20.

Fillmore, M.T., & Rush, C.R. (2002) Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence, 66*, 265-273.

Fillmore, M.T., Rush, C.R., & Hays, L. (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug and Alcohol Dependence, 67,* 157-167.

Fillmore, M.T., Rush, C.R., & Hays, L. (2005). Cocaine improves inhibitory control in human model of response conflict. *Experimental and Clinical Psychopharmacology, 13,* 327-335.

Fillmore, M.T., Rush, C.R., & Hays, L. (2006). Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. *Addiction, 101*, 1323-1332.

Fishbein, D.H., Krupitsky, E., Flannery, B.A., Langevin, D.J., Bobashev, G., Verbitskaya, E., Augustine, C.B., Bolla, K.I., Zvartau, E., Schech, B., Egorova, V., Bushara, N., & Tsoy, M. (2007). Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. *Drug and Alcohol Dependence, 90,* 25-38.

Fisk, J.E., & Sharp, C.A. (2004) Age-related impairments in executive functioning: Updating, inhibition, shifting and access. *Journal of Clinical and Experimental Neuropsychology, 26,* 874-890.

Flores, E.A., Aragón, C., Chicharro, J., Ezpeleta, D., Fernández, E., García, G., García, O., González, J., Iraurgi, I., Landa, N., Llanero, M., Lloves, M.A., López, A., Lorea, I., Olivar, A., Pedrero, E.J., Pérez, M., Puerta, C., Rojo, G., Ruiz, J.M., Sánchez, A., Sánchez, E., Secades, R., Tirapu, J., Verdejo, A. (2010) Documento de consenso para el abordaje de las adicciones desde las neurociencias. *Trastornos Adictivos, 11,* 243-246.

Foisy, M.L., Kornreich, C., Fobe, A., D'Hondt, L., Pelc, I., Hanak, C., Verbanck, P., & Philippot, P. (2007a). Impaired emotional facial expression recognition in alcohol dependence: do these deficits persist with midterm abstinence? *Alcoholism, Clinical and Experimental Research, 31,* 404-410.

Foisy, M.L., Kornreich, C., Petiau, C., Parez, A., Hanak, C., Verbanck, P., Pelc, I., & Philippot, P. (2007b). Impaired emotional facial expression recognition in alcoholics: are these deficits specific to emotional cues? *Psychiatry Research, 150,* 33-41.

Foisy, M.L., Philippot, P., Verbanck, P., Pelc, I., van der Straten, G., & Kornreich, C. (2005). Emotional facial expression decoding impairment in persons dependent on multiple substances: impact of a history of alcohol dependence. *Journal of Studies on Alcohol, 66,* 673-681.

Forman, S.D., Dougherty, G.G., Casey, B.J., Siegle, G.J., Braver, T.S., Barch, D.S., Stenger, V.A., Wick-Hull, C., Pisarov, L.A., & Lorensen, E. (2004) Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biological Psychiatry, 55*, 531-537.

Fox, H.C., Hong, K.I., Siedlarz, K., & Sinha, R. (2008). Enhanced sensitivity to stress and drug/alcohol craving in abstinent cocaine-dependent individuals compared to social drinkers. *Neuropsychopharmacology, 33,* 796-805.

Fox, H.C., McLean, A., Turner, J.J.D., Parrot, A.C., Rogers, R., & Sahakian, B.J. (2002). Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology, 162,* 203-214.

Franken, I.H. (2003). Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. *Progress in Neuropsychopharmacology & Biological Psychiatry, 27,* 563-579.

Franken, I.H.A., Nijs, I.M.T., Muris, P., & van Strien, J.W. (2007) Alcohol selectively reduces brain activity during the affective processing of negative information. *Alcoholism, Clinical and Experimental Research, 31*, 919-927.

Frederick, D.L., Ali, S.F., Gillam, M.P., Gossett, J., Slikker, W. Jr., & Paule, M.G. (1998). Acute effects of dexfenfluramine (d-FEN) and methylenedioxymethamphetamine (MDMA) before and after short-course, high-dose treatment. *Annals of the New York Academy of Sciences, 844,* 183-190

Frederick, D.L., Ali, S.F., Slikker, W. Jr, Gillam, M.P., Allen, R.R., & Paule, M.G. (1995). Behavioral and neurochemical effects of chronic methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. *Neorotoxicology and Teratology, 17,* 531-543

Fried, P.A., Watkinson, B., & Gray, R. (2005). Neurocognitive consequences of marihuana-a comparison with pre-drug performance. *Neorotoxicology and Teratology, 27,* 231-239.

Frigerio, E., Burt, D.M., Montagne, B., Murray, L.K., & Perrett, D.I. (2002). Facial affect perception in alcoholics. *Psychiatry Research, 113,* 161-171.

Friswell, J., Phillips, C., Holding, J., Morgan, C.J.A., Brandner, B. & Curran, H.V. (2008). Acute effects of opioids on memory functions on healthy men and women. *Psychopharmacology, 198,* 243-250.

Fuchs, R.A., Evans, K.A., Parker, M.P., & See, R.E. (2004). Differential involvement of orbitofrontal cortex subregions in conditioned cue-induced and cocaine-primed reinstatement of cocaine seeking in rats. *Journal of Neuroscience, 24,* 6600-6610.

Fusar-Poli, P., Landi, P., & O'Connor, C. (2009). Neurophysiological response to emotional faces with increasing intensity of fear: A skin conductance response study. *Journal of Clinical Neuroscience, 16,* 981-982

Galynker, I.I., Eisenberg, D., Matochik, J.A., Gertmenian-King, E., Cohen, L., Kimes, A.S., Contoreggi, C., Kurian, V., Ernst, M., Rosenthal, R.N., Prosser, J., London, E.D. (2007) Cerebral metabolism and mood in remitted opiate dependence. *Drug and Alcohol Dependence, 90,* 166-174.

Garavan H., & Stout, J.C. (2005). Neurocognitive insights into substance abuse. *Trends in Cognitive Sciences, 9,* 195-201.

Garavan, H. & Hester, R. (2007). The role of cognitive control in cocaine dependence. *Neuropsychology Review, 17,* 337-345.

Garavan, H., Kaufman, J.N. & Hester, R. (2008). Acute effects of cocaine on the neurobiology of cognitive control. *Philosophical Transactions of the Royal Society of London. Series B,* 363, 3267-3276.

García-Ogueta, M.I. (2001). Mecanismos atencionales y síndromes neuropsicológicos. *Revista de Neurología, 32*, 463-467.

Gauthier, C.T., Duyme, M., Zanca, M., & Capron, C. (2009) Sex and performance level effects on brain activation during a verbal fluency task: A functional magnetic resonance imaging study. *Cortex, 45*, 164-176.

George, O., Mandyam, C.D., Wee, S., & Koob, G.F. (2008) Extended access to cocaine self-administration produces long-lasting prefrontal cortex-dependent working memory impairments. *Neuropsychopharmacology, 33,* 2474-2482.

Gerra, G., Baldaro, B., Zaimovic, A., Moi, G., Bussandri, M., Raggi, M.A. & Brambilla, F., 2003. Neuroendocrine responses to experimentally-induced emotions among abstinence opioid-dependent subjetcs. *Drug and Alcohol Dependence, 71,* 25-35.

Gerra, G., Calbiani, B., Zaimovic, A., Sartori, R., Ugolotti, G., Ippolito, L., Delsignore, R., Rustichelli, P., & Fontanesi, B. (1998). Regional cerebral blood flow and comorbid diagnosis in abstinent opioid addicts. *Psychiatry Research: Neuroimaging Section, 83,* 117-126.

Gilbert, S.J., Spengler, S., Simons, J.S., Frith, C.D., & Burgess, P.W. (2006) Differential functions of lateral and medial rostral prefrontal cortex (area 10) revealed by brain-behavior associations. *Cerebral Cortex, 16,* 1783-1789.

Glass, J.M., Buu, A., Adams, K.M., Nigg, J.T., Puttler, L.I., Jester, J.M., & Zucker, R.A. (2009) Effects of alcoholism severity and smoking on executive neurocognitive function. *Addiction, 104,* 38-48.

Golden, C.J. (1978) *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Stoelting Co. Wood Dale, Illinois.

Goldman, A.I., & Sripada, C.S. (2005). Simulationist models of face-based emotion recognition. *Cognition, 94,* 193-213.

Goldstein, R.Z., Alia-Klein, N., Leskovjan, A.C., Fowler, J.S., Wang, G.J., Gur, R.C., Hitzemann, R., & Volkow, N.D. (2005). Anger and depression in cocaine addiction: association with the orbitofrontal cortex. *Psychiatry Research, 138,* 13-22.

Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S., Wang, G.J., Fowler, J.S., & Volkow, N.D. (2004). Severity of neuropsychological

impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia, 42,* 1447-1458.

Goldstein, R.Z., Tomasi, D., Rajaram, S., Cottone, L.A., Zhang, L., Maloney, T., Telang, F., Alia-Klein, N., & Volkow, N.D. (2007a). Role of the anterior cingulated and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience, 144,* 1153-1159.

Goldstein, R.Z., & Volkow, N.D. (2002). Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *The American Journal of Psychiatry, 159,* 1642-1652.

Goldstein, R.Z., Woicik, P.A., Lukasik, T., Maloney, T., & Volkow, N.D. (2007b). Drug fluency: A potential marker for cocaine use disorders. *Drug and Alcohol Dependence, 89,* 97-101.

González, R. (2007). Acute and Non-acute Effects of Cannabis on Brain Functioning and Neuropsychological Performance. *Neuropsychology Review, 17*, 347-361.

González, R., Bechara, A., & Martin, E.M. (2007). Executive functions among individuals with methamphetamine or alcohol as drugs of choice: preliminary observations. *Journal of Clincal and Experimental Neuropsychology, 29,*155-159.

González, R., Rippeth, J.D., Carey, C.L., Heaton, R.K., Moore, D.J., Shweinsburg, B.C., Cherner, M. & Grant, I. (2004). Neurocognitive performance of methamphetamine users discordante for history of marijuana exposure. *Drug and Alcohol Dependence, 76,* 181-190.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, J., Fimm, B. & Sass, H. (2000). Impaired cognitive performance in drug free users of

recreational ecstasy (MDMA). *Journal of Neurology, Neurosurgery and Psychiatry, 68,* 719-725.

Gouzoulis-Mayfrank, E., Thimm, B., Rezk, M., Hensen, G. & Daumann, J. (2003). Memory impairment suggest hippocampal dysfunction in abstinent ecstasy abusers. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 27,* 819-827.

Grace, J., Malloy, P.F. (2001). *Frontal Systems Behavior Scale (FrSBe): Professional Manual.* Lutz, FL: Psychological Assessment Resources.

Grant, I., Gonzalez, R., Carey, C. L., Natarajan, L. & Wolfson, T. (2003). Non-acute (residual) neurocognitive effects of cannabis use: A meta analytic review. *Journal of the International Neuropsychological Society, 9,* 679-689.

Gruber, S.A., Silveri, M.M., & Yurgelun-Todd, D.A. (2007) Neuropsychological consequences of opiate use. *Neuropsychology Review, 17,* 299-315.

Gruber, S.A., & Yurgelun-Todd, D.A. (2001). Neuropsychological correlates of drug abuse. In Kaufman, M.J. (Ed). *Brain imaging in substance abuse: research, clinical and forensic applications.* Human Press Inc. Totowa: New Jersey.

Gupta, R., Duff, M.C., Denburg, N.L., Cohen, N.J., Bechara, A., & Tranel, D. (2009) Declarative memory is critical for sustained advantageous complex decision-making. *Neuropsychologia, 47,* 1686-1693.

Hair, J.F.Jr, Anderson, R.E., Tatham, R.L., & Black, W.C. (2000) *Análisis Multivariante* (quinta edición, in spanish). Madrid: Prentice Hall Iberia.

Halpern, J.H., Pope Jr., H.G., Sherwood, A.R., Barry, S., Hudson, J.I., & Yurgelun-Todd, D. (2004). Residual neuropsychological effects of illicit 3,4-

methylenedioximethamphetamine in individuals with minimal exposure to other drugs. *Drug and Alcohol Dependence, 75,* 135-147.

Hammersley, R., Ditton, J., Smith, I., & Short, E. (1999). Patterns of ecstasy use by drug users. *The British Journal of Criminology, 39,* 625-647.

Hanlon, C.A., Wesley, M.J. & Porrino, L.J. (2009) Loss of functional specificity in the dorsal striatum of chronic cocaine users. *Drug and Alcohol Dependence, 102,* 88-94.

Hanson, K.L., Luciana, M., & Sullwold, K. (2008). Reward-related decision-making deficits and elevated impulsivity among MDMA and other drug users. *Drug and Alcohol Dependence, 96,* 99-110.

Hayes, S.C. (2004). Acceptance and commitment therapy, relational frame theory, and the third wave of behavioral and cognitive therapies. *Behavior Therapy, 35,* 639-665

Heath, R.G., Fitziarrell, A.T., Fontana, C.J., & Garey, R.E. (1980). Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. *Biological Psychiatry, 15,* 657-690.

Heaton, R.K., Grant, I. & Matthews, C.G. (1991). *Comprehensive norms for an expanded Halstead-Reitan Battery*. Odessa, FL: Psychological Assessment Resources.

Heil, S.H., Johnson, M.W., Higgins, S.T. & Bickel, W.K. (2006). Delay discounting in currently using and currently abstinent cocaine-dependent outpatients and non-drug-using matched controls. *Addictive Behaviors, 31*, 1290-1294.

Henry, J.D., Mazur, M., & Rendell, P.G. (2009). Social-cognitive difficulties in former users of methamphetamine. *British Journal of Clinical Psychology, 48,* 323-327.

Herkenham, M. (1992). Cannabinoid receptor localization in brain: Relationship to motor and reward systems. *Annals of the New York Academy of Sciences, 654,* 19-32.

Herndon, J.G., Moss, M.B., Rosene, D.L., & Killiany, R.J. (1997) Patterns of cognitive decline in aged rhesus monkeys. *Behavioral Brain Research, 87,* 25-34.

Hester R., & Garavan H. (2004). Executive dysfunction in cocaine addiction: evidence from discordant frontal, cingulate, and cerebellar activity. *The Journal of Neuroscience, 24,* 11017-11022.

Hoffman, W.F., Moore, M., Templin, R., McFarland, B., Hitzemann, R.J., & Mitchell, S.H. (2006). Neuropsychological function and delay discounting in methamphetamine-dependent individuals. *Psychopharmacology, 188,* 162-170.

Homer, B.D., Solomon, T.M., Moeller, R.W., Mascia, A., DeRaleau, L., & Halkitis, P.N. (2008). Methamphetamine abuse and impairment of social functioning: a review of the underlying neurophysiological causes and behavioral implications. *Psychological Bulletin, 134,* 301-310.

Hoppes, K. (2006). The application of mindfulness-based cognitive interventions in the treatment of co-occurring addictive and mood disorders. *CNS Spectrums, 11,* 829-851

Hoshi, R., Bisla, J., & Curran, H.V. (2004). The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expressions: preliminary findings. *Drug and Alcohol Dependence, 76,* 297-304.

Hoshi, R., Mullins, K., Boundy C., Brignell, C., Piccini, P., & Curran, H.V. (2007) Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naïve controls. *Psychopharmacology, 194,* 371-379.

Ilan, A.B., Smith, M.E., & Gevins, A. (2004). Effects of marijuana on neurophysiological signals of working and episodic memory. *Psychopharmacology , 176,* 214-222.

Jacobus, J., Bava, S., Cohen-Zion, M., Mahmood, O., & Tapert, S.F. (2009). Functional consequences of marijuana use in adolescents. *Pharmacology Biochemistry and Behavior, 92* (4), 559-565.

Jager, G., Kahn, R.S., van Den Brink, W., van Ree, J.M., & Ramsey, N.F. (2006) Long-term effects of frequent cannabis use on working memory and attention: An fMRI study. *Psychopharmacology, 185*, 358-368.

Jatlow, P., McCance, E.F., Bradberry, C.W., Elsworth, J.D., Taylor, J.R., & Roth, R.H. (1996). Alcohol plus Cocaine: The Whole Is More Than the Sum of Its Parts [Proceedings Of The Fourth International Congress Of Therapeutic Drug Monitoring And Clinical Toxicology]. *Therapeutic Drug Monitoring, 18,* 460-464.

Jentsch, J.D., & Taylor, J.R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology, 146,* 373-390.

Jentsch, JD., Olausson, P., De la Garza, R., & Taylor, JR. (2002). Impairments of reversal learning and response perseveration after repeated, intermittent cocaine administrations to monkeys. *Neuropsychopharmacology, 26*,183-190.

Jentsch, J.D., Verrico, C.D., Le, D., & Roth, R.H. (1998). Repeated exposure to Δ^9-tetrahydrocannabinol reduces prefrontal cortical dopamine metabolism in the rat. *Neuroscience Letters, 246*, 169-172.

Johnson, B.A., Ait-Daoud, N., & Wells, L.T. (2000). Effects of isradipine, a dihydropyridine-class calcium channel antagonist, on D-methamphetamine-induced cognitive and physiological changes in humans. *Neuropsychopharmacology, 22,* 504-512.

Jovanovski, D., Erb, S., & Zakzanis, K. (2005). Neurocognitive deficits in cocaine users: a quantitative review of the evidence. *Journal of Clinical and Experimental Neuropsychology, 27,* 189-204.

Kalechstein, A.D., Newton T.F., & Green, M. (2003). Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *The Journal of Neuropsychiatry and Clinical Neurosciences, 15,* 215-220.

Kaplan, R.F., Cohen, R.A., Moscufo, N., Guttmann, C., Chasman, J., Buttaro, M., Hall, C.H., & Wolfson, L. (2009) Demographic and biological influences on cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 31,* 1-9.

Karlinska, I., Siger, M., Lewanska, M., & Selmaj, K. (2008). Cognitive impairment in patients with relapsing-remitting multiple sclerosis. The correlation with MRI lesion volume. *Neurologia i neurochirurgia polska, 42,* 416-423.

Kemmis, L., Hall, J.K., Kingston, R., & Morgan, M.J. (2007). Impaired fear recognition in regular recreational cocaine users. *Psychopharmacology, 194,* 151-159.

Kirby, K.N., & Petry, N.M. (2004). Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction, 99,* 461-471.

Kirisci, L., Tarter, R.E., Reynolds, M., & Vanyukov, M. (2006). Individual differences in childhood neurobehavior disinhibition predict decision to desist substance use during adolescence and substance use disorder in young adulthood: A prospective study. *Addictive Behaviors, 31,* 686-696.

Kirisci, L., Vanyukov, M., & Tarter, R. (2005). Detection of youth at high risk for substance use disorders: A longitudinal study. Psychol. *Addictive Behaviors, 19,* 243-252.

Klintsova, A.Y., Helfer, J.L., Calizo, L.H., Dong, W.K., Goodlett, C.R., & Greenough, W.T. (2007). Persistent Impairment of Hippocampal Neurogenesis in Young Adult Rats Following Early Postnatal Alcohol Exposure. *Alcoholism, Clinical and Experimental Research, 31,* 2073-2082.

Koechlin, E., & Summerfield, C. (2007) An information theoretical approach to prefrontal executive function. *Trends in Cognitive Sciences, 11*, 229-235.

Koob, G.F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology, 24,* 97-129.

Kornreich, C., Blairy, S., Philippot, P., Hess, U., Noel, X., Streel, E., Le Bon, O., Dan, B., Pelc, I., & Verbanck, P. (2001). Deficits in recognition of emotional facial expression are still present in alcoholics after mid- to long-term abstinence. *Journal of Studies on Alcohol, 62,* 533-542.

Kornreich, C., Foisy, M.L., Philippot, P., Dan, B., Tecco, J., Noel, X., Hess, U., Pelc, I., & Verbanck, P. (2003). Impaired emotional facial expression recognition in alcoholics, opiate dependence subjects, methadone maintained subjects and mixed alcohol-opiate antecedents subjects compared with normal controls. *Psychiatry Research, 119,* 251-260.

Kornreich, C., Philippot, P., Foisy, M.L., Blairy, S., Raynaud, E., Dan, B., Hess, U., Noel, X., Pelc, I., & Verbanck, P. (2002). Impaired emotional facial expression recognition is associated with interpersonal problems in alcoholism. *Alcohol and Alcoholism, 37,* 394-400.

Krull, K.R., & Adams, R.L. (1997). Problems in neuropsychological research methodology. In: Maruish, M.E., Moses, J.A. (Eds.), *Clinical neuropsychology:*

theoretical foundations for practitioners. New Jersey: Lawrence Erlbaum Associates.

Kübler, A., Murphy, K., & Garavan, H. (2005) Cocaine dependence and attention switching within and between verbal and visuospatial working memory. *The European Journal of Neuroscience, 21,* 1984-1992.

Kufahl, P.R., Zhu Li, Risinger, R.C., Rainey, C.J., Wu, G., Bloom, A.S., & Li, S. (2005). Neural responses to acute cocaine administration in the human brain detected by fMRI. *Neuroimage, 28,* 904-914.

Kulisevsky, J., Pagonabarraga, J., Pascual-Sedano, B., Garcia-Sanchez, C., & Gironell, A. (2008). Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Movement Disorders, 23,* 1889-1896.

Kuypers, K.P., & Ramaekers, J.G. (2007). Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected. *Psychopharmacology, 189,* 557-563.

Kuypers, K.P.C., Wingen, M., Samyn, N., Limbert, N., & Ramaekers, J.G. (2007). Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night. *Psychopharmacology, 192,* 111-119.

Lane, R.D., Sechrest, L., Riedel, R., Shapiro, D.E., & Kaszniak, A.W. (2000). Pervasive emotion recognition deficit common to alexythimia and the repressive coping style. *Psychosomatic Medicine, 62,* 492-501.

Lane, S.D., Cherek, D.R., Tcheremissine, O.V., Lieving, L.M., & Pietras, C.J. (2005). Acute Marijuana Effects on Human Risk Taking. *Neuropsychopharmacology, 30,* 800-809.

Lawrence, A.D., Calder, A.J., McGowan, S.W., & Grasby, P.M. (2002). Selective disruption of the recognition of facial expressions of anger. *Neuroreport, 13,* 881-884.

Lawrence, A.D., Goerendt, I.K., & Brooks, D.J. (2007). Impaired recognition of facial expressions of anger in Parkinson's disease patients acutely withdrawn from dopamine replacement therapy. *Neuropsychologia, 45,* 65-74.

Leber, W.R., Parsons, O.A., & Nichols, N. (1985) Neuropsychological test results are related to ratings of men alcoholics' therapeutic progress: A replicated study. *Journal of Studies on Alcohol, 46,* 116-121.

Lee, T.M., & Pau, C.W. (2002) Impulse control differences between abstinent heroin users and matched controls. *Brain Injury, 16,* 885-889.

Leitz, J.R., Morgan, C.J.A., Bisby, J.A., Rendell, P.G., & Curran, V. (2009). Global impairment of prospective memory following acute alcohol. *Psychopharmacology, 205,* 379-387.

Leland, D.S., & Paulus, M.P. (2005). Increased risk-taking decision-making but not altered response to punishment in stimulant-using young adults. *Drug and Alcohol Dependence, 78*, 83-90.

Leppänen, J.M. (2006). Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry 19,* 34-39.

Levine, B., Dawson, D., Boutet, I., Schwartz, M.L., & Stuss, D.T. (2000) Assessment of strategic self-regulation in traumatic brain injury: Its relationship to injury severity and psychosocial outcome. *Neuropsychology, 14,* 491-500.

Lezak, M.D. (2004) *Neuropsychological Assessment* (4th edition). New York: Oxford University Press.

Li, C.S., Huang, C., Yan, P., Bhagwagar, Z., Milivojevic, V., & Sinha, R. (2008). Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology, 33,* 1798-1806.

Li, C.S., & Sinha, R. (2008). Inhibitory control and emotional stress regulation: Neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. *Neuroscience and Biobehavioral Reviews, 32,* 581-597.

Loeber, S., Duka, T., Welzel, H., Nakovics, H., Heinz, A., Flor, H., & Mann, K. (2009) Impairment of cognitive abilities and decision making after chronic use of alcohol: The impact of multiple detoxifications. *Alcohol and Alcoholism, 44,* 372-381.

López-Torrecillas, F., Godoy, J.F., Pérez-García, M., Godoy, D., & Sánchez-Barrera, M. (2001). Variables modulating stress and coping that discriminate drug consumers from low or not drug consumers. *Addictive Behaviors, 25,* 161-165.

Lubman, D.I., Yucel, M., & Pantelis, C. (2004) Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction, 99,* 1491-1502.

Lyons, M.J., Bar, J.L., Panizzon, M.S., Toomey, R., Eisen, S., Xian, H., & Tsuang, M.T. (2004). Neuropsychological consequences of regular marijuana use: a twin study. *Psychological Medicine, 34,* 1239-1250.

Lyoo, K., Pollack, M.H., Silveri, M.M., Ahn, K.H., Diaz, C.I., Hwang, J., Kim, S.J., Yurgelun-Tood, D.A., Kaufman, M.J., Renshaw, P.F. (2006). Prefrontal and temporal gray matter density decreases in opiate dependence. *Psychopharmacology, 184,* 139-144.

Lyvers, M., & Yakimoff, M. (2003) Neuropsychological correlates of opioid dependence and withdrawal. *Addictive Behaviors, 28,* 605-611.

Makris, N., Gasic, G.P., Seidman, L.J., Goldstein, J.M., Gastfriend, D.R., Elman, I., Albaugh, M.D., Hodge, S.M., Ziegler, D.A., Sheahan, F.S., Caviness, V.S., Tsuang, M.T., Kennedy, D.N., Hyman, S.E., Rosen, B.R., & Breiter, H.C. (2004). Decreased absolute amygdala volume in cocaine addicts. *Neuron, 44,* 729-740.

Mann, L.S., Wise, T.N., Trinidad, A., & Kohanski, R. (1995). Alexythimia, affect recognition, and five factors of personality in substance abusers. *Perceptual and Motor Skills, 81,* 35-40.

Markianos, M., & Stefanis, C. (1982). Effects of acute cannabis use and short-term deprivation on plasma prolactine and dopamine-beta-hydroxilase in long-term users. *Drug and Alcohol Dependence, 9,* 251-255.

Marlatt, G.A. (2002). Buddhist philosophy and the treatment of addictive behavior. *Cognitive and Behavioral Practice, 9,* 44-50

Marlatt, G. A., & Gordon, J. R. (1985). *Relapse prevention: Maintenance strategies in addictive behavior change.* New York: Guilford.

Marlatt, G., Witkiewitz, K., Dillworth, T.M., Bowen, S.W., Parks, G.A., Macpherson, L.M., Lonczak, H.S., Larimer, M.E., Simpson, T., Blume, A.W., & Crutcher, R. (2004). Vipassana mediation as a treatment for alcohol and drug use disorders. In: Hayes, S., Follette, V.M., Linehan, M.M. (eds). *Mindfulness and Acceptance.* New York: Guildford Press.

Martin, L., Clair, J., Davis, P., O'Ryan, D., Hoshi, R., & Curran, H.V. (2006). Enhanced recognition of facial expressions of disgust in opiate users receiving maintenance treatment. *Addiction, 101,* 1598-1605.

Massman, P.J., Sims, J., Cooke, N., Haverkamp, L.J., Appel, V., & Appel, S.H. (1996). Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 61,* 450-455.

McCann, U.D., Szabo, Z., Seckin, E., Rosenblatt, P., Mathews, W.B., Ravert, H.T., Dannals, R.F., & Ricaurte, G.A. (2005). Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. *Neuropsychopharmacology, 30,* 1741-1750.

McCaul, M.E., Svikis, D.S., & Moore, R.D. (2001). Predictors of outpatient treatment retention: patient versus substance use characteristics. *Drug and Alcohol Dependence, 62,* 9-17.

McHale, S., & Hunt, N. (2008). Executive function deficits in short-term abstinent cannabis users. *Human Psychopharmacology: Clinical and Experimental, 23,* 409-415.

Medina, K.L., Hanson, K.L., Schweinsburg, A.D., Cohen-Zion, M., Nagel, B.J., & Tapert S.F. (2007) Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence. *Journal of the International Neuropsychological Society, 13,* 807-820.

Medina, K.L., McQueeny, T., Nagel, B.J., Hanson, K.L., Schweinsburg, A.D., & Tapert, S. (2008). Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. *Alcohol, Clinical and Experimental Research, 32,* 386-394.

Medina, K.L., McQueeny, T., Nagel, B.J., Hanson, K.L., Yang, T.T., & Tapert, S.F. (2009). Prefrontal cotex morphometry in abstinent adolescent marijuana users: Subtle gender effects. *Addiction Biology, 14,* 457-468.

Metzger, D.S., Woody, G., Marmor, M., & Gross, M. (1996). Risk characteristics of injection drug users (IDUs) participating in the vaccine preparedness study (VPS). *International Conference on AIDS , 11,* 357.

Miller, N.S., Gold, M.S., & Belkin, B.M. (1990). The diagnosis of alcohol and cannabis dependence in cocaine dependence. *Advances in Alcohol & Substance Abuse, 8,* 33-42.

Mintzer, M.Z., Copersino, M.L., & Stitzer, M.L. (2005). Opioid abuse and cognitive performance. *Drug and Alcohol Dependence, 78,* 225-230.

Miranda, R., Jr., Meyerson, L.A., Myers, R.R., & Lovallo, W.R. (2003). Altered affective modulation of the startle reflex in alcoholics with antisocial personality disorder. *Alcoholism, Clinical and Experimental Research, 27,* 1901-1911.

Mittenberg, W., & Motta, S. (1993). Effects of chronic cocaine abuse on memory and learning. *Archives of Clinical Neuropsychology, 8,* 447-461.

Miyake, A., Friedman, N.P., Emerson, M.J., Witzky, A.H., & Howerther, A. (2000) The unity and diversity of executive function and their contribution to complex frontal lobe tasks: A latent variable analysis. *Cognitive Psychology, 41,* 49-100.

Moeller, F.G., Hasan, K.M., Steinberg, J.L., Kramer, L.A., Dougherty, D.M., Valdes, I., Swann, A.C., Barrat, E.S., & Narayana, P.A. (2005) Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. *Neuropsychopharmacology, 30,* 610-617.

Monastero, R., Bettini, P., Del Zotto, E., Cottini, E., Tincani, A., Balestrieri, G., Cattaneo, R., Camarda, R., Vignolo, L.A., & Padovani, A. (2001). Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without

overt neuropsychiatric manifestations. *Journal of the Neurological Sciences, 184,* 33-39.

Monterosso, J.R., Aron, A.R., Cordova, X., Xu, J., & London, E.D. (2005). Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug and Alcohol Dependence, 79,* 273-277.

Montgomery, C., Fisk, J.E., Newcombe, R., & Murphy, P.N. (2005). The differential effects of ecstasy/polydrug use on executive components: shifting, inhibition, updating and access to semantic memory. *Psychopharmacology, 182,* 262-276.

Moon, M., Do, K.S., Park, J., & Kim, D. (2007). Memory impairment in methamphetamine dependent patients. *International Journal of Neuroscience, 117,* 1-9.

Morgan, M.J. (1998). Recreational use of MDMA ("ecstasy") is associated with elevated impulsivity. *Neuropsychopharmacology, 19,* 252-264.

Morgan, M.J. (1999). Memory deficits associated with recreational use of 'ecstasy' (MDMA). *Psychopharmacology, 141,* 30-36.

Morgan, M.J., Impallomeni, L.C., Pirona, A. & Rogers, R.D. (2006) Elevated impulsivity and impaired decision-making in abstinent ecstasy MDMA users compared to polydrug and drug-naïve controls. *Neuropsychopharmacology, 31*, 1562-1573.

Moriyama, Y., Mimura, M., Kato, M., Yoshino, A., Hara, T., Kashima, H., Kato, A., & Watanabe, A. (2002). Executive dysfunction and clinical outcome in chronic alcoholics. *Alcoholism, Clinical and Experimental Research, 26,* 1239-1244.

Murphy, F.C., Nimmo-Smith, I., & Lawrence, A.D. (2003). Functional neuroanatomy of emotions: a meta-analysis. *Cognitive, Affective & Behavioral Neuroscience, 3,* 207-233.

Murphy, F.C., Smith, K.A., Cowen, P.J., Robbins, T.W., Sahakian, B.J. (2002). The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology, 163,* 42-53.

Nagai, T., Takuma, K., Dohniwa, M., Ibi, D., Mizoguchi, H., Kamei, H., Nabeshima, T., & Yamada, K. (2007). Repeated methamphetamine treatment impairs spatial working memory in rats: reversal by clozapine but not haloperidol. *Psychopharmacology, 194,* 2132.

Nava, F., Carta, G., Colombo, G., & Gessa, G.L. (2001). Effects of chronic Δ^9-tetrahydrocannabinol treatment on hippocampal extracellular acetylcholine concentration and alternation performance in the T-maze. *Neuropharmacology, 41,* 392, 399.

Nestor, L., Roberts, G., Garavan, H., & Hester, R. (2008) Deficits in learning and memory: Parahippocampal hyperactivity and frontocortical hypoactivity in cannabis users. *NeuroImage 40,* 1328-1339.

Niyuhire, F., Varvel, S.A., Martin, B.R., & Lichtman, A.H. (2007). Exposure to Marijuana Smoke Impairs Memory Retrieval in Mice. *The Journal of Pharmacology and Experimental Therapeutics, 322,* 1067-1075.

Noel, X., Van der Linden, M., Schmidt, N., Sferrazza, R., Hanak, C., Le Bon, O., De Mol, J., Kornreich, C., Pelc, I., & Verbanck, P. (2001). Supervisory attentional system in nonamnesic alcoholic men. *Archives of General Psychiatry, 58,* 1152-1158.

O'Leary-Moore, S.K., McMechan, A.P., Mathison, S.N., Berman, R.F., & Hannigan, J.H. (2006). Reversal learning after prenatal or early postnatal alcohol exposure in juvenile and adult rats. *Alcohol, 38,* 99-110.

O'Malley, S., Adamse, M., Heaton, R.K., & Gawin, F.H. (1992). Neuropsychological impairment in chronic cocaine abusers, *American Journal of Drug and Alcohol Abuse, 18,* 131-144.

Ornstein, T.J., Iddon, J.L., Baldacchino, A.M., Sahakian, B.J., London, M., Everitt, B.J., & Robbins, T.W (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. *Neuropsychopharmacology, 23,* 113-126.

Paine, T.A., Dringenberg, H.C., & Olmstead, M.C. (2003). Effects of chronic cocaine on impulsivity: relation to cortical serotonin mechanisms. *Behavioural Brain Research, 147,* 135-147.

Passetti, F., Clark, L., Mehta, M.A., Joyce, E., & King, M. (2008) Neuropsychological predictors of clinical outcome in opiate addiction. *Drug and Alcohol Dependence, 94,* 82-91.

Pau, C.W.H., Lee, T.M.C., & Chan, S.F. (2002). The impact of heroin on frontal executive functions. *Archives Clinical Neuropsychology, 17,* 663-670.

Paulus, M.P., Hozack, N., Frank, L., Brown, G.B., & Schuckit, M.A. (2003) Decision-making by methamphetamine-dependent subjects is associated with error-rate independent decrease in prefrontal and parietal activation. *Biological Psychiatry, 53,* 65-74.

Paulus, M.P., Hozack, N., Zauscher, B.E., Frank, L., Brown, G.B., Braff, D.L., & Schuckit, M.A. (2002) Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology, 26*, 53-63.

Paulus, M.P., Tapert, S.F., & Schuckit, M.A. (2005) Neural activation patterns of methamphetamine-dependent subjects during decision-making predicts relapse. *Archives of General Psychiatry, 62,* 761-768.

Pérez-García, M. (2009). *Manual de neuropsicología clínica.* Madrid: Pirámide.

Pfefferbaum, A., Desmond, J.E., Galloway, C., Menon, V., Glover, G.H., & Sullivan, E.V. (2001). Reorganization of frontal systems used by alcoholics for spatial working memory: An fMRI study. *Neuroimage, 14,* 7-20.

Picton, T.W., Stuss, D.T., Alexander, M.P., Shallice, T., Binns, M.A., & Gillingham, S. (2007) Effects of focal frontal lesions on response inhibition. *Cerebral Cortex, 17,* 826-838.

Pitel, A.L., Beaunieux, H., Witkowski, T., Vabret, F., Guillery-Girard, B., Quinette, P., Desgranges, B. & Eustache, F. (2007). Genuine episodic memory deficits and executive dysfunctions in alcoholics early in abstinence. *Alcoholism, 31,* 1169-1178.

Pitel, A.L., Rivier, J., Beaunieux, H., Vabret, F., Desgranges, B., & Eustache, F. (2009) Changes in the episodic memory and executive functions of abstinent and relapsed. Alcoholics over a 6-month period. *Alcoholism, Clinical and Experimental Research, 33,* 490-498.

Pope, H.G., Gruber, A.J., Hudson, J.L., Huestis, M.A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry, 58,* 909-915.

Porrino, L.J., Lyons, D., Smith, H.R., Daunais, J.B. & Nader, M.A. (2004). Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *The Journal of Neuroscience, 24,* 3554-3562.

Posner, M.I., & Petersen, S.E. (1990). The attention system of the human brain. *Annual Review of Neuroscience, 13*, 25-42.

Prosser, J., Cohen, L.J., Steinfeld, M., Eisenberg, D., London, E.D., & Galynker, I.I. (2006). Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment. *Drug and Alcohol Dependence, 84*, 240-247.

Pu, L., Bao, GB., Xu, NJ., Ma, L., & Pei, G. (2002). Hippocampal Long-Term Potentiation Is Reduced by Chronic Opiate Treatment and Can Be Restored by Re-Exposure to Opiates. *The Journal of Neuroscience, 22,* 1914-1921.

Quednow, B.B., Kuhn, K.U., Hoppe, C., Westheide, J., Maier, W., & Wagner, M. (2006). Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. *Psychopharmacology,* 20, 373-384.

Quednow, B.B., Kühn, K.U., Hoppe, C., Westheide, J., Maier, W., Daum, I., & Wagner, M. (2007). Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). *Psychopharmacology, 189,* 517-530.

Ramaekers, J.G., Kauert, G., van Ruitenbeek, P., Theunissen, E.L., Schneider, E., & Moeller, M.R. (2006). High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology, 31,* 2296-2303.

Ramaekers, J.G. & Kuypers, K.P.C. (2006). Acute effects of 3,4-Methylenedioxymethamphetamine (MDMA) on behavioural measures of impulsivity: alone and in combination with alcohol. *Neuropsychopharmacology, 31,* 1048-1055.

Ranganathan, M., & D'Souza, D.C. (2006). The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology, 188,* 425-444.

Ratti, M.T., Bo, P., Giardini, A., & Soragna, D. (2002). Chronic alcoholism and the frontal lobe: which executive functions are imparied? *Acta Neurologica Scandinavica, 105,* 276-281.

Ray, S., & Bates, M.E. (2006). Acute Alcohol Effects on Repetition Priming and Word Recognition Memory with Equivalent Memory Cues. *Brain and Cognition, 60,* 118-127.

Reay, J.L., Hamilton, C., Kennedy, D.O., & Scholey, A.B. (2006). MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgement processes. *Journal of Psychopharmacology, 20,* 385-388.

Redish, A.D., Jensen, S., & Johnson, A. (2008). A unified framework for addiction: Vulnerabilities in the decision process. *Behavioral and Brain Sciences, 31,* 415-487.

Rendell, P.G., Mazur, M., & Henry, J.D. (2009). Prospective memory impairment in former users of methamphetamine. *Psychopharmacology, 203,* 609-616.

Reynolds, B., & Schiffbauer, R. (2004). Measuring state changes in human delay discounting: an experiential discounting task. *Behavioural Processes, 67,* 343-356.

Ricaurte, GA., Yuan, J., Hatzidimitriou, G., Cord, B.J., & McCann, U.D. (2002). Severe Dopaminergic Neurotoxicity in Primates After a Common Recreational Dose Regimen of MDMA ("Ecstasy"). *Science, 297,* 2260-2263.

Rice, F.P. (1997). *Desarrollo humano: estudio del ciclo vital.* México: Prentice-Hall Hispanoamericana.

Risinger, R.C., Salmeron, B.J., Ross, T.J., Amen, S.L., Sanfilipo, M., Hoffmann, R.G., Bloom, A.S., Garavan, H. & Stein, E.A. (2005). Neural correlates of high and

craving durgin cocaine self-administration using BOLD fMRI. *Neuroimage, 26,* 1097-1108.

Robbins, T.W., Ersche, K.D., & Everitt, B.J. (2008) Drug addiction and the memory systems of the brain. *Annals of the New York Academy of Sciences, 1141,* Issue Addiction Reviews, 1-21.

Roberts, A.C., Robbins, T.W., & Weiskrantz, L. (1998). *The prefrontal cortex: executive and cognitive functions.* New York: Oxford University Press.

Robinson, J.E., Heaton, R.K. & O´Malley, S.S. (1999). Neuropsychological functioning in cocaine abusers with and without alcohol dependence. *Journal of the International Neuropsychological Society, 5,* 10-19.

Robinson, T.E., & Berridge, K.C., 2003. Addiction. *Annual Review of Psycholgy, 54,* 25-53.

Robinson, T.E., & Kolb, B. (2004). Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacology, 47,* 33-46.

Roiser, J.P., Rogers, R.D., & Sahakian, B.J. (2007). Neuropsychological function in ecstasy users: a study controlling for polydrug use. *Psychopharmacology, 189,* 505-516.

Rose, J.S., Branchey, M., Buydens-Branchey, L., Stapleton, J.M., Chasten, K., Werrell, A., & Maayan, M.L. (1996). Cerebral perfusion in early and late opiate withdrawal: a technetium-99-m-HMPAO SPECT study. *Psychiatry Research: Neuroimaging Section, 67,* 39-47.

Roselli, M., & Ardila, A. (1996). Cognitive effects of cocaine and polydrug abuse. *Journal of Clinical and Experimental Neuropsychology, 18,* 122-135.

Rounsaville, B.J., Foley, S., Carroll, K., Budde, D., Prusoff, B.A., & Gawin, F.H. (1991). Psychiatric diagnosis of treatment seeking cocaine abusers. *Archives of General Psychiatry, 48,* 43-51.

Rounsaville, B.J., Tierney, T., Crits-Christoph, K., Weissman, M.M., & Kleber, H.D. (1982). Predictors of outcome in treatment of opiate addicts: evidence for the multidimensional nature of addicts' problems. *Comprehensive Psychiatry, 23,* 462-478.

Ruff, R.M. (1996) Ruff Figural Fluency Test: Professional Manual. Lutz, FL: Psychological Assessment Resources. Salthouse TA (2009) When does age-related cognitive decline begin? *Neurobiology of Aging, 30,* 507-514.

Salloum, J.B., Ramchandani, V.A., Bodurka, J., Rawlings, R., Momenan, R., George, D., & Hommer, D.W. (2007). Blunted rostral anterior cingulate response during a simplified decoding task of negative emotional facial expressions in alcoholic patients. *Alcoholism, Clinical and Experimental Research, 31,* 1490-1504.

Salo, R., Nordahl, T.E., Galloway, G.P., Moore, C.D., Waters, C., & Leamon, M.H. (2009). Drug abstinence and cognitive control in methamphetamine-dependent individuals. *Journal of Substance Abuse Treatment, 37,* 292-297.

Salo, R., Nordahl, T.E., Possin, K., Leamon, M., Gibson, D.R., Galloway, G.P., Flynn, N.M., Henik, A., Pfefferbaum, A., & Sullivan, E.V. (2002). Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. *Psychiatry Research, 111,* 65-74.

Sánchez-Tutret, M. (1997). Alcohol y alcoholismo. En Gómez-Jarabo, G. (ed.). *Farmacología de la conducta. Manual básico para psicoterapeutas y clínicos.* Madrid: Síntesis.

Santucci, A.C., Capodilupo, S., Bernstein, J., Gómez-Ramírez, M., Milefsky, R., & Mitchell, H. (2004). Cocaine in adolescent rats produces residual memory impairments that are reversible with time. *Neurotoxicology and Teratology, 26,* 651-661.

Schecklmann, M., Ehlis, A.C., Plichta, M.M., Boutter, H.K., Mezger, F.G., & Fallgatter, A.J. (2007) Altered frontal brain oxygenation in detoxified alcohol dependent patients with unaffected verbal fluency performance. *Psychiatry Research: Neuroimaging, 156,* 129-138.

Schilt, T., de Win, M.M.L, Jager, G., Koeter, M.W., Ramsey, N.F., Schmand, B., & van den Brink, W. (2008). Specific effects of ecstasy and other illicit drugs on cognition in poly-substance users. *Psychological Medicine, 38,* 1309-1317.

Schoenbaum, G., Saddoris, M.P., Ramus, S.J., Shaham, Y., & Setlow, B. (2004) Cocaine-experienced rats exhibit learning deficits in a task sensitive to orbitofrontal cortex lesions. *European Journal of Neuroscience, 19,* 1997-2002.

Schottenbauer, M.A., Hommer, D., & Weingartner, H. (2007). Memory Deficits Among Alcoholics: Performance on a Selective Reminding Task. Aging Neuropsychology and Cognition, 14, 505-516.

Schütz, C.G., Vlahov, D., Anthony, J.C., & Graham, N.M.H. (1994). Comparison of self-reported injection frequencies for past 30 days and 6 months among intravenous drug users. *Journal of Clinical Epidemiology, 47,*191-195.

Schweinsburg A., Nagel, B., Schweinsburg, B., Park, A., Theilmann, R., & Tapert, S. (2008). Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. Psychiatry Research: Neuroimaging, *163* (1) 40-51.

Sedó, M. (2005) *Test de los Cinco Dígitos: Five Digit Test.* Madrid: TEA Ediciones.

Sedó, M., Levenson, R., & Leonard, A. (1995) Reading-free Stroop Interference Tests: automatic and effortful processing. In *Proceedings of the 17th Midyear Conference of the International Neuropsychological Society*. Angers, France.

Silber, B. Y., Croft, R. J., Papafotiou, K., & Stough, C. (2006). The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology, 187,* 154-169.

Simon, N.W., Mendez, I.A., & Setlow, B. (2007). Cocaine exposure causes long-term increases in impulsive choice. *Behavioral Neuroscience, 121,* 543-549.

Solowij, N., & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: a review. *Current Drug Abuse Reviews, 1,* 81-98.

Spain, J.W., & Newsom, G.C. (1991). Chronic opioids impair acquisition of both radial maze and Y-maze choice escape. *Psychopharmacology, 105,* 101-106.

Spiro, R.J., & Jehng, J. (1990). Cognitive flexibility and hypertext: Theory and technology for the non-linear and multidimensional traversal of complex subject matter. D. Nix & R. Spiro (eds.), *Cognition, Education, and Multimedia.* Hillsdale, New Jersey: Erlbaum.

Spreen, S., & Strauss, E. (1991). *A compendium of neuropsychological test: Administration, norms and commentary.* New York: Oxford University Press.

Sprengelmeyer, R. (2007). The neurology of disgust. *Brain, 130,* 1715-1717.

Squire, L. R., & Knowlton, B. J. (2000). The medial temporal lobe, the hippocampus, and the memory systems of the brain. In Gazzaniga M. (Ed.): *The new cognitive neurosciences* (2nd edition). Cambridge, MA: MIT Press

Stalnaker, T.A., Roesch, M.R., Franz, T.M., Burke, K.A., & Schoenbaum, G. (2006) Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. *European Journal of Neuroscience, 24,* 2643-2653.

Stalnaker, T.A., Takahashi, Y., Roesch, M.R., & Schoenbaum, G. (2009). Neural substrates of cognitive inflexibility after chronic cocaine exposure. *Neuropharmacology, 56,* 63-72.

Stout, J.C., Ready, R.E., Grace, J., Malloy, P.F., & Paulsen, J.S. (2003). Factor analysis of the Frontal Systems Behavior Scale (FrSBe). *Assessment, 10,* 79-85.

Streeter, C.C., Terhune, D.B., Whitfield, T.H., Gruber, S., Sarid-Segal, O., Silveri, M.M., Tzilos, G., Afshar, M., Rouse, E.D., Tian, H., Renshaw, P.F., Ciraulo, D., & Yurgelun-Todd, D.A. (2008) Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology, 33,* 827-836.

Stuss, D.T., & Alexander, M.P. (2007) Is there a dysexecutive syndrome? *Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 29,* 901-915.

Stuss, D.T., & Knight, R.T. (2002). *Principles of frontal lobe functioning*. New York: Oxford University Press.

Swan, G.E., & Lessov-Schlaggar, C.N. (2007) The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychology Review, 17,* 259-273.

Taffe, M.A., Davis, S.A., Yuan, J., Schroeder, R., Hatzidimitriou, G., Parsons, L.H., Ricaurte, G.A., & Gold, L.H. (2002). Cognitive performance of MDMA-treated rhesus monkeys: sensitivity to serotonergic challenge. *Neuropsychopharmacology, 27,* 993-1005.

Taffe, M.A., Huitron-Resendiz, S., Schroeder, R., Parsons, L.H., Henriksen, S.J., & Gold, L.H. (2003). MDMA exposure alters cognitive and electrophysiological sensitivity to rapid tryptophan depletion in rhesus monkeys. *Pharmacology, Biochemistry, and Behavior, 76,* 141-152.

Tapert, S.F., Brown, G.G., Baratta, M.V., & Brown, S.A. (2004). fMRI BOLD response to alcohol stimuli in alcohol dependent young women. *Addictive Behaviors, 29,* 33-50.

Tarter, R.E., Kirisci, L., Habeych, M., Reynolds, M., & Vanyukov, M. (2004). Neurobehavior disinhibition in childhood predisposes boys to substance use disorder by young adulthood: direct and mediated etiologic pathways. *Drug and Alcohol Dependence, 73,* 121-132.

Teasdale, J.D., Williams, J.M., Soulsby, J.M., Segal, Z.V., Ridgeway, V.A., & Lau, M.A. (2000) Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *Journal of Consulting and Clinical Psychology, 68,* 615-623

Teichner, G., Horner, M.D., Roitzsch, J.C., Herron, J., & Thevos, A. (2002) Substance abuse treatment outcomes for cognitively impaired and intact outpatients. *Addictive Behaviors, 27,* 751-763.

Tobit, J. (1958). Estimation of relationship for limited dependent variables. *Econometrica 26,* 24-36.

Townshend, J.M., & Duka, T. (2003). Mixed emotions: alcoholics' impairments in the recognition of specific emotional facial expressions. *Neuropsychologia 41,* 773-782.

Troyer, A.K., Moscovitch, M., Winocur, G., Alexander, M.P., & Stuss, D. (1998) Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia, 36,* 499-504.

Tucker, K.A., Potenza, M.N., Beauvais, J.E., Browndyke, J.N., Gottschalk, C., & Kosten, T.R. (2004). Perfusion abnormalities and decision-making in cocaine dependence. *Biological Psychiatry, 56,* 527-530.

Turner, T.H., LaRowe, S., Horner, M.D., Herron, J., & Malcolm, R. (2009) Measures of cognitive functioning as predictors of treatment outcome for cocaine dependence. *Journal of Substance Abuse Treatment, 37,* 328-334.

UNODC: United Nations Office on Drugs and Crime (2008). *United Nations World Drug Report.* Retrieved from http://www.unodc.org/unodc/en/data-and-analysis/WDR-2008.html

UNODC: United Nations Office on Drugs and Crime (2009). *United Nations World Drug Report.* Retrieved from http://www.unodc.org/unodc/en/data-and-analysis/WDR-2009.html

van der Elst, W., van Boxtel, M.P.J., van Breukelen, G.J.P., & Jolles, J. (2006) The Stroop color-word test. Influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment, 13,* 62-79.

van der Plas, E.A.A., Crone, E.A., van den Wildenberg, W.P.M., Tranel, D., & Bechara, A. (2009). Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women. *Journal of Clinical and Experimental Neuropsychology, 31,* 706-719.

van Gorp, W.G., Wilkins, J.N., Hinkin, C.H., Moore, L. H., Hull, J., Horner, M.D., & Plotkin, D. (1999). Declarative and procedural memory functioning in abstinent cocaine abusers. *Archives of General Psychiatry, 56,* 85-89.

Vanderploeg, R.D. (2000). *Clinician's guide to neuropsychological assessment* (2nd edition). Hillslade, New Jersey: Lawrence Erlbaum Associates.

Velligan, D.I., Ritch, J.L., Sui, D., DiCocco, M., & Huntzinger, C.D. (2002). Frontal systems behavior scale in schizophrenia: relationships with psychiatric symptomatology, cognition and adaptive function. *Psychiatry Research, 113,* 227-236.

Verdejo-García, A., Aguilar de Arcos, F., & Pérez-García, M. (2004). Alterations in the decision making processes linked to the ventromedial prefrontal cortex in drug-abusing patients. *Revista de Neurologia, 38,* 601-606.

Verdejo-García, A., Alcázar-Córcoles, M.A., Gómez-Jarabo, G.A., & Pérez-García, M. (2004). Pautas para el desarrollo científico y profesional de la neuropsicología forense. *Revista de Neurología, 39,* 60-73.

Verdejo-García, A., & Bechara, A. (2009). A somatic marker theory of addiction. *Neuropharmacology, 56,* 48-62.

Verdejo-García, A., Bechara, A., Recknor, E.C., & Pérez-García, M. (2006). Decision-making and the Iowa gambling task: ecological validity in individuals with substance dependence. *Psychologica Belgica, 46*, 55-78.

Verdejo-Garcia, A., Benbrook, A., Funderburk, F., David, P., Cadet, J.L., & Bolla, K.I. (2007c) The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug and Alcohol Dependence, 90,* 2-11.

Verdejo-García, A., Lawrence, A.J., & Clark, L. (2008) Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neuroscience and Biobehavioral Reviews, 32,* 777-810.

Verdejo-García, A. J., López-Torrecillas, F., Aguilar de Arcos, F., & Pérez-García, M. (2005b). Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. *Addictive Behaviors, 30,* 89-101.

Verdejo-García, A., López-Torrecillas, F., Giménez, C.O., & Pérez-García, M. (2004). Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. *Neuropsychology Review, 14,* 1-41.

Verdejo-García, A., Perales, J.C., & Pérez-García, M. (2007a). Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addictive Behaviors, 32,* 950-966.

Verdejo-García, A., & Pérez-García, M. (2007a). Profile of executive deficits in cocaine and heroin polysubstance users: common and differential effects on separate executive components. *Psychopharmacology, 190,* 517-530.

Verdejo-García, A., & Pérez-García, M. (2007b). Ecological assessment of executive functions in substance dependent individuals. *Drug and Alcohol Dependence*, *90,* 48-55.

Verdejo-García, A., & Pérez-García, M. (2008). Substance abusers' self-awareness of the neurobehavioral consequences of addiction. *Psychiatry Research, 158,* 172-180.

Verdejo-García, A., Pérez-García, M., & Bechara, A. (2006). Emotion, Decision-Making and Substance Dependence: A Somatic-Marker Model of Addiction. *Current Neuropharmacology, 4,* 17-31.

Verdejo-García, A., Rivas-Pérez, C., López-Torrecillas, F., & Pérez-García, M. (2006). Differential impact of severity of drug use on frontal behavioral symptoms. *Addictive Behaviors, 31,* 1373-1382.

Verdejo-García, A., Rivas-Pérez, C., Vilar-López, R., & Pérez García, M. (2007b). Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug and Alcohol Dependence, 86,* 139-146.

Verdejo-García, A., Toribio, C., Orozco, K., Puente, K., & Pérez-García, M. (2005a). Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. *Drug and Alcohol Dependence, 78,* 283-288.

Verhaeghen, P., & Cerella, J. (2002) Aging, executive control, and attention: a review of meta-analyses. *Neuroscience and Biobehavioral Reviews, 26,* 849-857.

Vericco, C.D., Jentsch, J.D., & Roth, R.H. (2003). Persistent and anatomically selective reduction in prefrontal cortical dopamine metabolism after repeated, interminttent, cannabinoid administration to rats. *Synapse, 49,* 61-66.

Verrico, C.D., Jentsch, J.D., Roth, R.H., & Taylor, J.R. (2004) Repeated, intermittent 9-tetrahydrocannabinol administration to rats impairs acquisition and performance of a test of visuospatial divided attention. *Neuropsychopharmacology, 29,* 522-529.

Volkow, N. D., Chang, L., Wang, G., Fowler, J. S., Ding, Y., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C., & Pappas, N.

(2001). Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *American Journal of Psychiatry, 158,* 2015-2021.

Volkow, N. D., Chang, L., Wang, G., Fowler, J. S., Franceschi, D., Sedler, M. J., Gatley, S. J., Hitzerman, R., Ding, Y., Wong, C. & Logan, J. (2001). Higher cortical and lower subcortical metabolism in detoxified methamphetamine abusers. *American Journal of Psychiatry, 158,* 383-389.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Franceschi, D., Sedler, M., Gatley, S.J., Miller, E., Hitzemann, R.., Ding, Y.S. & Logan, J. (2001) Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *The Journal of Neuroscience, 21,* 9414-9418.

Volkow, N.D., Fowler, J.S., & Wang, G.J. (2004). The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology, 47,* 3-13.

Volkow, N., Fowler, J.S., Wang, G.J., Telang, F., Logan, J., Jayne, M., Ma, Y., Pradhan, K. & Wong, C. (2009). Cognitive control over craving in cocaine abusers decreased metabolism in right ventral striatum and medial orbitofrontal cortex. *Journal of nuclear medicine, 50,* 78.

Volkow, N.D., Gillespie, H., Mullani, N., Tancredi, L., Grant, C., Valentine, A., & Hollister, L. (1996). Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. *Psychiatry Research: Neuroimaging Section, 67,* 29-38.

Volkow, N.D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Hitzeman, R., Chen, A. D., Dewey, S. L., & Pappas, N. (1997). Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. *Nature, 386,* 830-833.

Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J., Childress, A.R., Jayne, M., Ma, Y., Wong, C. (2006). Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *The Journal of Neuroscience, 26,* 6583-6588.

Vollenweider, F.X., Lechti, M.E., & Paulus, M.P. (2005). MDMA affects both error-rate dependent and independent aspects of decision-making in a two-choice prediction task. *Journal of Psychopharmacology, 19,* 366-374.

Wadsworth, E.J.K., Moss, S.C., Simpson, S.A., & Smith, A.P. (2006) Cannabis use, cognitive performance and mood in a sample of workers. *Journal of Psychopharmacology, 20,* 14-23.

Wang, G.J., Volkow, N.D., Chang, L., Miller, E., Sedler, M., Hitzemann, R., Zhu, W., Logan, J., Ma, Y., & Fowler, J.S. (2004). Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. *American Journal of Psychiatry, 161,* 242-248.

Ward, J., Hall, K., & Haslam, C. (2006). Patterns of memory dysfunction in current and 2-year abstinent MDMA users. *Journal of Clinical and Experimental Neuropsychology, 28,* 306-324.

Wareing, M., Fisk, J.E., Murphy, P., & Montgomery, C. (2004). Verbal working memory deficits in current and previous users of MDMA. Human Psychopharmacology, 19, 225-234.

Wareing, M., Fisk, J.E., Murphy, P., & Montgomery, C. (2005). Visuo-spatial working memory deficits in current and former users of MDMA ('ecstasy'). *Human Psychopharmacology, 20,* 115-123.

Wechsler, D. (1997a). *Wechsler adult intelligence scale, 3rd Edition.* The Psychological Corporation. San Antonio, Texas.

Wechsler, D. (1997b). *Wechsler memory scale, 3rd Edition*. The Psychological Corporation. San Antonio, Texas.

Wendt, P.E., & Risberg, J. (2001) Ethanol reduces rCFB activation of left dorsolateral prefrontal cortex during a verbal fluency task. *Brain and Language, 77,* 197-215.

Whitlow, C.T., Liguori, A., Livengood, L.B., Hart, S.L., Mussat-Whitlow, B.J., & Lamborn, C.M. (2004) Long-term heavy marijuana users make costly decisions on a gambling task. *Drug and Alcohol Dependence, 76,* 107-111.

Wilson, B.A., Alderman, N.A., Burgess, P.W., Ernslie, H., & Evans, J.J. (1996). *Behavioural Assessment of the Dysexecutive Syndrome.* Thames Valley Test Company. Bury St. Edmunds.

Wilson, S.J., Sayette, M.A., & Fiez, J.A. (2004). Prefrontal responses to drug cues: a neurocognitive analysis. *Natural Neuroscience, 7,* 211-214.

Woicik, P.A., Moeller, S.J., Alia-Klein, N., Maloney, T., Lukasik, T.M., Yeliosof, O., Wang, G.J., Volkow, N.D., & Goldstein, R.Z. (2008). The neuropsychology of cocaine addiction: recent cocaine use masks impairment. *Neuropsychopharmacology, 34,* 1112-1122.

Wood, S.C., Fay, J., Sage, J.R., & Anagnostaras, S.G. (2007). Cocaine and Pavlovian fear conditioning: dose-effect analysis. *Behavioural Brain Research, 176,* 244-250.

Woods, SP., Rippeth, JD., Conover, E., Gongvatana, A, González, R., Carey, CL, Cherner, M., Heaton, RK., & Grant, I. (2005). Deficient strategic control of verbal encoding and retrieval in individuals with methamphetamine dependence. *Neuropsychology, 19,* 35-43.

Wrase, J., Makris, N., Braus, D.F., Mann, K., Smolka, M.N., Kennedy, D.N., Caviness, V.S., Hodge, S.M., Tang, L., Albaugh, M., Ziegler, D.A., Davis, O.C., Kissling, C., Schumann, G., Breiter, H.C., & Heinz, A. (2008). Amygdala volume associated with alcohol abuse relapse and craving. *The American Journal of Psychiatry, 165,* 1179-1184.

Wu, L.T., Parrott, A.C., Ringwalt, C.L., Patkar, A.A., Mannelli, P., & Blazer, D.G. (2009). The high prevalence of substance use disorders among recent MDMA users compared with other drug users: Implications for intervention. *Addictive Behaviors, 34,* 654, 661.

Yang, L., Sun, Z.S., & Zhu, Y.P. (2007) Proteomic analysis of rat prefrontal cortex in three phases of morphine-induced conditioned place preference. *Journal of Proteome Research, 6,* 2239-2247.

Yip, J., & Lee, T. (2005). Effect of ecstasy use on neuropsychological function: a study in Hong Kong. *Psychopharmacology, 179,* 620-628

Young, A.W., Perrett, D.I., Calder, A.J., Sprengelmeyer, R., Ekman, P. (2002). *Facial expressions of emotion: stimuli and tests (FEEST).* Thames Valley Test Company, Bury St. Edmunds.

Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., & Lubman, D.I. (2008) Regional brain abnormalities associated with long-term heavy cannabis use. *Archives of General Psychiatry, 65,* 694-701.

Yurgelun-Todd, D.A., Gruber, S.A., Hanson, R.A., Baird, A.A., Renshaw, P., & Pope, H.G. (1999). Residual effects of marijuana use: a fMRI study. Proceedings of the 60 th annual scientific meeting of the college on problems of drug dependence. *NIDA Research Monograph, 179,* 78.

Zakzanis, K.K. (2001) Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effects size analyses for neuropsychological researchers. *Archives of Clinical Neuropsychology, 16,* 653-677.

Zakzanis, K.K., Campbell, Z., & Jovanovski, D. (2007). The neuropsychology of ecstasy (MDMA) use: a quantitative review. *Human Psychopharmacology, 22,* 427-435.

Zakzanis, K.K., & Young, D.A. (2001). Executive function in abstinent MDMA ('ecstasy') users. Medicine Science Monitor, 7, 1292-1298.

Zakzanis, KK., Young, DA., & Campbell, Z. (2003). Prospective memory impairment in abstinent MDMA ("ecstasy") users. *Cognitive Neuropsychiatry, 8,* 141-153.

Zelazo, P.D., Carter, A., Reznick, J.S., & Frye, D. (1997) Early development of executive function: A problem-solving framework. *Review of General Psychology, 1,* 198-226.

Zgierska, A., Rabago, D., Zuelsdorff, M., Coe, C., Miller, M., & Fleming, M. (2008) Mindfulness meditation for alcohol relapse prevention: a feasibility pilot study. *Journal of Addiction Medicine, 2,* 165-173

ANEXOS

Anexo I

Elsevier Editorial System(tm) for Neuroscience & Biobehavioral Reviews
Manuscript Draft

Manuscript Number: NEUBIOREV-D-09-00180R1

Title: What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance?

Article Type: Review Article

Keywords: cannabis, psychostimulants, opioids, alcohol, polysubstance use, neuropsychology, emotion, memory, executive functions.

Corresponding Author: MsC Maria Jose Fernandez-Serrano,

Corresponding Author's Institution: Universidad de Granada

First Author: Maria Jose Fernandez-Serrano

Order of Authors: Maria Jose Fernandez-Serrano; Miguel Perez-Garcia; Antonio Verdejo-Garcia

Abstract: Most substance abusers simultaneously use and abuse more than one substance, even when there is a clear drug of choice. This pattern creates a great challenge in relating neuropsychological findings in drug users to a certain drug. This review aims to: (i) discuss results from neuropsychological studies using different research methodologies that may improve our understanding of specific vs. generalized effects of different drugs on neuropsychological performance; and (ii) determine which neuropsychological mechanisms are impaired in the same way by the use of different drugs, and which impairments are specific to certain substances, including cannabis, psychostimulants, opioids and alcohol. We review evidence from human studies in chronic substance abusers using three methodologies: (i) studies on 'pure' users of one particular substance, (ii) studies that methodologically control the effects of drugs co-abused, and (iii) studies contrasting subgroups of polysubstance users with different drugs of choice. Converging evidence from these approaches indicates that all the drugs studied are commonly associated with significant alterations in the neuropsychological domains of episodic memory, emotional processing, and the executive components of updating and decision-making. However, there is evidence of a greater reliability in the association of certain substances with specific neuropsychological domains. Specifically, there are relatively more robust effects of psychostimulants and alcohol use on impulsive action and cognitive flexibility, of alcohol and MDMA use on spatial processing, perceptual speed and selective attention, cannabis and methamphetamine on prospective memory deficits, and cannabis and MDMA on processing speed and complex planning. The magnitude of both generalized and specific neuropsychological effects is overall attenuated in samples achieving long-term abstinence, but there are persistent psychostimulant-related effects on updating, inhibition, flexibility and emotional processing, and opioid-related effects on updating and decision-making.

What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance?

Maria Jose Fernández-Serrano[*a], Miguel Pérez-García [a,b], & Antonio Verdejo-García[*a,b].

[a] Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Granada, Campus de Cartuja, s/n, 18071 Granada, Spain

[b] Institute of Neurosciences F. Oloriz, Universidad de Granada, Spain

*Corresponding authors:

Maria Jose Fernández-Serrano/ Antonio Verdejo-García

Departamento de Personalidad, Evaluacion y Tratamiento Psicologico, Facultad de Psicologia de la Universidad de Granada, Campus de Cartuja, s/n, 18071 Granada, Spain. Tel.: +34-958-242-948; fax: +34-958-243-749.

E-mail address: mjfser@ugr.es (M.J. Fernández-Serrano)/ averdejo@ugr.es (A. Verdejo-García).

Abstract

Most substance abusers simultaneously use and abuse more than one substance, even when there is a clear drug of choice. This pattern creates a great challenge in relating neuropsychological findings in drug users to a certain drug. This review aims to: (i) discuss results from neuropsychological studies using different research methodologies that may improve our understanding of specific vs. generalized effects of different drugs on neuropsychological performance; and (ii) determine which neuropsychological mechanisms are impaired in the same way by the use of different drugs, and which impairments are specific to certain substances, including cannabis, psychostimulants, opioids and alcohol. We review evidence from human studies in chronic substance abusers using three methodologies: (i) studies on 'pure' users of one particular substance, (ii) studies that methodologically control the effects of drugs co-abused, and (iii) studies contrasting subgroups of polysubstance users with different drugs of choice. Converging evidence from these approaches indicates that all the drugs studied are commonly associated with significant alterations in the neuropsychological domains of episodic memory, emotional processing, and the executive components of updating and decision-making. However, there is evidence of a greater reliability in the association of certain substances with specific neuropsychological domains. Specifically, there are relatively more robust effects of psychostimulants and alcohol use on impulsive action and cognitive flexibility, of alcohol and MDMA use on spatial processing, perceptual speed and selective attention, cannabis and methamphetamine on prospective memory deficits, and cannabis and MDMA on processing speed and complex planning. The magnitude of both generalized and specific neuropsychological effects is overall attenuated in samples achieving long-term abstinence, but there are persistent psychostimulant-related effects on updating, inhibition, flexibility and emotional processing, and opioid-related effects on updating and decision-making.

Key words: cannabis, psychostimulants, opioids, alcohol, polysubstance use, neuropsychology, emotion, memory, executive functions.

1. Introduction

The use of psychoactive substances is associated with neuropsychological deficits in mechanisms related to emotion, memory and executive functions. Impairment of these functions does not only interfere with the cognitive performance of drug users in a general manner (thus influencing their quality of life, their academic/work performance, or their ability to receive cognitive treatment), but they also affect the core aspect of addiction: the tendency to continue drug use despite its increasingly negative consequences. The interaction between: (1) motivational and memory mechanisms, which amplify the reinforcing value associated with the substance, and (2) poor performance of the executive control mechanisms, in charge of regulating automated behaviors, is at the root of the dependence on different drugs (Bechara, 2005; Garavan and Hester, 2007; Goldstein and Volkow, 2002; Verdejo-García and Bechara, 2009). Therefore, one possibility is that all drugs of abuse produce generalized impairments in these neuropsychological mechanisms. In this case, the specific neuropsychological effects of a substance (e.g., a stimulant) and those produced by another substance (e.g., an opioid) would overlap, even though their pharmacological effects are quite different. This possibility would reduce the scientific interest in studying a certain substance in isolation, and it would support the explanatory power of studies performed on polysubstance users (which are most of those found in the literature). The alternative possibility is that each substance, depending on its characteristic pharmacological effects, produces a specific neuropsychological profile differing from the neuropsychological profiles of other drugs. This hypothesis would reduce the explanatory value of the research on polysubstance use, as it would mask the characteristic effects of each drug on neuropsychological performance. Although studies with animals have elegantly addressed this question, research with humans is clearly hindered by the difficulties to select 'pure' users of one drug only. In spite of this limitation, some studies have dealt with the problem by sampling populations with cultural peculiarities (Fishbein et al., 2007; Halpern et al., 2004), investigating substances with a relatively low co-abuse rate (e.g., alcohol or cannabis) (Fein et al., 2004; Fried et al., 2005), or controlling polysubstance use through methodological designs or statistical techniques (Bolla et al., 2000; Morgan et al., 1999, 2006). The objectives of this review are: (1) to critically examine neuropsychological studies carried out on drug users from both approaches and (2) to determine which neuropsychological mechanisms are impaired in

the same manner by the use of different drugs, and which deficits are specific to certain substances. Given these fundamental objectives, this will be a systematic review analyzing both specific and general neuropsychological effects of the abuse of cannabis, stimulants (cocaine and methamphetamine), 3, 4-Methylenedioxymethamphetamine (MDMA; "Ecstasy"), opioids (heroin and methadone) and alcohol on mechanisms of emotion, memory and executive control. Due to the inherent diversity of the concept of "executive control", the review will be approached from a multi-component perspective, encompassing mechanisms of updating (including tests of working memory, controlled access and production of information and reasoning), inhibition (including tests of impulsive action –response inhibition and self-regulation, and impulsive choice –reflection-impulsivity, time estimation, delay discounting), flexibility (including attentional/set-shifting and reversal learning tests) and decision-making (including probabilistic choice and gambling decision tests) (Verdejo-García and Pérez-García, 2007). We present a brief definition of each of the neuropsychological domains addressed in the review, and a list of the neuropsychological tests typically used to measure them, in Table 1. It is important to mention that dysfunctions in some of these neuropsychological domains (e.g., inhibition or decision-making) have been proposed to precede initial drug use and to predispose certain individuals to being attracted to different drugs (Dalley et al., 2007; Verdejo-García et al., 2008); therefore, although this review is focused on neuropsychological effects of drugs use, we prevent ourselves about providing strong causal assumptions throughout the text.

Insert Table 1 here

In the first part of the manuscript, we shall briefly present relevant evidence about specific effects of these substances based on animal and pharmacological studies using controlled drug administration in healthy individuals. In the second part of the manuscript, we perform a systematic review of neuropsychological studies investigating specific vs. generalized effects of these drugs through three different research approaches that can shed light on our objectives: (i) studies on selected samples of 'pure' users of certain substances, (ii) studies with methodological control of the effect of the co-abuse of drugs other than the one of interest, and (iii) studies on polysubstance users with different main drugs of choice. Finally, we will integrate the results, in order to provide insights about which skills are affected indistinctly by all drugs and which skills are differentially affected by specific substances taking into account the time line of drug effects (i.e., acute, short-term, mid-term and long-term).

2. Methods.

First, in Section 3, we narratively review relevant findings from animal and human controlled drug-administration studies selected by the authors with the aim of providing a background about the selective pharmacological/ neuropsychological effects of each of the individual substances studied.

For Sections 4 to 6, we performed a systematic review of peer-reviewed studies tracked from the PubMed and PsycInfo databases. These studies stemmed from searches combining the following terms:

DRUG (OR SUBSTANCE) ABUSE,

DRUG (OR SUBSTANCE) DEPENDENCE,

DRUG (OR SUBSTANCE) ADDICTION,

CANNABIS (+ABUSE/DEPENDENCE/ADDICTION),

PSYCHOSTIMULANTS (+ABUSE/DEPENDENCE/ADDICTION),

COCAINE (+ABUSE/DEPENDENCE/ADDICTION),

AMPHETAMINE (+ABUSE/DEPENDENCE/ADDICTION),

METHAMPHETAMINE (+ABUSE/DEPENDENCE/ADDICTION),

MDMA (+ABUSE/DEPENDENCE/ADDICTION),

ECSTASY (+ABUSE/DEPENDENCE/ADDICTION),

OPIATES (+ABUSE/DEPENDENCE/ADDICTION),

OPIOIDS (+ABUSE/DEPENDENCE/ADDICTION),

HEROIN (+ABUSE/DEPENDENCE/ADDICTION),

METHADONE (+ABUSE/DEPENDENCE/ADDICTION),

ALCOHOL (+ABUSE/DEPENDENCE/ADDICTION).

AND

COGNITION, NEUROPSYCHOL*, MEMORY, ATTENTION, EXECUTIVE FUNCTIONS, WORKING MEMORY, FLUENCY, REASONING, FLEXIBILITY, IMPULSIVITY, (DIS)INHIBITION, DELAY

DISCOUNTING, DECISION MAKING, EMOTION PERCEPTION, EMOTION EXPERIENCE, EMOTION PROCESSING, (PSYCHO)MOTOR PROCESSING, (VISUAL)SPATIAL PROCESSING.

Next, we reviewed the resulting papers according to the inclusion criteria detailed below and distributed them, based on their methodological approach, in one of the three main sections: studies in 'pure' users, studies with methodological control of polysubstance use, or studies in polysubstance users (these latter studies were subdivided in two subgroups: studies comparing polysubstance users with healthy controls, and studies comparing polysubstance users of one drug of choice with polysubstance users of another drug of choice). The inclusion/exclusion criteria for the systematic search were:

- Manuscripts published between 1999 and 2009 (including papers ahead of print available at databases before January 2010): this criteria was meant to review only those studies published during the last decade, encompassing the period after the surge of contemporary neuroscientific models of addiction (e.g., Everitt and Robbins, 2005; Goldstein and Volkow, 2002; Koob and LeMoal, 2001) and filtering earlier studies, many of which had important methodological drawbacks (see Verdejo-García et al., 2004 for review).
- Studies conducted in individuals with substance use disorders with no psychiatric comorbidities.
- Studies in which the main aim was neuropsychological assessment (excluding neuroimaging studies in which neurocognitive paradigms are adapted to be administered inside the scanner and studies using cognitive psychology tests not validated for use in neuropsychology).
- Studies including at least one psychometrically validated neuropsychological measure of the domains of interest (see Table 1 for a definition of the domains of interest).
- Participants had to have a minimum abstinence of 24 hours, since our main interest was to review non-acute neuropsychological effects of drugs of abuse and to rule out effects of drug-related intoxication.
- They had to include at least one comparison group of non-drug using individuals (with the exception of methodologically controlled subtraction studies –Section 5, where the control group of interest is, by definition, formed by other drug-using groups). These comparison groups had to be demographically matched to the drug using groups, or in case there were differences in demographic characteristics, they had to be statistically controlled.

We present the resulting selected studies organized according to the duration of abstinence in the drug user participants throughout the text; this is the key variable to differentiate between short-term (>48 hours<30 days of abstinence), mid-term (1 to 6 months of abstinence) and long-term (>6 months of abstinence) neuropsychological effects of drug use. In Tables (Tables 2 to 6) studies are organized in the same way. In these Tables we also provide, for each study, information about the number, main drug of choice and treatment status (i.e., non-treatment seekers, community treatment or residential treatment patients) of drug using participants, about the neuropsychological tests employed, and about which neuropsychological domains were found to be impaired vs. intact. With this information, readers can differentiate between domains that were assessed but found to be intact vs. domains that were not taxed by the neuropsychological test batteries. We have marked **in bold** those domains that were found to be impaired by each study. Furthermore, we have marked *in italics* those domains that were found to be impaired by different studies on the same drug, and we have underlined those domains that were found to be impaired across different studies addressing the effects of different drugs. Therefore, in each Table, those domains that are marked **in bold and underlined** represent generalized effects of different drugs, whereas those domains marked ***in bold and italics*** (not underlined) are the ones that have been shown to be associated with one specific drug by two or more studies (an index of consistent exclusive effects). These marks have been included to provide readers with shortcuts and rules to interpret the often quite diverse research findings in the field.

Finally, in Section 7 we provide a quantitative estimation of the mean magnitude of the neuropsychological effects (specific vs. generalized) of different drugs on different domains by calculating mean effect sizes obtained by studies using each of the three methodologies reviewed. We also provide a quantitative estimation of the mean magnitude of the neuropsychological effects of different drugs according to abstinence duration (short-, mid- or long-term). These results are displayed in Tables 6 and 7. These results are also used to build up the *Summary* subsections placed at the end of each section, where we only comment on neuropsychological effects reaching at least an average medium effect size (mean Cohen´s $d \geq 0.5$). Finally, we integrate the overall results and provide quantitatively-lead insights about the specific vs. generalized neuropsychological effects of different drugs.

3. Specific action mechanisms of each drug: animal studies and studies of acute drug administration in humans.

3.1. Cannabis

Cannabis produces its psychoactive effects in the brain by acting on the CB1 receptors. Animal evidence showed that the cannabinoid receptors are distributed in the brain in a similar way to the dopaminergic receptors, with high concentrations in the basal ganglia and hippocampus, although the highest concentrations of cannabinoid receptors are found in the cerebellum (Herkenham, 1992). Human imaging techniques have shown that the human brain also contains high densities of cannabinoid CB1 receptors in the frontal cortical regions, including the posterior cingulate cortex, superior frontal gyrus and orbitofrontal cortex (Burns et al., 2007). Cannabis stimulates the production of dopamine (DA) in an indirect way through the action of the CB1 receptors on the neurons of the GABA neurotransmitters and glutamate in the ventral tegmental area and the striatum (Camí and Farré, 2003).

Studies performed on mice (Niyuhire et al., 2007) and rats (Deadwyler et al., 2007; Fadda et al., 2004; Jentsch et al., 1998; Nava et al., 2001) reveal that administration of cannabis produces important alterations in working memory when doing the delayed-non-match-to-sample, radial maze, T maze, delay and Morris swimming pool navigation tasks. In rhesus monkeys, exposure to cannabis produced chronic changes in brain structures related to memory and emotion (hippocampus and amygdala) (Heath et al. 1980), and in rats THC exposure induced selective and persistent reductions in medial prefrontal cortex dopamine turnover (a key system for reward learning and decision-making) (Vericco et al., 2003).

Regarding the effects of acute cannabis administration, a review by Ranganathan and D'Souza (2006) concluded that the most consistent impairments were found on measures of episodic memory, both immediate and delayed free recall. Regarding executive functions, several studies have shown that at the acute level cannabis produces alterations in working memory (Ilan et al., 2004), response inhibition (Ramaekers et al., 2006) and decision-making (Lane et al., 2005; Ramaekers et al., 2006) in healthy subjects.

3.2. Psychostimulants (cocaine and methamphetamine)

From a neurochemical point of view, cocaine's most important action is the blockage of the monoamine transporters, inhibiting the reuptake of dopamine (DA), serotonin (5HT) and norepinephrine (NE). In their acute stage, methamphetamine blocks the reuptake of DA, producing depletion of DA and, to a lesser extent, 5HT, in the long term. In addition, methamphetamine exposure is associated with lower levels of dopamine in the striatum and a tendency toward a decrease in this neurotransmitter in the prefrontal cortex (Clemens et al., 2005).

Animal models have shown that repeated administration of cocaine leads to impairment in cognitive flexibility, specifically in perseveration and reversal learning linked to orbitofrontal cortex functioning (Jentsch et al., 2002; Schoenbaum et al., 2004; Stalnaker et al., 2006, 2009). Other authors have observed the existence of impairments in short term and long term memory and an increase in impulsivity, specifically in the delayed reinforcement paradigm, in rats exposed to cocaine (Paine et al., 2003; Santucci et al., 2004; Simon et al., 2007). In rats, methamphetamine produce various types of alterations, including alterations in time perception, time-based prospective memory, reversal learning, and spatial working memory (Cheng et al., 2007; Nagai et al., 2007).

Acute cocaine administration produces functional magnetic resonance imaging (fMRI)-indexed alterations in brain regions involved in reward processing, executive functions and emotional regulation, including mesolimbic and mesocortical regions, prefrontal cortex, and orbitofrontal cortex (Kufahl et al., 2005). Contradictory results have been found regarding the effects of acute cocaine administration on response inhibition, with some studies showing detrimental effects (Fillmore et al., 2002), while others found paradoxical improvements (Fillmore et al., 2005), mainly as a function of the dose (Fillmore et al., 2006). A recent fMRI study showed that acute cocaine-induced performance improvements were associated with increases in activation in the medial and lateral prefrontal regions, which may be chronically dysregulated in chronic users (Garavan et al., 2008). Acute administration of methamphetamine has been associated with transient improvements in psychomotor functioning, attention and perceptual speed, as well as an increase in risky decision-making (Johnson et al., 2000; Silber et al., 2006).

3.3. MDMA ('Ecstasy')

The most relevant component of ecstasy, MDMA causes alterations in the serotonergic brain system. Neurochemical and anatomical studies carried out using Positron Emission Tomography (PET) in humans and animals, specifically monkeys and baboons, reveal that the use of MDMA produces significant reductions in the 5HT transporter in different cortical and subcortical brain regions (McCann et al., 2005; Ricaurte et al., 2002).

Studies performed on non-human primates exposed to repeated doses of MDMA showed the existence of major behavioral impairments related to the serotonergic system (Frederick et al. 1998; Taffe et al., 2002, 2003). Long-lasting impairments were observed in the performance of MDMA-treated monkeys on impulsivity and memory domains measured with time estimation, learning and short-term memory tests (Frederick et al., 1995).

With regard to the acute effects of MDMA, various studies have shown that controlled low-dose administration of the drug produces acute alterations in selective attention, spatial memory, response inhibition and decision-making (Kuypers et al., 2007; Kuypers and Ramaekers, 2007; Ramaekers and Kuypers, 2006; Vollenweider et al., 2005). Other authors have also observed the existence of alterations in episodic memory as a result of co-administration of MDMA and alcohol (Dumont et al., 2008), and high motor activation as a result of the acute administration of MDMA alone (Dumont et al., 2007).

3.4. Opioids

Opioids produce their effects by stimulating the opioid receptor system (mu, delta and kappa). They also increase the levels of dopamine, but through an indirect route, by reducing the inhibitory activity of the GABA in the ventral tegmental area (Camí and Farré, 2003).

Studies performed on rats have shown that opioid exposure produces impairment in learning on the Morris swimming pool tasks and in performance across different spatial memory tasks (radial and Y maze) (Pu et al., 2002; Spain and Newsom, 1991).

Although difficult to perform for ethical reasons, studies on acute opioid administration in humans have observed impairments in working memory, episodic memory (Curran et al., 2001; Friswell et al., 2008) and emotional processing (Aguilar de Arcos et al., 2008).

3.5. Alcohol

Alcohol favors the synaptic inhibition produced by the GABA transmitter. The anesthetic effect occurs mainly through the inhibitory action it performs on the NMDA receptors of the glutamate neurotransmitter (see Sánchez-Tutret, 1997). Alcohol inhibits the release of oxytocin, vasopressin and possibly other hypothalamic peptides in a concentration within pharmacological limits. As for the stimulant effect of alcohol, at a neurochemical level it has been associated with increases in the release of dopamine in the ventral tegmental area and in the nucleus accumbens (Sánchez-Tutret, 1997).

Studies performed on animals have shown that postnatal exposure of rats to different doses of alcohol produces alterations in cerebral structures related to memory in the adult stage, specifically in hippocampal areas (Klintsova et al., 2007). Other studies performed on rats have shown that mice exposed to alcohol experienced difficulties in reversing previously acquired learning (reversal learning tasks, O'Leary-Moore et al., 2006).

Acute effects of alcohol exposure in adults include dissociated alterations in the memory systems. Alterations have been observed in the recognition of explicit, but not implicit, memory contents, in prospective memory and in response inhibition (Corbin and Cronce, 2007; Leitz et al., 2009; Ramaekers and Kuypers, 2006; Ray and Bates, 2006). Alcohol-exposed subjects also showed a slowing of the motor skills and alterations in emotional processing, specifically in the processing of unpleasant information (Franken et al, 2007).

4. Studies on samples of relatively 'pure' users.

In spite of the fact that they are quite difficult to conduct, since most drug users tend to use several substances simultaneously, studies on samples of mostly 'pure' users of one specific substance are ideally suited to reveal the neuropsychological effects of that particular substance.

4.1. Cannabis

Only one study of 'pure' cannabis users met criteria for inclusion. The study by Fried et al. (2005) used a non-treatment-seeker sample of 113 young probands: 19 current heavy users, 19 current light users, 16 former regular users and 59 controls. They were assessed yearly up to age 7 and once during each of the 9-12, 13-16 and 17-21 year intervals using neuropsychological tests measuring IQ, processing speed, memory and reasoning. This is a particularly strong design, since it allowed authors to disentangle current marijuana-related cognitive deficits from potential premorbid alterations. The period of abstinence of current users was 24 hours, whereas the abstinence duration of former users was of at least 3 months. The results of this study showed that, after controlling for premorbid cognitive function, current marijuana use produced alterations in episodic memory, both immediate and delayed, and in visual processing speed, with these subjects also showing a significantly lower IQ than the subjects who were not marijuana users. However, none of these deficits were observed in former users.

4.2. Psychostimulants

No studies of 'pure' cocaine users met criteria for inclusion. Two consecutive studies by Bolla et al. (2003) and Verdejo-García et al. (2007a) revealed decision-making deficits measured with the Iowa Gambling Task in the same sample of 'pure' cocaine users (with carefully monitored abstinence duration of 25 days). However, in both studies behavioral performance was obtained while subjects performed the task inside the scanner, and therefore results are not entirely comparable to those obtained using standard neuropsychological measures outside the scanner.

With regard to methamphetamine, three studies taxing the neuropsychological effects of this drug in 'pure' users during mid- and long-term abstinence met criteria for inclusion. All these studies were conducted in individuals following residential treatment or on probation. Volkow et al. (2001) conducted a neuropsychological and dopamine-transporter-binding PET imaging study that retested five methamphetamine-abusing individuals after a 12- to 17-month period of abstinence. Their imaging results showed significant increases in basal ganglia dopamine transporters availability at follow-up. However, re-test of cognitive performance showed only mild (non-significant) improvements in gross motor skills and episodic memory, but persistent deficits on fine-

grained psychomotor function and executive-based interference during memory encoding. Moon et al. (2007) studied verbal and visual episodic memory in 19 methamphetamine dependent subjects with a mean abstinence of 1.79 years (although with a high variability) and 18 non-drug users. The results showed that mid-term abstinent methamphetamine users had intact performance on verbal memory, but impaired performance on the visual memory task (an adaptation of the Rey Complex Figure Test), which involves visual memory as well as planning and organizational skills. More recently, Salo et al. (2009) evaluated performance differences on the Stroop test between methamphetamine users who recently initiated abstinence (n=38, average abstinence of 2.6 months), methamphetamine users who had a long-term abstinence duration (n=27, average abstinence of 31.5 months), and non-users (n=33). The results showed that methamphetamine users with mid-term abstinence exhibited greater deficits in response inhibition compared to both the non-user group and methamphetamine users who had long-term abstinence; long-term abstinent methamphetamine users did not differ from controls. This finding may be interpreted as a sign of recovery of response inhibition skills with protracted methamphetamine abstinence.

4.3. MDMA ('Ecstasy')

Two recent studies that have managed to sample relatively 'pure' MDMA users met criteria for inclusion. Halpern et al., (2004) examined the effects of exclusive MDMA use on executive functions, specifically on working memory and response inhibition. The sample of non-treatment seeker exclusive MDMA users was recruited in a region of the United States where religious traditions strongly discouraged alcohol, tobacco, and any other illicit drug use. More specifically, the sample of users was made up of two subgroups: light MDMA users (n=12) who presented a lifetime consumption ranging from 22 to 50 pills, and heavy MDMA users (n=11) who presented a lifetime consumption of more than 50 pills. Both groups were evaluated after 10 days of abstinence. The results of the study showed the existence of statistically significant cognitive deficits only among users who consumed more than 50 pills. These users showed alterations on the Stroop test, where they performed more slowly on all parts of the task and had a greater number of interference errors, demonstrating alterations in cognitive processing speed and higher impairment in response inhibition. Moreover, they presented alterations in their performance on a multitasking self-regulation test, the Revised Strategy Application Task (R-SAT), as they used inappropriate strategies, in spite of beginning the task more quickly than the other groups.

This response pattern in the R-SAT indicates poor inhibition, as well as alterations in the ability to self-regulate prepotent response, since MDMA users were unable to reverse a response pattern yielding initial benefits that would progressively disappear. A second study on the effects of MDMA use after mid-term abstinence was conducted in Hong Kong by Yip and Lee (2005) in a sample of non-treatment seeker 'pure' users. These authors investigated the effects of MDMA on episodic memory and on the updating component of executive functions, specifically in tests of working memory, fluency and selective attention. They compared 100 controls to a sample of 100 regular ecstasy users who were not users of any other substance and had an average abstinence of 2.23 months. The results showed that ecstasy users presented alterations on both verbal and non-verbal tasks of episodic memory, selective attention, and on the updating component of executive functions, specifically for working memory and verbal fluency measures, but not figural fluency, where they performed better than controls.

4.4. Opioids

There has been little research on the neurocognitive effects produced by heroin in pure users of this substance, probably because heroin is a 'late-stage' drug that users get to after an extensive use of other substances. Nonetheless, one recent study, conducted in a selected sample of Russian heroin users following residential treatment, met the proposed criteria for inclusion. Fishbein et al. (2007) contrasted the cognitive performance of four groups of participants: pure users of heroin (n=100), co-users of heroin and alcohol (n=60), pure alcohol users (n=102), and non-users (n=160), on measures of episodic memory and different components of executive functions, including working memory, decision-making, planning/problem solving, response inhibition, and cognitive flexibility. Users were evaluated after 3 weeks of abstinence. The data showed that heroin users had impaired performance on decision-making (measured by the Cambridge Decision Making Task); as their decisions were riskier in spite of taking more time to make them. However, performance of 'pure' heroin users on visual episodic memory and problem-solving tasks was better than that of the other two groups, heroin+alcohol and alcohol. It seems, therefore, that visual memory and reasoning/problem solving alterations would be more closely linked to alcohol rather than heroin use, whereas there is a significant association between heroin use and decision-making alterations.

4.5. Alcohol

Several studies have addressed the neuropsychological effects produced by exclusive alcohol use, most of them conducted in samples of alcohol-dependent individuals following residential-treatment. A first group of these studies investigated cognitive performance during short-term abstinence (<30 days). Bjork et al. (2004) found significant alterations in different forms of impulsivity (including response inhibition, delay discounting and risk-taking) in 130 alcohol dependent subjects who had been alcohol abstinent for 1 week. Interestingly, when alcohol users were subdivided according to age at onset of alcohol use and family history (Type I vs. Type II), early onset alcoholics (Type II) had poorer performance on response inhibition, but both groups performed similarly on delay discounting and risk taking measures. These results suggest that alcohol-related deleterious effects relate to impulsive choice and decision-making, whereas alterations in impulsive action might be premorbid. A study by Ratti et al. (2002) showed that a group of alcoholics (n=22 with 3 weeks of abstinence) who were not users of other substances presented impairments in abstraction, problem-solving, cognitive flexibility, attention and perceptual motor speed. They also had higher impulsivity levels than non-users in different dimensions, including motor inhibition alterations on reaction time tasks and a significant increase in the preference for immediate reward options in a delay-discounting task. A study by Schottenbauer et al. (2007) evaluated memory alterations in a group of alcoholics (n=176) who had not used any other drugs for at least 6 months prior to the study and who had been alcohol abstinent for 3 weeks. The results showed that the alcohol-using subjects presented an altered performance on a word-learning memory task; they needed more time to learn the word list and had more difficulties to retrieve what they had learned.

When considering alcohol effects observed after a mid-term abstinence period, Errico et al. (2002) employed a comprehensive neuropsychological battery of memory and executive functions measures, but only found alterations in verbal episodic memory in alcoholic subjects abstinent for 32 days. When considering the effects of this substance at long-term, two consecutive studies from the same group have provided some keys to reveal potential recovery of cognitive functioning across abstinence. The first study by Fein et al. (2004) specifically assessed decision-making performance (measured by the Iowa Gambling Task). The sample was composed by 44 long-term abstinent alcoholics (average abstinence of 6.6 years), who were non-treatment seekers, and 58 healthy subjects. Results showed that, after this period of abstinence, alcoholic users had yet a poorer decision-

making performance than controls. A later study by Fein et al. (2006), employing a much more comprehensive neuropsychological assessment to explore cognitive flexibility, attention, auditory working memory, immediate and delayed episodic memory, psychomotor function, reaction time, spatial processing and verbal skills, showed that long-term abstinent alcoholics (average abstinence of 6.7 years, n=48), non-treatment seekers and ex-residential treatment participants, performed similarly to non alcohol users (n=48) in all the domains assessed, except for the spatial processing domain. These results show that protracted abstinence can resolve most of the neurocognitive deficits associated with alcoholism, except for persistent deficits in spatial processing and decision-making.

Insert Table 2 here

4.6. Summary

According to the studies on samples of relatively 'pure' users of one particular drug, the most consistent generalized effects across substances are: episodic memory, showing large mean effect sizes for cannabis, methamphetamine and MDMA, and medium mean effect sizes for opioids and alcohol; and impulsive action, showing large mean effect sizes for methamphetamine and medium mean effect sizes for MDMA and alcohol. Interestingly, the effects of methamphetamine and alcohol on impulsive action covary with their effects on psychomotor functioning, possibly indicating generalized neural substrates of both substances. Recent imaging work indicates that these deficits are related to dysfunction of the brain system formed by the pre-supplementary motor area, the inferior frontal gyrus and the basal ganglia (Aron et al., 2007). With regard to episodic memory, although all drugs seem to impair this function, they could be tapping on different subprocesses. For example, the effects of methamphetamine on episodic memory appear to be related to altered executive monitoring of encoding strategies during verbal learning (Volkow et al., 2001) and to altered planning/organization skills during visual memory (Moon et al., 2007). Reasoning deficits are shared by pure users of heroin and alcohol, although mean effect sizes are larger for alcohol. Similarly, processing speed deficits are shared by alcohol and cannabis users, although they only seem to persist during mid-term abstinence in alcohol-using individuals. As for exclusive effects of different drugs, results from this methodology indicate robust exclusive effects of alcohol use on spatial processing and cognitive flexibility –set-shifting, and of MDMA use on verbal fluency. Nonetheless, these conclusions should be qualified by the fact that there are not available studies in 'pure' users' studies of drugs like cocaine, which is also significantly linked to updating and set-shifting abnormalities. The

same limitation (due to the lack of available studies) applies to the domain of decision-making, which has been only explored by studies in 'pure' users of alcohol and cocaine, preventing us from drawing strong conclusions about this ability. Future studies should aim to address these gaps in the literature. Finally, the most robust long-term effects (>6 months of abstinence) are visual-spatial and decision-making deficits in alcoholics, and episodic memory and psychomotor functioning deficits in methamphetamine abusers.

5. Methodologically controlled studies for studying specific effects

The obvious difficulties in recruiting samples of 'pure' users of any drug have favored the development of studies that attempt to control for polysubstance use through methodological strategies. One of the most commonly used designs for this purpose is that in which researchers compare one group of polysubstance users of the drug of interest with a comparison group of polysubstance users of the same drugs except for the drug under study. In this way, potential differences between the two groups can be attributed to the drug of interest, which is the only one that the two groups do not have in common. This strategy, which has been used by various studies, employs a subtraction rationale where the effects of the other drugs used are subtracted from those of the main drug by using matched polydrug control groups.

5.1. Psychostimulants:

- *Cocaine+Alcohol*

Cocaine and alcohol are a combination of substances frequently consumed by drug users. Numerous studies have tried to investigate the neuropsychological effects of each substance separately. However, given the high frequency of their combined consumption, many authors have recently examined whether the concurrence of the two can produce combined effects on neuropsychological performance. Several studies have revealed that the combination of cocaine and alcohol produces a metabolite called cocaethylene that produces further deterioration than the use of each substance separately (Andrews, 1997; Carroll, 1993; Jatlow et al., 1996). Our systematic review identified two neuropsychological studies conducted in cocaine+alcohol users after short-term abstinence that yielded results consistent with this notion. Goldstein et al. (2004) contrasted the neuropsychological performance of three groups: a group of crack/cocaine users who also used alcohol (n=42; average abstinence of 22.9 days), a group of alcohol users (n=40; average abstinence of 16.9 days), and a group

of non drug users (n=72). The cocaine/alcohol groups were formed by community and residential treatment participants. The results showed that the cocaine group had significantly generalized neuropsychological impairments, although of a moderate nature, in the neuropsychological domains studied: verbal knowledge, episodic memory, including visual and verbal memory, attention and executive functions, specifically on cognitive flexibility measures. The specific analysis of the performance associated with cocaine use (controlling the use of alcohol) showed an association of this substance with verbal memory impairments. In contrast, alcohol use was associated with a greater effect on attention and executive functions; cocaine users who also consumed alcohol performed worse on these measures than those who did not use alcohol. Bolla et al. (2000) used regression techniques in a non-treatment seeking sample including cocaine users who did not consume alcohol (n=29) and cocaine users who did (n=27), in order to dissociate the effects of the two substances on the different neuropsychological functions. Subjects were assessed twice, after 1-3 days of abstinence and after 28-29 days of abstinence. After 1-3 days of abstinence, they found dose related associations between cocaine dose and alcohol dose and neuropsychological performance. Specifically, processing speed and executive function, including cognitive flexibility and planning, were affected by the use of alcohol, while episodic memory, verbal learning and attention were affected by cocaine. The authors observed that these alterations persisted after 4 weeks of abstinence, although with somewhat different results depending on the dose. Specifically, they found a decline in the Stroop test relative to baseline in participants who reported mid-range cocaine use together with mid-range alcohol use. This decline was not found in those who reported using small amounts of cocaine in conjunction with heavy drinking or those who used heavy amounts of cocaine together with light drinking. These results suggest that a moderate amount of both cocaine and alcohol is required to produce a maximum synergy that might exert more deleterious and persistent effects on the brain. Thus, the neuropsychological effects of the combined consumption of both substances would be additive.

A second group of studies have found evidence of the opposite notion, i.e. alcohol co-abuse may decrease cocaine-induced neuropsychological deficits. Two studies supporting this notion met criteria for inclusion, one conducted during short-term abstinence and one carried out during mid-term abstinence. Abi-Saab et al. (2005) investigated the effects of co-abuse during short-term abstinence. Participants were 22 cocaine users and 71 cocaine and alcohol users, both groups' non-treatment seekers, with an average abstinence of 4.82 days. These

authors observed that the two groups presented alterations on measures of episodic memory, attention and manual dexterity. The magnitude of alterations in both groups was quite similar, although it was slightly higher in the cocaine group for all the measures and considerably higher on the memory tests. When considering mid-term abstinence duration, Robinson et al. (1999) evaluated community and residential treatment groups of cocaine users (n=30) vs. users of cocaine and alcohol (n=30) with a mean cocaine abstinence of 95.8 days and a mean alcohol abstinence of 72.9 days. These authors observed that the individuals who consumed both substances performed better than those who only consumed cocaine on global neuropsychological functioning, including measures of psychomotor functioning and manual dexterity, where they found significant differences between the two groups. The authors suggested that this superior performance was due to the vasodilator effect produced by alcohol, which would counteract the vasoconstriction produced by cocaine. This effect would mean an improved functioning of the subject as a result of the combination of the two substances. One possible explanation for the discrepancy between the results of these studies and those mentioned previously can be the differences in parameters of severity (i.e., dose, frequency or duration) of the drugs used among these studies. When inspecting the duration of alcohol use, we observe that, while in the Bolla and Goldstein study the users of cocaine and alcohol presented duration of use ranging from 15 to 23 years, those in the Robinson and Abi-Saab study ranged between 5 and 17 years. Moreover, the period of abstinence in the studies by Bolla and Goldstein varied between 1 and 29 days, while in the Robinson and Abi-Saab study the period of abstinence ranged from 1 to 95 days. Therefore, the severity of alcohol and cocaine abuse and the duration of abstinence may modulate their relative contribution to neuropsychological deficits in mixed cocaine and alcohol users.

In spite of these findings, most of the studies that met inclusion criteria in our systematic review found that alcohol did not increase the cognitive performance decrements associated with cocaine, nor did it seem to attenuate its effects. The study by Colzato et al. (2009) was conducted in cocaine+alcohol polysubstance users vs. non-cocaine polysubstance users during short-term abstinence. Participants were non-treatment seekers. This study was focused only in selective attention skills, and found that cocaine polysubstance users performed poorer than alcohol users on this domain. Addressing a longer mid-term abstinence, Fein et al. (2002) found that the two groups of drug users, cocaine (n=17) and cocaine+alcohol (n=29), both following residential treatment with an average abstinence of 6 weeks, did not differ from each other in the different domains; both showed

alterations in episodic memory, reasoning, flexibility, selective attention, spatial processing and processing speed. Di Sclafani et al. (2002) found similar results when studying the neuropsychological performance of crack users (n=20) vs. crack and alcohol co-users (n=37) with different abstinence periods: 6 weeks and 6 months. The results showed that both groups had comparable alterations on episodic memory, specifically on measures of immediate and delayed recall, selective attention, spatial processing, reasoning and cognitive flexibility –set-shifting. The most robust effects were found on measures of spatial processing, and indices of the executive components of reasoning and cognitive flexibility. These effects were present at both 6 weeks and 6 months. On the other hand, some improvements were observed in immediate recall, possibly due to the effect of practice.

- *Methamphetamine+Cannabis*

Only one study meeting inclusion criteria used this type of subtraction design. González et al. (2004) carried out a study to test whether cannabis can produce an attenuation of the effects of methamphetamine during short-term abstinence. For this purpose, they compared two subgroups from a mixed sample of non-treatment seeker and residential treatment-enrolled methamphetamine users: methamphetamine+cannabis co-users (n=27) and users of methamphetamine alone (n=26), both with an abstinence of 1 to 30 days. Although there were no significant differences between the groups, they found that methamphetamine users performed worse than methamphetamine and cannabis co-users, above all with regard to episodic memory, specifically on measures of delayed memory and learning. It seems, therefore, that while cannabis may not necessarily improve the neuropsychological effects caused by methamphetamine, at least it does not make them worse.

5.2. MDMA ('Ecstasy'):

- *MDMA + cannabis*

It is common for MDMA users to consume also other substances, the most frequent of which is cannabis (Wu et al., 2009). We found four studies that have tried to dissociate the neuropsychological effects stemming from the MDMA and cannabis co-use by means of subtraction techniques. Since MDMA use rarely generates addiction treatment demands, all of these studies are conducted in non-treatment seeking samples. The first of these studies investigated these effects during short-term abstinence. Gouzoulis-Mayfrank et al. (2000) compared a sample of ecstasy and cannabis co-users (n=28) to another group who used only cannabis (n=28) and a group of non-users

(n=28). The average abstinence period was 41 days for the use of ecstasy and 4 days for the use of cannabis. The results of the study showed that the MDMA and cannabis co-user group was the most affected, especially on measures of episodic memory and learning, selective and divided attention, and executive functions such as fluency, working memory, reasoning, and problem solving. Importantly, the heavier the use of ecstasy (around 100 units) and cannabis, the worse the performance, with longer reaction times on verbal memory and divided attention, as well as poorer working memory. In contrast, the groups that only used cannabis showed a very similar performance to that of the non drug using subjects. De Sola et al. (2008) investigated the effects of MDMA + cannabis use across a period of two years. They examined a group of polysubstance users with regular co-abuse of ecstasy and cannabis (n=37), another group of cannabis using subjects who were not polysubstance users (n=23), and a third group of non drug users (n=34). The results revealed that 72 hours after the last use, ecstasy and cannabis co-users showed specific impairments in semantic verbal fluency, and those who were heavier ecstasy users throughout their lifetime (more than 100 units) presented alterations in visual episodic memory, visual working memory and processing speed. Moreover, after six, 12 and 24 months, ecstasy users had persistently poorer performance than non-drug users on measures of word fluency, working memory and processing speed.

Although these studies clearly point to ecstasy use as being mainly responsible for the alterations found, other studies have obtained contradictory results. Two studies supporting this notion met criteria for inclusion, both conducted during short-term abstinence. Croft et al. (2001) compared the performance of a group of cannabis users (n=18), a second group who used cannabis and an average of less than 50 units of ecstasy (n= 11), and a third group of non drug users (n= 31). The users had at least 17 hours of cannabis abstinence and at least 1 week of MDMA abstinence. The results showed that both groups of drug users presented alterations in memory, verbal fluency, working memory, learning, processing speed and manual dexterity, with no significant differences between them. However, the covariate models that analyzed the isolated contribution of each substance indicated that MDMA contributed differentially to impairments in processing speed, whereas cannabis contributed to impairments in fluency and verbal learning. Both substances were related to deficits in working memory and manual dexterity. Dafters et al. (2004) found similar results when using four groups, cannabis users (n=15), cannabis users who consumed less than 50 units of ecstasy (n=19), cannabis users who consumed more than 50

units of ecstasy (n=16) and non drug users (n=19). All the subjects stated that they had abstained from MDMA use for at least 7 days and from cannabis use for 48 hours prior to testing. The results showed that the groups that consumed cannabis, whether or not they used ecstasy, demonstrated impairments in episodic memory (free immediate, and delayed recall), which seems to indicate that the effects were due to the use of cannabis. In both the study by Dafters and the one by Croft, the authors observed that the subjects used other substances (cocaine, alcohol, amphetamines, etc.); thus, once again the problem of polysubstance use may be confusing the results obtained from various studies. Furthermore, the period of abstinence from using cannabis in these studies varied between 17 and 48 hours, whereas MDMA abstinence was about one week; therefore some of the specific effects observed for cannabis could be acute or sub-acute and transient.

- *MDMA + polysubstance use*

In trying to dissociate the effects of polysubstance use from those produced by the use of MDMA, several studies have contrasted performance of groups of polysubstance users who used MDMA with that of polysubstance users who did not use MDMA. Four of the studies selected were conducted during short-term abstinence. In a sample including 20 polysubstance users with MDMA use and at least 2 weeks of abstinence, 20 polysubstance non MDMA users, and 20 non-drug users, Fox et al. (2002) found that the ecstasy group presented impairments in verbal learning, visual memory, spatial working memory and verbal fluency (but not on planning, impulsive action, cognitive flexibility or risky decision-making). Dafters et al. (2006) examined three groups: 18 MDMA + cannabis users, 18 cannabis users and 18 drug-free controls using tests of impulsive action and set-shifting. The duration of abstinence for cannabis was of 48 hours, whereas MDMA abstinence was of 5 days. The results showed that MDMA use was specifically associated with cognitive flexibility/set-shifting deficits. Morgan et al. (2006) found that after a mean abstinence of 23 days, MDMA users presented alterations on impulsive choice (measured by the Matching Familiar Figures Test) and risky decision-making (measured by the Risky Decision-Making task). There is a certain degree of discrepancy between the findings from these studies, especially with regard to the domains of cognitive flexibility and risky decision-making, which may be explained by the use of different assessment instruments (e.g., Stroop-shifting vs. CANTAB ID/ED or Cambridge Gamble vs. Risk tasks) with slightly different cognitive demands. A recent study by Schilt et al. (2008) as a part of the Netherlands XTC Toxicity (NeXT) study, the first large-scale ecstasy study which,

through the use of imaging techniques and a combination of both cross-sectional and longitudinal approaches, constitutes the gold standard in ecstasy studies (de Win et al., 2005), have compared the performance of 31 polysubstance users who used MDMA to that of 36 polysubstance non MDMA users with a minimum drug abstinence of 2 weeks for MDMA and 1 week for alcohol. Using regression techniques to separate the ecstasy effects from the effects of other drugs, the results showed that ecstasy use had a specific significant dose-related negative effect on verbal delayed recall after adjusting for the use of other drugs.

When considering results obtained after mid-term abstinence we identified three different studies meeting inclusion criteria. Butler and Montgomery (2004) found that in a sample of recreational users with a mean abstinence of 5 weeks, the group of polysubstance users who consumed more than 20 pills of MDMA (n=18) presented a greater preference for risky options on a decision-making task than those polysubstance users who did not take MDMA (n=37) or those who did not use as much (n=28). A first study by Morgan (1998)* found that polysubstance users who had used MDMA had more prominent impairments in impulsivity than non-MDMA polysubstance users, especially on a measure of reflection-impulsivity (Matching familiar figures test, MFFT), and these impairments persisted after 65 days of abstinence (Morgan, 1998). In a subsequent study that tested part of the same sample, Morgan et al. (1999) compared a group of 25 polysubstance users who used MDMA with 22 polysubstance users who did not use it, both with an average MDMA abstinence period of from less than 1 month to 6 months. The results showed impairment in episodic memory in the group that used MDMA, both immediate and delayed recall, which was not observed in the other group. These memory impairments were also associated with the amount of ecstasy consumed per session and, in the case of immediate recall, with the number of years it was used as well. The study also reflected the persistence of the impairments produced by the MDMA up to 6 months after its use.

However, the studies conducted on MDMA polysubstance abusers presenting long-term abstinence duration have provided little evidence of the existence of durable neuropsychological effects associated with the use of MDMA (Hoshi et al., 2007; Roiser et al., 2007). Specifically, the study by Hoshi et al. (2007) found that current MDMA users (n=25; mean abstinence of 14 days) and polysubstance users (n=29) presented alterations on verbal learning and episodic memory measures, as well as on impulsive action. However, these alterations were

not observed among former users (n=28; mean abstinence of 2.78 years). Furthermore, there were no differences between the groups on measures of the executive component of updating, including attention, working memory and verbal fluency measures, or on cognitive flexibility. Using a similar methodological design, Roiser et al. (2007) compared the performance of a group of 30 current MDMA users (mean abstinence of 75 days), 20 ex-MDMA users (mean abstinence of 2.79 years), 30 polysubstance users who did not consume MDMA, and a group of 30 non users on a series of neuropsychological tests. The results only showed the existence of subtle differences on a spatial ability task between former users of MDMA and non users.

5.3. Opioids

Regarding opioid users, only one study corresponding to this methodology met our inclusion criteria. Verdejo-García et al. (2005a) carried out a study with two groups of opioid users, one group enrolled in methadone maintenance treatment (n=18) and another group of former heroin users (n=23), during a period of at least 15 days of abstinence. Given that the subjects had different histories of substance use, with the subjects in the methadone group having higher scores on both amount and duration of use of cannabis and heroin, the authors used multiple regression techniques to subtract the effects of the use of these substances from the scores obtained by the subjects on the neuropsychological measures employed. After controlling for the co-abuse of other drugs the results showed that, compared to the heroin group, subjects in the methadone group performed more slowly on measures of processing speed, visuospatial attention and cognitive flexibility, and they performed worse on measures of the executive component of updating, including measures of working memory and analogical reasoning. Thus, the results showed that it was the use of methadone itself that was associated with the cognitive impairments found in these participants.

Insert Table 3 here

5.4. Summary

The bulk of evidence stemming from this research methodology focuses on the neuropsychological effects of psychostimulants (cocaine and MDMA) vs. alcohol, cannabis and polysubstance use. With regard to the direct comparison of alcohol and cocaine, the overall conclusion is that alcohol co-abuse is associated with increased motor and executive functions deficits (including fluency, selective attention and set-shifting), which reach medium effect sizes at mid-term abstinence. However most of the studies indicate that, during long-term

abstinence, there are only mild persistent neuropsychological effects of cocaine and alcohol (small effect sized decrements in spatial processing, selective attention, episodic memory, reasoning and set-shifting), and that the relative contributions of each substance are indistinguishable. With regard to the generalized and specific effects of MDMA vs. cannabis and polysubstance abuse, results show that: (i) at short-term abstinence, MDMA is associated with medium sized effects indicating greater impairments in selective/divided attention, updating and response speed; (ii) at mid-term abstinence, MDMA is associated with low sized effects indicating mildly increased deficits in episodic memory and impulsive choice; and (iii) at long-term abstinence, the differential effects of MDMA are of low-to-medium size (*d* values of 0.3-0.5), and relate to deficits on response speed, spatial processing, episodic memory and motor/impulsive action. The lack of correspondence between results at the different time points is partly related to the fact that certain cognitive abilities (e.g., set-shifting, impulsive choice or decision-making) were measured by several studies during short- and mid-term but are not well-represented in studies addressing long-term abstinence. Finally, with regard to the specific effects of opioids, the results from the only study that met inclusion criteria revealed medium-large additive specific effects of methadone on speed, working memory, reasoning and set-shifting skills.

The results provided by these studies must be interpreted with caution due to the inherent limitations of the type of designs used to subtract the neuropsychological effects of different drugs. We have repeatedly observed a lack of consensus among studies that use similar designs to study the effects of joint use of cocaine and alcohol, MDMA and cannabis, or MDMA and many other substances. This lack of consensus may be related to several factors, including the non-homogeneous assessment protocols, or the differences in the duration of abstinence of the main drugs contrasted (e.g., in MDMA vs. cannabis studies, cannabis abstinence is usually shorter than MDMA abstinence). In addition, the dose-related effects of the severity of drugs use on several of the neurocognitive decrements observed may also contribute to disparity of findings. Some of these dose-related effects have been well-documented; for example, there are significant detrimental effects of severity of MDMA used on episodic memory, processing speed and executive functions (De Sola et al., 2008), and detrimental effects of severity of alcohol and psychostimulants use on impulsive action and decision-making (Verdejo-García et al., 2005b; Verdejo-García et al., 2007a). Future studies using this methodology should assess to what extent the different degrees of drug exposure contribute to generalized vs. differential drug effects.

6. Neuropsychological studies in polysubstance users with different principal drugs of choice

Most drug users are frequently users of more than one substance and even take more than one substance in the same session (National Institute of Drug Abuse, 1998). Regarding cocaine, Robinson et al. (1999) found that subjects who use this substance usually develop dependence on many other substances of a sedative nature, usually alcohol (Miller et al, 1990; Rounsaville et al, 1991). On the other hand, cocaine and heroin are often consumed together using freebase administration. Some studies suggest that the incidence of this type of polysubstance use is relatively high in the United States (Metzger et al., 1996; Schütz et al., 1994) and in the European Union (EMCDDA Annual Report, 2008). Similarly, a study by Butler et al. (2004) revealed that in a broad sample of ecstasy users, all of them had used other illegal substances, especially stimulants and hallucinogens. Hammersley et al. (1999) did not find even one subject who had consumed ecstasy and had not used other drugs.

Furthermore, we sometimes encounter studies in which there is little information about the possible polysubstance use of the samples under study. This lack of information may be due to the fact that the subjects' history of drug use was not thoroughly explored, or to the reliability of the data provided by the subjects about their drug use, or to the heterogeneous profile of the subjects found in treatment centers. For one reason or another, the reality is that most studies on drug dependence use samples of subjects who are 'main users' of one substance. Among them, we can distinguish between two types of studies. On the one hand, there are those that study the effects of the different abused drugs in polysubstance users who have a principal drug of choice, comparing their performance with that of healthy subjects. On the other hand, we have those studies that also seek to study the effects of the different drugs, but they do so by comparing the performance of two or more groups of polysubstance users who have different drugs of choice, also comparing their performance with that of healthy subjects. Although both types of studies are useful to contrast the neuropsychological performance of drug users, the latter are better suited to address the question of which effects are specific and which effects are common to the use of the different drugs of choice compared in the study.

6.1. Studies comparing polysubstance users with a principal drug of choice and drug-free controls:

6.1.1. Cannabis

Five studies meeting inclusion criteria have contrasted the neuropsychological performance of individuals who use mainly cannabis and that of non drug users. Three of these studies were conducted during early/short-term abstinence (24h to 7 days) employing measures of psychomotor functioning, episodic memory and executive functions (McHale et al., 2008; Pope et al., 2001; Wadsworth et al., 2006). Their results showed that during the first day of abstinence, deficits are observed in psychomotor skills, episodic, prospective memory and the updating component of executive functions. However, after 7 days of abstinence, only fluency and episodic memory deficits are still observable. According to Pope et al. (2001), up to 28 days after cannabis use ceased, none of the significant differences between users and controls remain significant. This conclusion is at odds with the results from Medina et al. (2007) on mid-term cannabis effects in adolescent users (after 30 days of abstinence). These authors showed decreased performance of abstinent cannabis users on tests of spatial processing, speed, episodic memory, selective attention and planning. Their results also showed that the frequency of cannabis use was significantly associated with poorer performance on these tests (even after controlling for alcohol use). Therefore, potential differences on patterns of severity of cannabis use, or adolescence-related brain developments may contribute to explain the discrepancies between the findings of these two studies, The only available study addressing long-term cognitive effects related to cannabis use was carried out with twins who were discordant for regular cannabis use; the twin-pair regular users group had been abstinent for almost 20 years (Lyons et al., 2004). These authors used a comprehensive neuropsychological test battery, and only found significant differences between cannabis users and their non-using co-twins on one measure of planning and perceptual organization (block design subtest, WAIS). These results indicate an absence of marked residual effects of cannabis use on cognitive abilities at the very long-term.

6.1.2. Psychostimulants:

- Cocaine

Ten studies contrasting neuropsychological performance between cocaine polysubstance users and drug-free controls met criteria for inclusion. Four of these studies investigated performance during short-term abstinence

using non-treatment seeker participants. Two of these four focused specifically on impulsive action (measured with the Stop-signal task) (Colzato et al., 2007; Fillmore and Rush, 2002) and one of them focused specifically on decision-making (measured by the Iowa Gambling Task) (Tucker et al., 2004). All of them found significant differences between cocaine users and controls on these domains. The other study by Woicik et al. (2008) employed a more comprehensive neuropsychological battery and found significant deficits in episodic memory, selective attention and working memory, which were less prominent in cocaine users who had recently used the substance, consistent with neuroimaging data (Garavan et al., 2008).

A second group of five studies have assessed neuropsychological performance in cocaine polysubstance users during mid-term abstinence. Three of these studies focused on specific domains and found significant decrements in cocaine users performing episodic memory (van Gorp et al., 1999), impulsive choice –measured with the delay-discounting task (Heil et al., 2006), and emotional decoding (i.e., recognition of facial emotional expressions). The other two employed more thorough neuropsychological assessments. Bolla et al. (1999) in a sample of non-treatment seeker cocaine abusers observed performance decrements in tests of speed, episodic memory, selective attention, psychomotor functioning, impulsive action and set-shifting. Similarly, Verdejo-García et al. (2007b) found significant decrements in cocaine users performing tests of impulsive action/set-shifting, decision-making and emotional decoding in residential treatment participants. In the only study addressing long-term effects of cocaine abuse (after 7 months of abstinence), Fernández-Serrano et al. (2010a) showed that deficits on emotional decoding remained significant during protracted abstinence. It is important to keep in mind that in all the studies mentioned, the experimental group used, in addition to cocaine, other addictive substances, usually alcohol, which may have significantly affected the results.

- *Methamphetamine*

Six studies contrasting neuropsychological performance between methamphetamine polysubstance users and drug-free controls met criteria for inclusion. Two of these studies investigated performance during short-term abstinence, both using non-treatment seeker participants. Monterosso et al. (2005) specifically focused on the domain of impulsive action (taxed by the Stop-signal task) and found that methamphetamine users display longer stop signal reaction time (i.e., the latency to inhibit an initiated motor response) after 5-7 days of

abstinence. On the other hand, Kalechstein et al. (2003) administered a more comprehensive neuropsychological battery including motor, attentional and executive measures and observed that methamphetamine users had decreased performance on tests of psychomotor functioning, episodic memory and verbal fluency.

Two other studies investigated neuropsychological performance during methamphetamine mid-term abstinence. Both of them used a mixed-sample of non-treatment seekers and in-treatment participants and both focused on specific cognitive domains: impulsive action (measured with the Stroop) (Salo et al., 2002) and verbal episodic memory (Woods et al., 2005). Both domains were significantly impaired in methamphetamine users after an abstinence interval ranging between two and four months.

Finally, three recent studies have examined neuropsychological performance in methamphetamine users during long-term abstinence (6 months) (Henry et al., 2009; Hoffman et al., 2006; Rendell et al., 2009). All of them examined community treatment participants and administered comprehensive protocols taxing memory and executive functions. However, the significant differences between groups were only found on certain cognitive/emotional functions that were assessed only by each of them: prospective memory (Rendell et al., 2009), emotional processing (Henry et al., 2009) and impulsive choice (measured by the delay-discounting task) (Hoffman et al., 2006). These studies indicate that gross deficits on memory and executive functions are not durable in methamphetamine users; however, specific deficits on some complex aspects of prospective memory/planning ahead, impulsive choice and emotion processing can be persistently altered in these individuals. Again, we have to take into account that these studies either did not exclude subjects with a history of co-abuse of other substances (Hoffman et al., 2006) or the subjects actually self-reported being co-users of other substances (Henry et al., 2009; Monterosso et al., 2005; Rendell et al., 2009; Woods et al., 2005).

6.1.3. MDMA ('Ecstasy'):

Eleven studies contrasting neuropsychological performance between MDMA polysubstance users and drug-free controls met criteria for inclusion; all of them were performed in non-treatment seeker individuals. Only one study addressed early residual MDMA effects during the first four days of abstinence (Hoshi et al., 2004). This study focused on emotional decoding, finding that MDMA users have residual alterations in the recognition of

fear. Two studies investigated neuropsychological performance of MDMA users during the first month of abstinence (short-term). One of them specifically focused on memory assessments and found significant decrements in tests of semantic memory, prospective memory (Zakzanis et al., 2003). The second study, by Gouzoulis-Mayfrank et al. (2003) used a slightly more comprehensive assessment including measures of memory and executive functions. Results showed that the only domain significantly affected in MDMA users was episodic memory.

A second group of four studies have assessed neuropsychological performance in MDMA polysubstance users during mid-term abstinence. All of these studies administered short cognitive batteries focused on selective aspects of memory and executive functions (mainly related to the updating component). Two studies from the same group found convergent declines on working memory performance by using different probes assessing this domain (Fisk and Montgomery, 2009; Montgomery et al., 2005). On the other hand, Bhattachary and Powell (2001) found significant declines in episodic memory and fluency (but not in working memory, which was assessed using a task that only taxed the maintenance but not the manipulation component of this domain). Finally, Zakzanis and Young (2001), using an ecologically-valid battery of complex executive functions (the Behavioural Assessment of the Dysexecutive Syndrome Battery; Wilson et al., 1996) found significant alterations of the planning skills of MDMA users. Although apparently disparate these results seem to point out that MDMA mid-term effects are related to the updating component of executive functions (Verdejo-García and Pérez-García 2007), which may underlie performance decrements in episodic memory, fluency, working memory and planning tests.

Finally, three studies have examined neuropsychological performance in MDMA polysubstance users during long-term abstinence. All of them focused on two aspects of memory/executive functions interplay: episodic and working memory. Results from two of the three studies, performed by the same group, observed significant working memory declines after six-months abstinence (Wareing et al., 2004, 2005). The third study only detected episodic memory alterations after 2 years of abstinence (Ward et al., 2006).

6.1.4. Opioids:

Seven studies contrasting neuropsychological performance between opioid polysubstance users and drug-free controls met criteria for inclusion. In this case all the studies were conducted on residential treatment participants. Three of these studies explored cognition and emotion during the first days of abstinence, thus taxing residual or sub-acute effects. In heroin users, Aguilar et al. (2008) found that recent heroin consumption is associated with alterations of emotional experience, characterized by a flattening of the arousal response towards pleasant arousing stimuli and a hypersensitisation of the arousal response towards highly unpleasant stimuli. When assessing cognition in methadone-maintained patients (MMP), Mintzer et al. (2004) demonstrated that methadone use is associated with greater declines in episodic memory, psychomotor functioning and set-shifting measures. Compared to MMP, former opioid abusers (abstinence duration between 6 weeks and 12 months) showed a performance level between that of MMP and non users, suggesting that cognitive functioning can be restored in heroin users during abstinence. Brand et al. (2008), who administered a remarkably comprehensive battery of attention and executive tests, demonstrated that 14-days abstinent heroin polysubstance users had significant performance decrements on tests of sustained attention (an exclusive heroin effect), reasoning, impulsive action, flexibility –set-shifting and risky decision-making.

Two selected studies have assessed cognitive performance in opioid users during mid-term abstinence. In a way similar to the Aguilar et al. (2008) study, Gerra et al. (2003) specifically focused on the domain of experienced emotion. Their results showed that 84-days abstinent heroin users also showed an altered pattern of emotional reactivity towards emotionally-laden stimuli: they displayed reduced reactivity to pleasant stimuli and increased reactivity to unpleasant stimuli. On the other hand, they showed intact performance on an abstract reasoning/rule shifting cognitive test (the Category Test). In the second study, aimed to assess cognitive functioning using a short battery of tests of visual memory, word fluency and response inhibition, Prosser et al. (2006) observed significant deficits of episodic memory and impulsive action in 3-months abstinent heroin users.

Finally, two selected studies have targeted neuropsychological performance in heroin users during long-term abstinence (around 1 year). Both of them used similarly-shaped cognitive batteries assessing attention and executive functions, but significant results were obtained on measures that did not overlap between studies: verbal fluency (Davis et al., 2002) and impulsive action (Pau et al., 2002). More studies using comprehensive

neuropsychological tests protocols are warranted to reveal which of the wide range of functions impaired in heroin users at short-term remain significantly impaired at the very long-term. So far, studies contrasting current MMP and former heroin users indicate some recovery of verbal fluency and cognitive flexibility impairments correlated with abstinence duration.

6.1.5. Alcohol:

Three studies contrasting neuropsychological performance between alcohol polysubstance users and drug-free controls met criteria for inclusion. The first of them was conducted during short-term alcohol abstinence -11 days (Pitel et al., 2007). These authors employed a quite thorough assessment protocol aimed to measure different aspects of memory and executive functions. Results showed that alcohol abusers had significant declines on tests of episodic memory, working memory, reasoning, impulsive action and cognitive flexibility – set-shifting.

The other two studies were conducted during mid-term abstinence, but they used less comprehensive neuropsychological protocols. Beatty et al. (2000) found significant alterations in psychomotor functioning, semantic memory and reasoning. On the other hand, Foisy et al. (2007) were selectively focused on different aspects of facial perception (testing both visual-spatial and emotional skills related to the processing of faces). Their results showed specific effects on the emotional decoding of facial expressions in the alcoholic group.

Insert Table 4 here

6.1.6. Summary

Results regarding generalized vs. specific effects stemming from this methodological approach indicate that most cognitive/emotional deficits are shared by a number of groups of polysubstance abusers differing on main drug of choice. Medium to large effect sized differences in episodic memory are shared by MDMA, heroin and alcohol users. Decrements on semantic memory are shared by MDMA (large effects) and alcohol (medium effects) users. Declines in verbal fluency are shared by cannabis, methamphetamine (large effects) and methadone (medium effects) users. Deficits in working memory are shared by cocaine, methamphetamine, MDMA and methadone users (all medium effect sizes). Decrements in impulsive action are shared by cocaine, methamphetamine, alcohol (all large effects) and heroin (medium effects) users, similar to deficits on

psychomotor functioning (shared by the same type of drugs). Finally, deficits in emotional processing are shared by methamphetamine (large effects), cocaine and alcohol (medium effects) polysubstance users, and maintained throughout protracted abstinence.

More specifically, decrements in prospective memory are shared by cannabis and methamphetamine users; reasoning deficits are shared by heroin and alcohol users; and declines in cognitive flexibility –set-shifting are shared by heroin and alcohol users (medium effects).

As for exclusive effects, there is a small magnitude exclusive effect of cannabis use on planning function (maintained across long-term abstinence); there are significant medium magnitude exclusive effects of MDMA use on processing speed, and of methamphetamine use on cognitive flexibility –reversal learning; and there is a significant large magnitude exclusive effect of psychostimulants use (i.e., cocaine and amphetamine) on impulsive choice, which is persistent across abstinence in the case of methamphetamine users.

6.2. Comparisons of polysubstance users with different principal drugs of choice

A number of studies have directly contrasted the neuropsychological performance of two groups of polysubstance users with different drugs of choice. Despite the limitations associated with the interpretation of the neuropsychological results obtained by polysubstance users, this type of studies provides indirect evidence about alterations that are more typical of using one main substance vs. others.

6.2.1. MDMA ('Ecstasy') vs. Cannabis

Three studies contrasting neuropsychological performance between MDMA and cannabis polysubstance users met criteria for inclusion. The first two studies (conducted by the same group in the same sample) were carried out during very short abstinence, thus measuring sub-acute or residual effects of these drugs. Quednow et al. (2006) carried out an analysis of cognitive subprocesses involved in a verbal memory test using a sample of polysubstance users whose preferred drug of choice was MDMA (n=19, average abstinence of 3 days), polysubstance users whose preferred drug of choice was cannabis (n=19, average abstinence of 3 days), and control subjects (n=19). The results showed that, while cannabis users performed similarly to controls, MDMA

users presented alterations in general indices of learning, memory consolidation, recall and recognition, as well as alterations in sub-indices indicative of working memory deficits, organization of information during learning, and retroactive interference, which are linked to executive processes and prefrontal cortex functioning. Furthermore, they observed positive correlations between memory alterations and the amount of MDMA used. Using this same sample, Quednow et al. (2007) also showed that after 3 days of abstinence, MDMA users presented selective alterations on impulsive choice (MFFT) and decision-making measures. In this case, the amount and duration of MDMA use was also significantly related to the performance on these measures. The third study (Clark et al., 2009) contrasted performance of one group of MDMA users with short-term abstinence (n=46, 21 days), one group of cannabis users with short-term abstinence (n=15, 21 days), a third group of former MDMA users with long-term abstinence (n=14, 12 months), and a drug-free control group (n=19). The cognitive assessment focused on one single measure of impulsive choice (the Information Sampling Task –Clark et al., 2006) and results showed that the only group showing abnormal performance, as compared to controls, was the short-term abstinent cannabis group. These findings stand in contrast with those of Quednow et al. (2007). This discrepancy might be explained by the different patterns of severity of MDMA use in both samples or by the additional cognitive demands of the MFFT, which requires working memory and attentional skills on top of the impulsive choice response tendencies.

6.2.2. Psychostimulants vs. Opioids

Six studies contrasting neuropsychological performance between psychostimulant and opioid polysubstance users met criteria for inclusion. Most of these studies were conducted with residential treatment participants. The first of them was conducted during very early abstinence, just after resolving withdrawal symptoms. Ornstein et al. (2000) compared the performance of two groups of drug users with different drugs of choice, 23 amphetamine vs. 22 heroin users, and a third group of non-drug users. Participants were assessed after resolving withdrawal symptoms by using memory and executive function tests. They observed an important dissociation on a test of reinforced learning and flexibility (intra/extradimensional set-shifting), which consists of a first part in which the reinforcement contingencies are learned according to a criterion, and a second part in which the reinforcement criterion changes and it is necessary to use a flexible behavior. The results showed that subjects who used heroin presented alterations in the acquisition of the initial reinforcement contingencies, while

amphetamine users showed alterations in the second part of the test only, when they had to adjust their response pattern to the new criterion. However, both groups presented impairments on a recognition memory test. Nevertheless, the authors mention that the experimental groups were also heavy polysubstance users, especially of cannabis, and within each group there were users of the principal drug of the other group; within the heroin group there were subjects who had used amphetamines and vice versa.

Two other studies (from the same group) examined neuropsychological performance in psychostimulants vs. opioids polysubstance users during mid-term abstinence (4-6 months) using comprehensive assessments of cognitive impulsivity and executive functions respectively. Verdejo-García et al. (2007c) contrasted the performance of three groups made up of polysubstance users of cocaine (n=34, average abstinence of 17.18 weeks), polysubstance users of opioids (n=25 average abstinence of 25.04 weeks) and controls (n=27) on tasks of cognitive impulsivity. In this case, the degree of polysubstance use in the opioid group was superior to that of the cocaine group. In contrast, the results showed that cocaine users performed significantly worse on tasks of selective attention and impulsive action. However, performance on decision-making (measured with the IGT) was equivalent in the two groups of users, but worse than that of the controls. In an extension of this study with the same design but a broader sample and a comprehensive executive functions assessment battery (Verdejo-García and Pérez-García, 2007a), the results also showed that the cocaine group performed significantly worse than the opioid group on tests of response inhibition and cognitive flexibility. Nonetheless, both groups of polysubstance users performed worse than the controls on updating measures of fluency, working memory and reasoning, and on decision-making.

Finally, three other studies examined neuropsychological performance in psychostimulants vs. opioids polysubstance users during long-term abstinence (by including a mixed group of former polysubstance psychostimulant and opioid users abstinent for 8 years). Ersche et al. (2006) contrasted the neuropsychological performance of four groups: current amphetamine users (n=25), current opioid users (n=42), former amphetamine and/or opioid users (n=26, average abstinence=8.2 years), and non-drug users (n=27). All the drug-user groups had used drugs other than the main substance of choice. The results showed that the performance of former users was not significantly different from that of the current amphetamine users, as both

groups showed more significant alterations than the opioid group on tests of spatial planning, pattern recognition memory and cognitive flexibility –set-shifting. In an extension of this study in which they included an additional group of current cocaine polysubstance users (n=27) and specifically analyzed the performance on a probabilistic task of reversal learning (i.e., flexibility is more related to a change in reinforcement pattern than to a change in external criterion), the results showed that polysubstance users of cocaine showed a significantly higher number of perseverations than the other consumer groups (amphetamines, opioids and ex-users) (Ersche et al., 2008). A related study in a similar sample, by Clark et al. (2006), contrasted the performance of similarly shaped four groups: current amphetamine users (n=24), current opioid users (n=40), former amphetamine and/or opioid users (n=24, average abstinence=8 years), and non-drug users (n=26), in a specific probe of impulsive choice (Information Sampling Task). Results showed that both current and former amphetamine and opioid drug groups displayed more impulsive choice responses.

6.2.3. Psychostimulants vs. Opioids vs. Alcohol

Only one study met criteria for inclusion that corresponded to this subsection. Kirby and Petry (2004) contrasted the delay-discounting performance of three groups of current users and three groups of abstinent users of cocaine, heroin and alcohol respectively. Abstinence duration in the ex-users groups was of 14 days (short-term). Results showed that during current use both cocaine and heroin users have steeper delay-discounting compared to controls. However, after 14-days of abstinence, significant differences only remained for the cocaine group.

6.2.4. Psychostimulants vs. Alcohol

Two studies met criteria for inclusion that corresponded to this subsection. Both of them were conducted during short-term abstinence in samples of residential treatment participants. González et al. (2007) contrasted the performance of alcohol (n=17) and methamphetamine users (n=16), and drug-free controls, on typical measures of working memory (delayed-non-matched-to-sample) and decision-making (Iowa Gambling Task). Results showed that methamphetamine users, but not alcohol users had significantly decreased performance on both neuropsychological indices. More recently, van der Plas et al. (2009) contrasted the performance of alcohol users (n=33), cocaine users (n=38), methamphetamine users (n=27) and drug-free controls (n=36) on a selective neuropsychological battery assessing relevant aspects of executive functions. Results showed that both cocaine

and methamphetamine users performed significantly poorer than alcohol users and controls on measures of working memory, cognitive flexibility –set-shifting and decision-making.

6.2.5. Opioids vs. Alcohol

Only one study met criteria for inclusion that corresponded to this subsection. Kornreich et al., (2003) contrasted the performance of four drug using groups and drug-free controls on a measure of emotional processing (Decoding of facial emotional expressions). Groups were formed by alcohol users (n=30, 21 days of abstinence), opioid users following methadone treatment (n=30), opioid users not following methadone treatment (n=30, 3.8 months of abstinence), and former users of both alcohol and opioids (n=30, alcohol abstinence of 21 days and heroin abstinence of 11 months), as compared with healthy controls (n=30). Results showed that both shortly-abstinent alcohol users and current and former opioid users displayed poorer emotion recognition in the task.

Insert Table 5 here

6.2.6. Summary

Results regarding generalized vs. specific effects stemming from this methodological approach indicate that some neuropsychological deficits can be dissociated between groups of polysubstance users with different main drug of choice. As for generalized effects, results indicate that deficits on episodic memory are shared by cannabis, MDMA and methamphetamine users (all medium effect sizes). Declines on the updating component of executive functions and on impulsive choice are both shared by cocaine and heroin polysubstance users, in contrast to less significant decrements in alcohol users.

As for relatively exclusive neuropsychological effects of different substances, results indicate that psychostimulants abuse is associated with selectively decreased performance on tests of planning, impulsive action and cognitive flexibility –both set-shifting and reversal learning (medium to large effect sizes), especially when compared to opioid users.

According to evidence from this methodological approach, psychostimulants-related deficits on episodic memory, planning and cognitive flexibility are the more persistent ones, remaining significant after several years of abstinence.

7. Correspondence between methodologies and quantitatively-derived estimations of neuropsychological effects of drug use: Insights on generalized vs. specific effects.

This final section provides an integration of the review's findings through the quantitative evaluation of the results obtained by the different research methodologies about the issues of (i) generalized vs. specific neuropsychological effects of different drugs of abuse (see Table 6), and (ii) which of these neuropsychological effects are durable across abstinence (see Tables 7). In the text and tables of this section, we mainly highlight findings that achieved an average medium effect size (Cohen's $d \geq 0.5$).

Insert Tables 6 and 7 here

With regard to cannabis use, there is a relative lack of correspondence between results stemming from the different research methodologies; pure users' studies seem to be superior to reveal significant deficits on episodic memory and processing speed, but this data mainly stem from single-studies that need to be replicated. Only episodic memory and planning deficits seem to persist at mid-term in cannabis users. No effects are observable at long-term abstinence.

With regard to cocaine-related effects, there is consistency in the results from at least two of the different research methodologies with regard to significant declines in the domains of working memory, impulsive action, impulsive choice and decision-making. Some relevant domains, such as emotional processing, have been only examined by one particular methodology (polysubstance users, showing consistency across 4 different studies) and should be addressed by other methods in future studies. Significant deficits in the updating component of executive functions, impulsive action, decision-making and emotional processing persists at mid-term abstinence. At long-term abstinence, only mild deficits in reversal learning and emotional processing have been detected, but there is a lack of studies examining other skills.

For methamphetamine, there is consistency in the results from at least two of the different research methodologies with regard to significant decrements in episodic memory, fluency, working memory and impulsive action. Some relevant domains, such as planning, have only been studied by one particular methodology (comparison between groups of polysubstance users, showing consistency across 2 different

studies) and should be addressed by other methods in future studies. Significant deficits in episodic memory, prospective memory, fluency, working memory, impulsive action and choice and emotional processing persist at long-term abstinence.

For MDMA, there is consistency in the results from at least two of the different research methodologies with regard to significant deficits in processing speed, episodic memory, fluency and selective attention. There is also consensus between the four methodologies for deficits in working memory, but these are of low-to-medium size (not reaching 0.5). Significant deficits in spatial processing, episodic memory, updating, planning, selective and divided attention and impulsive choice persist at mid-term abstinence. Only mild deficits in processing speed, working memory and episodic/semantic memory persist at long-term abstinence.

For opioids, there is consistency in the results from at least two of the different research methodologies with regard to significant deficits in fluency, working memory and reasoning. There is also consensus between the four methodologies for deficits in emotional processing, but these are of low-to-medium size (not reaching 0.5). Significant deficits in episodic memory, selective attention, impulsive action, fluency and emotional processing persist at mid-term abstinence. At long-term abstinence, the updating component of executive functions and decision-making seem to be pervasively altered.

For alcohol, there is consistency in the results from at least two of the different research methodologies with regard to significant deficits in selective attention, cognitive flexibility –set-shifting, psychomotor functioning/impulsive action, and emotional processing. Significant deficits in speed, semantic memory, selective attention and emotional processing seem to persist at mid-term. No deficits persist at long-term abstinence.

Overall, the studies discussed in this systematic quantitative review point to generalized effects of different types of drugs on episodic memory, the updating component of executive functions, decision-making and emotional processing. On the other hand, alcohol and psychostimulants use seem to be particularly associated with deficits in impulsive action and cognitive flexibility; alcohol and MDMA use with perceptual speed, spatial processing

and selective attention declines; cannabis and methamphetamine with prospective memory deficits; and cannabis and MDMA with alterations in processing speed and complex planning. The magnitude of both generalized and specific neuropsychological effects is generally attenuated in samples achieving long-term abstinence, but there are persistent psychostimulant-related effects on updating, inhibition, flexibility and emotional processing, and opioid-related persistent effects on updating and decision-making. Importantly, these specific effects are overall consistent with results from animal and controlled drug-administration studies.

A more detailed account of generalized vs. specific effects of different drugs, taking into account the time-line of these alterations across abstinence, is displayed in Figure 1. Similar to other findings summarized in this section, Figure 1 only depicts results with effect sizes ≥0.5. As the Figure displays, when we focus on mid-term abstinence –probably the most relevant interval for addiction treatment, there are generalized effects of different drugs on episodic memory, selective attention, selective components of updating (fluency and reasoning), planning, impulsive action and emotional processing. On the other hand, there are relatively specific effects of psychostimulants on impulsive choice/decision-making (but these domains have not been tested in cannabis, opioid or alcohol users during this period), of cocaine use on working memory, of MDMA use on spatial processing and divided attention, and of alcohol use on processing speed and semantic memory. Nonetheless, it is important to take into account that evidence about specific effects at mid-term abstinence mostly stems from single studies that need to be replicated. Moreover, when we focus on long-term abstinence –the most relevant interval to understand long-term recovery of neuropsychological functioning, there are generalized effects of different drugs on the updating component of executive functions (fluency and working memory). On the other hand, there are specific effects of methamphetamine on emotional processing, episodic and prospective memory, impulsive action and choice, and of heroin use on divided attention, reasoning and decision-making. However, these specific effects should be interpreted with particular caution because most of them stem from single studies (with the exception of memory and impulsive action findings on methamphetamine users), and because some of the domains (e.g., reasoning, inhibition or decision-making) have not been properly tested in users of other substances. The obvious implication of these observations is that, in spite of the abundant literature on the topic, there is a selective scarcity of studies on the neuropsychological effects of different drugs during mid-term and

long-term abstinence. More studies are warranted to gain insights about the generalized vs. specific effects of different drugs during these periods that are critical for addiction treatment and recovery.

Insert Figure 1 here

Even though there is a reasonable degree of correspondence between the three different methodologies discussed, especially when considering only robust medium-to-large effect sizes, none of them is completely satisfactory to unravel the specific vs. generalized effects associated with the use of different drugs. Studies with 'pure' users can provide more direct evidence, but their samples introduce important biases (e.g., cultural, socio-demographic), and therefore the possibility of generalizing results to the entire population of drug users is hindered. Furthermore, studies of this nature are quite difficult to implement in users of substances like cocaine or opioids (i.e., it is virtually impossible to find users of these substances who have not previously consumed alcohol or cannabis), although epidemiological changes in drug use patterns could increase their significance in the future. In contrast, subtraction studies are useful in cases of substances with frequent patterns of co-abuse (cocaine vs. alcohol, MDMA vs. cannabis), but they are difficult to apply in some substances (e.g., cannabis vs. other substances). Furthermore, results stemming from these studies have provided very contradictory findings (Bolla et al., 2000; Robinson et al., 1999), and they often vary depending on the plan of analysis (De Sola et al., 2008; Croft et al., 2001). Future studies using this methodology should attempt to match relevant variables (e.g., severity of use or duration of abstinence) with regard to the main drugs of interest. As for the studies with polysubstance users, paradoxically, we found that some of these studies have produced more indicative evidence of specific effects of certain substances than the 'pure' user models have. In this regard, various studies of polysubstance users with different drugs of choice indicate that the use of psychostimulants is related to especially robust alterations in impulsive action and choice and cognitive/affective flexibility. However, these models present obvious limitations when interpreting potential selective effects. A related limitation of these designs is that they might obscure the neuropsychological correlates of other earlier-stage drugs co-abused (e.g., alcohol or cannabis). Therefore, they are not appropriate to draw conclusions about these quite commonly abused drugs.

Several other factors should also be taken into account when interpreting these findings. Among the studies reviewed, we observed a great variability of results that may be related to key factors that vary between studies, including the demographic and clinical background of participants, the type of neuropsychological measures selected, the amount and duration of use of the different drugs studied, and the ranges of the periods of abstinence. These differences make it difficult to neatly determine the specific and generalized effects produced by the different drugs. For example, we found a remarkably high number of studies with non-demographically matched comparison groups (see Tables 2 to 6). Although most of these studies used covariance models to control the potential influence of these variables, there is increasing evidence indicating that this method is not ideally suited to address mismatch of demographics or IQ variables in neuropsychological research (Adams et al., 1985; Krull et al., 1997). This is especially true in the case of substance addiction, which might be viewed as a marker for a whole cluster of educational, occupational and health-related factors (e.g., accelerated aging) that negatively impact neuropsychological performance. In addition, a clearly noticeable bias related to demographic background is the preponderance of studies conducted in men vs. women. Although this is partly due to the greated prevalence of substance use disorders among males, more studies are warranted to understand the nature and relevance of neuropsychological effects of drug use in women, especially in light of increasing evidence of gender differences in the brain correlates of drug use (see Medina et al., 2008, 2009). A related issue is that of heterogeneity in the clinical background of participants, with marked differences concerning the treatment status of participants across different drugs (e.g., MDMA or cannabis participants are rarely treatment seekers) and across studies. There is evidence that indicates that the brain substrates of certain addiction-related symptoms, such as craving, sharply differ as a function of treatment status (see Wilson et al., 2004); thus this variable might also contribute to explain the diversity of results across neuropsychological studies.

With regard to the neuropsychological tests used, as Table 1 illustrates, there is a great degree of variability in the type of instruments used in the field. This is especially relevant because there is evidence to reckon that certain tests are more sensitive than others to detect particular deficits in this population (see Fernández-Serrano et al., 2010c). The development of evidence-based consensus on the best-suited neuropsychological instruments for this population could importantly optimize research headways on the field. There is also a bias to perform studies on particular neuropsychological domains (e.g., inhibition or decision-making) while neglecting others in

spite of the fact that comprehensive neuropsychological test batteries assessing all relevant domains are much more informative. Moreover, we observed that several of the studies reviewed employed tests that tap into various neurocognitive domains simultaneously (i.e. IGT, R-SAT, BADS). This approach complicates the possibility of providing a straightforward link between impaired task performance and dysfunction of any specific domain. However, these tests usually have greater ecological validity (Verdejo-García et al., 2006; Verdejo-García and Pérez-García, 2007a), which makes them quite useful for measuring and predicting the problems that can arise in the daily functioning of drug users. On the other hand, it should be noted that some studies that have adapted classical neuropsychological tests to incorporate drug-related context (e.g., drug Stroop-like tasks, drug verbal fluency or episodic memory tasks) have shown improvements in the performance of addicted individuals on this kind of tests (Beatty and Borrell, 2000; Goldstein et al., 2007a,b). This effect may indicate that drug abusers become more cognitively active when drug-related information is pertinent, and maybe more cognitive dysfunctional in neutral conditions because drug contents overload their memory, attentional or executive resources (see Field and Cox, 2008 for a discussion on the attentional bias effect). This possibility should be further explored in order to better characterize the neuropsychological deficits more prominent in drug users when they find themselves in drug-related contexts. Nonetheless, we should take into account that the exposure degree to drug-related contexts rapidly decrease during drug abstinence, and therefore findings on neutral conditions are equally important to predict off-drug clinical and everyday functioning in drug users.

Parameters of amount and duration of drug use must also be considered. In this paper we have observed associations between the severity of cannabis use and memory, learning and decision-making deficits, and between the severity of MDMA use and memory, processing speed, impulsive action and choice, and decision-making deficits. Alongside these lines, several studies have shown consistent associations between patterns of severity of use of a number of substances and neuropsychological deficits; for example, between the severity of cocaine use and alterations in response inhibition, working memory, reasoning and set-shifting measures (Bolla et al., 2000; Fernández-Serrano et al., 2010b; Fillmore and Rush, 2002; Roselli and Ardila, 1996; Verdejo-García et al., 2005b), and between the severity of opioid consumption and cognitive flexibility and impulsive choice (Fernández-Serrano et al., 2010b; Lyvers and Yakimoff, 2003). Future studies could contribute to an

improved delimitation of the alterations associated with similar parameters of use among the users of different drugs.

Additionally to these limitations we must refer one that is inherent to research on the neurocognitive effects of substance misuse. Most of the data reviewed here stem from cross-sectional designs, and therefore do not allow us to determine whether these alterations precede drug use, or if they occur as a consequence of the effects of continued substance use. A growing line of evidence from animal and human studies indicates that pre-existing executive dysfunctions may predate the onset of drug use and constitute vulnerability markers for liability to addiction (see Verdejo-García et al., 2008 for review). In fact, neurobehavioral disinhibition (a latent construct including neuropsychological and self-report indices of neurocognitive inhibition and trait impulsivity) during childhood is associated with earlier age of onset and rapid progression of substance user disorders across a variety of drugs (Clark, D.B., et al., 2005; Kirisci et al., 2005, 2006; Tarter et al., 2004). Of all the studies reviewed, only those included in NeXT, the study by Fried et al. (2005) and the one by Lyons et al. (2004), use longitudinal designs that allow to control this variable, which in the case of the Lyons study is also controlled by the use of a sample composed of twins.

Overall, the results obtained indicate that the objective of determining specific vs. generalized neuropsychological effects of different drugs requires the integration of data emerging from the different methodologies reviewed. Moreover, a very useful contribution comes from meta-analysis techniques on the effects of specific substances, and the use of regression models in sufficiently large samples to obtain conclusive results. As for the use of meta-analysis, we must highlight that the conclusions of our review are coherent with several meta-analyses describing medium/large effects of the learning/memory impairments in cannabis users (Grant et al., 2003; Solowij and Battisti, 2008), and memory and executive function in psychostimulant users (Jovanovski et al., 2005; Zakzanis et al., 2007). As for regression models, efforts to increase sample sizes or use neuropsychological measures in epidemiological studies can yield important advances on this issue.

Acknowledgements

This work is supported by the Spanish Ministry of Science and Innovation (MICINN), under the FPU national plan (grant ref. AP 2005-1411) and Research Project SEJ 2006-08278, and the Junta de Andalucía through the Research Project P07.HUM 03089. This study complies with current Spanish law and all international ethical guidelines for human studies.

References

Abi-Saab, D., Beauvais, J., Mehm, J., Brody, M., Gottschalk, C., Kosten, T.R., 2005. The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. Am. J. Addict. 14, 2, 166, 178.

Adams, K.M., Brown, G.G., Grant, I., 1985. Analysis of covariance as a remedy for demographic mismatch of research subject groups: some sobering simulations. J. Clin. Exp. Neuropsychol. 7, 4, 445, 462.

Aguilar de Arcos, F., Verdejo-García, A., Ceverino, A., Montañez-Pareja, M., López-Juárez, E., Sánchez-Barrera, M., López-Jiménez, A., Pérez-García, M., 2008. Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. Psychopharmacology, 198, 159, 166.

Andrews, P., 1997. Cocaethylene toxicity. J. Addict. Dis. 16, 3, 75, 84.

Aron, A.R., Behrens, T.E., Smith, S., Frank, M.J., Poldrack, R.A. 2007. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J. Neurosci. 27, 14, 3743, 3752.

Beatty, W.W., Borrel, G.K. 2000. Forms of knowledge, cognitive impairment and drug abuse: a demonstration. Prog. Neuropsychoparmacol. Biol. Psychiatry. 24, 17, 22.

Beatty, W.W., Tivis, R., Stott, H.D., Nixon, S.J., Parsons, O.A.., 2000. Neuropsychological Deficits in Sober Alcoholics: Influences of Chronicity and Recent Alcohol Consumption. Alcohol. Clin. Exp. Res. 24, 2, 149, 154.

Bechara, A. 2005., Decision-making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat. Neurosci. 8, 1458, 1463.

Bhattachary, S., Powell, J. H., 2001. Recreational use of 3-4-methyledioxymethanphetamine (MDMA) or "ecstasy": evidence for cognitive impairment. Psychol. Med. 31, 647, 658.

Bjork, J., Hommer, D., Grant, S., Danube, C., 2004. Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1–/type 2–like traits. Alcohol, 34, 2-3, 133, 150.

Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouraditis, M., Contoreggi C, Matochik, J.A., Kurian, V., Cadet, J-L., Kimes, A.S., Fundeburk, F.R., Ernst, M., 2003. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19, 1085, 1094.

Bolla, K.I., Funderburk, F.R., Cadet, J., 2000. Differential effects of cocaine and cocaine alcohol on neurocognitive performance. Neurology 54, 12, 2285, 2292.

Bolla, K.I., Rothman, R., Cadet, J.L., 1999. Dose-related neurobehavioral effects of chronic cocaine use. J. Neuropsychiatry. Clin. Neurosci. 11, 361, 369.

Brand, M., Roth-Bauer, M., Driessen, M., Markowitsch, H.J., 2008. Executive functions and risky decision-making in patients with opiate dependence. Drug Alcohol Depend. 7, 64, 72.

Burns, H.D., Van, L.K., Sanabria-Bohorquez, S., Hamill, T.G., Bormans, G., Eng, W.S., Gibson, R., Ryan, C., Connolly, B., Patel, S., Krause, S., Vanko, A., Van, H.A., Dupont, P., De I, L., Rothenberg, P., Stoch, S.A., Cote, J., Hagmann,W.K., Jewell, J.P., Lin, L.S., Liu, P., Goulet, M.T., Gottesdiener, K., Wagner, J.A., de, H.J., Mortelmans, L., Fong, T.M., Hargreaves, R.J., 2007. [18F]MK-9470, a positron emission tomography (PET) tracer for in vivo human PET brain imaging of the cannabinoid-1 receptor. Proc. Natl. Acad. Sci. U. S. A. 104, 9800, 9805.

Butler, G.K., Montgomery, A.M., 2004. Impulsivity, risk taking and recreational "ecstasy" (MDMA) use. Drug Alcohol Depend., 76, 55, 62.

Camí, J., Farré, M., 2003. Drug addiction. N. Engl. J. Med. 349, 975, 986.

Carroll, K., Ziedonis, D., O'Malley, S., McCance-Katz, E., Gordon, L., Rounsaville, A., 1993. Pharmacologic Interventions for Alcohol- and Cocaine-Abusing Individuals: A Pilot Study of Disulfiram vs. Naltrexone. Am. J. Addict. 2 (1), 77, 79.

Cheng, R.K., Etchegaray, M., Meck, W.H., 2007. Impairments in timing, temporal memory, and reversal learning linked to neurotoxic regimens of methamphetamine intoxication. Brain Res. 1186 (19), 255, 266.

Clark, D.B., Cornelius, J.R., Kirisci, L., Tarter, R.E. 2005. Childhood risk categories for adolescent substance involvement: a general liability typology. Drug Alcohol Depend. 77, 13, 21.

Clark, L., Robbins, T.W., Ersche, K.D., Sahakian, B.J., 2006. Reflection impulsivity in current and former substance users. Biol. Psychiatry 60, 5, 515-522.

Clark, L., Roiser, J.P., Robbins, T.W., Sahakian, B.J., 2009. Disrupted 'reflection' impulsivity in cannabis users but not current or former ecstasy users. J. Psychopharmacol. 23, 1, 14, 22.

Clemens, K.J., Cornish, J.L., Kong, M.L., Kunt, G.E., McGregor, I.S., 2005. MDMA ('Ecstasy') and methamphetamine combined: Order of administration influences hyperthermic and long-term adverse effects in female rats. Neuropharmacology, 49 (2), 195, 207.

Colzato, L.S., van den Wildenberg, W.P.M, Hommel, B., 2007. Impaired inhibitory control in recreational cocaine users. PLos ONE 2, 11, e1143

Colzato, L.S., van den Wildenberg, W.P.M., Hommel, B., 2009. Reduced attentional scope in cocaine polydrug users. PlosOne 4, 6, 6043.

Corbin, W.R., Cronce, J.M., 2007. Alcohol Effects on Behavioral Control: The Impact of Likelihood and Magnitude of Negative Consequences. Alcohol. Clin. Exp. Res. 31, 6, 955,964.

Croft, R.J., Mackay, A.J., Mills, A.T.D., Gruzelier, J.G.H., 2001. The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology 153, 373, 379.

Curran, H.V., Kleckham, J., Bearn, J., Strang, J., Wanigaratne, S., 2001. Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose response study. Psychopharmacology 154, 153,160.

Dafters, R.I., 2006. Chronic ecstasy (MDMA) use is associated with deficits in task-switching but not inhibition or memory updating executive functions. Drug Alcohol Depend. 83, 3, 181, 184.

Dafters, R.I., Hoshi, R., Talbot, A.C., 2004. Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. Psychopharmacology 173, 405, 410.

Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Laane, K., Pena, Y., Murphy, E.R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F.I., Richards, H.K., Hong, Y., Baron, J.C., Everitt, B.J., Robbins, T.W., 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315, 1267–1270.

Davis, P. E., Liddiard, H., McMillan, T. M., 2002. Neuropsychological deficits and opiate abuse. Drug Alcohol Depend. 67, 105, 108.

Deadwyler, S.A., Goonawardena, A.V., Hampson, R.E. 2007. Short-term memory is modulated by the spontaneous release of endocannabinoids: evidence from hippocampal population codes. Behav. Pharmacol. 18, 571, 580.

De Sola, S., Miguelez-Pan, M., Peña-Casanova, J., Poudevida, S., Farré, M., Pacifini, R., Böhm, P., Abanades, S. Verdejo-García, A., Zuccaro, P., De la Torre, R., 2008. Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study. J. Psychopharmacol. 200, 425, 437.

de Win, M.M.L., Jager, G., Verkaeke, H.K.E., Schilt, T., Reneman, L., Booij, J., Verhulst, F.C., Den Heeten, G.J., Ramsey, N.F., Korf, D.J., Van den Brink, W., 2005. The Netherlands XTC Toxicity (NeXT) study: objectives and methods of a study investigating causality, course, and clinical relevance. Int. J. Methods Psychiatr. Res. 14, 167, 185.

Di Sclafani, V., Tolou-Shams, M., Price, L.J., Fein, G., 2002. Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. Drug Alcohol Depend. 66, 161, 171.

Dumont, G.J.H., Valkenberg, M.M.G.J., Schoemaker, R., Buitelaar, J.K., van Gerven, J.M.A, Verkes, R.J., 2007. Acute MDMA and ethanol interaction effects on psychomotor performance. Br. J. Clin. Pharmacol. 63, 503.

Dumont, G.J.H., Wezenberg, E., Valkenberg, M.M.G.J., de Jong C.A.J., Buitelaar, J.K., van Gerven, J.M.A., Verkes, R.J., 2008. Acute neuropsychological effects of MDMA and etanol (co-) administration in healthy volunteers. Psychopharmacology, 197, 465-474.

Errico, A.L., King, A.C., Lovallo, W.R., Parsons, O.A., 2002. Cortisol dysregulation and cognitive impairment in abstinent male alcoholics. Alcohol. Clin. Exp. Res. , 26, 1198, 1204.

Ersche, K.D., Clark, L., London, M., Robbins, T.W. Sahakian, B.J. 2006. Profile of executive and memory function associated with amphetamine and opiate dependence. Neuropsychopharmacology, 31, 1036, 1047.

Ersche, K.D., Roiser, J.P., Robbins, T.W., Sahakian, B.J,. 2008. Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans. Psychopharmacology 197, 3, 421, 431.

European Monitoring Centre for Drugs and Drug Addiction. Annual Report 2008: the state of the drugs problem in the European Available at http://www.emcdda.eu Lisbon: EMCDDA 2008.

Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement of drug addiction: from actions to habits to compulsion. Nat. Neurosci. 8, 1481, 1489.

Fadda, P., Robinson, L., Fratta, W., Pertwee, RG., Riedel, G., 2004. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. Neuropharmacology, 47, 8, 1170, 1179.

Fein, G., Di Sclafani, V., Meyerhoff, D. J., 2002. Prefrontal cortical volume reduction associated with frontal cortex function deficit in 6-week abstinent crack-cocaine dependent men. Drug Alcohol Depend. 68, 87, 93.

Fein, G., Klein, L., Finn, P., 2004. Impairment on a simulated gambling task in long-term abstinent alcoholics. Alcohol. Clin. Exp. Res. 28, 10, 1487, 1491.

Fein, G., McGillivray, S., 2007. Cognitive performance in long-term abstinent elderly alcoholics. Alcohol Clin. Exp. Res. 31, 1788, 1799.

Fein, G., Torres, J., Price, L.J., Di Sclafani, V., 2006. Cognitive performance in long-term abstinent alcoholics. Alcohol. Clin. Exp. Res. 30, 1538, 1544.

Fernández-Serrano, M.J., Lozano, O., Pérez-García, M., Verdejo-García, A., 2010a Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. in press.

Fernández-Serrano, M.J., Pérez-García, M., Perales, J.C., & Verdejo-García. A., 2010c. Prevalence of executive dysfunction in cocaine, heroin and alcohol users enrolled in therapeutic communities. Eur. J. Pharmacol. 626, 104, 112.

Fernández-Serrano, M.J., Pérez-García, M., Schmidt Río-Valle, J., Verdejo-García. A., 2010b. Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. J. Psychopharmacol. in press.

Field, M., Cox, W. M. 2008. Attentional bias in addictive behaviors: A review of its development, causes, and consequences. Drug Alcohol Depend. 97, 1, 20.

Fillmore, M.T., Rush, C.R., 2002. Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend., 66, 265, 273.

Fillmore, M.T., Rush, C.R., Hays, L., 2002. Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug Alcohol Depend., 67, 157, 167.

Fillmore, M.T., Rush, C.R., Hays, L., 2005. Cocaine improves inhibitory control in human model of response conflict. Exp. Clin. Psychopharmacol. 13, 327, 335.

Fillmore, M.T., Rush, C.R., Hays, L., 2006. Acute effects of cocaine in two models of inhibitory control: implications of non-linear dose effects. Addiction 101, 9, 1323, 1332.

Fishbein, D.H., Krupitsky, E., Flannery, B.A., Langevin, D.J., Bobashev, G., Verbitskaya, E., Augustine, C.B., Bolla, K.I., Zvartau, E., Schech, B., Egorova, V., Bushara, N., Tsoy, M., 2007. Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. Drug Alcohol Depend. 90, 25, 38.

Foisy, M.L., Kornreich, C., Fobe, A., D'Hondt, L., Pelc, I., Hanak, C., Verbanck, P., Philippot, P., 2007. Impaired Emotional Facial Expression Recognition in Alcohol Dependence: Do These Deficits Persist With Midterm Abstinence? Alcohol. Clin. Exp. Res. 31, 3, 404, 410.

Fox, H.C., McLean, A., Turner, J.J.D., Parrot, A.C., Rogers, R., Sahakian, B.J., 2002. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. Psychopharmacology 162, 203, 214.

Franken, I.H.A., Nijs, I.M.T., Muris, P., Van Strien, J.W., 2007. Alcohol Selectively Reduces Brain Activity During the Affective Processing of Negative Information. Alcohol. Clin. Exp. Res. 31, 6, 919, 927.

Frederick, D.L., Ali, S.F., Gillam, M.P., Gossett, J., Slikker, W. Jr., Paule, M.G., 1998. Acute effects of dexfenfluramine (d-FEN) and methylenedioxymethamphetamine (MDMA) before and after short-course, high-dose treatment. Ann. NY. Acad. Sci. 844, 183, 190

Frederick, D.L., Ali, S.F., Slikker, W. Jr, Gillam, M.P., Allen, R.R., Paule, M.G., 1995. Behavioral and neurochemical effects of chronic methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. Neorotoxicol. Teratol. 17, 531, 543

Fried, P.A., Watkinson, B., Gray, R., 2005. Neurocognitive consequences of marihuana-a comparison with pre-drug performance. Neurotoxicol. Teratol. 27, 231, 239.

Friswell, J., Phillips, C., Holding, J., Morgan, C.J.A., Brandner, B., Curran, H.V., 2008. Acute effects of opioids on memory functions on healthy men and women. Psychopharmacology 198, 243, 250.

Garavan, H., Hester, R., 2007. The role of cognitive control in cocaine dependence. Neuropsychol. Rev. 17 3, 337, 345.

Garavan, H., Kaufman, J.N., Hester, R., 2008. Acute effects of cocaine on the neurobiology of cognitive control. Phil. Trans. R. Soc. B, 363, 3267, 3276.

Gerra, G., Baldaro, B., Zaimovic, A., Moi, G., Bussandri, M., Raggi, M.A., Brambilla, F., 2003. Neuroendocrine responses to experimentally-induced emotions among abstinence opioid-dependent subjetcs. Drug Alcohol Depend. 71, 1, 25, 35.

Goldstein R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G., Fowler, J.S., Volkow, N.D., 2004. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 42, 1447, 1458.

Goldstein, R.Z., Tomasi, D., Rajaram, S., Cottone, L.A., Zhang, L., Maloney, T., Telang, F., Alia-Klein, N., Volkow, N.D., 2007a. Role of the anterior cingulated and medial orbitofrontal cortex in processing drug cues in cocaine addiction. Neuroscience 144, 1153, 1159.

Goldstein, R.Z., Volkow, N.D., 2002. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. Am. J. Psychiatry 159, 1642, 1652.

Goldstein, R.Z., Woicik, P.A., Lukasik, T., Maloney, T., Volkow, N.D., 2007b. Drug fluency: A potential marker for cocaine use disorders. Drug Alcohol Depend. 89, 97, 101.

González, R., Bechara, A., Martin, E.M., 2007. Executive functions among individuals with methamphetamine or alcohol as drugs of choice: preliminary observations. J. Clin. Exp. Neuropsychol. 29, 2, 155-159.

González, R., Rippeth, J.D., Carey, C.L., Heaton, R.K., Moore, D.J., Shweinsburg, B.C., Cherner, M., Grant, I., 2004. Neurocognitive performance of methamphetamine users discordante for history of marijuana exposure. Drug Alcohol Depend. 76, 181, 190.

Gouzoulis-Mayfrank, E., Daumann, J., Tuchtenhagen, F., Pelz, S., Becker, S., Kunert, J., Fimm, B., Sass, H., 2000. Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). J. Neurol. Neurosurg. Psychiatr. 68, 719, 725.

Gouzoulis-Mayfrank, E., Thimm, B., Rezk, M., Hensen, G., Daumann, J., 2003. Memory impairment suggest hippocampal dysfunction in abstinent ecstasy abusers. Prog. Neuropsychopharmacol. Biol. Psychiatry. 27, 819, 827.

Grant, I., González, R., Carey, C.L., Natarajan, L., Wolfson, T., 2003. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. J. Int. Neuropsychol. Soc. 9, 679, 689.

Hammersley, R., Ditton, J., Smith, I., Short, E. (1999). Patterns of ecstasy use by drug users. Br. J. Criminol. 39, 625-647.

Halpern, J.H., Pope, H.G., Sherwood, A.R., Barry, S., Hudson, J.I., Yurgelun-Todd, D., 2004. Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. Drug Alcohol Depend. 75, 135, 147.

Heath, R.G., Fitziarrell, A.T., Fontana, C.J., Garey, R.E., 1980. Cannabis sativa: effects on brain function and ultrastructure in rhesus monkeys. Biol. Psychiatry, 15, 5, 657, 690.

Heil, S.H., Johnson, M.W., Higgins, S.T., Bickel, W.K., 2006. Delay discounting in currently using and currently abstinent cocaine-dependent outpatients and non-drug-using matched controls. Addict. Behav. 31, 7, 1290, 1294.

Henry, J.D., Mazur, M., Rendell, P.G., 2009. Social-cognitive difficulties in former users of methamphetamine. Br. J. Clin. Psychol. 48, 323-327.

Herkenham, M., 1992. Cannabinoid receptor localization in brain: Relationship to motor and reward systems. Ann. N. Y. Acad. Sci. 654, 19, 32.

Hoffman, W.F., Moore, M., Templin, R., McFarland, B., Hitzemann, R.J., Mitchell, S.H., 2006. Neuropsychological function and delay discounting in methamphetamine-dependent individuals. Psychopharmacology, 188, 162, 170.

Hoshi, R., Bisla, J., Curran, H.V., 2004. The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expressions: preliminary findings. Drug Alcohol Depend. 76, 297, 304.

Hoshi, R., Mullins, K., Boundy C., Brignell, C., Piccini, P., Curran, H.V., 2007 Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naïve controls. Psychopharmacology, 194, 371, 379.

Ilan, A.B., Smith, M.E., Gevins, A., 2004. Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology , 176, 214, 222.

Jatlow, P., McCance, E.F., Bradberry, C.W., Elsworth, J.D., Taylor, J.R., Roth, R.H., 1996. Alcohol plus Cocaine: The Whole Is More Than the Sum of Its Parts [Proceedings Of The Fourth International

Congress Of Therapeutic Drug Monitoring And Clinical Toxicology]. Ther. Drug Monit. 18 (4), 460, 464.

Jentsch, JD., Olausson, P., De la Garza, R., Taylor, JR., 2002. Impairments of reversal learning and response perseveration after repeated, intermittent cocaine administrations to monkeys. Neuropsychopharmacology, 26, 2,183, 190.

Jentsch, JD., Verrico, CD., Le, D., Roth, RH., 1998. Repeated exposure to Δ^9-tetrahydrocannabinol reduces prefrontal cortical dopamine metabolism in the rat. Neurosci. Lett. 246 (3), 169, 172.

Johnson, B. A., Ait-Daoud, N., Wells, L.T., 2000. Effects of isradipine, a dihydropyridine-class calcium channel antagonist, on D-methamphetamine-induced cognitive and physiological changes in humans. Neuropsychopharmacology, 22, 504, 512.

Jovanovski, D., Erb, S., Zakzanis, K., 2005. Neurocognitive deficits in cocaine users: a quantitative review of the evidence. J. Clin. Exp. Neuropsychol. 27, 189, 204.

Kalechstein, A.D., Newton T.F., Green, M., 2003. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. J. Neuropsychiatry Clin. Neurosci. 15, 2, 215-220.

Kemmis, L., Hall, J.K., Kingston, R., Morgan, M.J., 2007. Impaired fear recognition in regular recreational cocaine users. Psychopharmacology 194, 2, 151, 159.

Kirisci, L., Tarter, R.E., Reynolds, M., Vanyukov, M. 2006. Individual differences in childhood neurobehavior disinhibition predict decision to desist substance use during adolescence and substance use disorder in young adulthood: A prospective study. Addict. Behav. 31, 686-696.

Kirisci, L., Vanyukov, M., Tarter, R. 2005. Detection of youth at high risk for substance use disorders: A longitudinal study. Psychol. Addict. Behav. 19, 243-252.

Klintsova, A.Y., Helfer, J.L., Calizo, L.H., Dong, W.K., Goodlett, C.R., Greenough, W.T., 2007. Persistent Impairment of Hippocampal Neurogenesis in Young Adult Rats Following Early Postnatal Alcohol Exposure. Alcohol. Clin. Exp. Res. 31, 12, 2073, 2082.

Kornreich, C., Foisy, M.L, Philippot, P., Dan, B., Tecco, J., Noël, X., Hess, U., Pelc, I., Verbanck, P., 2003. Impaired emotional facial expression recognition in alcoholics, opiate dependence subjects, methadone

maintained subjects and mixed alcohol-opiate antecedents subjects compared with normal controls. Psychiatry Res. 119, 3, 251, 260.

Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology, 24, 97-129.

Krull, K.R., Adams, R.L., 1997. Problems in neuropsychological research methodology, in: Maruish, M.E., Moses, J.A. (Eds.), Clinical neuropsychology: theoretical foundations for practitioners.

Kufahl, P.R., Zhu Li, Risinger, R.C., Rainey, C.J., Wu, G., Bloom, A.S., Li, S., 2005. Neural responses to acute cocaine administration in the human brain detected by fMRI. Neuroimage 28, 4, 904, 914.

Kuypers, K.P., Ramaekers, J.G., 2007. Acute dose of MDMA (75 mg) impairs spatial memory for location but leaves contextual processing of visuospatial information unaffected. Psychopharmacology 189, 557, 563.

Kuypers, K.P.C., Wingen, M., Samyn, N., Limbert, N., Ramaekers, J.G., 2007. Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night. Psychopharmacology 192, 1, 111, 119.

Kirby, K.N., Petry, N.M., 2004. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction, 99, 461, 471.

Lane, S.D., Cherek, D.R., Tcheremissine, O.V., Lieving, L.M., Pietras, C.J., 2005. Acute Marijuana Effects on Human Risk Taking. Neuropsychopharmacology 30, 800, 809.

Leitz, J.R., Morgan, C.J.A., Bisby, J.A., Rendell, P.G., Curran, V., 2009. Global impairment of prospective memory following acute alcohol. Psychopharmacology 205, 3, 379-387.

Lyons, M.J., Bar, J.L., Panizzon, M.S., Toomey, R., Eisen, S., Xian, H., Tsuang, M.T., 2004. Neuropsychological consequences of regular marijuana use: a twin study. Psychol. Med. 34, 1239, 1250.

Lyvers, M., Yakimoff, M., 2003. Neuropsychological correlates of opioid dependence and withdrawal. Addict. Behav. , 28, 605, 611.

McCann, U.D., Szabo, Z., Seckin, E., Rosenblatt, P., Mathews, W.B., Ravert, H.T., Dannals, R.F., Ricaurte, G.A., 2005. Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. Neuropsychopharmacology 30, 1741, 1750.

McHale, S., Hunt, N., 2008. Executive function deficits in short-term abstinent cannabis users. Hum. Psychopharmacol. Clin. Exp. 23, 409, 415.

Medina, K.L., Hanson, K.L., Schweinsburg, A.D., Cohen-Zion, M., Nagel, B.J., Tapert, S.F., 2007. Neuropsychogical functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence. J. Int. Neuropsychol. Soc. 13, 807, 820.

Medina, K.L., McQueeny, T., Nagel, B.J., Hanson, K.L., Schweinsburg, A.D., Tapert, S., 2008. Prefrontal cortex volumes in adolescents with alcohol use disorders: unique gender effects. Alcohol Clin. Exp. Res., 32, 3, 386, 394.

Medina, K.L., McQueeny, T., Nagel, B.J., Hanson, K.L., Yang, T.T., Tapert, S.F., 2009. Prefrontal cotex morphometry in abstinent adolescent marijuana users: Subtle gender effects. Addict. Biol., 14, 4, 457, 468.

Metzger, D.S., Woody, G., Marmor, M. and Gross, M., 1996. Risk characteristics of injection drug users (IDUs) participating in the vaccine preparedness study (VPS). Int. Conf. AIDS, 11, 357.

Miller, N.S., Gold, M.S., Belkin, B.M., 1990. The diagnosis of alcohol and cannabis dependence in cocaine dependence. Adv. Alcohol Subst. Abuse 8, 33, 42.

Mintzer, M.Z., Copersino, M.L., Stitzer, M.L., 2005. Opioid abuse and cognitive performance. Drug Alcohol Depend. 78, 225, 230.

Monterosso, J.R., Aron, A.R., Cordova, X., Xu, J., London, E.D., 2005. Deficits in response inhibition associated with chronic methamphetamine abuse. Drug Alcohol Depend. 79, 273, 277.

Montgomery, C., Fisk, J.E., Newcombe, R., Murphy, P.N., 2005. The differential effects of ecstasy/polydrug use on executive components: shifting, inhibition, updating and access to semantic memory. Psychopharmacology, 182, 262, 276.

Moon, M., Do, KS., Park, J., Kim, D., 2007. Memory impairment in methamphetamine dependent patients. Intern. J. Neuroscience 117, 1, 9.

Morgan, M.J., 1998. Recreational use of MDMA ("ecstasy") is associated with elevated impulsivity. Neuropsychopharmacology 19, 252, 264

Morgan, M.J., 1999. Memory deficits associated with recreational use of 'ecstasy' (MDMA). Psychopharmacology 141, 30, 36.

Morgan, M.J., Impallomeni, L.C., Pirona, A., Rogers, R.D., 2006. Elevated impulsivity and impaired decision-making in abstinent ecstasy (MDMA) users compared to polydrug and drug-naïve controls. Neuropsychopharmacology 31, 1562, 1573.

Nagai, T., Takuma, K., Dohniwa, M., Ibi, D., Mizoguchi, H., Kamei, H., Nabeshima, T., Yamada, K., 2007. Repeated methamphetamine treatment impairs spatial working memory in rats: reversal by clozapine but not haloperidol. Psychopharmacology 194, 1, 21, 32.

Nava, F., Carta, G., Colombo, G., Gessa, G.L,. 2001. Effects of chronic Δ^9-tetrahydrocannabinol treatment on hippocampal extracellular acetylcholine concentration and alternation performance in the T-maze. Neuropharmacology, 41, 3, 392, 399.

Niyuhire, F., Varvel, S.A., Martin, B.R., Lichtman, A.H., 2007. Exposure to Marijuana Smoke Impairs Memory Retrieval in Mice. J. Pharmacol. Exp. Ther. 322, 1067, 1075.

O'Leary-Moore, S.K., McMechan, A.P., Mathison, S.N., Berman, R.F., Hannigan, J.H., 2006. Reversal learning after prenatal or early postnatal alcohol exposure in juvenile and adult rats. Alcohol, 38, 2, 99, 110.

Ornstein, T.J., Iddon, J.L., Baldacchino, A.M., Sahakian, B.J., London, M., Everitt, B.J., Robbins, T.W., 2000. Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology 23, 113, 126.

Paine, T.A., Dringenberg, H.C., Olmstead, M.C., 2003. Effects of chronic cocaine on impulsivity: relation to cortical serotonin mechanisms. Behavioral Brain. Res. 147, 135, 147.

Pau, C.W.H., Lee, T.M.C., Chan, S.F., 2002. The impact of heroin on frontal executive functions. Arch. Clin. Neuropsychol. 17, 663, 670.

Pitel, A.L., Beaunieux, H., Witkowski, T., Vabret, F., Guillery-Girard, B., Quinette, P., Desgranges, B., Eustache, F., 2007. Genuine episodic memory deficits and executive dysfunctions in alcoholics early in abstinence. Alcoholism, 31, 7, 1169, 1178.

Pope, H.G., Gruber, A.J., Hudson, J.L., Huestis, M.A. Yurgelun-Todd, D., 2001. Neuropsychological performance in long-term cannabis users. Arch. Gen. Psychiatry, 58, 909, 915.

Prosser, J., Cohen, L.J., Steinfeld, M., Eisenberg, D., London, E.D., Galynker, I.I., 2006. Neuropsychological functioning in opiate-dependent subjects receiving and following methadone maintenance treatment. Drug Acohol Depend. 84, 3, 240, 247.

Pu, L., Bao, GB., Xu, NJ., Ma, L., Pei, G., 2002. Hippocampal Long-Term Potentiation Is Reduced by Chronic Opiate Treatment and Can Be Restored by Re-Exposure to Opiates. J. Neurosci. 22, 1914, 1921.

Quednow, BB., Kühn, KU., Hoppe, C., Westheide, J., Maier, W., Daum, I., Wagner, M., 2007. Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). Psychopharmacology, 189, 4, 517, 530.

Quednow, B.B., Kuhn, K.U., Hoppe, C., Westheide, J., Maier, W., Wagner, M., 2006. Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. Psychopharmacology 20, 1, 14.

Ramaekers, J.G., Kauert, G., van Ruitenbeek, P., Theunissen, E.L., Schneider, E., Moeller, M.R., 2006. High-potency marijuana impairs executive function and inhibitory motor control. Neuropsychopharmacology 31, 2296, 2303.

Ramaekers, J.G., Kuypers, K.P.C., 2006. Acute effects of 3,4-Methylenedioxymethamphetamine (MDMA) on behavioural measures of impulsivity: alone and in combination with alcohol. Neuropsychopharmacology 31, 1048, 1055.

Ranganathan, M., D'Souza, D.C., 2006. The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology 188, 425, 444.

Ratti, M.T., Giardini, P., Soragna, D., 2002. Chronic alcoholism and the frontal lobe: which executive functions are imparied? Acta Neurol. Scand. 105, 4, 276, 281.

Ray, S., Bates, ME., 2006. Acute Alcohol Effects on Repetition Priming and Word Recognition Memory with Equivalent Memory Cues. Brain Cogn. 60, 2,118, 127.

Rendell, P.G., Mazur, M., Henry, J.D., 2009. Prospective memory impairment in former users of methamphetamine. Psychopharmacology 203, 609-616.

Ricaurte, GA., Yuan, J., Hatzidimitriou, G., Cord, BJ., McCann, UD., 2002. Severe Dopaminergic Neurotoxicity in Primates After a Common Recreational Dose Regimen of MDMA ("Ecstasy"). Science 297, 2260, 2263.

Robinson, J.E., Heaton, R.K., O´Malley, S.S., 1999. Neuropsychological functioning in cocaine abusers with and without alcohol dependence. J. Int. Neuropsychol Soc. 5, 10, 19.

Roiser, J.P., Rogers, R.D., Sahakian, B.J., 2007. Neuropsychological function in ecstasy users: a study controlling for polydrug use. Psychopharmacology 189, 505, 516.

Roselli, M., Ardila, A., 1996. Cognitive effects of cocaine and polydrug abuse. J. Clin. Exp. Neuropsychol. 18, 122, 135.

Rounsaville, B.J., Foley, S., Carroll, K., Budde, D., Prusoff, B.A., Gawin, F.H., 1991. Psychiatric diagnosis of treatment seeking cocaine abusers. Arch. Gen. Psychiatry 48, 43, 51.

Salo, R., Nordahl, T.E., Galloway, G.P., Moore, C.D., Waters, C., Leamon, M.H., 2009. Drug abstinence and cognitive control in methamphetamine-dependent individuals. J. Subst. Abuse Treat. 37, 292-297.

Salo, R., Nordahl, T.E., Possin, K., Leamon, M., Gibson, D.R., Galloway, G.P., Flynn, N.M., Henik, A., Pfefferbaum, A., Sullivan, E.V., 2002. Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. Psychiatry Res. 111, 1, 65, 74.

Sánchez-Tutret, M., 1997. Alcohol y alcoholismo. En Gómez-Jarabo, G. (ed.). Farmacología de la conducta. Manual básico para psicoterapeutas y clínicos. Madrid: Síntesis, S.A.

Santucci, AC., Capodilupo, S., Bernstein, J., Gómez-Ramírez, M., Milefsky, R., Mitchell, H., 2004. Cocaine in adolescent rats produces residual memory impairments that are reversible with time. Neurotoxicol. Teratol. 26, 5, 651, 661.

Schilt, T., de Win, M.M.L, Jager, G., Koeter, M.W., Ramsey, N.F., Schmand, B. and van den Brink, W., 2008. Specific effects of ecstasy and other illicit drugs on cognition in poly-substance users. Psychol. Med. 38, 1309, 1317.

Schoenbaum, G., Saddoris, MP., Ramus, SJ., Shaham, Y., Setlow, B., 2004. Cocaine-experienced rats exhibit learning deficits in a task sensitive to orbitofrontal cortex lesions. Eur. J. Neurosci. 19, 1997, 2002.

Schottenbauer, M.A., Hommer, D., Weingartner, H., 2007. Memory Deficits Among Alcoholics: Performance on a Selective Reminding Task. Aging Neuropsychol. Cogn. 14, 505, 516.

Schütz, C.G., Vlahov, D., Anthony, J.C., Graham, N.M.H., 1994. Comparison of self-reported injection frequencies for past 30 days and 6 months among intravenous drug users. J. Clin. Epidemiol. 47,191, 195.

Silber, B. Y., Croft, R. J., Papafotiou, K., Stough, C., 2006. The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. Psychopharmacology 187, 154, 169.

Simon, NW., Mendez, I.A., Setlow, B., 2007. Cocaine exposure causes long-term increases in impulsive choice. Behav. Neurosci. 121, 3, 543, 549.

Solowij, N., Battisti, R., 2008. The chronic effects of cannabis on memory in humans: a review. Curr. Drug Abuse Rev. 1, 81, 98.

Spain, J.W., Newsom, G.C., 1991. Chronic opioids impair acquisition of both radial maze and Y-maze choice escape. Psychopharmacology 105, 101, 106.

Stalnaker, T.A., Roesch, M.R., Franz, T.M., Burke, K.A., Schoenbaum, G., 2006. Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. Eur. J. Neurosci. 24, 2643, 2653.

Stalnaker, T.A., Takahashi, Y., Roesch, M.R., Schoenbaum, G., 2009. Neural substrates of cognitive inflexibility after chronic cocaine exposure. Neuropharmacology 56, 63, 72.

Taffe, M.A., Davis, S.A., Yuan, J., Schroeder, R., Hatzidimitriou, G., Parsons, L.H., Ricaurte, G.A., Gold, L.H., 2002. Cognitive performance of MDMA-treated rhesus monkeys: sensitivity to serotonergic challenge. Neuropsychopharmacology 27, 993, 1005.

Taffe, M.A., Huitron-Resendiz, S., Schroeder, R., Parsons, L.H., Henriksen, S.J., Gold, L.H., 2003. MDMA exposure alters cognitive and electrophysiological sensitivity to rapid tryptophan depletion in rhesus monkeys. Pharmacol. Biochem. Behav. 76, 141, 152.

Tarter, R.E., Kirisci, L., Habeych, M., Reynolds, M., Vanyukov, M. 2004. Neurobehavior disinhibition in childhood predisposes boys to substance use disorder by young adulthood: direct and mediated etiologic pathways. Drug Alcohol Depend. 73, 121, 132.

Tucker, K.A., Potenza, M.N., Beauvais, J.E., Browndyke, J.N., Gottschalk, C., Kosten, T.R., 2004. Perfusion abnormalities and decision-making in cocaine dependence. Biol. Psychiatry 56, 527, 530.

van Gorp, W.G., Wilkins, J.N., Hinkin, C.H., Moore, L. H., Hull, J., Horner, M.D., Plotkin, D., 1999. Declarative and procedural memory functioning in abstinent cocaine abusers. Arch. Gen. Psychiatry 56, 85-89.

van der Plas, E.A.A., Crone, E.A., van den Wildenberg, W.P.M., Tranel, D., Bechara, A., 2009. Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women. J. Clin. Exp. Neuropsychol. 31, 706, 719.

Verdejo-García A, Bechara, A., 2009. A somatic marker theory of addiction. Neuropharmacology, 56, 48, 62.

Verdejo-García A., Bechara, A., Recknor, E.C., Pérez García, M., 2006. Decision-making and the Iowa gambling task: ecological validity in individuals with substance dependence. Psychol. Belg. 46, 55, 78.

Verdejo-García, A., Benbrook, A., Funderburk, F., David, P., Cadet, J.L., Bolla, K.I., 2007a. The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. Drug Alcohol Depend. 90, 2, 11.

Verdejo-García, A., Lawrence, A.J., Clark, L., 2008. Impulsivity as a vulnerability marker for substance-use disorders: review of findings from high-risk research, problem gamblers and genetic association studies. Neurosci. Biobehav. Rev. 32, 777, 810.

Verdejo-García, A., López-Torrecillas, F., Giménez, C.O., Pérez-García, M., 2004. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. Neuropsychol Rev. 14, 1, 1, 41.

Verdejo-García, A., López Torrecillas, F., Aguilar de Arcos, F., Pérez García, M., 2005b. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: A multiple regression analysis. Addict. Behav. 30, 1, 89, 101.

Verdejo-García, A., Perales, J.C., Pérez-García, M., 2007c. Cognitive impulsivity in cocaine and heroin polysubstance abusers. Addict. Behav. 32, 950, 966.

Verdejo-García, A., Pérez-García, M., 2007. Profile of executive deficits in cocaine and heroin polysubstance users: common and differential effects on separate executive components. Psychopharmacology 190, 517, 530.

Verdejo-García, A., Pérez-García, M. 2007a. Ecological assessment of executive functions in substance dependent individuals. Drug Alcohol Depend. 90, 48, 55.

Verdejo-García, A., Rivas-Pérez, C., Vilar-López, R., Pérez García, M., 2007b. Strategic self-regultaion, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. Drug Alcohol Depend. 86, 139, 146.

Verdejo-García, A., Toribio, C., Orozco, K., Puente, K., Pérez García, M., 2005a. Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. Drug Alcohol Depend. 78, 283, 288.

Vericco, C.D., Jentsch, J.D., Roth, R.H. 2003. Persistent and anatomically selective reduction in prefrontal cortical dopamine metabolism after repeated, interminttent, cannabinoid administration to rats. Synapse 49, 61, 66.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Franceschi, D., Sedler, M., Gatley, S.J., Miller, E., Hitzemann, R.., Ding, Y.S., Logan, J., 2001 Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. J. Neurosci. 21, 9414, 9418.

Vollenweider, F.X., Lechti, M.E., Paulus, M.P., 2005. MDMA affects both error-rate dependent and independent aspects of decision-making in a two-choice prediction task. J. Psychopharmacol. 19, 366, 374.

Wadsworth, E.J.K., Moss, S.C., Simpson, S.A., Smith, A.P., 2006. Cannabis use, cognitive performance and mood in a sample of workers. J. Psychopharmacol. 20, 1,14, 23.

Ward, J., Hall, K., Haslam, C., 2006. Patterns of memory dysfunction in current and 2-year abstinent MDMA users. J. Clin. Exp. Neuropsychol. 28, 306-324.

Wareing, M., Fisk, J.E., Murphy, P., Montgomery, C., 2004. Verbal working memory deficits in current and previous users of MDMA. Hum. Psychopharmacol. Clin. Exp., 19, 225-234.

Wareing, M., Fisk, J.E., Murphy, P., Montgomery, C., 2005. Visuo-spatial working memory deficits in current and former users of MDMA ('ecstasy'). Hum. Psychopharmacol. Clin. Exp., 20, 115-123.

Wilson, B.A., Alderman, N.A., Burgess, P.W., Ernslie, H., Evans, J.J., 1996. Behavioural Assessment of the Dysexecutive Syndrome. Thames Valley Test Company. Bury St. Edmunds.

Wilson, S.J., Sayette, M.A., Fiez, J.A., 2004. Prefrontal responses to drug cues: a neurocognitive analysis. Nat. Neurosci. 7, 3, 211, 214.

Woicik, P.A., Moeller, S., Alia-Klein, N., Maloney, T., Lukasik, T.M., Yeliosof, O., Wang, G.J., Volkow, ND., Goldstein, RZ., 2008. The neuropsychology of cocaine addiction: recent cocaine use masks impairment. Neuropsychopharmacology 1, 11.

Woods, SP., Rippeth, JD., Conover, E., Gongvatana, A, González, R., Carey, CL, Cherner, M., Heaton, RK., Grant, I., 2005. Deficient Strategic Control of Verbal Encoding and Retrieval in Individuals With Methamphetamine Dependence. Neuropsychology 19, 1, 35, 43.

Wu, L.T., Parrott, A.C., Ringwalt, C.L., Patkar, A.A., Mannelli, P., Blazer, D.G., 2009. The high prevalence of substance use disorders among recent MDMA users compared with other drug users: Implications for intervention. Addict. Behav. 34, 8, 654, 661.

Yip, J., Lee, T., 2005. Effect of ecstasy use on neuropsychological function: a study in Hong Kong. Psychopharmacology 179, 620, 628

Zakzanis, K.K., Campbell, Z., Jovanovski, D., 2007. The neuropsychology of ecstasy (MDMA) use: a quantitative review. Hum. Psychopharmacol. 22, 7, 427, 435.

Zakzanis KK, Young DA., 2001. Executive function in abstinent MDMA ('ecstasy') users. Med. Sci. Monit. 7, 1292, 1298.

Zakzanis, KK., Young, DA., Campbell, Z., 2003. Prospective memory impairment in abstinent MDMA ("ecstasy") users. Cogn. Neuropsychiatry, 8 (2), 141, 153.

DOMAINS	COMPONENTS	MEASURES[a]
MEMORY	Declarative memory (explicit): involves the conscious recollection of past events or experiences and is typically measured through recall or recognition. It includes semantic and episodic memory. -Episodic memory (EM): acquisition and retention of knowledge about personally experienced events and their temporal relations in subjective time and the ability to mentally "travel back" in time. -Semantic memory (SM): capability of internally representing states of the world that is not perceptually present. The memory of meanings of words, facts or rules. Prospective memory (PrM): capability to remember to do something in the future, or remembering to perform an intended action. Non-declarative memory (implicit) (IM): capability to remember something without being aware that you are remembering it.	EM: BSRT, RAVLT, RCFT, CAVLT, WMS (Logical memory, verbal paired association, visual reproduction, inmmediate memory, general memory), AFLT, CVLT, PAL, HRDT, MC: (story recall, wordlist2, address), WRMT, CLDL, FRT, RBMT, BVRT, SMT, FMT, HVLT-R, BVMT-R, VLMT, VIG, PSR, PRM PAL, IDPR, IFRT, DFRT, BCSR, LGT-3, AMIPB, FCSRT, ECM, DPT, ST, SpT, PMT, SDPALT SM: SPT, BNT, WAIS (Vocabulary), SILS-V, PPVT PrM: RBMT, Virtual week WSC
ATTENTION	-Divided attention (DAT): the ability to respond simultaneously to multiple tasks or multiple task demands -Selective attention (SAT): the capacity to maintain a behavioral or cognitive set in the face of distracting or competing stimuli. -Sustained attention (SUAT): the ability to maintain a consistent behavioral response during continuous and repetitive activity.	DAT: TAP (subtest 5), TMT, CTT. CalCap (RT2) SAT: TAP (subtest 6), FAT, SAT, CTT, RSCT, DCT, MC: alphabet, numbers forward, numbers reversed, wordlist1, SDMT, DVT, CPT, ACPT, RT, SSPT, ANT, Stroop SUAT: TEA, SSST, Stroop

Table 1 (continued)

EXECUTIVE FUNCTION	Updating: online monitoring and manipulation of different information modalities -Fluency (UP-Fl): capacity of the individual to initiate his/her behavior in a fluid way in response to a new order. -Analogical reasoning/abstraction/problem solving (UP-Rs): non deductive reasoning that consists of reaching a conclusion based on premises in which a comparison or analogy is established between elements or sets of different elements. -Working memory (UP-WM): a system for temporarily storing and managing the information required to carry out complex cognitive tasks, such as learning, reasoning and comprehension.	UP-FI: FAS, RFFT, VFT, WF, SFVF, D-KEFS (verbal fluency), COVF, CWF UP-Rs: Sim, CANTAB_SC, LPS-4, CT, ACatT, SOC ,BCT, MC (analogies), IT, SILS-A, CLAT UP-WM: FBDS, FDST, BDST, WMS (working memory), PASAT, DMS (Spatial span), WAIS (digit forwards, digit backward), CBTT, SWM, TileMT, SST, KTT, CS, VRT, 2-back, Tic tac
	Cognitive flexibility: ability to flexibly change forward and backward in relation to different tasks, mental operations, or schemas -Set shifting (CogFlx-SS): ability to switch between perceptive or attentional or perceptual sets or criteria. -Reversal learning (CogFlx-RL): ability to switch between reinforcement patterns.	CogFlx-SS: WCST, TMT, TEA, MC (object match), OT, ASST, TDIDED, AAT (alternate response),CTT CogFlx-RL: PRL
	Inhibition: ability to inhibit in a controlled way the production of prepotent, automatic, or impulsive responses when necessary Impulsive action (ImpAC): -Response Inhibition: the ability to inhibit inappropriate responses -Self regulation: the regulation of one's own behavior without external control or monitoring Impulsive choice (ImpCH): -Reflection-impulsivity: the tendency to gather and evaluate information before making a decision -Time estimation: the ability to estimate and pace the passage of time -Delay discounting: a greater preference for immediate rewards, even when they are less advantageous than other rewards	ImpAC: Go-No go, Stroop, R-SAT, SCT, IMT, DelayedMT, RLG, FDT, HSCT, PMQS, CRT ImpCH: TCDDT,DDT,MFFT,TEP, CARROT, IST, MCQ
	Decision-making: the ability to select the most adaptive course of action for the organism among a set of possible behavioral alternatives.	DMK: IGT, CDMT, RTT, SGT, The Bets 16, DMT, GDT, CBT
	Planning/Organization/Sequencing: the process of setting goals, developing strategies, and outlining tasks and schedules to accomplish goals	PLAN: CANTAB_SC, TOL, TMT, WAIS (mosaic test, block design), TileMT, D-KEFS (towers), BADS, TOH

Table 1 (continued)

PSYCHOMOTOR FUNCTIONING	Psychomotor performance, encompasses motor strength, hand-eye coordination, balance, dexterity, tracking and other skills (MOT) -Manual dexterity: fine motor skills of hands (or fingers) -Psychomotor speed: the amount of time it takes a person to process a signal, prepare a response and execute that response	MOT: FOT, FTT, GPT, DSST, HRNTB, WAIS (digit symbol), SDMT, CalCAP, DVT, MC (timers), GSM, PRT, D-KEFS, SRTT, FAT, CST, Timed gait, TPT, FAB, HDT
SPATIAL PROCESSING	The ability to accurately judge the relationship between visual stimuli (SPA)	SPA: WAIS (block design, pictures, cubes, object assembling), MC : Tic Tac, clocks, SDMT, MRT, JoLO, OT, CCSE, VST
PROCESSING SPEED	The ability to process information automatically and therefore speedily, without intentional thinking through (Speed)	Speed: SDMT, FDT, SRT. CalCAP
EMOTION PROCESSING	The ability to recognize, experience, and express valence specific emotion (PrEMO)	PrEMO: FEEST, DERS, PFA, ME, BFRT, EFE, Eyes task, ICERE

Table 1.

Definition of neuropsychological domains and list of neuropsychological instruments used to measure them in the field of neuropsychology and addiction. Neuropsychological instruments are listed in alphabetical order.

[a] AAT: Attentional assessment test, ACatT: Adult category test; ACPT: Auditory Continuous Performance Test, AFLT: Aggie figures learning test; AMIPB: Adult memory and information processing battery; ANT: Attention network test, ASST:Attentional Set-Shifting task; BCSR: Babcock story recall, BCT: Booklet Categories Test, BD: Block design; BDST: Backward digit span test; BFRT: Benton facial recognition test, BNT, Boston naming test, BSRT: The Buschke Selective Reminding Task; BVMT-R: Brief visuospatial memory test, BVRT: Benton visual retention test, CalCAP: California computerized assessment package; CANTAB: DMS, Delayed Matching to Sample, CANTAB_SC: Stocking of Cambridge; CAVLT: Chinese auditory verbal learning test; CBT: Cognitive bias task, CBTT: Corsi block tapping test, CCSE: Cognitive capacity screening examination, CDMT: Cambridge decision making task; ; CLAT: Conceptual levels analogies; CLDL: Coughlan list and design learning; COVF: Controlled oral verbal fluency,COWAT: Controlled Oral Word Association Test, CPT: Continuous Performance Test; CRTT: Choice reaction time task (stop-signal), CS: computation span, CST: Categoric search task; CT: Category test; CTT: Colour trails test; CVLT: California verbal learning test, CWF: Chicago word fluency, DCT: Digit cancellation test, DDT: Delay discounting task; DelayedMT: Delayed memory task; DERS: Difficulties emotional regulation scale, DFRT: Delayed free recall task; D-KEFS: Delis-Kaplan Executive function system, DMT: Decision making task; DPT Doors and people test; DSST: Digit symbol substitution test; DVT: Digit vigilance test, ECM: Ecological contextual memory, EFE: Emotional facial expressions recognition task, FAB: Fregly Ataxia Battery; FAS: Oral word association test; FAT: Focused attention task, FBDS: Forward and backward digit span; FCSRT: Free and cued selective reminding test; FDST: Forward digit span test; FDT: Five digit test, FEEST: Facial expressions of emotions: stimuli and tests; FMT: Figure memory test, FOT: Finger oscillation test; FRT: Free recall test, FTT: Finger tapping test;GDT: Game of dice task, GSM: Gibson's spiral maze, GPT: Grooved pegboard test; HDT: Hand Dynamometer Test, HRDT: Hebbs recurring digits test, HRNTB: Halstead-Reitan Neuropsychological test battery; HSCT: Hayling sentence completion test,HVLT-R: Hopkins verbal learning test;ICERE: Clinical Instrument for Emotional Response Evaluation, IDPR: Immediate and delayed prose recall;IGT: Iowa gambling task; IFRT: Immediate free recall task; IMT: Immediate memory task; IST: Information sampling test, IT: Integration task; JoLO: Judgment of Line Orientation, KTT: Keep Track Task, LGT-3: Lern-und Gedachtnistest learning and memory test, LPS-4: Leistungsprüfsystem, abstract logical thinking; MC: MicroCog assessment of cognitive functioning; MCQ: Monetary choice questionnaire, ME: Mind in the Eyestest; MFFT: Matching familiar figures test; MRT: Mental rotation task, OT: Oral trails,PAL, Paired Associate learning, PASAT: Paced Auditory Serial Addition Test, PFA: Pictures of facial affect, PMQS: Porteus maze test; PMT: Pictorial associative memory task, PPVT: Peabody picture vocabulary test, PRL: Probabilistic reversal learning; PRM: Delayed pattern recognition memory; PRT: Pursuit rotor task, PSR: Pattern and spatial recognition; RAVLT: Rey Auditory Verbal Learning Test; RBMT: Rivermead behavioural memory test; RCFT: Rey-Osterrieth Complex Figure Test, RFFT: Ruff figural fluency test; RLG: Random letter generation, R-SAT: Revised strategy applications test; RSCT (BADS): Rule shift cards test (Behavioural assessment of the dysexecutive syndrome); RT: Rhytm test, RTT: Risk taking task; SAT: Visuo-auditory selective attention task, SCT: Stop Change Task, SDMT: Symbol Digit Modalities Test, SDPALT: Symbol digit paired associate learning test; SFVF: Semantic and phonemic verbal fluency SGT: Simulated gambling task, SILS-A: Abstraction scale, SILS-V: Vocabulary scale, Sim: Similarites subtest (WAIS), SMT: Story memory test, SN-SALT: Spatial and non-spatial associative learning test; SOC: Speed of Comprehension; SOT, Stocking of Cambridge, SpT: Spondee test, SPT: Semantic processing task; SRT: Simple reaction time; SSPT: Speech sounds perception test; SSST: Serial seven subtraction test, ST: shaped test; SWM: Spatial working memory,TAP: Test of attentional performance; TCDDT: Two choice delay discounting task; TDIDED: Three dimensional IDED; TEA: Test of everyday attention, TEP: Time estimation and production; TileMT: Tile manipulation test,TMT: Trail making test; TOH: Tower of Hanoi; TOL: Tower of London; TPT: Tactual performance test,VFT: Verbal fluency test; VIG: Visuospatial memory, VLMT: Verbal learning memory test, VRT: Verbal reasoning task; VST: Visuo-spatial strategy task; WCST: Wisconsin card sorting test; WF: Word fluency, WRMT: Warrington recognition memory tests for words and faces; WSC: Word stem completation

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
Cannabis	Fried et al., 2005 (SAC/MT)	NTxS: 19 current heavy users, 19 current light users, 16 former regular users; 59 controls	Current: 24 h Former: at least 3 months	Vocabulary, AcatT, WAIS (General IQ, Block design, Picture completion, Digit symbol), WMS (IMI, GMI)	IQ, SM, UP-Rs, **speed**, **EM**: 24 hours
Psychostimulants	Bolla et al., 2003 (ST)	NTxS: 13 cocaine users; 13 controls [#]	25 days	IGT	***DMK***
	Verdejo et al., 2007a (ST)	NTxS: 12 cocaine users; 13 controls [#]	25 days	IGT	***DMK***
	*Volkow et al., 2001 (MT/LT)	RESTx: 5 methamphetamine users; 11 controls	3 months 12-17 months	RAVLT, GPT	***EM***, **MOT**: After 3 months
	Salo et al., 2009 (MT/LT)	COMTx: 38 methamphetamine mid abstinence, 27 methamphetamine long abstinence; 33 non users [+]	78 days 31.5 months	Stroop Attention Task	**ImpAC**: After 2.6 months
	Moon et al., 2007 (LT)	19 methamphetamine users, 18 controls	1.79 years	RAVLT, RCFT	***EM***
MDMA	Halpern et al., 2004 (ST)	NTxS: 23 MDMA users (12 light users with consumption between 22-50 pills, 11 heavy users with more than 50 pills consumption); 16 controls	10 days	Vocabulary, Digit symbol, Digit span, Block design (WAIS-III), Stroop, RPM, Mental control, Logical memory, Verbal paired associates, Spatial span, Visual reproduction (WMS-II), COWAT, RCFT, WCST, TMT, CVLT-II, R-SAT	IQ, SUAT, SPA, MOT, SM, EM, UP-WM, UP-Fl, Cogflx-SS, **ImpAC**, **speed**
	Yip & Lee 2005 (MT)	NTxS: 100 MDMA users; 100 controls	67 days	FDST, BDST, CAVLT, Stroop, AFLT, CTT, SDMT, VFT, RFFT	SPA, Cogflx-SS, ImpAC, **EM**, **SAT**, **UP-WM**, **UP-Fl**
Opioids	Fishbein et al., 2007 (ST)	RESTx: 100 heroin users, 102 alcohol users, 60 alcohol and heroin users; 160 controls [+]	21 days	CANTAB test battery: DMS, PAL, SOC; E-Prime battery: Stroop, CDMT, SCT	UP-WM, ImpAC, ***EM*** (alcohol), ***UP-Rs*** (alcohol), **DMK** (heroin)
Alcohol	Bjork et al., 2004 (ST)	RESTx: 130 alcohol dependent patients; 41 controls [+]	7 days	IMT, DelayedMT, RTT, TTDDT	DMK, **ImpAC**, **ImpCH**
	Ratti et al., 2002 (ST)	RESTx: 22 alcohol users; 22 controls	21 days	Digit symbol, TMT, Stroop, Digit cancellation test, Choice Reaction time, WCST	SUAT, speed, ImpAC, **MOT**, **SAT**, ***UP-Rs***, **Cogflx-SS**
	Schottenbauer et al., 2007 (ST)	RESTx: 176 alcohol users; 35 controls [+]	Alcohol: 21 days Other substances: 6 months	The Buschke selective reminding task, WAIS: Vocabulary, Block design	IQ, ***EM***
	Errico et al., 2002 (MT)	RESTx: 48 alcohol users; 30 controls	32 days	WMS: Logical memory, Wechsler immediate and delayed visual reproduction subtests, RCFT, HRDT, CBTT WCST	CogFlx-SS, UP-WM, ***EM***
	Fein et al., 2004 (LT)	NTxS: 44 long term abstinent; 58 controls	6.6 years	SGT	**DMK**
	Fein et al., 2006 (LT)	NTxS and ex-RESTx: 48 long term abstinent; 48 controls	6.7 years	MicroCog, RCFT, TMT, Symbol Digit Modalities Test, AMNART, COWAT, PASAT, Block Design (WAIS-R), Stroop, FAB, SGT	IQ, MOT, SAT, EM, UP-WM, UP-Fl, Cogflx-SS, ImpAC, speed, **SPA**

Table 2.
Neuropsychological studies on relatively ‘pure’ users of one substance (excluding nicotine and minimal alcohol use).

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] RPM: Raven’s progressive matrices; AMNART: American version of the Nelson Adult Reading Test.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models; [#] Comparison groups were not demographically matched but these variables were not correlated with neuropsychological measures and were no longer considered.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
Psychostimulants	Bolla et al. 2000 (SAC/ST)	NTxS: 29 cocaine users, 27 cocaine and alcohol users	1-3 days 28 days	Shipley IQ, WAIS-R, RAVLT, Digit Symbol (WAIS-R), TMT Stroop, Block design (WAIS-R), CalCAP, GPT.	IQ, ***MOT*** (alcohol), ***SAT*** (cocaine), ***EM*** (cocaine), ***CogFlx-SS*** (alcohol), **PLAN** (alcohol)
	Abi-Saab et al. 2005 (ST)	NTxS and COMTx: 22 cocaine users, *71 cocaine and alcohol users; 16 controls [+]	Cocaine and alcohol: 5 days	Digit span, Digit symbol (WAIS-R), DVT, PASAT, TMT, FOT, GPT, RAVLT, COWAT.	UP-WM, CogFlx-SS, UP-Fl, Cocaine and alcohol: ***MOT, SAT, EM***
	Colzato et al., 2009 (ST)	NTxS: 18 polysubstance (non cocaine users), 18 polysubstance (cocaine users)	14 days	Raven's Progressive Matrices, Global local task	IQ, ***SAT***
	Goldstein et al, 2004 (ST)	RESTx and COMTx: 42 crack+alcohol users, 40 alcohol users; 72 controls [#]	Crack: 23 days Alcohol: 17 days	COWAT, BNT, Similarities (WAIS-R), CVLT, WMS, BVRT, DCT, SDMT, TMT, WCST, Stroop, BCT, WRAT, RPM	IQ, SM, MOT, UP-Rs, ImpAC*, ***SAT*** (alcohol), ***EM*** (crack), ***CogFlx-SS*** (alcohol)
	*Fein et al., 2002 (MT)	RESTx: 17 cocaine users, 29 cocaine and alcohol users; 20 controls	24 days	MC: numbers forward, numbers reversed, alphabet, word list, analogies, object match, tic tac, clock, story, word list, address, timers.	UP-WM, Cocaine and alcohol: ***MOT, SPA, SAT, EM, UP-Rs, CogFlx-SS***
	Di Sclafani et al., 2002 (MT)	RESTx: 20 crack users, 37 crack and alcohol users; 29 controls	24 days 6 months	MC, RCFT, TMT, SDMT, COWAT, GPT, SCT, Stroop.	MOT, UP-Fl, ImpAC*, Cocaine and alcohol: ***SPA, SAT*, EM, UP-Rs*, CogFlx-SS***
	Robinson et al. 1999 (MT)	RESTx and COMTx: 30 cocaine users, 30 cocaine and alcohol users; 30 controls	Cocaine: 96 days Alcohol: 73 days	HRNTB (CT, TMT, TPT,RT, SSPT, FTT), WAIS-R, GPT, SMT, FMT, HDT	SAT, CogFlx-SS Cocaine and alcohol: improve global neuropsychological, ***MOT*** (cocaine)
	González et al., 2004 (ST)	RESTx and NTxS: 26 methamphetamine users, 27 methamphetamine and cannabis users; 41 controls	1-30 days	FAS, CT, TMT, Letter and number (WAIS), PASAT, HVLT-R, BVMT-R, SMT, FMT, GPT	MOT, UP-WM, UP-Fl, Up-Rs, CogFlx-SS, ***EM***
MDMA	Dafters et al., 2006 (ST)	NTxS: 18 cannabis and MDMA users, 18 cannabis users; 18 non users	MDMA: 5 days Cannabis: 48 h	Stroop, Stroop (task switching version), Keep Track Task	SAT, ImpAC, CogFlx-SS, UP-WM **Cog-Flx-SS** (MDMA)
	Croft et al., 2001(Cannabis SAC, MDMA ST)	NTxS: 18 cannabis users, 11 cannabis and MDMA users; 31 controls	Cannabis: 17 h MDMA: 7 days	WRMT, GPT, SN-SALT, FBDS, VFT, Stroop, CLDL, NART.	SAT, SPA, ImpAC, ***speed*** (MDMA), **MOT** (MDMA and cannabis), ***UP-Fl*** (cannabis), ***UP-WM*** (MDMA and cannabis)
	Dafters et al., 2004 (ST)	NTxS: 19 cannabis and MDMA users (light), 16 cannabis and MDMA users (heavy), 15 cannabis users; 19 controls	Cannabis: 48 h MDMA: 7 days	FDST, FRT, RBMT (immediate and delayed), RSCT (BADS), TEA, MFFT.	SAT, CogFlx-SS, UP-WM, ImpCH, ***EM*** (cannabis)
	Morgan 2006 (ST)	NTxS: 12 polysubstance users (non MDMA users), 20 MDMA users; 20 controls	23 days	MFFT, CARROT, Risky decision making	***ImpCH, DMK***
	Schilt et al., 2008 (ST)	NTxS: 31 polysubstance users (MDMA users), 36 polysbustance users (non MDMA users)	Psychoactive drugs: 14 days Alcohol: 7 days	PASAT, Digit span, RAVLT, Memory for design test, Mental rotation task, Judgment of Line Orientation (JoLO)	SPA, UP-WM, ***EM*** (MDMA)
	Fox et al., 2002 (ST)	NTxS: 20 polysubstance users (non MDMA users), 20 polysubstance users (MDMA users)	14 days	VFT, SWM, 3-D IDED (CANTAB), PSR, PAL, Go-nogo, One touch TOL, DMT.	Cog Flx-SS, ImpAC, DMK, PLAN, MDMA: ***EM, UP-WM, UP-Fl***
	Gouzoulis-Mayfrank, 2000 (MT MDMA, ST Cannabis)	NTxS: 28 cannabis users, 28 cannabis and MDMA users; 28 controls	MDMA: 41 days Cannabis: 4 days	TAP (1,6,5,8,12), Stroop, Digit span (WAIS), VLMT, VIG, WF, LPS-4, Mosaic test (WAIS), General knowledge (WAIS).	IQ, ImpAC, Cannabis and MDMA: **SAT, *EM*, *UP-Fl*, *UP-WM*, UP-Rs, PLAN, DAT**

Table 3 (continued)

MDMA	Butler and Montgomery 2004 (MT)	NTxS: 37 polysubstance users, 28 polysubstance users (light MDMA users), 18 polysubstance users (heavy MDMA users), 55 cannabis users; 116 controls	35 days	The Bets16.	***DMK*** (MDMA)
	Morgan et al. 1999 (MT)	NTxS: 22 polysubstance users (non MDMA users), 25 polysubstance users (MDMA users); 19 controls	1-6 months	RBMT	***EM*** (MDMA)
	Morgan 1998 (MT)	NTxS: 12 polysubstance users (non MDMA users), 16 polysubstance users (MDMA users); 16 controls	65 days	TOL, MFFT	PLAN ***ImpCH***
	De Sola et al., 2008 (ST/LT)	NTxS: 37 polydrug users (MDMA and cannabis), 23 cannabis users; 34 non-users	72 h 24 months	Vocabulary (WAIS), CALCAP, TOL, WF, SDMT, CVLT, RCFT, CBT, Letter and number (WAIS)	SM, DAT, PLAN, 72 h cannabis and MDMA: ***speed, EM, UP-Fl, UP-WM,*** 24 months MDMA: ***speed, UP-Fl, UP-WM***
	Hoshi et al., 2007 (ST/LT)	NTxS: 25 current MDMA users, 28 ex MDMA users, 29 polydrug users; 27 non users	Current MDMA: 14 days Ex MDMA: 1017 days	IDPR, BSRT, Go/No go task, SST, SFVF, TMT, CANTAB spatial working memory, stockings of Cambridge, GSM	MOT*, UP-WM*, UP-Rs, CogFlx-SS*, Current MDMA and polydrug users: ***EM*, ImpAC****
	Roiser et al., 2007 (MT/LT)	NTxS: 30 current MDMA users, 20 ex MDMA users, 30 polydrug users; 30 non users	Current MDMA: 75 days Ex MDMA: 2 years and 10 months	Tile manipulation test, Mental rotation task, DMT, Pattern recognition memory, DMS	EM, UP-WM, DKM, PLAN, **SPA** (MDMA)
Opioids	Verdejo et al., 2005a (ST)	RESTx: 23 heroin users, 18 methadone patients	Heroin: 15 days	FAS, Letter Number Sequencing (WAIS), Oral trails, Stroop, Similarities, FDT, WCST	UP-Fl, ImpAC, Methadone: **speed, UP-WM, UP-Rs, CogFlx-SS,**

Table 3.
Neuropsychological studies implementing methodological control of co-abused drugs.

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] NART: National adult reading test; HRNTB: Halstead-Reitan Battery; SCT: Short category test (Booklet format); RPM: Raven´s progressive matrices.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models; [#] Comparison groups were not demographically matched but these variables were not correlated with neuropsychological measures and were no longer considered.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
Cannabis	*Wadsworth et al., 2006 (SAC)	NTxS: 34 cannabis users; 85 controls [+]	24 h	SRTT, FAT, CST, IFRT, DFRT, VRT, SPT	PLAN, **MOT**, ***EM***, **UP-WM**
	Mc Hale et al., 2008 (SAC/ST)	Study 1: NTxS, 12 cannabis acute abstinence, 25 cannabis short abstinence; 23 controls; Study 2 & 3: NTxS, 18 acute abstinence; 20 controls	24 h 7 days	Study 1: Verbal fluency, Phonemic verbal fluency task Study 2: Doors and People test, Shapes test Study 3: RBMT (belonging)	1 week abstinence: **UP-Fl** 1 day: ***EM*****, PrM**
	Pope et al., 2001 (SAC/ST)	NTxS: 63 current heavy cannabis users, 45 former heavy cannabis users; 72 non users [+]	0, 1, 7, 28 days	WAIS, CPT, ACPT, BSRT, BVRT, WCST, WMS, block design (WAIS-R), COWAT, Stroop, RPM	IQ, AT, CogFlx-SS, SPA, UP-Fl, ImpAC, ***EM*** (after 7 days)
	Medina et al., 2007 (MT)	NTxS: 65 cannabis users; 65 controls	30 days	D-KEFS (verbal fluency, towers), TMT, WAIS (Letter and Lumber sequencing, digit symbol, arithmetic, digit span bakwards) CVLT-II, PASAT, WMS (verbal story, logical memory), RCFT, WASI (block design)	UP-Fl, UP-WM, **speed**, **SPA**, **SAT,** ***EM***, ***PLAN***,
	Lyons et al., 2004 (LT)	NTxS: 54 twin pairs, 54 former cannabis users, 54 non cannabis users	20 years	WAIS, RPM, WRAT, CT, CPT, TMT, WMS (logical memory, visual reproduction), CVLT, RCFT, WCST, Stroop, FTT, GP	IQ, SPA, SAT, DAT, EM, UP-Rs, UP-WM, CogFlx-SS, MOT, ***PLAN***
Psychostimulants	*Tucker et al., 2004 (ST)	NTxS: 17 cocaine users; 14 non users [+]	3 days	IGT	***DMK***
	Woicik et al., 2008 (ST)	NTxS: 64 cocaine users; 64 controls [+]	3-25 days	COWAT, Digit span, Letter and Sequencing (WAIS-III), SDMT, TMT, WCST, Stroop, ANT, IGT, CVLT-II, Ekman faces, BFRT, Timed gait, Finger Tapping, GP	MOT, PrEMO, UP-Fl, , CogFlx-SS, ImpAC, DMK, **UP-WM, *SAT*, *EM***
	Fillmore & Rush., 2002 (ST)	NTxS: 22 cocaine users; 22 controls	7 days	Choice reaction time task (stop-signal paradigm)	***ImpAC***
	Colzato et al., 2007 (ST)	NTxS: 13 recreational cocaine users; 13 controls	7 days	Stop-signal task	***ImpAC***
	Bolla et al., 1999 (MT)	NTxS: 21 cocaine; 20 control	30 days	Shipley-IQ, COVF, WMS (logical memory), RAVLT, RCFT, SDPAL, Cancellation test, WAIS (digit symbol, block design), TMT, Stroop, WCST, JoLO, CalCAP, FTT, GP	IQ, SPA, UP-Fl, **speed, *SAT*, MOT**, ***EM***, **CogFlx-SS**, ***ImpAC***,
	Heil et al., 2006 (MT)	COMTx: 21 abstinent cocaine users (30 days), 21 current cocaine users; 21 controls	30 days	Delay discounting task	***ImpCH***
	Van Gorp et al., 1999 (MT)	RESTx: 37 cocaine; 27 controls [++]	45 days	CAVLT, RCFT, Pursuit Rotor Task	MOT, ***EM***
	Kemmis et al., 2007 (ST/MT)	NTxS: 30 occasional cocaine, 48 regular recreational cocaine; 21cocaine naïve participants [+]	Ocassional: 6 months Regular: 4 days	EFE Recognition task, Eyes task	***PrEMO***
	Verdejo et al., 2007b (MT)	RESTx: 30 poly-substance abusers; 35 controls	4 months	Ekman Faces Test, R-SAT, IGT	***ImpAC*****, *DMK*, *PrEMO***
	Fernandez-Serrano et al., 2010b (LT)	RESTx: 65 polydrug users; 30 non-users [+]	7 months	Ekman Faces Test, FrsBe	***PrEMO***
	Monterosso et al., 2005 (ST)	NTxS: 11 methamphetamine users; 43 controls [++]	5-7 days	Stop-signal task	***ImpAC***

Table 4 (continued)

Psychostimulants	Kalechstein et al., 2003 (ST)	NTxS: 27 methamphetamine; 18 controls	5-14 days	COWAT, WAIS(Letter and number, VMS), RFFT, RAVLT, WMS (logical memory), RCFT, Stroop, SDMT, TMT	SUAT, UP-WM, CogFlx-SS, ImpAC, ***MOT***, ***EM***, **UP-Fl**
	Salo et al., 2002 (MT)	COMTx and NTxS: 8 methamphetamine; 12 controls +	56-112 days	Stroop	***ImpAC***
	Woods et al., 2005 (MT)	RESTx and NTxS: 87 methamphetamine users; 71 controls	4 months	HVLT-R	***EM***
	Rendell et al., 2009 (LT)	RESTx and COMTx: 20 methamphetamine; 20 controls	6 months	Visual week, FAS, HSCT, RAVLT, Digit forwards, digit bakwards	EM, UP-WM, UP-Fl, ImpAC, **PrM**
	Henry et al., 2009 (LT)	RESTx: 20 methamphetamine, 20 controls	6 months	PFA, ME, FAS, HSCT, RAVLT	EM, UP-Fl, ImpAC, ***PrEMO***
	Hoffman et al., 2006 (LT)	RESTx: 41 methamphetamine users, 41 controls +	6 months	Shipley-IQ, RCFT, Babcock story recall, RAVLT, TMT, GP, Stroop, WCST, Delay discounting task	IQ, SUAT, MOT, EM, SM, CogFlx-SS, ImpAC, ***ImpCH***
MDMA	Hoshi et al., 2004 (SAC/ST)	NTxS: 16 MDMA users; 21 controls +	0-4 days	FEEST	**PrEMO**
	Zakzanis et al., 2003 (ST)	NTxS: 15 MDMA users; 17 controls	14 days	RBMT, Vocabulary (WAIS), WSC.	EM, IM, **SM, PrM**
	Gouzoulis-Mayfrank et al., 2003 (ST)	NTxS: 30 MDMA users (heavy +80 pills), 30 MDMA (light -80); 30 controls	28 days	WAIS (General Knowledge) Go-no go, Visual scanning, Plan-A-Day, Digit span backwards, 2-back, LGT-3	IQ, UP-WM, ImpAC, PLAN, ***EM***
	Bhattachary and Powell, 2001 (MT)	NTxS: 18 new users MDMA, 26 regular users MDMA, 16 past users MDMA; 20 controls	60 days	Quick test, Prose recall test, RCFT, Reversed digit span, COWAT, Verbal Fluency test.	IQ, UP-WM, ***EM***, **UP-Fl**
	Montgomery et al., 2005 (MT)	NTxS: 27 MDMA users; 34 controls	35 days	Letter span, Consonant updating, Computation span, Semantic fluency, CWF	UP-Fl, ***UP-WM***
	Fisk & Montgomery, 2009 (AC/MT)	NTxS: 14 heavy MDMA, 39 light MDMA; 28 non users +	Heavy: 38 days Light: 28 days Others: 24 hours	Letter span, Digits span, Spatial span, Updating task, Computation span, Random Letter Generation	ImpAC, ***UP-WM*** (MDMA)
	Zakzanis and Young, 2001 (MT)	NTxS: 24 MDMA users; 24 controls +	4 months	BADS	SAT, **PLAN**
	Wareing et al., 2004 (AC/ST/LT)	NTxS: 42 current MDMA, 17 former MDMA; 31 controls +	Current: 7 days MDMA, 24 h other drugs, Former: 6 months MDMA, 24 h other	Reading span, Computation span, Raven's Progressive Matrices (word, digit span).	***UP-WM*** (current and former MDMA)
	Wareing et al., 2005 (ST/LT)	NTxS: 36 current MDMA, 12 former MDMA; 31 controls +	Current: 7 days Former: 6 months	SWM, Spatial span task, Computation task, Digit span	***UP-WM*** (current and former MDMA)
	Ward et al., 2006 (ST/LT)	NTxS: 31 current MDMA, 30 former MDMA; 30 controls +	Current: 7 days Former: 2 years	WMS	UP-WM, ***EM*** (current and former MDMA)
Opioids	Mintzer et al., 2005 (SAC)	RESTx: 20 former heroin users, 18 methadone patients; 21 controls	24 h	DSST, TMT, 2-back, Recognition memory, Free recall, IGT	UP-WM, DMK, **MOT**, ***EM***, ***CogFlx-SS***
	*Aguilar et al., 2008 (ST)	RESTx: 22 current opioid users, 41 abstinent opioid users ++	Current: 24 h Abstinent: 14 days	Clinical Instrument for Emotional Response Evaluation	***PrEMO*** current)
	Brand et al., 2008 (ST)	RESTx: 18 opiate dependence; 18 controls	14 days	Game of Dice Task, MCST, FAS, FWIT (Stroop), LPS (reasoniing subtest), Tower Hanoi, ME	PrEMO, UP-Fl, PLAN, **SUAT, UP-Rs**, ***CogFlx-SS***, ***ImpAC***, **DMK**
	Prosser et al., 2006 (MT)	RESTx: 29 former heroin actual methadone, 29 former heroin; 29 controls +	3 months	WAIS (Vocabulary), Stroop, COWAT, Benton visual retention test	SAT, SM, UP-Fl, ***ImpAC*** (former), ***EM*** (former and actual)

Table 4 (continued)

Opioids	*Gerra et al., 2003 (MT)	RESTx: 12 heroin users; 12 controls	84 days	Pictures from the International Affective System	***PrEMO***
	Davis et al., 2002 (MT/LT)	RESTx: 15 methadone patients, 16 former opiate users; 14 controls [+]	42 days-12 months	AMIPB, Test of everyday attention, WAIS (comprehension, similarities, block design, object assembly), COWAT	SPA*, EM*, UP-Rs*, **UP-Fl**
	Pau et al., 2002 (LT)	RESTx: 30 heroin users; 25 controls [+]	13 months	SSST, CTT, PMQS, WCST	DAT, SUAT, CogFlx-SS, ***ImpAC***
Alcohol	Pitel et al., 2007 (ST)	RESTx: 40 alcohol users; 55 controls	11 days	FCSRT, ECM, Integration task, Spondee test, Verbal fluency tasks, Stroop, Attentional assessment test, N-Back (N-2) paradigm	UP-Fl, **EM**, **UP-WM**, **CogFlx-SS**, **ImpAC**, ***UP-Rs***
	Beatty et al., 2000 (ST/MT)	RESTx and COMTx: 55 alcohol users (4 - 9 years), 107 alcohol users (more than 10 years); 165 controls [+]	14- 42 days	SILS-V, SILS-A, Digit symbol (WAIS), CLAT, Six verbal fluency test.	UP-Fl, **SM**, **MOT**, ***UP-Rs***
	Foisy et al., 2007 (ST/MT)	RESTx: 22 abstinent alcoholic, 27 dropping alcoholic; 22 controls	21-60 days	Emotional facial expression test, WAIS (picture completion, cubes, objects assembling), CCSE, Benton facial recognition test	SPA, **PrEMO**

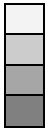
Table 4.
Neuropsychological studies on polysubstance users of the different drugs studied.

Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] RPM: Raven's progressive matrices; WRAT: Wide range achievement test; BDI: Beck depression inventory; MCST: Modified card sorting test, FWIT: Farbe wort interferenz test, LPS: Leistungs Prüfsystem.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models; [++] Comparison groups were not demographically matched and these variables were controlled through covariance models; [#] Comparison groups were not demographically matched but these variables were not correlated with neuropsychological measures and were no longer considered.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

SUBSTANCE	ARTICLE	PARTICIPANTS	ABSTINENCE	TASKS[a]	ASSESSED/**IMPAIRED FUNCTIONS**
MDMA & Cannabis	Quednow et al., 2006 (ST)	NTxS: 19 abstinent MDMA users, 19 abstinent cannabis users; 19 drug-naïve control	3 days	VMLT/RAVLT	MDMA: **EM, UP-WM***
	Quednow et al., 2007 (ST)	NTxS: 19 abstinent MDMA users, 19 abstinent cannabis users; 19 drug-naïve control	3 days	Go/no go task, Matching Familiar Figures Test, Decision making task	ImpAC, **DMK** (MDMA), **ImpCH** (MDMA)
	Clark et al., 2009 (ST/LT)	NTxS: 46 current MDMA users, 14 ex MDMA users, 15 current cannabis users; 19 controls	Current: 21 days Ex users: 1 year	IST, NART, IVE, BDI	IQ, **ImpCH** (cannabis)
Opioids & Psychostimulants & Alcohol	Kirby et al., 2004 (SAC/ST)	NTxS and COMTx: 14 current alcohol users, 19 ex alcohol users, 20 current cocaine users, 21 ex cocaine users, 7 current heroin users, 20 ex heroin users; 44 controls	Ex users: 14 days	MCQ, Shipley (vocabulary, abstract reasoning), IVE, ZSS, BIS	IQ, ***ImpCH*** (current cocaine, ex cocaine, current heroin)
Opioids & Alcohol	Kornreinch et al., 2003 (Alcohol ST, Opiate MT/LT)	RESTx: 30 alcohol users, 30 opiate users with methadone, 30 opiate abstinent users, 30 ex opiates and alcohol users; 30 controls [+]	Alcohol users: 21 days Opiate abstinents: 3.8 months Ex opiates and alcohol: 11 months for opiates, 21 days for alcohol	EFE	**PrEMO** (alcohol and opiates)
Psychostimulants & Alcohol	González et al., 2007 (ST)	RESTx: 17 alcohol users, 16 methamphetamine; 19 controls [+]	14 days	IGT, Delayed non match to sample task	***DMK, UP-WM*** (methamphetamines)
	Van der Plas et al., 2009 (ST)	RESTx: 33 alcohol users, 38 cocaine, 27 methamphetamine; 36 controls [+]	15 days	IGT, Tic Tac Toe, Cognitive flexibility, WCST, Response inhibition task	ImpAC, Cocaine and metham: ***UP-WM, CogFlx-SS, DMK***
Psychostimulants & Opioids	Ornstein et al., 2000 (SAC)	RESTx: 22 heroin users, 23 amphetamines users (9 heroin dependent); 3 control groups x 22)	After withdrawal symptoms	FAS, Category fluency (animals), Attentional Set-Shifting task, Spatial working memory task, O-TTOLT, Visuospatial strategy task.	SPA, UP-Fl, UP-WM, PLAN, Heroin: **EM** Amphetamines: ***EM, CogFlx-SS,***
	Verdejo-García y Pérez-García, 2007 (Cocaine MT, Heroin LT)	RESTx: 45 cocaine polysubstance abusers, 28 heroin polysubstance abusers, 8 alcohol polysubstance abusers; 37 controls	Cocaine: 4 months Heroin: 6 months	FAS, RFFT, WAIS (letter-number sequencing, arithmetic, digit, similarities, WMS (spatial span), Stroop, FDT, Go/no go task, Category test, WCST, CBT, IGT	Cocaine: ***CogFlx-SS, ImpAC*** Cocaine and Heroin: ***UP-WM, DMK,*** **UP-Rs, UP-Fl**
	Verdejo-García et al., 2007c (Cocaine MT, Heroin LT)	RESTx: 34 cocaine polysubstance abusers, 25 heroin polysubstance abusers; 27 controls	Cocaine: 4 months Heroin: 5.8 months	TWAT, Stroop, FDT, Go/no go task, IGT	IQ, Cocaine and Heroin: ***DMK*** Cocaine: ***ImpAC***
	Ersche et al., 2006 (LT)	COMTx and NTxS: 25 chronic amphetamine users, 42 chronic opiate users, 26 former drug users of psychostimulants and opiates; 27 controls	Former users: 8 years	O-TTOL, Three dimensional IDED, PAL, PRM	Former and current amphetamine users: **PLAN, *CogFlx-SS*, *EM***
	Ersche et al., 2008 (LT)	COMTx and NTxS: 30 chronic amphetamine users, 27 chronic cocaine users, 42 chronic opiate, 26 former drug users of psychostimulants and opiates; 25 controls [+]	Former: 8 years	Probabilistic Reversal-Learning	Cocaine: **CogFlx-RL**
	Clark et al., 2006 (LT)	NTxS: 24 current amphetamines users, 40 current opiates users, 24 former users of amphetamines and opiates; 26 controls	Former: 8 years	NART, IST, BDI, BIS	IQ, ***ImpCH*** (current and former amphetamines users, current and former opiates users)

Table 5.
Neuropsychological studies comparing performance of polysubstance users with different principal drug of choice.



Studies in sub-acute abstinent users
Studies in short-term abstinent users
Studies in mid-term abstinent users
Studies in long-term abstinent users

Notes.
In bold: domains found to be impaired. *In italics*: domains found to be impaired by different studies on the same drug. Underlined: domains found to be impaired across different studies addressing the effects of different drugs.
SAC: Sub-acute abstinence; ST: Short-term abstinence; MT: Mid-term abstinence; LT: Long-term abstinence; NTxS: Non treatment seekers; COMTx: Community treatment; RESTx: Residential treatment.
[a] VLMT/RAVLT: Verbaler Lern- und Merkfähigkeitstest; O-TTOLT: One-touch tower of London task; TWAT: Test word accentuation test; NART: National adult reading test; BDI: Beck depression inventory; BIS: Barratt Impulsivity Scale; IVE: Eysenck Impulsiveness Venturesomeness Empathy questionnaire; ZSS: Zuckerman sensation seeking scale.
[+] Comparison groups were not demographically matched and these variables were controlled through covariance models.
*Insufficient information to calculate effect sizes for the study (when the mark is in the ARTICLE column), for one particular group of participants (when the mark is in the PARTICIPANTS column) or for one particular neuropsychological measure (when the mark is in the ASSESSED/IMPAIRED FUNCTIONS column).

	CANNABIS				COCAINE				METHAMPHETAMINES				MDMA				HEROIN				METHADONE				ALCOHOL			
	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP
EM	**2.21**	0.33	0.36	0.42		0.36	0.27		**0.87**		0.46	**0.51**	**1.04**	0.49	**0.52**	**1.06**	0.48		**0.52**	0.12			0.16		0.35	0.28	**0.54**	
	(1)	(1)	(4)	(1)		(1)	(3)		(1)		(5)	(2)	(2)	(8)	(3)	(1)	(1)		(2)	(1)			(2)		(3)	(2)	(1)	
SM	**3**					0.16					0.27		**0.50**	0.49	**0.94**				0.32	0.28				0.23			**0.54**	
	(1)					(1)					(1)		(2)	(1)	(1)				(1)	(2)				(1)			(1)	
PrM			**0.95**								**1.25**				0.43													
			(1)								(1)				(1)													
IM															0.41													
															(1)													
SAT			0.15			0.38	0.45						**1.40**	**0.56**	**0.53**				**0.83**				0.36		**0.83**	**0.56**		
			(2)			(2)	(2)						(1)	(4)	(1)				(1)				(1)		(2)	(4)		
DAT			0.05											**0.52**					**0.53**									
			(1)											(2)					(1)									
SUAT											0.43		**0.51**						0.42						**1.03**			
											(2)		(1)						(2)						(1)			
UP-Fl		0.17	**1.05**			0.49	0.11	**0.83**			**1.11**	**0.68**	**0.63**	0.39	**0.76**				**0.60**	**0.78**		0.16	**0.64**		0.05	**0.52**	0.35	
		(1)	(3)			(2)	(2)	(1)			(3)	(2)	(2)	(4)	(2)				(3)	(2)		(1)	(2)		(1)	(1)	(2)	
UP-Rs	0.39	0.40	0.16			0.13		**1.79**						**0.60**			**0.71**		**1**	**1.81**		**0.89**			0.10		**0.69**	
	(1)	(1)	(1)			(1)		(1)						(2)			(1)		(1)	(1)		(1)			(1)		(2)	
UP-WM		0.15	0.14	0.44		**0.56**	**0.79**	**1.19**			**0.71**	**0.73**	0.40	0.25	0.47	0.44	**0.53**		0.17	**1.06**		**0.63**	**0.53**		0.28	0.43	**0.56**	
		(1)	(2)	(1)		(1)	(1)	(2)			(2)	(3)	(2)	(8)	(7)	(1)	(1)		(1)	(2)		(1)	(1)		(2)	(1)	(1)	
CogFlx-		0.47	0.38			0.20	0.26	0.30			0.36	0.33	0.35	**0.65**					**0.62**	0.36		**0.76**	0.46	0.05	0.45	**0.55**	**0.53**	0.31
SS		(1)	(2)			(1)	(2)	(2)			(2)	(3)	(1)	(3)					(3)	(3)		(1)	(1)	(1)	(3)	(2)	(1)	(1)

Table 6 (continued)

	CANNABIS				COCAINE				METHAMPHETAMINES				MDMA				HEROIN				METHADONE				ALCOHOL			
	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP	PU	MC	PS	PP
CogFlx-RL								0.43 (1)			**0.57** (1)	0.24 (1)							0.37 (1)	0.25 (1)				0.26 (1)				
ImpAC			0.28 (1)	0.10 (1)			**0.93** (5)	**0.55** (2)	**0.82** (1)		**1.12** (6)	0.37 (1)	**0.54** (1)	0.31 (5)	0.15 (2)	0.13 (1)	0.27 (1)		**0.84** (3)	0.24 (1)		0.40 (1)	**0.66** (1)		0.49 (3)		**0.87** (1)	0.37 (1)
ImpCH				0.39 (2)			**1.92** (1)	**0.90** (1)			**0.81** (1)	0.09 (1)		0.44 (3)		0.35 (2)				**0.60** (2)				0.03 (1)	0.17 (1)			0.22 (1)
DMK					**0.63** (2)		0.33 (2)	0.49 (2)				0.40 (1)		0.19 (4)		**0.69** (1)	0.38 (1)		0.29 (2)	0.46 (2)			**0.51** (1)		0.26 (2)			0.47 (2)
PLAN			0.37 (2)	0.06 (1)								**0.89** (2)		0.26 (5)	0.42 (2)				0.19 (1)	0.42 (2)				**0.92** (1)		**0.82** (1)		
MOT		0.20 (1)	0.22 (1)			0.49 (2)	0.25 (3)				**0.61** (2)		0.27 (1)	0.49 (2)					**0.51** (1)				**0.98** (1)		**0.74** (2)	0.47 (4)	**0.69** (1)	
SPA			0.12 (3)			**0.96** (1)	0.25 (1)			0.10 (1)		0.41 (1)	**0.96** (2)	0.28 (3)						0.34 (1)					0.33 (1)	0.19 (3)	**0.61** (1)	
Speed	**1.20** (1)		0.16 (1)				0.28 (1)						**0.58** (1)	**0.51** (2)								**0.65** (1)			**0.84** (1)			
PrEMO							**0.58** (4)				**2.03** (1)				0.45 (1)				0.41 (1)	0.45 (1)				**0.57** (1)			**0.59** (1)	**1.18** (1)

Table 6. Summary of mean effect sizes (Cohen´s *d*) of the neuropsychological deficits related to different drugs according to the three different methodological approaches reviewed. Numbers in parentheses represent the number of studies used to calculate the mean effect size for each drug/domain.

Notes.

PU, Pure Users, MC, Methodological Control, PS, Polysubstance, PP, Comparison of Polysubstance Users, EM, Episodic Memory, SM, Semantic Memory, PrM, Prospective Memory, IM, Implicit Memory, SAT, Selective Attention, DAT, Divided Attention, SUAT, Sustained Attention, UP-Fl, Updating Fluency, UP-Rs, Updating Reasoning, UP-WM, Updating Working Memory, CogFlx-SS, Cognitive Flexibility Self-shifting, CogFlx-RL, Cognitive Flexibility Reversal Learning, ImpAC, Impulsive Actions, ImpCH, Impulsive Choice, DMK, Decision Making, PLAN, Planning, MOT, Psychomotor Functioning, SPA, Spatial Processing, Speed, Processing Speed, PrEMO, Emotional Processing.

In bold: Mean effect sizes reaching at least a medium magnitude (mean Cohen´s $d \geq 0.5$) across studies. Significant mean effect sizes are reported regardless of the statistical significance (p value) of the results reported in the original studies.

	CANNABIS				COCAINE				METHAMPHETAMINES				MDMA				HEROIN				METHADONE				ALCOHOL			
	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT
EM	**1.1**	0.31	0.23	0.14		0.38	0.34		**1**	**0.85**	0.41	**0.7**		**0.55**	**0.86**	0.46	**0.51**	0.48	**1.39**	0.12	0.29					**0.53**	0.3	0.27
	(4)	(3)	(1)	(1)		(2)	(2)		(1)	(1)	(1)	(5)		(9)	(5)	(3)	(2)	(1)	(1)	(1)	(1)					(4)	(2)	(1)
SM	**3**					0.16						0.27		**0.69**		0.49			0.32								**0.54**	
	(1)					(1)						(1)		(3)		(1)			(1)								(1)	
PrM	**0.95**											**1.25**		0.43														
	(1)											(1)		(1)														
IM														0.41														
														(1)														
SAT			0.19	0.08		**0.69**	0.29							0.23	**1.08**				**0.83**							**0.99**	**0.51**	0.23
			(1)	(1)		(3)	(1)							(3)	(2)				(1)							(2)	(1)	(1)
DAT				0.05										0.04	**1.01**	0.06				**0.53**								
				(1)										(1)	(1)	(1)				(1)								
SUAT										**0.62**		0.34		0.49				**0.75**		0.22						**1.03**		
										(1)		(1)		(1)				(1)		(1)						(1)		
UP-Fl	**2.30**	**1.01**	0.22			0.10	0.44		**0.68**	**0.77**		**0.79**		0.38	**0.82**	0.24	0.49	**0.52**	**0.61**	**1.08**		0.16	**1.09**			**0.62**	0.3	0.05
	(2)	(3)	(1)			(1)	(2)		(1)	(1)		(2)		(4)	(3)	(1)	(1)	(1)	(1)	(1)		(1)	(1)			(1)	(2)	(1)
UP-Rs	0.39	0.40		0.16		0.13	**1.79**							0.36	**0.84**			**0.85**		**1.81**		**0.89**				**0.53**	0.48	
	(1)	(1)		(1)		(1)	(1)							(1)	(1)			(2)		(1)		(1)				(3)	(1)	
UP-WM		0.35	0.12	0.17		**0.79**	**1.07**		**0.53**	**0.57**		**0.84**		0.41	0.35	0.4	0.35	**0.53**		**1.19**	0.47	**0.63**				**0.52**	0.37	0.19
		(2)	(1)	(1)		(1)	(1)		(1)	(3)		(1)		(13)	(5)	(5)	(2)	(1)		(1)	(1)	(1)				(2)	(1)	(1)
CogFlx-	0.40	0.43		0.06		0.14	0.31		**0.53**	0.38		0.22		**0.66**	0.35		**0.57**	**0.96**		0.38	**0.64**	**0.76**				**0.7**	0.38	0.12
SS	(1)	(2)		(1)		(2)	(2)		(1)	(2)		(2)		(4)	(1)		(2)	(1)		(3)	(1)	(1)				(3)	(2)	(1)

Table 7 (continued)

	CANNABIS				COCAINE				METHAMPHETAMINES				MDMA				HEROIN				METHADONE				ALCOHOL			
	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT	SAC	ST	MT	LT
CogFlx-RL								0.43 (1)												0.25 (1)								
ImpAC	0.16 (1)	0.17 (2)				**1.05** (3)	**0.82** (4)			**0.56** (3)	**0.94** (2)	**1.21** (3)		0.23 (7)	0.26 (3)			**0.79** (2)	**1.2** (1)	0.49 (2)		0.4 (1)				**0.65** (4)		0.18 (1)
ImpCH		0.39 (2)				**0.9** (1)	0.36 (1)					**0.81** (1)		0.36 (4)	**0.61** (1)			**1.1** (1)		0.11 (1)						0.19 (2)		
DMK						0.46 (3)	**0.51** (3)			0.47 (2)				0.41 (3)	0.24 (2)	0.12 (1)	0.23 (1)	**0.8** (1)		**0.85** (1)	**0.6** (1)					0.32 (2)		0.4 (1)
PLAN	0.35 (1)		**0.55** (1)	0.19 (1)					**0.85** (1)			0.15 (1)		0.31 (3)	**0.52** (3)	0.33 (2)	**1.21** (1)	0.19 (1)		0.1 (1)						**0.6** (1)		
MOT		0.20 (1)		0.22 (1)		0.13 (2)	0.37 (2)			**0.96** (1)		0.44 (1)		0.48 (2)			**0.51** (1)				**0.98** (1)					1 (2)	0.49 (3)	0.24 (1)
SPA	0.07 (1)	0.19 (1)	0.03 (1)	0.21 (1)			0.25 (1)		0.41 (1)					0.28 (3)	**0.81** (2)	0.17 (1)	0.34 (1)										0.39 (2)	0.33 (1)
Speed	**1.20** (1)		0.16 (1)				0.28 (1)							**0.58** (2)		0.46 (1)						**0.65** (1)				**0.84** (1)	**0.75** (1)	0.26 (1)
PrEMO						0.35 (2)	**0.66** (1)	0.45 (2)				**2.03** (1)	0.47 (1)					0.4 (2)					**0.57** (1)			**1.18** (1)	**0.59** (1)	

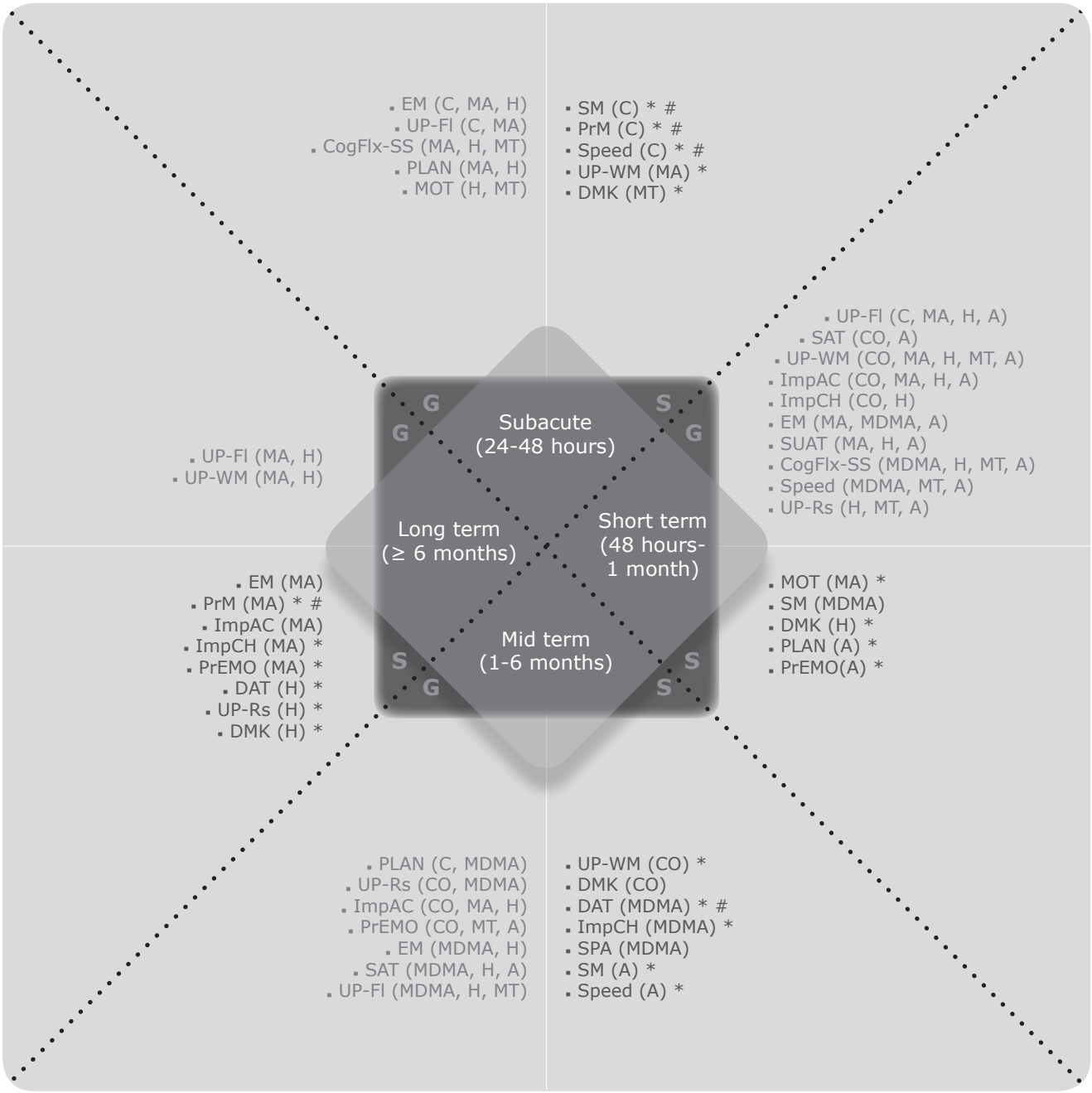
Table 7. Summary of mean effect sizes (Cohen´s *d*) of the neuropsychological deficits related to different drugs according to the time-line of abstinence duration. Numbers in parentheses represent the number of studies used to calculate the mean effect size for each drug/domain.

Notes.

SAC, Sub-acute abstinence, ST: Short-term abstinence, MT, Mid-term abstinence, LT, Long-term abstinence , EM, Episodic Memory, SM, Semantic Memory, PrM, Prospective Memory, IM, Implicit Memory, SAT, Selective Attention, DAT, Divided Attention, SUAT, Sustained Attention, UP-Fl, Updating Fluency, UP-Rs, Updating Reasoning, UP-WM, Updating Working Memory, CogFlx-SS, Cognitive Flexibility Self-shifting, CogFlx-RL, Cognitive Flexibility Reversal Learning, ImpAC, Impulsive Actions, ImpCH, Impulsive Choice, DMK, Decision Making, PLAN, Planning, MOT, Psychomotor Functioning, SPA, Spatial Processing, Speed, Processing Speed, PrEMO, Emotional Processing.

In bold: Mean effect sizes reaching at least a medium magnitude (mean Cohen´s $d \geq 0.5$) across studies. Significant mean effect sizes are reported regardless of the statistical significance (p value) of the results reported in the original studies.

Figure(s)


▪ EM (C, MA, H)
▪ UP-Fl (C, MA)
▪ CogFlx-SS (MA, H, MT)
▪ PLAN (MA, H)
▪ MOT (H, MT)
▪ SM (C) * #
▪ PrM (C) * #
▪ Speed (C) * #
▪ UP-WM (MA) *
▪ DMK (MT) *
▪ UP-Fl (C, MA, H, A)
▪ SAT (CO, A)
▪ UP-WM (CO, MA, H, MT, A)
▪ ImpAC (CO, MA, H, A)
▪ ImpCH (CO, H)
▪ EM (MA, MDMA, A)
▪ SUAT (MA, H, A)
▪ CogFlx-SS (MDMA, H, MT, A)
▪ Speed (MDMA, MT, A)
▪ UP-Rs (H, MT, A)
▪ UP-Fl (MA, H)
▪ UP-WM (MA, H)
G
G
S
G
Subacute
(24-48 hours)
Long term
(≥ 6 months)
Short term
(48 hours-
1 month)
Mid term
(1-6 months)
S
G
S
S
▪ EM (MA)
▪ PrM (MA) * #
▪ ImpAC (MA)
▪ ImpCH (MA) *
▪ PrEMO (MA) *
▪ DAT (H) *
▪ UP-Rs (H) *
▪ DMK (H) *
▪ MOT (MA) *
▪ SM (MDMA)
▪ DMK (H) *
▪ PLAN (A) *
▪ PrEMO(A) *
▪ PLAN (C, MDMA)
▪ UP-Rs (CO, MDMA)
▪ ImpAC (CO, MA, H)
▪ PrEMO (CO, MT, A)
▪ EM (MDMA, H)
▪ SAT (MDMA, H, A)
▪ UP-Fl (MDMA, H, MT)
▪ UP-WM (CO) *
▪ DMK (CO)
▪ DAT (MDMA) * #
▪ ImpCH (MDMA) *
▪ SPA (MDMA)
▪ SM (A) *
▪ Speed (A) *

Figure(s)

Figure 1.

Time-line of specific vs. generalized neuropsychological effects associated with cannabis, cocaine, methamphetamines, MDMA, heroin, methadone and alcohol abuse.

Note. G: generalized, S: specific, C: cannabis, CO: cocaine, MA: methamphetamines, MDMA: ecstasy, H: heroin, MT: methadone, A: alcohol, EM, Episodic Memory, SM, Semantic Memory, PrM, Prospective Memory, IM, Implicit Memory, SAT, Selective Attention, DAT, Divided Attention, SUAT, Sustained Attention, UP-Fl, Updating Fluency, UP-Rs, Updating Reasoning, UP-WM, Updating Working Memory, CogFlx-SS, Cognitive Flexibility Self-shifting, CogFlx-RL, Cognitive Flexibility Reversal Learning, ImpAC, Impulsive Actions, ImpCH, Impulsive Choice, DMK, Decision Making, PLAN, Planning, MOT, Psychomotor Functioning, SPA, Spatial Processing, Speed, Processing Speed, PrEMO, Emotional Processing.

* Results obtained from a single study.

Neuropsychological domain tested only for this substance.

Anexo II

European Journal of Pharmacology 626 (2010) 104–112

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Behavioural Pharmacology

Prevalence of executive dysfunction in cocaine, heroin and alcohol users enrolled in therapeutic communities

María José Fernández-Serrano [a,*], Miguel Pérez-García [a,b], José C. Perales [c], Antonio Verdejo-García [a,b,*]

[a] Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de Psicología de la Universidad de Granada, Campus de Cartuja, s/n, 18071 Granada, Spain
[b] Institute of Neurosciences F. Olóriz, Universidad de Granada, Spain
[c] Departamento de Psicología Experimental y Fisiología del Comportamiento, Universidad de Granada, Spain

ARTICLE INFO

Article history:
Received 7 May 2009
Received in revised form 3 August 2009
Accepted 9 October 2009
Available online 15 October 2009

Keywords:
Prevalence
Executive function
Cocaine
Heroin
Alcohol
Therapeutic community

ABSTRACT

Many studies have observed relevant executive alterations in polysubstance users but no data have been generated in terms of prevalence of these alterations. Studies of the prevalence of neuropsychological impairment can be useful in the design and implementations of interventional programs for substance abusers. The present study was conducted to estimate the prevalence of neuropsychological impairment in different components of executive functions in polysubstance users enrolled in therapeutic communities. Moreover, we estimated the effect size of the differences in the executive performance between polysubstance users and non substance users in order to know which neuropsychological tasks can be useful to detect alterations in the executive functions. Study results showed a high prevalence of executive function impairment in polysubstance users. Working memory was the component with the highest impairment proportion, followed by fluency, shifting, planning, multi-tasking and interference. Comparisons between user groups showed very similar executive impairment prevalence for all the analyzed executive components. The best discriminating task between users and controls was Arithmetic (Wechsler Adult Intelligence Scale, WAIS-III). Moreover FAS and Ruff Figural Fluency Test was discriminating for fluency, Category Test for shifting, Stroop Colour–Word Interference Test for interference, Zoo Map (Behavioural Assessment of the Dysexecutive Syndrome, BADS) for planning and Six Elements (BADS) for multi-tasking. The existence of significant prevalence of executive impairment in polysubstance users reveals the need to redirect the actuation policies in the field of drug-dependency towards the creation of treatments addressed at the executive deficits of the participants, which in turn would facilitate the individuals' compliance and final rehabilitation.

1. Introduction

The progressive increase of drug consumption-related problems has yielded an important number of research projects aimed at detecting neuropsychological alterations in drug-users' executive functions. Executive functions are an integrated group of abilities involved in the generation, supervision and monitoring of behaviours directed towards goals (Roberts et al., 1998; Stuss and Knight, 2002; Verdejo-Garcia and Perez-Garcia, 2007a). Several research papers agree in the existence of alterations in different components of these executive functions in polysubstance users with a main consumption of cocaine (Fillmore et al., 2002; Bolla et al., 2003; Kubler et al., 2005; Verdejo-Garcia and Perez-Garcia, 2007a), heroin (Lee and Pau, 2002; Pau et al., 2002; Verdejo-García et al., 2005b; Fishbein et al., 2007; Brand et al., 2008) or alcohol (Ratti et al., 2002; Bjork et al., 2004). Moreover, these alterations negatively affect the users' family and social relations as well as their occupational status (Bechara et al., 2001; Moriyama et al., 2002). In addition, executive functions are also essential for the success of interventional programs that are carried out with substance users. Treatment of addiction-related disorders requires many intervention types some of which imply cognitive requirements, such as working memory, problem solving and abstract reasoning (Teichner et al., 2002). Other executive processes, such as inhibition and decision-making, have been associated with relapse occurrence in substance-dependent individuals (Franken, 2003; Tapert et al., 2004; Paulus et al., 2005). A number of studies agree that the existence of executive function alterations in users may interfere in the success of interventional programs undertaken within therapeutic communities (Fals-Stewart and Schafer, 1992; Bowden-Jones et al., 2005; Passetti et al., 2008). These findings reveal the necessity to design and implement programs tailored to the individuals' executive function limitations, since these may influence and condition the rehabilitation process itself.

Despite the fact that many studies have observed relevant executive alterations in terms of extension (number of affected regions) and

* Corresponding authors. Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de Psicología de la Universidad de Granada, Campus de Cartuja, s/n, 18071 Granada, Spain. Tel.: +34 958 242 948; fax: +34 958 243 749.
E-mail addresses: mjfser@ugr.es (M.J. Fernández-Serrano), averdejo@ugr.es (A. Verdejo-García).

0014-2999/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2009.10.019

magnitude (effect size) in drug-users vs. non-users, no data have been generated to date in terms of prevalence of these alterations among users using several therapeutic contexts, including therapeutic communities. Studies on the prevalence of neuropsychological impairment have been undertaken for other disorders, such as Parkinson disease (Kulisevsky et al., 2008), multiple sclerosis (Massman et al., 1996; Karlinska et al., 2008), lupus (Carbotte et al., 1986; Monastero et al., 2001) and HIV (Cysique et al., 2004). These have proved useful in the design and implementation of interventional programs for the relevant patient populations. In the same fashion, studies on the prevalence of neuropsychological impairment in drug-users using therapeutic communities could be very useful and constitute the foundations for political actions aiming at supporting suitable programs according to the neuropsychological profile of the consuming population. Furthermore, it would be interesting to learn which tools have a higher discriminating potential in detecting alterations in the executive functions of substance-dependent individuals, since this could make both clinical assessment and research in the drug-dependence field easier.

Previous studies in our laboratory have shown alterations in several components of executive functions in polysubstance users under treatment (Verdejo-Garcia et al., 2005a,b; Verdejo-Garcia et al., 2006; Verdejo-Garcia et al., 2007a,b; Verdejo-Garcia and Perez-Garcia, 2007a,b; Verdejo-Garcia and Perez-Garcia, 2008). In this paper we will use data from these studies and successive samples to establish the prevalence of executive impairment in polysubstance-dependent individuals as a reference for the potential application of specific interventions in order to address these impairments in the treatment setting. The specific goals of this paper are: (i) estimate the prevalence of the neuropsychological impairment in executive functions in polysubstance users enrolled in therapeutic community, taking as a reference the performance in the tests of a large group of non-drug-users; (ii) estimate the prevalence of executive impairment in several groups of polysubstance users classified according to their main drug consumed, and (iii) estimate the extent of the effect size of the differences in the executive performance of polysubstance users vs. non-users, and between the several groups of polysubstance users.

2. Method and materials

2.1. Participants

One hundred twenty-three poly-substance-dependent individuals (thirteen women), aged 18–58 years, and 67 healthy control individuals (eight women), aged 18–50 years, participated in this study. Poly-substance-dependent individuals and control participants were matched on variables of age, educational level and gender (see Table 1). Poly-substance-dependent individuals were recruited during their treatment at the therapeutic communities "Proyecto Hombre" and "Cortijo Buenos Aires", in Granada-Spain. Both centers are residential therapeutic communities that provide psychological treatment and educational/occupational counseling in a controlled environment during an extended period of time. The dependent individuals sample was principally composed of polysubstance users who requested treatment for: cocaine, heroin, heroin + cocaine or alcohol use. According to the main substance leading to treatment, within the dependent individuals sample we can distinguish 4 groups of polysubstance users: cocaine poly-substance-dependents (CPSD; $n=74$), heroin poly-substance-dependents (HPSD; $n=34$) and alcohol dependents ($n=15$). In the HPSD sub-group we can distinguish in turn two sub-groups of users: heroin dependents ($n=17$), composed by those individuals who were users mainly of heroin, and heroin + cocaine dependents ($n=17$) composed by those individuals who were initially users mainly of heroin but at some point started to consume it along with cocaine, which made polyconsumption of both substances the reason for demanding treatment. All of the polysubstance users had a minimum abstinence duration of 15 days before testing, although the mean duration of abstinence in the group was 23.79 (S.D. = 18.19) weeks, so that it was possible to rule out the presence of alterations associated with the acute or short term effects of the drugs. None of them were following methadone maintenance treatment or any other pharmacological substitution treatment during the course of the neuropsychological testing. Urine analyses for cannabis, benzodiazepines, cocaine, and heroin metabolites were conducted to confirm abstinence. Potential participants who had previously been diagnosed with any disorder from DSM-IV Axes I and II (other than substance dependence) were not included in the target sample. Those potential participants who had been previously diagnosed with traumatic brain injury, neurological disorders or HIV were also excluded.

Control participants were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these control participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than ten drinks per week), (ii) absence of documented major psychiatric disorders, (iii) absence of documented head injury or neurological disorder and (iv) not being on any medication affecting Central Nervous System. The mean amount of alcohol use in control participants was 35.91 units/month (S.D. = 71.82) and the mean of alcohol duration consumption was 7.79 years (S.D. = 7.63).

2.2. Instruments and assessment procedures

2.2.1. Background information

Data regarding lifetime amount and duration of use of the different drugs was self-reported by participants and collected using the Interview for Research on Addictive Behavior (IRAB; Verdejo-García et al., 2005a). This interview provides an estimation of monthly use of each substance (amount per month) and total duration of use of each substance (in years). The descriptive scores for these variables in the present sample are presented in Table 2.

2.2.2. Neuropsychological tests

We initially designed a battery of neuropsychological tests aimed to assess a number of aspects associated with executive functioning, including fluency, working memory, inhibition, shifting, and decision-making. After evaluating our preliminary results, we decided to add to this battery a number of tests originally designed to enhance the ecological validity of executive functions assessment, including complex planning and multi-tasking tasks (e.g., the BADS and the Revised Strategy Application Test). In this report we include results from both the initial and the extended battery; therefore, the number of participants vary across tests and will be stated in each case. We have not included results from the decision-making test (the Iowa Gambling Task); previous studies have shown that this test is poorly performed by roughly 15% of the healthy population (Bechara et al., 2001), and therefore is inadequate to estimate prevalence of

Table 1
Descriptive scores for the socio-demographic characteristics of poly-substance-dependent individuals (PSD) and controls (CON).

Socio-demographic variables		PSD		CON		t/chi-square [a,b]	p
		Mean	S.D.	Mean	S.D.		
Age		31.05	7.73	30.11	8.48	0.77[a]	0.442
Educational level (%)	Primary	7.8		1.5		3.57[b]	0.167
	Secondary	74.2		76.1			
	Superior	18		22.4			
Gender (%)	Men	89.4		88.05		0.08[b]	0.811
	Women	10.6		11.95			

[a] value of Student's t;
[b] value of Chi-square χ^2.

neuropsychological impairment based on a comparison group. Previous reports have provided a detailed description of the instruments used (Verdejo-Garcia et al., 2005a; Verdejo-Garcia et al., 2007b; Verdejo-Garcia and Perez-Garcia, 2007a,b); here we provide a summarized description.

2.2.2.1. Fluency tests

- FAS, Animals and Fruits: for semantic and phonological fluency assessment. We used the number of animals, the number of fruits and the sum of the number of words beginning with F, A, and S produced in a 60-s period as the primary dependent measures from this test. All participants ($n=190$) were assessed with these tasks.
- Ruff Figural Fluency Test (RFFT) (Ruff, 1996): for figural fluency assessment. The dependent variable used in this test was the total number of original figures produced. All participants ($n=190$) were assessed with this task.

2.2.2.2. Working memory

- Letter Number Sequencing (LNS) (WAIS-III, Wechsler, 1997a): the dependent variable used on this test was the number of correct answers. All participants ($n=190$) were assessed with this task.
- Arithmetic (WAIS-III, Wechsler 1997a): the dependent measure was the number of correct answers. All participants ($n=190$) were assessed with this task.
- Digits (WAIS-III, Wechsler 1997a): the dependent measure was the total number of correct answers on "digit forward" and "digit backward". All participants ($n=190$) were assessed with this task.
- Spatial Span (Wechsler Memory Scale—WMS-III, Wechsler, 1997b): for visuo-spatial working memory assessment. We used the total number of correct responses as the primary dependent measures from this test. One hundred nineteen poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.
- Rule Shift Cards (Behavioural Assessment of the Dysexecutive Syndrome—BADS, Wilson et al., 1996): the performance index on this task was the profile score from the test which is obtained according to the number of errors made (with a range between 0 and 4). Seventy-six poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.

2.2.2.3. Shifting

- Wisconsin Card Sorting Test (WCST): for cognitive flexibility assessment. We used the percentage of perseverative errors as primary dependent measure. One hundred and twenty two poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.
- Category Test (DeFilippis, 2002): for cognitive flexibility assessment. A computerized version of this test was administered. The main index of performance on the test was the total number of errors on the seven subtests. One hundred nineteen poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.
- Five Digit Test (Sedó, 2005): for cognitive flexibility assessment. We used the differential "shifting" score (time on part 4 minus mean time on parts 1 and 2) as the primary dependent measure from this test. All participants ($n=190$) were assessed with this task.
- Oral Trail Making (Sedó et al., 1995): for cognitive flexibility assessment. The dependent measure was the shifting score obtained by subtracting time in part 1 from time in part 2 (OT 2 − 1). One hundred twenty two poly-substance-dependent individuals and sixty six controls were assessed with this task.

2.2.2.4. Interference

- Stroop Colour–Word Interference Test (Golden, 1978): for selective attention/interference assessment. The main dependent variable used in this test was the interference score (Golden, 1978). One hundred twenty one poly-substance-dependent individuals and the entire control sample were assessed with this task.
- Five Digit Test (Sedó, 2005): for interference assessment. We used the differential "interference" score (time on part 3 minus mean time on parts 1 and 2) as the primary dependent measure from this test.
- Go/no go task: for motor response inhibition assessment. The main dependent variable used in this test was the total number of commission errors made. One hundred eleven poly-substance-

Table 2
Descriptive scores for patterns of quantity and duration of drug use in the group of cocaine poly-substance-dependents (CPSD), heroin poly-substance-dependents (HPSD) and alcohol dependents (ALCO).

Substances	Variables	CPSD		HPSD		ALCO	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Cannabis	Joints/month	161.35	203.67	200.22	204.77	38.53	86.18
	Duration	5.58	5.97	11.35	6.94	4.86	8.78
Cocaine	Grams/month	61.01	46.41	37.58	43.58	6.33	15.75
	Duration	7.41	4.49	9.26	5.90	4.93	7.75
Heroin	Grams/month	5.82	22.78	51.63	46.05	2.00	7.74
	Duration	0.72	2.27	9.16	6.10	0.20	0.77
Methadone	Mililiters/month	12.16	104.62	676.82	1111.74	0.00	0.00
	Duration	0.01	0.11	1.35	2.99	0.00	0.00
MDMA	Units/month	13.70	24.87	16.82	35.78	2.60	7.06
	Duration	1.64	2.56	2.26	4.24	0.20	0.56
Alcohol	Units/month	385.40	415.72	269.23	331.34	944.00	452.72
	Duration	7.84	5.92	10.77	8.11	15.26	7.42
Amphetamines	Units/month	2.79	8.95	4.67	17.46	3.06	10.33
	Duration	0.70	1.71	0.41	1.04	1.06	2.84
Benzodiazepines	Units/month	5.48	19.12	20.00	39.68	34.28	90.71
	Duration	0.20	0.65	0.24	0.66	2.85	7.55
Abstinence (weeks)		22.50	14.69	26.53	26.31	23.85	10.39

dependent individuals and sixty six controls were assessed with this task.

2.2.2.5. Planning

- Key Search (BADS, Wilson et al., 1996): application of strategies to solve a problem. The performance index on this task was the raw score from the test, which is obtained according to the appropriateness and efficacy of the strategy developed (with a range from 0 to 16). Seventy-six poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.
- Zoo Map (BADS, Wilson et al., 1996): planning. The performance index on the test was the raw score (sum of parts 1 and 2, based on the efficacy of the plan designed, with a range from 0 to 16). Seventy-six poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.

2.2.2.6. Multi-tasking

- Six Elements (BADS, Wilson et al., 1996): the performance index on this test was the raw score, which was obtained based on the number of tasks attempted minus the number of rule violations committed (with a range from 0 to 6). Seventy-six poly-substance-dependent individuals and the entire control sample ($n=67$) were assessed with this task.
- Revised Strategy Application Test (Levine et al., 2000): self-regulation in a multi-tasking task. The dependent variable from the R-SAT was the proportion of brief items completed (not including the first page of each stack) with regard to the total number of items attempted. Sixty-five poly-substance-dependent individuals and sixty six controls were assessed with this task.

2.3. Procedure

Participants were assessed individually between March 2003 and December 2007 in a single session that lasted approximately 3 h and 45 min (including breaks) or on two consecutive days, depending on the rehabilitation center availability. Test administration was arranged to alternate between verbal and non-verbal tasks and between more and less demanding tasks. All of the participants in the study were informed about the objectives, benefits, and possible inconveniences associated with the research protocol. Likewise, all the participants signed an informed consent form certifying their voluntary participation. The poly-substance-dependents and the control participants who requested it received a neuropsychological report about their performance on the tests. In addition, the control participants were paid €18 for their collaboration to ensure motivation.

2.4. Data analysis

To calculate the prevalence of impairment, scores directly obtained by polysubstance users in each of the neuropsychological tests were transformed into a *Z*-score, taking as a reference the mean and standard deviation (S.D.) obtained by the non-user group in each test. We then codified *Z*-scores according to two levels of neuropsychological impairment based on the criteria of Heaton et al., 1991: (i) mild impairment: if the scores were 1.5 S.D. below those of the normative group, and (ii) moderate to severe impairment: if the scores were 2 S.D. below those of the normative group. Next, we classified the individuals according to the existence of impairment of each of the analyzed components in only one test, or in two or more tests. To do so, we followed the criteria of both mild and moderate–severe impairment. A series of χ^2 analyses were undertaken to find out whether there were differences in the impairment proportions of each of the groups according to the adopted criteria.

Also, a global executive impairment index was calculated by adopting the criterion of (mild or moderate–severe) impairment in at least 3 of the 6 executive components assessed.

Finally we calculated the effect size in each of the neuropsychological tests by using Cohen's δ, following the formulae by Zakzanis (2001). The effect size of each task was obtained for the comparisons between differents analyzed groups, comparing effect sizes between poly-substance-dependent individuals and controls, and between the different groups of substance users: (i) between the CPSD and HPSD groups, and (ii) between the CPSD, heroin, heroin + cocaine and alcohol dependents groups. Overlap proportions between the compared groups for the dependent variables in each of the tests were obtained from the δ values.

3. Results

3.1. Poly-substance-dependents vs. controls

The results obtained from the comparison between poly-substance-dependent individuals vs. healthy controls individuals in terms of prevalence of mild and moderate–severe neuropsychological impairment, global impairment index and Cohen's Deltas obtained for each of the neuropsychological are detailed in Table 3.

3.1.1. Prevalences

Results obtained from the application of the mild impairment criterion (1.5 S.D.) revealed that it was working memory the component where a higher poly-substance-dependents proportion (62%) showed impairment in the performance of 2 or more tests. The moderate–severe criterion (2 S.D.) also showed that working memory was the component with the most poly-substance-dependents (48.4%) with impairment in the performance of at least 1 test. As for the global impairment index, results revealed that, under the mild impairment criterion, 68.8% of poly-substance-dependents showed global impairment in executive functions. Under the moderate–severe criterion, it was 32.8% of poly-substance-dependents that showed a global impairment of their executive functions.

3.1.2. Effect size (Cohen's Delta)

When comparing performance of poly-substance-dependent individuals vs. controls in the different tests, we observed that effect size (Cohen's δ) was over 0.8, which indicates a high effect size (Cohen, 1988) in 45% of the tests, including fluency process, working memory and shifting measures. Specifically for fluency components, δ values ranged from 1.07 to 0.65. The most discriminating tasks were phonologic FAS and RFFT (41.1% of overlap between groups). As for working memory component, δ ranged from 1.69 to 0.81. For this component, the arithmetic test was the most discriminating (24.6% of overlap). For the shifting component, values ranged from 1.17 to 0.38. Category Test was the most discriminating (37.8% of overlap). For the interference component, values ranged from 0.75 to 0.42, Stroop being the most discriminating test (57% of overlap). For the planning component, values ranged from 0.63 to 0.093. Zoo Map was the most discriminating task for this component (61.8% of overlap). Finally, values for multi-tasking ranged from 0.69 to 0.66, Six Elements being the task with a higher discrimination (57% of overlap).

3.2. Cocaine poly-substance-dependents vs. heroin poly-substance-dependents

The results obtained from the comparison between CPSD vs. HPSD in terms of prevalence of mild and moderate–severe neuropsychological impairment, global impairment index and Cohen's Deltas obtained for each of the tasks are detailed in Table 4.

Table 3
Prevalence of neuropsychological impairment, global impairment index and effect size in the neuropsychological tests in poly-substance-dependents (PSD) and controls (CON).

		1.5 S.D.[a]		2 S.D.		Cohen's *d* [b,c,d,e]	
		PSD	CON	PSD	CON		
Fluency	1 task	**57**	**19.4**	**34.4**	**10.4**	Anim fas	0.65 (CON)[d]
						Phono fas	−1.07 (PSD)[e]
	2 task	**33.6**	**7.5**	7.8	1.5	Fruits fas	−0.96 (PSD)[e]
						Rfft	−1.07 (PSD)[e]
Working memory	1 task	**84.4**	**22.4**	**48.4**	**4.5**	Lns	−1.51 (PSD)[e]
						Arithm	−1.69 (PSD)[e]
						Digit	−1.27 (PSD)[e]
	2 task	**62.2**	**7.5**	**19.7**	**3.0**	Span	−1.03 (PSD)[e]
						Rule	−0.81 (PSD)[e]
Shifting	1 task	**64.8**	**22.4**	**43**	**14.9**	Wcst	0.57 (PSD)[d]
						Category	1.17 (PSD)[e]
	2 task	**27.3**	**4.5**	**13.4**	**4.5**	5dt shift	0.49 (PSD)[d]
						Otm	0.38 (PSD)
Interference	1 task	**38.3**	**19.4**	**20.3**	**9**	Stroop	−0.75 (PSD)[d]
						5dt interf	0.42 (PSD)[d]
	2 task	**8.6**	**1.5**	3.9	0	Go/no go	0.48 (PSD)[d]
Planning	1 task	**56.8**	**23.9**	**29**	**6**	Key	−0.093 (PSD)
	2 task	**16**	**0**	**7.4**	**0**	Zoo	−0.63 (PSD)[d]
Multi-tasking	1 task	**66.3**	**22.4**	**40.3**	**6**	Six	−0.69 (PSD)[d]
	2 task	11.3	6	1.5	0	R-sat	−0.66 (PSD)[d]
% Global impairment		**68.8**	**19.4**	**32.8**	**4.5**		

[a] In bold significative differences between groups.
[b] Between parentheses groups with the worse execution in that task.
[c] Anim fas: animals FAS; Phono fas: phonological FAS; Rfft: Ruff figural fluency task; Lns: Letter and numbers (WAIS-III); Arithm: Arithmetic (WAIS-III); Digit: Digits (WAIS-III); Span: Spatial span (WMS-III); Rule: Rule shift cards (BADS); Wcst: Wisconsin card sorting test; Category: Category test; 5dt shift: Five digit test shifting score; Otm: Oral trail making; Stroop: Stroop colour–word interference test; 5dt interf: Five digit test interference score; Key: Key search (BADS); Zoo: Zoo map (BADS); Six: Six elements (BADS); R-sat: Revised strategy application test.
[d] Effect size ≥0.4.
[e] Effect size ≥0.8.

3.2.1. Prevalences

Results obtained from the application of the mild impairment criterion (1.5 S.D.) revealed that it was working memory the component where a higher CPSD proportion (64.4%) showed impairment in the performance of 2 or more tests. Among HPSD individuals it was working memory the component with a greater number of individuals with impairment (58.8%). Results obtained from the application of the moderate–severe (2 S.D.) criterion revealed that shifting was the component with the more CPSD (47.3%) with impairment in at least 1 task. As for the HPSD group, planning was the component with more impaired individuals (57.1%). As for the global impairment index, results obtained from the application of the mild impairment criterion revealed that 66.2% of CPSD showed global impairment in executive functions vs. 67.6% of HPSD. Results obtained from the application of the moderate–severe impairment showed that 33.8% of CPSD showed global impairment vs. 29.4% of HPSD.

3.2.2. Effect size (Cohen's Delta)

Comparison of performance in neuropsychological tests obtained by sub-groups CPSD and HPSD cast Cohen's Deltas below 0.4 (with an overlap range between groups ranging from 100% to 72.6%) in all tasks involving fluency, working memory, shifting and multi-tasking components. For the interference component, we observed that δ values ranged from 0.40 to 0.00. Five Digit Test was the most discriminating task (72.6% of overlap between groups) where the CPSD group showed the poorest performance. For the planning component, δ values ranged from 0.54 to 0.00. In this case, Zoo Map was the most discriminating task (66.6% of overlap) where HPSD group showed a poorer performance.

3.3. Cocaine poly-substance vs. heroin vs. heroin + cocaine vs. alcohol dependents

Results obtained from comparing CPSD vs. heroin vs. heroin + cocaine vs. alcohol dependents in terms of prevalence of mild and severe–moderate neuropsychological impairment and global impairment index are detailed in Table 5 below. Table 6 shows Cohen's Deltas obtained from comparing performance of different groups in the used tasks.

3.3.1. Prevalences

Results obtained from the application of the mild impairment criterion (1.5 S.D.) revealed that fluency and working memory were the components where a higher heroin dependents proportion (47.1%) showed impairment in the performance of 2 or more tests. Both for heroin + cocaine dependents and alcohol dependents, working memory was the component with a higher number of impaired individuals (heroin + cocaine = 70.6%; alcohol = 66.7%). Results obtained from the application of the moderate–severe impairment criterion (2 S.D.) revealed that it was planning the component where a higher heroin dependents proportion (60%) showed impairment in the performance of 1 or more tests. Both for heroin + cocaine dependents and alcohol dependents, working memory was the component with a higher number of impaired individuals (heroin + cocaine = 64.7%; alcohol = 53.3%). As for the global impairment index, results obtained from the application of the mild impairment criterion revealed that 70.6% of heroin dependents showed global impairment vs. 64.7% of heroin + cocaine dependents and 80% of alcohol dependents. However, when applying the moderate–severe criterion, 35.3% of heroin dependents showed

Table 4
Prevalence of neuropsychological impairment, global impairment index and effect size in the neuropsychological tests in cocaine poly-substance-dependents (CPSD) and heroin poly-substance-dependents (HPSD).

		1.5 S.D.[a]		2 S.D.		Cohen's *d* [b,c,d]	
		CPSD	HPSD	CPSD	HPSD		
Fluency	1 task	56.8	64.7	31.1	41.2	Anim fas	−0.11 (CPSD)
						Phono fas	0.07 (HPSD)
	2 task	31.1	41.2	6.8	11.8	Fruits fas	−0.00 (CPSD)
						Rfft	0.36 (HPSD)
Working memory	1 task	**89.2**	**73.5**	45.9	52.9	Lns	0.23 (HPSD)
						Arithm	0.25 (HPSD)
						Digit	0.05 (HPSD)
	2 task	64.4	58.8	17.8	26.5	Span	−0.18 (CPSD)
						Rule	−0.16 (CPSD)
Shifting	1 task	63.5	61.8	47.3	41.2	Wcst	−0.35 (HPSD)
						Category	0.25 (CPSD)
	2 task	29.7	26.5	13.5	15.2	5dt shift	0.10 (CPSD)
						Otm	0.03 (CPSD)
Interference	1 task	36.5	41.2	21.6	23.5	Stroop	−0.00 (CPSD)
						5dt interf	0.40 (CPSD)[d]
	2 task	12.2	2.9	6.8	0	Go/no go	0.14 (CPSD)
Planning	1 task	**45.8**	**85.7**	34.7	57.1	Key	−0.00 (CPSD)
	2 task	12.5	21.4	6.1	7.1	Zoo	0.54 (HPSD)[d]
Multi-tasking	1 task	60.9	80	44.2	36.4	Six	0.10 (HPSD)
	2 task	10.9	6.7	2.5	0	R-sat	0.09 (HPSD)
% Global impairment		66.2	67.6	33.8	29.4		

[a] In bold significative differences between groups.
[b] Between parentheses groups with the worse execution in that task.
[c] Anim fas: animals FAS; Phono fas: phonological FAS; Rfft: Ruff figural fluency task; Lns: Letter and numbers (WAIS-III); Arithm: Arithmetic (WAIS-III); Digit: Digits (WAIS-III); Span: Spatial span (WMS-III); Rule: Rule shift cards (BADS); Wcst: Wisconsin card sorting test; Category: Category test; 5dt shift: Five digit test shifting score; Otm: Oral trail making; Stroop: Stroop colour–word interference test; 5dt interf: Five digit test interference score; Key: Key search (BADS); Zoo: Zoo map (BADS); Six: Six elements (BADS); R-sat: Revised strategy application test.
[d] Effect size ≥0.4.

Table 5
Prevalence of neuropsychological impairment and global impairment index in cocaine poly-substance-dependents (CPSD), heroin dependents (HERO), heroin + cocaine dependents (HERO + COCA) and alcohol dependents (ALCO).

		1.5 S.D.				2 S.D.			
		CPSD	HERO	HERO + COCA	ALCO	CPSD	HERO	HERO + COCA	ALCO
Fluency	1 task	56.8	58.8	70.6	40	31.1	41.2	41.2	33.3
	2 task	31.1	47.1	35.3	26.7	6.8	17.6	5.9	6.7
Working memory	1 task	89.2	64.7	82.4	80	45.9	41.2	64.7	53.3
	2 task	64.4	47.1	70.6	66.7	17.8	23.5	29.4	13.3
Shifting	1 task	63.5	64.7	58.8	73.3	47.3	52.9	29.4	26.7
	2 task	29.7	29.4	23.5	26.7	13.5	12.5	17.6	13.3
Interference	1 task	36.5	47.1	35.3	46.7	21.6	35.3	11.8	13.3
	2 task	12.2	0	5.9	6.7	6.8	0	0	0
Planning	1 task	45.8	90	75	71.4	34.7	60	50	42.9
	2 task	12.5	10	50	28.6	6.1	10	0	14.3
Multi-tasking	1 task	60.9	90	60	64.3	44.2	28.6	50	30.8
	2 task	10.9	0	20	14.3	2.5	0	0	0
% Global impairment		66.2	70.6	64.7	80	33.8	35.3	23.5	40

global impairment vs. 23.5% of heroin + cocaine dependents and 40% of alcohol dependents.

3.3.2. Effect size (Cohen's Delta)

Comparison of CPSD vs. heroin dependents sub-group showed Cohen's Deltas below 0.4 (with an overlap ranging from 100% and 78.7%) in all fluency, working memory and shifting component measures. For the interference component, δ values ranged from 0.42 to 0.08. Five Digit Test was the most discriminating task (72.6% of overlap) where the CPSD group showed the poorest performance. For the planning component, values ranged from 0.51 to 0.13. Zoo Map was the most discriminating task (66.6% of overlap) where the heroin dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 0.52 to 0.20, R-SAT being the task with a higher discrimination (66.6% of overlap). For this test, CPSD was the group with the poorest performance.

Comparison of CPSD vs. heroin + cocaine dependents sub-groups showed Cohen's Deltas below 0.4 (with an overlap ranging from 92.3% and 72.6%) in all fluency, working memory and interference component measures. For the fluency component, Cohen's Deltas ranged from 0.63 to 0.02. RFFT was the most discriminating task (61.8% of overlap) where the heroin + cocaine dependents group showed the poorest performance. For the shifting component, δ values ranged from 0.49 to 0.05. WCST was the most discriminating task (66.6% of overlap) where the heroin + cocaine dependents group showed the poorest performance. For the planning component, values ranged from 0.59 to 0.31. Zoo Map was the most discriminating task (61.8% of overlap) where the heroin + cocaine dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 1.04 to 0.08. R-SAT was the most discriminating task (44.6% of overlap) where the heroin + cocaine dependents group showed the poorest performance.

Comparison of heroin dependents vs. heroin + cocaine dependents sub-groups showed Cohen's Deltas below 0.4 (with an overlap ranging from 100% to 72.6%) in all fluency, working memory and interference component measures. For the fluency component,

Table 6
Effect size in the neuropsychological tests in cocaine poly-substance-dependents (CPSD), heroin dependents (HERO), heroin + cocaine dependents (HERO + COCA) and alcohol dependents (ALCO).

	Cohen's d [a,b,c,d]	CPSD vs. HERO	CPSD vs. HERO + COCA	CPSD vs. ALCO	HERO vs. HERO + COCA	HERO vs. ALCO	HERO + COCA vs. ALCO
Fluency	Anim fas	−0.17 (CPSD)	−0.05 (CPSD)	−0.58 (CPSD)[c]	0.12 (HERO + COCA)	−0.32 (HERO)	−0.05 (HERO + COCA)
	Phono fas	0.17 (HERO)	−0.02 (CPSD)	−0.21 (CPSD)	−0.20 (HERO)	−0.34 (HERO)	−0.18 (HERO + COCA)
	Fruits fas	−0.26 (CPSD)	0.26 (HERO + COCA)	−0.19 (CPSD)	0.48 (HERO + COCA)[c]	0.05 (ALCO)	−0.40 (HERO + COCA)[c]
	Rfft	0.09 (HERO)	0.63 (HERO + COCA)[c]	−0.10 (CPSD)	0.67 (HERO + COCA)[c]	−0.19 (HERO)	−0.85 (HERO + COCA)[c]
Working	Lns	0.06 (HERO)	0.38 (HERO + COCA)	−0.47(CPSD)[c]	0.34 (HERO + COCA)	−0.47 (HERO)[c]	−0.69 (HERO + COCA)[c]
memory	Arithm	0.13 (HERO)	0.37 (HERO + COCA)	−0.41(CPSD)[c]	0.24 (HERO + COCA)	−0.48 (HERO)[c]	−0.76 (HERO + COCA)[c]
	Digit	0.00 (HERO)	0.10 (HERO + COCA)	−0.06(CPSD)	0.09 (HERO + COCA)	−0.07 (HERO)	−0.16 (HERO + COCA)
	Span	−0.10 (CPSD)	−0.24 (CPSD)	0.24 (ALCO)	−0.15 (HERO)	0.34 (ALCO)	0.41 (ALCO)[c]
	Rule	−0.15 (CPSD)	−0.20 (CPSD)	−0.25 (CPSD)	−0.04 (HERO)	−0.08 (HERO)	−0.03 (HERO + COCA)
Shifting	Wcst	−0.20 (HERO)	−0.49 (HERO + COCA)[c]	−0.10 (ALCO)	−0.29 (HERO + COCA)	0.08 (HERO)	0.36 (HERO + COCA)
	Category	0.29 (CPSD)	0.21 (CPSD)	−0.28 (ALCO)	−0.06 (HERO + COCA)	−0.64 (ALCO)[c]	−0.52 (ALCO)[c]
	5dt Shift	0.06 (CPSD)	0.14 (CPSD)	0.08 (CPSD)	0.07 (HERO)	0.01 (HERO)	−0.07 (ALCO)
	otm	0.01 (CPSD)	0.05 (CPSD)	0.03 (CPSD)	0.05 (HERO)	0.01 (HERO)	−0.04 (ALCO)
Interference	Stroop	−0.08 (CPSD)	0.06 (HERO + COCA)	0.46 (ALCO)[c]	0.15 (HERO + COCA)	0.54 (ALCO)[c]	0.42 (ALCO)[c]
	5dt interf	0.42 (CPSD)[c]	0.36 (CPSD)	0.03 (CPSD)	−0.06 (HERO + COCA)	−0.55 (ALCO)[c]	−0.40 (ALCO) [c]
	Go/no go	0.11 (CPSD)	0.16 (CPSD)	0.11 (CPSD)	0.05 (HERO)	−0.00 (ALCO)	−0.08 (ALCO)
Planning	Key	−0.13 (CPSD)	0.31 (HERO + COCA)	0.18 (ALCO)	0.45 (HERO + COCA)[c]	0.30 (ALCO)	−0.11 (HERO + COCA)
	Zoo	0.51 (HERO)[c]	0.59 (HERO + COCA)[c]	0.44 (ALCO)[c]	0.04 (HERO + COCA)	−0.10 (HERO)	−0.19 (HERO + COCA)
Multi-tasking	Six	0.20 (HERO)	0.08 (HERO + COCA)	0.10 (ALCO)	− 0.49 (HERO)[c]	−0.10 (HERO)	0.25 (ALCO)
	R-sat	−0.52 (CPSD)[c]	1.04 (HERO +COCA)[d]	−0.21 (CPSD)	1.09 (HERO + COCA)[d]	0.35 (ALCO)	−1.07 (HERO + COCA)[d]

[a] Between parentheses groups with the worse execution in that task.
[b] Anim fas: animals FAS; Phono fas: phonological FAS; Rfft: Ruff figural fluency task; Lns: Letter and numbers (WAIS-III); Arithm: Arithmetic (WAIS-III); Digit: Digits (WAIS-III); Span: Spatial span (WMS-III); Rule: Rule shift cards (BADS); Wcst: Wisconsin card sorting test; Category: Category test; 5dt shift: Five digit test shifting score; Otm: Oral trail making; Stroop: Stroop colour–word interference test; 5dt interf: Five digit test interference score; Key: Key search (BADS); Zoo: Zoo map (BADS); Six: Six elements (BADS); R-sat: Revised strategy application test.
[c] Effect size ≥0.4.
[d] Effect size ≥0.8.

Cohen's Deltas ranged from 0.67 to 0.12. RFFT was the most discriminating task (57% of overlap) where the heroin + cocaine dependents group showed the poorest performance. For the planning component, values ranged from 0.45 to 0.04. Key Search was the most discriminating task (72.6% of overlap) where the heroin + cocaine dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 1.09 to 0.49, R-SAT being the task with a higher discrimination (41.1% of overlap). For this test, heroin + cocaine dependents was the group with the poorest performance.

Comparison of CPSD vs. alcohol dependent sub-groups showed Cohen's Deltas below 0.4 (with an overlap ranging from 100% to 78.7%) in all shifting and multi-tasking component measures. For the fluency component, Cohen's Deltas ranged from 0.58 to 0.10. FAS test for animals was the most discriminating task (61.8% of overlap) where the CPSD group showed the poorest performance. As for working memory component, Cohen's Deltas ranged from 0.47 to 0.06. Letter Number Sequencing was the most discriminating test (66.6% of overlap) where the CPSD group showed the poorest performance. For the interference component, δ values ranged from 0.46 to 0.03. Stroop was the most discriminating task (66.6% of overlap) where the alcohol dependents group showed the poorest performance. Finally, for the planning component, values ranged from 0.44 to 0.18. Zoo Map was the most discriminating task (72.6% of overlap) where the alcohol dependents group showed the poorest performance.

Comparison of heroin vs. alcohol dependents yielded Cohen's Deltas below 0.4 (with an overlap range from 100% to 78.7%) in all fluency, planning and multi-tasking measures. As for working memory component, Cohen's Deltas ranged from 0.48 to 0.07. Arithmetic was the most discriminating task (66.6% of overlap) where the heroin dependents group showed the poorest performance. For the shifting component, δ values ranged from 0.64 to 0.01. Category Test was the most discriminating task (61.8% of overlap) where the alcohol dependents group showed the poorest performance. Finally, for the planning component, values ranged from 0.54 to 0.00. Five Digit Test was the most discriminating task (66.6% of overlap) where the alcohol dependents group showed the poorest performance.

Finally, when comparing heroin + cocaine vs. alcohol dependents, Cohen's Delta values were below 0.4 (with an overlap range from 92.3% to 85.3%) in all tests of the planning component. For the fluency component, Cohen's Deltas ranged from 0.85 to 0.05. RFTT was the most discriminating test (52.6% of overlap) where heroin + cocaine dependents showed the poorest performance. As for working memory component, Cohen's Deltas ranged from 0.76 to 0.03. Arithmetic was the most discriminating test (52.6% of overlap) where heroin + cocaine dependents showed the poorest performance. For the shifting component, values ranged from 0.52 to 0.04. Category Test was the most discriminating task (66.6% of overlap) where the alcohol dependents group showed the poorest performance. For the interference component, δ values ranged from 0.42 to 0.08. Stroop was the most discriminating task (72.6% of overlap) where the alcohol dependents group showed the poorest performance. Finally, values for multi-tasking ranged from 1.07 and 0.25, R-SAT being the most discriminating task (41.1% of overlap) where the heroin + cocaine dependents group showed the worst performance.

4. Discussion

Study results showed a high prevalence of executive function impairment in polysubstance users vs. non substance users. Working memory was the component with the highest impairment proportion, followed by fluency, shifting, planning, multi-tasking and interference. Comparisons between user groups showed very similar executive impairment prevalence for all the analyzed components. Nonetheless, higher impairment prevalence was observed in shifting for CPSD and planning for HPSD when applying a moderate–severe impairment criterion. Arithmetic was the best discriminating index between users and controls; Zoo Map for CPSD vs. HSPD, where the latter had a more impaired performance; and R-SAT for the several user sub-groups, allowing us to discriminate performance of the heroin + cocaine group from that of the rest of users.

As for the first goal of our study, estimation of prevalence of executive function impairment in polysubstance users, results revealed that about 70% of the individuals showed global impairment in executive functions when applying a mild impairment criterion (1.5 S.D. below the normative group) and about 35% when applying the moderate–severe impairment criterion (2 S.D.). Working memory was the component where a higher number of poly-substance-dependent individuals showed impairment in the performance or 2 or more tasks (about 60% when applying the mild impairment criterion, and 20% when applying the moderate–severe), followed by fluency (35% mild, and 8% moderate–severe), shifting (30% mild, and 15% moderate–severe), planning (15% mild, and 10% moderate–severe), multi-tasking (10% mild, and 1% moderate–severe), and interference (10% mild, and 5% moderate–severe). These findings are coherent with previous research having proved impairment in many executive function components among users of several substances, including impairment in working memory (Beatty et al., 2000; Mintzer et al., 2005; Kubler et al., 2005), fluency (Noel et al., 2001; Davis et al., 2002; Verdejo-Garcia and Perez-Garcia, 2007a), shifting (Ratti et al., 2002; Fishbein et al., 2007; Ersche et al., 2008), planning (Pau et al., 2002; Verdejo-Garcia and Perez-Garcia, 2007b), and multi-tasking (Verdejo-Garcia et al., 2007b; Verdejo-Garcia and Perez-Garcia, 2007b). Alterations in each of these components could have important effects in the compliance and success of therapeutic programs addressed at drug-dependent individuals. Deficits in working memory may be associated with difficulties in retaining complex instructions, selecting relevant information in clinical sessions or group interactions, as well as generalizing specific learning to other familiar and social interactive activities (Verdejo-García et al., 2005a). Alterations in fluency and planning skills may be limiting the users' effectiveness to motivate in attaining the program's goals, and to start and plan new activities to help them rehabilitate. Also, for a good compliance of interventional programs the individual must be able to inhibit a previously-accustomed and reinforced response pattern, such as consumption, and modify it for another pattern that would in turn allow them reach the intervention's goals. Interference and self-regulation components could therefore have an essential role in treatment. Some of these deficits have collectively been associated with inferior clinical progression levels (Leber et al., 1985), a lower level of participation and implication in the treatment (Fals-Stewart and Lucente, 1994) and a higher discontinuation rate in this programs (Aharonovich et al., 2003, 2006; Teichner et al., 2002). For this reason, one of the most relevant implications of our study lies in the fact that it shows the need to design and implement treatment programs considering executive function impairments of polysubstance users using therapeutic communities. Programs adapted to these impairments will contribute to users' maximal benefit of the intervention (Teichner et al., 2002). This would facilitate their rehabilitation process and avoid potential relapses (Franken, 2003; Tapert et al., 2004; Paulus et al., 2005).

The second goal of our study was to estimate the executive impairment prevalence rates in different groups of polysubstance users. When comparing these, we observed that CPSD individuals had a global executive impairment very similar to that of HPSD individuals (70% under the mild impairment criterion, and 30% under the moderate–severe impairment criterion). When comparing the several user sub-groups, results showed very similar impairment proportions, around 65–80% under the mild impairment criterion and 25–40 under the moderate–severe impairment criterion. If we consider the executive components analyzed, we observe that working memory was the component with the highest impairment prevalence in all user groups. When applying a moderate–severe impairment criterion, we

observed that shifting was the component with the highest impairment prevalence for the CPSD group, whereas for HPSD and the heroin dependents sub-group that was the planning component. These results are coherent with those of other studies having found the highest impairment in the shifting component for polysubstance users of cocaine and heroin (Ersche et al., 2008; Ornstein et al., 2000; Verdejo-Garcia and Perez-Garcia, 2007a). In the same fashion, other studies have related consumption of heroin with the occurrence of difficulties in planning (Pau et al., 2002). Our results are also in line with the clinics of these patients, characterized by the persistence of answers that are no longer adaptive in cocaine users (Ersche et al., 2008) and by the slowness in the onset of response (motor sluggishness) in heroin users (Fishbein et al., 2007). However, a global vision of the results allows us to see a great similitude among user groups, which may indicate that the different analyzed drugs produce common impairments in the neuropsychological mechanisms under study. Recent data from regression studies with polysubstance users have found common effects of substances such as cocaine and alcohol on verbal fluency and decision-making executive processes (Fernandez-Serrano et al., in press).

The third and last goal of this study was to detect the most discriminating instruments for performance among the groups. In this sense, Arithmetic was the most discriminating task as to performance of users vs. control individuals. The best discriminators for performance in the remaining components were phonologic FAS and RFFT for fluency, Category Test for shifting, Stroop for interference, Zoo Map for planning, and Six Elements for multi-tasking. These tests may be proposed as an abbreviated clinical batch for reference to clinical assessment and research in the field of drug-dependency. When comparing CPSD vs. HPSD, Zoo Map was the most discriminating task, where HPSD group showed the poorest performance, in line with the highest impairment for planning observed in heroin users. In the several comparisons among the user sub-groups, we can observe that R-SAT was the test that most often allowed differentiate performance among groups, specifically for the heroin + cocaine dependents groups, where performance was more impaired compared with the rest of sub-groups (CPSD, heroine users, alcohol users). This result may show the existence of an addictive effect of heroin + cocaine consumption, which would become evident in the behavior self-regulation processes implied in the performance of this test. Studies with polysubstance users, with a relevant proportion of heroin + cocaine users, have yielded similar results for performance in R-SAT, which is coherent with this finding (Verdejo-Garcia et al., 2007b).

As limitations of our study we could elicit the lack of data of some individuals in BADS and R-SAT, due to the late incorporation of these tests to the evaluation protocol, along with small sample size for the heroin, heroin + cocaine and alcohol sub-groups. These circumstances may influence the impairment prevalence obtained. In addition, considering that the sample of participants in our study had very specific characteristics regarding treatment, since they were users of therapeutic communities, future research could study the prevalence of executive impairment in samples of polysubstance users involved in different treatment programs. Research undertaken with users under out-patient treatment programs has shown association between these individuals' executive functions and discontinuation of treatment (Aharonovich et al., 2003, 2006; Teichner et al., 2002). Therefore, it would be interesting to study the executive function prevalence grade in polysubstance users receiving this sort of treatments. It would also be interesting to extend these studies to polysubstance users with different socio-cultural characteristics to those of the sample, since some studies suggest that these characteristics may influence the success of treatment programs (Rounsaville et al., 1982; McCaul et al., 2001; Bernstein et al., 2006).

5. Conclusions

The study showed the existence of significant prevalence of executive impairment in polysubstance users using therapeutic communities. This reveals the need to redirect the actuation policies in the field of drug-dependency towards the creation of treatments addressed at the executive deficits of the participants, which in turn would facilitate the individuals' compliance and final rehabilitation.

Acknowledgements

This work is supported by the Spanish Ministry of Science and Innovation (MICINN), under the FPU national plan (grant ref. AP 2005-1411) and Research Project SEJ 2006-08278, and with funds from the Junta de Andalucía through the Research Project P07.HUM 03089. This study complies with the current Spanish laws and all international ethical guidelines for human studies.

References

Aharonovich, E., Nunes, E., Hasin, D., 2003. Cognitive impairment, retention and abstinence among cocaine abusers in cognitive–behavioral treatment. Drug Alcohol Depend. 71, 207–211.
Aharonovich, E., Hasin, D.S., Brooks, A.C., Liu, X., Bisaga, A., Nunes, E.V., 2006. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug Alcohol Depend. 81, 313–322.
Beatty, W.W., Tivis, R., Stott, H.D., Nixon, S.J., Parsons, O.A., 2000. Neuropsychological deficits in sober alcoholics: influences of chronicity and recent alcohol consumption. Alcohol Clin. Exp. Res. 24, 149–154.
Bechara, A., Dolan, S., Denburg, N., Hindes, A., Anderson, S.W., Nathan, E., 2001. Decision-making deficits, linked to a dysfunctional ventromedial prefrontal cortex, revealed in alcohol and stimulant abusers. Neuropsychologia 39, 376–389.
Bernstein, J., Bernstein, E., Shepard, D.S., Valentine, A., Heeren, T., Winter, M., Levenson, S., Beaston-Blaakman, A., Tassiopoulos, K., Hingson, R., 2006. Racial and ethnic differences in health and health care: lessons from an inner-city patient population actively using heroin and cocaine. J Ethn. Subst. Abuse 5, 35–50.
Bjork, J.M., Hommer, D.W., Grant, S.J., Danube, C., 2004. Impulsivity in abstinent alcohol-dependent patients: relation to control subjects and type 1-/type 2-like traits. Alcohol 34, 133–150.
Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Funderburk, F.R., Ernst, M., 2003. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19, 1085–1094.
Bowden-Jones, H., McPhillips, M., Rogers, R., Hutton, S., Joyce, E., 2005. Risk-taking on tests sensitive to ventromedial prefrontal cortex dysfunction predicts early relapse in alcohol dependency: a pilot study. J. Neuropsych. Clin. Neurosci. 17, 417–420.
Brand, M., Roth-Bauer, M., Driessen, M., Markowitsch, H.J., 2008. Executive functions and risky decision-making in patients with opiate dependence. Drug Alcohol Depend. 7, 64–72.
Carbotte, R.M., Denburg, S.D., Denburg, J.A., 1986. Prevalence of cognitive impairment in systemic lupus erythematosus. J Nerv. Ment. Dis 174, 357–364.
Cysique, L.A., Maruff, P., Brew, B.J., 2004. Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: a combined study of two cohorts. J. Neurovirol. 10, 350–357.
Cohen, J., 1988. Statistical power analysis for the behavioral sciences (2nd ed.), Lawrence Erbaum Association Publishers, New York.
Davis, P.E., Liddiard, H., McMillan, T.M., 2002. Neuropsychological deficits and opiate abuse. Drug Alcohol Depend 67, 105–108.
DeFilippis, N.A., 2002. Category Test: Computer Version Research Edition. Psychological Assessment Resources Lutz, Florida.
Ersche, K.D., Roiser, J.P., Robbins, T.W., Sahakian, B.J., 2008. Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans. Psychopharmacology (Berl) 197, 421–431.
Fals-Stewart, W., Lucente, S., 1994. The effect of neurocognitive status and personality functioning on length of stay in residential substance abuse treatment: an integrative study. Psychol. Addict. Behav. 8, 1–12.
Fals-Stewart, W., Schafer, J., 1992. The relationship between length of stay in drug-free therapeutic communities and neurocognitive functioning. J. Clin. Psychol. 48, 539–543.
Fernandez-Serrano, M.J., Perez-Garcia, M., Schmidt, J., Verdejo-Garcia, A., in press. Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. J. Psychopharmacol.
Fillmore, M.T., Rush, C.R., Hays, L., 2002. Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug Alcohol Depend. 67, 157–167.
Fishbein, D.H., Krupitsky, E., Flannery, B.A., Langevin, D.J., Bobashev, G., Verbitskaya, E., Augustine, C.B., Bolla, K.I., Zvartau, E., Schech, B., Egorova, V., Bushara, N., Tsoy, M., 2007. Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. Drug Alcohol Depend. 90, 25–38.
Franken, I.H., 2003. Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. Prog. Neuropsychopharmacol. Biol. Psych. 27, 563–579.
Golden, C.J., 1978. Stroop color and word tests: a manual for clinical and experimental uses. Stoelting Co Wood Dale, Illinois.

Heaton, R.K., Grant, I., Matthews, C.G., 1991. Comprehensive norms for an expanded Halstead–Reitan battery. Psychological Assessment Resources, Inc., Odessa, FL.
Karlinska, I., Siger, M., Lewanska, M., Selmaj, K., 2008. Cognitive impairment in patients with relapsing–remitting multiple sclerosis. The correlation with MRI lesion volume. Neurol. Neurochir. Pol 42, 416–423.
Kubler, A., Murphy, K., Garavan, H., 2005. Cocaine dependence and attention switching within and between verbal and visuospatial working memory. Eur. J. Neurosci. 21, 1984–1992.
Kulisevsky, J., Pagonabarraga, J., Pascual-Sedano, B., Garcia-Sanchez, C., Gironell, A., 2008. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. Mov. Disord. 23, 1889–1896.
Leber, W.R., Parsons, O.A., Nichols, N., 1985. Neuropsychological test results are related to ratings of men alcoholics' therapeutic progress: a replicated study. J. Stud. Alcohol 46, 116–121.
Lee, T.M., Pau, C.W., 2002. Impulse control differences between abstinent heroin users and matched controls. Brain Inj. 16, 885–889.
Levine, B., Dawson, D., Boutet, I., Schwartz, M.L., Stuss, D.T., 2000. Assessment of strategic self-regulation in traumatic brain injury: its relationship to injury severity and psychosocial outcome. Neuropsychology 14, 491–500.
Massman, P.J., Sims, J., Cooke, N., Haverkamp, L.J., Appel, V., Appel, S.H., 1996. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psych. 61, 450–455.
McCaul, M.E., Svikis, D.S., Moore, R.D., 2001. Predictors of outpatient treatment retention: patient versus substance use characteristics. Drug Alcohol Depend. 62, 9–17.
Mintzer, M.Z., Copersino, M.L., Stitzer, M.L., 2005. Opioid abuse and cognitive performance. Drug Alcohol Depend. 78, 225–230.
Monastero, R., Bettini, P., Del Zotto, E., Cottini, E., Tincani, A., Balestrieri, G., Cattaneo, R., Camarda, R., Vignolo, L.A., Padovani, A., 2001. Prevalence and pattern of cognitive impairment in systemic lupus erythematosus patients with and without overt neuropsychiatric manifestations. J. Neurol. Sci 184, 33–39.
Moriyama, Y., Mimura, M., Kato, M., Yoshino, A., Hara, T., Kashima, H., Kato, A., Watanabe, A., 2002. Executive dysfunction and clinical outcome in chronic alcoholics. Alcohol Clin. Exp. Res 26, 1239–1244.
Noel, X., Van der Linden, M., Schmidt, N., Sferrazza, R., Hanak, C., Le Bon, O., De Mol, J., Kornreich, C., Pelc, I., Verbanck, P., 2001. Supervisory attentional system in nonamnesic alcoholic men. Arch. Gen. Psych. 58, 1152–1158.
Ornstein, T.J., Iddon, J.L., Baldacchino, A.M., Sahakian, B.J., London, M., Everitt, B.J., Robbins, T.W., 2000. Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology 23, 113–126.
Passetti, F., Clark, L., Mehta, M.A., Joyce, E., King, M., 2008. Neuropsychological predictors of clinical outcome in opiate addiction. Drug Alcohol Depend. 94, 82–91.
Pau, C.W., Lee, T.M., Chan, S.F., 2002. The impact of heroin on frontal executive functions. Arch. Clin. Neuropsychol. 17, 663–670.
Paulus, M.P., Tapert, S.F., Schuckit, M.A., 2005. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. Arch. Gen. Psych. 62, 761–768.
Ratti, M.T., Bo, P., Giardini, A., Soragna, D., 2002. Chronic alcoholism and the frontal lobe: which executive functions are impaired? Acta Neurol. Scand. 105, 276–281.
Roberts, A.C., Robbins, T.W., Weiskrantz, L., 1998. The Prefrontal Cortex: Executive and Cognitive Functions. Oxford University Press, New York.
Rounsaville, B.J., Tierney, T., Crits-Christoph, K., Weissman, M.M., Kleber, H.D., 1982. Predictors of outcome in treatment of opiate addicts: evidence for the multidimensional nature of addicts' problems. Compr. Psych. 23, 462–478.
Ruff, R.M., 1996. Ruff Figural Fluency Test: Professional Manual. Psychological Assessment Resources Lutz, Florida.
Sedó, M., 2005. Test de los cinco dígitos: Five digit test. TEA Ediciones, Madrid.
Sedó, M., Levenson, R., Leonard, A., 1995. Reading-free Stroop interference tests: automatic and effortful processing In: Proceedings of the 17th Midyear Conference of the International Neuropsychological Society. Angers, France (Abstract).
Stuss, D.T., Knight, R.T. (Eds.), 2002. Principles of Frontal Lobe Functioning. Oxford University Press, New York.
Tapert, S.F., Brown, G.G., Baratta, M.V., Brown, S.A., 2004. fMRI BOLD response to alcohol stimuli in alcohol dependent young women. Addict. Behav. 29, 33–50.
Teichner, G., Horner, M.D., Roitzsch, J.C., Herron, J., Thevos, A., 2002. Substance abuse treatment outcomes for cognitively impaired and intact outpatients. Addict. Behav. 27, 751–763.
Verdejo-Garcia, A., Perez-Garcia, M., 2007a. Profile of executive deficits in cocaine and heroin poly-substance users: common and differential effects on separate executive components. Psychopharmacology (Berl) 190, 517–530.
Verdejo-Garcia, A., Perez-Garcia, M., 2007b. Ecological assessment of executive functions in substance dependent individuals. Drug Alcohol Depend 90, 48–55.
Verdejo-Garcia, A., Perez-Garcia, M., 2008. Substance abusers' self-awareness of the neurobehavioral consequences of addiction. Psychiatry Res 158, 172–180.
Verdejo-Garcia, A.J., Lopez-Torrecillas, F., Aguilar de Arcos, F., Perez-Garcia, M., 2005a. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict. Behav. 30, 89–101.
Verdejo-Garcia, A., Toribio, I., Orozco, C., Puente, K.L., Perez-Garcia, M., 2005b. Neuropsychological functioning in methadone maintenance patients versus abstinent heroin abusers. Drug Alcohol Depend. 78, 283–288.
Verdejo-Garcia, A., Rivas-Perez, C., Lopez-Torrecillas, F., Perez-Garcia, M., 2006. Differential impact of severity of drug use on frontal behavioral symptoms. Addict. Behav. 31, 1373–1382.
Verdejo-García, A., Perales, J.C., Pérez-García, M., 2007a. Cognitive impulsivity in cocaine and heroin polysubstance abusers. Addict. Behav. 32, 950–966.
Verdejo-Garcia, A., Rivas-Perez, C., Vilar-Lopez, R., Perez-Garcia, M., 2007b. Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. Drug Alcohol Depend. 86, 139–146.
Wechsler, D., 1997a. Wechsler Adult Intelligence Scale, 3rd Edition. The Psychological Corporation San Antonio, Texas.
Wechsler, D., 1997b. Wechsler Memory Scale, 3rd Edition. The Psychological Corporation San Antonio, Texas.
Wilson, B.A., Alderman, N.A., Burgess, P.W., Ernslie, H., Evans, J.J., 1996. Behavioural Assessment of the Dysexecutive Syndrome. Thames Valley Test Company, Bury St. Edmunds.
Zakzanis, K.K., 2001. Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effects size analyses for neuropsychological researchers. Arch. Clin. Neuropsychol. 16, 653–677.

Anexo III

J Psychopharmacol OnlineFirst, published on December 9, 2009 as doi:10.1177/0269881109349841

Oiginal Paper

Neuropsychological consequences of alcohol and drug abuse on different components of executive functions

Psychopharm

Journal of Psychopharmacology
0(00) 1–16

DOI: 10.1177/0269881109349841
jop.sagepub.com
SAGE

María José Fernández-Serrano[1], Miguel Pérez-García[1,2], Jacqueline Schmidt Río-Valle[3] and Antonio Verdejo-García[1,2]

Abstract

Several studies have shown alterations in different components of executive functioning in users of different drugs, including cannabis, cocaine and heroin. However, it is difficult to establish a specific association between the use of each of these drugs and executive alterations, since most drug abusers are polysubstance abusers, and alcohol is a ubiquitous confounding factor. Moreover, in order to study the association between consumption of different drugs and executive functioning, the patterns of quantity and duration of drugs used must be considered, given the association between these parameters and the executive functioning alteration degree. Based on the multicomponent approach to executive functions, the aims of the present study were: (i) to analyse the differential contribution of alcohol versus cocaine, heroin and cannabis use on executive functions performance; and (ii) to analyse the contribution made by the severity of the different drugs used (quantity and duration patterns) on these functions in a sample of polysubstance abusers that requested treatment for cannabis-, cocaine- or heroin-related problems. We administered measures of fluency, working memory, analogical reasoning, interference, cognitive flexibility, decision-making and self-regulation to two groups: 60 substance-dependent individuals (SDIs) and 30 healthy control individuals (HCIs). SDIs had significantly poorer performance than HCIs across all of the executive domains assessed. Results from hierarchical regression models showed the existence of common correlates of the use of alcohol, cannabis and cocaine on verbal fluency and decision-making; common correlates of quantity of cannabis and cocaine use on verbal working memory and analogical reasoning; common correlates of duration of cocaine and heroin use on shifting; and specific effects of duration of cocaine use on inhibition measures. These findings indicate that alcohol abuse is negatively associated with fluency and decision-making deficits, whereas the different drugs motivating treatment have both generalized and specific deleterious effects on different executive components.

Keywords

alcohol, cannabis, cocaine, executive functions, heroin, severity of use

Introduction

Drug use has increased notably among the world population, according to the United Nations World Drug Report 2008 (from the United Nations Office of Drugs and Crime, UNODC, 2008). It has been estimated that 4.9% of the world's population aged 15–64 have used drugs at least once over 2007–2008, and 0.6% of the world's population have drug-related problems, poly-consumption of diverse substances, such as heroin, cocaine, cannabis, amphetamines and ecstasy (MDMA), being the predominant abuse pattern (UNODC, 2008) especially in those individuals that demand treatment (European Monitoring Centre for Drugs and Drug Addiction, EMCDDA, 2008). In parallel with the increase of drug-related problems, there is increasing consensus on the notion of addiction as a brain disorder characterized by longstanding changes in cognitive functioning, especially in so-called executive functions (i.e. higher-order skills responsible for selection, monitoring and fine-tuning of goal-directed behaviour) (Goldstein and Volkow, 2002; Lubman et al., 2004). Recent evidence from animal and human studies indicate that specific components of executive functions, including dysfunctional impulsivity and decision-making, may predate initiation of drug use and mediate the transition between drug use and drug dependence (Belin et al., 2008; Dalley et al., 2007; Tarter et al., 2003). Accordingly, human studies have shown mild executive deficits in recreational users of cannabis and psychostimulants (De Win et al., 2007; Leland and Paulus, 2005). On the other hand, there is evidence that intensive exposure leading to dependence to different drugs, including cannabis, psychostimulants and opioids, dose-dependently impair several domains of executive functions (i.e. selective attention, inhibition, flexibility) and prefrontal cortex structure and function in animals (Jentsch et al., 2002; Stalnaker et al., 2009; Verrico et al., 2004; Yang et al., 2007) and humans (Bolla et al., 2003, 2004, 2005;

[1]Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Granada, Campus de Cartuja, s/n, 18071 Granada, Spain.
[2]Institute of Neurosciences F Olóriz, Universidad de Granada, Spain.
[3]Departamento de Enfermería, Escuela de Ciencias de la Salud, Universidad de Granada, Spain.

Corresponding author:
María José Fernández-Serrano and Antonio Verdejo-García, Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de Psicología de la Universidad de Granada, Campus de Cartuja, s/n, 18071 Granada, Spain. Email: mjfser@ugr.es and averdejo@ugr.es

Verdejo-Garcia et al., 2004; Whitlow et al., 2004). As compared with recreational users, executive deficits in individuals with substance dependence are more generalized (i.e. affecting mechanisms of access, working memory, inhibition, planning, flexibility and decision-making) and greater in magnitude (i.e. effect sizes ranging 0.5–2.2) (Verdejo-García and Pérez-García, 2007). Executive dysfunction is especially relevant in the context of substance dependence treatment, since performance on indices of executive functioning has been strongly associated with treatment retention and drug relapse (Aharonovich et al., 2006, 2008; Passetti et al., 2008; Streeter et al., 2008). Currently, cannabis, heroin and cocaine are the illegal drugs that generate more treatment demands in the European Union (EMCDDA 2008), and therefore there is a need to better understand the selective effects of these drugs on executive functions among substance dependents.

Despite being traditionally considered as a general cognitive domain (Denckla and Reiss, 1997; Zelazo et al., 1997), the literature agrees on the existence of a number of executive components or sub-functions (such as access, working memory, inhibition, flexibility or decision-making) (Fisk and Sharp, 2004; Miyake et al., 2000; Verdejo-García and Pérez-García, 2007). Evidence from lesion research and functional neuroimaging studies has supported this view by showing that discrete executive mechanisms are endorsed by differentiated neural systems. Hence, there is evidence of the prominent roles of the dorsolateral prefrontal cortex in working memory (D'Esposito et al., 1999), the inferior frontal gyrus and supplementary motor area in response inhibition (Aron et al., 2003; Picton et al., 2007), the lateral orbitofrontal cortex in cognitive flexibility (Cools et al., 2002), the frontal pole (Area 10) in multitasking (Dreher et al., 2008; Gilbert et al., 2006) and the medial orbitofrontal cortex in decision-making (Bechara et al., 1994). Although distinct, these processes are flexibly assembled in response to complex task demands (Collette et al., 2005). Therefore, the abuse of different drugs may both selectively and commonly impair these separate but interrelated executive components. In the last few years, several studies have shown decrements in differentiated components of executive functioning in cannabis, cocaine and heroin abusers/dependents, the type of addicted individuals forming our sample. Studies have found impairments in working memory, decision-making, attention and planning in cannabis abusers/dependents (Bolla et al., 2005; Medina et al., 2007; Verdejo-García et al., 2007a; Wadsworth et al., 2006), impairments in decision-making, working memory and inhibition in cocaine abusers/dependents (Bolla et al., 2003; Fillmore et al., 2002; Kübler et al., 2005; Verdejo-García et al., 2007a) and impairments in decision-making, inhibition and flexibility in heroin abusers/dependents (Brand et al., 2008; Fishbein et al., 2007; Lee and Pau, 2002; Pau et al., 2002; Verdejo-García et al., 2005a). However, it is difficult to establish a selective association between decrements in separate executive tasks and the abuse/dependence of any given drug, since virtually all of these studies have been conducted in polysubstance using groups. Along with the potential detrimental effects of aging and lower education on executive decline (Van der Elst et al., 2006; Verhaeghen and Cerella, 2002), one of the main confusing variables in most of these studies is co-abuse of alcohol, which is ubiquitous among polysubstance abusers. Alcohol abuse and dependence are related to long-lasting executive impairments affecting fluency, working memory, inhibition, flexibility and decision-making, and decreases in prefrontal cortex structure (Chanraud et al., 2007; Loeber et al., 2009; Pitel et al., 2009). Furthermore, there is evidence of dose-dependent effects of severity of alcohol use on executive performance decrements (Glass et al., 2009). More importantly, there is some evidence that alcohol abuse may be more strongly associated with certain aspects of executive dysfunction (i.e. sustained attention, planning or flexibility) than the co-abuse of other drugs, such as cocaine (Bolla et al., 2000; Goldstein et al., 2004) or heroin (Fishbein et al, 2007). Therefore, alcohol co-abuse is a relevant confounding variable that complicates the interpretation of previously observed associations between cannabis, cocaine or heroin abuse and impairment of separate executive processes (Abi-Saab et al., 2005; Di Sclafani et al., 2002; Fishbein et al., 2007; Robinson et al., 1999). Nicotine is also a relevant confounding variable, but its neurocognitive effects appear to be more related to processing speed and memory functioning, with less deleterious effects on executive functions (Swan and Lessov-Schlaggar, 2007). On the other hand, in order to examine the association between abuse/dependence of different drugs and executive functioning, the patterns of quantity and duration of use of these drugs must be considered. As we explained earlier, there is a strong association between the intensity of drug use (in terms of both quantity and duration of use) and the degree of executive functions impairment and frontal cortex dysfunction (see Beveridge et al., 2008). In this regard, several studies have shown consistent associations between the severity of cannabis use and alterations in inhibition, flexibility and decision-making (Bolla et al., 2002, 2005; Verdejo-García et al., 2005b), between the severity of cocaine use and inhibition impairments (Bolla et al., 2000; Fillmore and Rush, 2002; Roselli and Ardila, 1996; Verdejo-García et al., 2005b) and between the severity of opioid consumption and cognitive flexibility decrements (Lyvers and Yakimoff, 2003).

Therefore, based on the multicomponent approach to executive functions, this study is aimed at: (i) analysing the independent impact of the three main drugs motivating treatment demand (cocaine, heroin and cannabis) versus the impact of alcohol co-abuse on polysubstance dependents' executive functions performance, and (ii) analysing the contribution made by the quantity and duration of consumption of the different drugs analysed on executive functions performance. We expect that alcohol and other drugs of abuse have a differential contribution in the separate components of the executive functions analysed. To reach both aims, we chose to make a three-stage multiple regression approach aimed to differentiate between detrimental effects due to the effects of demographic variables (age and education), those related to the effects of alcohol, and those related to the effects of the main drugs of choice motivating treatment (especially after discounting demographic and alcohol effects).

Method and materials

Participants

Sixty substance-dependent individuals (SDIs) (eight female), aged 21–49 years, and 30 healthy control individuals (HCIs)

(six female), aged 18–49 years, participated in this study. All participants were Spaniards (European background) and spoke Spanish as their native language. SDIs and HCIs participants were matched for gender, but not for age or education level, which were used as independent variables in regression analyses. In Table 1, we present the main sociodemographic characteristics of both groups. SDIs were selected during their treatment at the 'Proyecto Hombre' rehabilitation centre, an intreatment therapeutic community in Granada, Spain. This centre provides a controlled environment for dishabituation and treatment of drug abuse. SDIs were in a situation of controlled abstinence and urine toxicology screening (One Step Syva rapid tests for alcohol, cannabis-THC, amphetamines, benzodiazepines, cocaine and opiates) was conducted on these individuals weekly, allowing us to rule out drug use throughout the entire period of abstinence. Selection criteria for participants in the SDIs group were: (i) meeting the DSM-IV criteria for substance dependence; (ii) absence of documented comorbid mood or personality disorders as assessed by clinical reports; (iii) absence of documented head injury or neurological disorders; (iv) not being enrolled in opioid substitution treatment; and (v) minimum abstinence duration of 15 days before testing, although the median duration of abstinence for any drug in the group was of 32 weeks, so that it was possible to rule out the presence of alterations associated with the acute or short-term effects of the drugs. The SDIs sample was principally composed of polysubstance abusers who requested treatment for cocaine, heroin or cannabis use. Although five SDIs showed high level of MDMA use (a lifetime consumption of more than 50 pills), none of them requested treatment for this MDMA consumption. In Table 2, we present the consumption characteristics of the SDIs group.

Control participants were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these control participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than six units of alcohol per week); (ii) absence of documented major psychiatric disorders; (iii) absence of documented head injury or neurological disorder; and (iv) not being on any medication affecting the central nervous system (CNS), including antidepressants, mood stabilizers, anxiolytics, antiepileptics or antipsychotics. The mean amount of alcohol use in male HCIs was 5.43 units/month (SD = 5.24) and the mean of alcohol duration consumption was 6.12 years (SD = 6.06). In female HCIs the mean amount of alcohol use was 5.33 units/month (SD = 8.35) and the mean of alcohol duration consumption was 9.00 years (SD = 11.45).

Instruments and assessment procedures

Background information: In order to examine the lifetime use of different substances, we used the *Interview for Research on Addictive Behaviour* (IRAB) (López-Torrecillas et al., 2001). This instrument evaluates the dosing, frequency (consumption episodes per month) and duration of use of a number of substances. For every substance the subject had actually consumed, including cannabis, alcohol, cocaine, heroin, amphetamines, benzodiazepines and MDMA, the following information was requested:

(1) The average amount of each target drug taken in each episode of use (number of joints for cannabis; number of grams for cocaine and heroin; and number of units for alcohol, considering that a glass of Scotch whisky equals one unit, while a glass of wine or beer equals 0.5 units), and the frequency of these consumption episodes per month (daily, between one and three times per week, once a week, between one and three times per month or once a month).
(2) The number of years elapsed since the onset of use.

Table 2. Descriptive scores for patterns of quantity and duration of drug use in the group of substance-dependent individuals (SDIs)

		SDIs	
Substances	Variables	Mean	SD
Cocaine	Grams/month	49.53	42.22
	Duration (years)	8.07	5.57
Cannabis	Joints/month	148.65	179.87
	Duration (years)	8.27	7.63
Heroin	Grams/month	10.90	24.05
	Duration (years)	1.90	4.14
Alcohol	Units/month	506.98	445.58
	Duration (years)	10.40	7.17
	Abstinence (weeks)	33.28	Median = 32.00

Table 1. Descriptive scores for the sociodemographic characteristics of substance-dependent individuals (SDIs) and healthy control individuals (HCIs)

	SDIs		HCIs			
Socio-demographic variables	Mean	SD	Mean	SD	t/χ^2	*p*-value
Age	30.58	7.08	26.40	8.03	2.52*	0.013
Years of education	9.88	2.48	11.63	2.04	−3.33*	0.001
Gender (%)					0.67**	0.538
Men	86.7		80			
Women	13.3		20			

*Value of Student's *t*.
**Value of chi-squared χ^2.

From these data, two independent measures of *quantity* (average amount taken in each episode of use × monthly frequency) and *duration* (years) of consumption were calculated for each drug abused by the participants.

Neuropsychological tests: We used a selective battery of neuropsychological tests designed to assess several components of executive functions, including fluency, working memory, analogical reasoning, interference and cognitive flexibility (which have been associated with the functioning of different sections of the lateral prefrontal cortex) (Koechlin and Summerfield, 2007), and decision-making and self-regulation during multitasking (which are proposed to relate to more medial and rostral sections of the prefrontal cortex) (Bechara et al., 2000; Levine et al., 2000). Below we describe the tasks used grouped by executive components.

Fluency tests:

- FAS (verbal fluency) (Lezak, 2004): participants were asked to produce in 1 min the greatest possible number of words that start first with the letter 'F', next with the letter 'A' and finally with the letter "S". The main dependent variable was the sum of the words produced with these three letters.
- Ruff figural fluency test (RFFT) (Ruff, 1996): consists of five parts that present a similar structure, made up of 35 boxes with five dots in each. Participants were required to draw as many different figures as possible joining with straight lines at least two of the five dots each box contains. The main dependent variable used in this test was the total number of original figures produced.

Working memory tests:

- Letter number sequencing (LNS) (Wechsler adult intelligence scale, WAIS-III) (Wechsler, 1997a): the participant is read a sequence in which letters and numbers are combined, and they are asked to reproduce the sequence heard, first placing the numbers in ascending order and then the letters in alphabetical order. The test consists of seven elements, and each element consists of three tries. In each element, the sequence is read at one letter or number per second. The administration is stopped when the participant misses three tries in the same element. The main dependent variable used on this test was the number of correct answers.
- Spatial span (Wechsler memory scale, WMS-III) (Wechsler, 1997b): this task consists of a platform on which a series of 10 three-dimensional cubes are placed and organized according to a pre-determined pattern. The test consists of two parts: forward and backward span. In both cases the evaluator touches a series of cubes (whose number increases in successive trials) with his finger, and the participant must touch the same cubes as the evaluator (1) in the same order (forward span) or (2) in inverse order (backward span). The main dependent variable used in these tests was the total number of correct responses.

Analogical reasoning tests:

- Similarities (WAIS-III) (Wechsler, 1997a): pairs of words that represent common objects or concepts are read, and participants have to indicate how these objects/concepts are similar. This task consists of 19 pairs of words. The administration is stopped when the participant misses four consecutive elements. The main dependent variable analysed in this test was the number of correct answers.
- Category test (DeFilippis, 2002): a computerized version of this test was administered. The task consists of 208 stimuli that have different types of designs (squares, triangles, circles, letters, etc.) grouped in seven subtests with different rules. For all of the stimuli included in the same subtest, there is an underlying rule that determines the appropriateness of the responses throughout this subtest. However, this rule changes in the next subtest, so that the participant's performance on the test depends on the ability to infer these rules, and modify them when they are no longer valid. Test instructions are intentionally ambiguous: we explained to the participant that different types of designs will appear consecutively on the screen, and that each design is associated with one of the first four numbers: 1, 2, 3 or 4. For each stimulus the participant must press the key with the number they think is associated with that design, and the computer provides auditory feedback related to the correctness or incorrectness of the response provided. The main index of performance on the test was the total number of errors on the seven subtests.

Tests of interference and shifting:

- Stroop: this test consists of three forms, each of which contains 100 elements distributed in five columns of 20 elements each. The first form (WORDS condition) is made up of the words 'RED', 'GREEN' and 'BLUE' ordered randomly and printed in black ink. In this condition the participant is asked to read aloud, as quickly as possible, the words written on this page in a time set at 45 s. The second form consists of strings of 'XXXX' (COLORS condition) printed in red, blue or green ink. In this condition, the participant is asked to read aloud as quickly as possible the colour of these elements with a time limit of 45 s. The third form (COLOR-WORD condition) introduces the condition of interference, and it consists of the words from the first form printed in the colours of the second. In this condition, the subject is asked to name the colour of the ink the word is written in, ignoring the word, also in 45 s. The main dependent variable used in this test was the interference score, obtained by subtracting subjects' response latency to WORDS and COLOR (using the formula: WORDS*COLORS/WORDS + COLORS) from their response latency to the COLOR-WORD condition (Golden, 1978).
- Five digit test (5DT) (Sedó, 2005): this consists of four parts of independent application, in which a series of 50 boxes are presented, each of which contains one to five digits (parts 1, 3 and 4) or stars (part 2), organized in

patterns similar to those on domino pieces or playing cards. In part 1 (reading), the participant is asked to read as quickly as possible the digit each box contains. In part 2 (counting), they are asked to count how many stars each box contains. In part 3 (interference), they are asked to count the number of digits each box contains, producing an effect of interference as the boxes present groups of digits that do not correspond to their arithmetic value (e.g. in a box with five twos, the correct response would be five and not two). Finally, in part 4 (shifting), the participant is asked to count, just as in part 3, or read, as in part 1, depending on whether the outline of the box is normal (count, 80% of the stimuli) or of double thickness (read, 20% of the stimuli). Parts 1 and 2 constitute basic measures of attention and processing speed. In contrast, parts 3 and 4 are sensitive to executive processes of inhibition. Therefore, the main dependent variables used in this test were the difference between the performance time on part 3 and the mean of parts 1 and 2 (differential 'interference' score), and the difference between the performance time on part 4 and the means of parts 1 and 2 (differential 'shifting' score).

- Oral Trail Making (OTM) (Sedó et al., 1995): this test includes two independent parts. The first part (OT 1) assesses visuo-spatial and naming abilities. It contains 20 items consisting of numbers (1–20) paired with four familiar fruit images (apple, banana, grapes and orange). The items (containing the number and the paired fruit represented together in 20 little boxes) are spread all over the test form. Participants are asked to visually search for the items by number, and to name the fruit paired with each item (one apple, two orange and so forth). The second part (OT 2) assesses visuo-spatial and cognitive flexibility skills. This portion of the test uses a presentation identical to that in the first part, except that the fruits paired with the numbers are printed in different non-natural colours, in such a way that the shape and the colour of the fruit are always incongruent (e.g. red banana). Participants are asked to visually search for each item by number and to name the fruit paired according to the colour and not the shape (thus, a red banana should be named as 'apple'). The dependent measure was the interference score obtained by subtracting time in part 1 from time in part 2 (OT 2−1).

Decision making:

- Iowa gambling task (IGT) (Bechara et al., 1994): this is a computerized task that factors several aspects of decision-making including uncertainty, risk, and evaluation of reward and punishing events. The IGT involves four decks or cards, decks A′, B′, C′ and D′. Participants were instructed to win as much money as possible by picking one card at a time from each of the four decks in any order until the computer instructed them to stop (after the selection of the 100th card). Each time a participant selects a card, a specified amount of play money is awarded. However, interspersed among these rewards, there are probabilistic punishments (monetary losses with different amounts). Two of the decks of cards, decks A′ and B′, produce high immediate gains; however, in the long run, these two decks will take more money than they give, and are therefore considered to be the disadvantageous decks. The other two decks, decks C′ and D′, are considered advantageous, as they result in small, immediate gains, but will yield more money than they take in the long run. The main dependent variable used on this task was the difference between the number of advantageous and disadvantageous choices [(C + D)−(A + B)] on each of the five blocks of 20 trials of the task.

Self-regulation:

- Revised Strategy Application Test (R-SAT) (Levine et al., 2000; Spanish adaptation by Verdejo-García et al., 2007b): this is an unstructured paper-and-pencil multitasking test sensitive to disturbed self-regulation. It consists of three simple activities: figure tracing, sentence copying and object numbering. Each activity has to be performed in two different stacks (A and B), each containing 10 pages with approximately 12 items each. The items differed in two dimensions: size (they can be large or small) and time required to complete them (they can be brief, taking a couple of seconds, medium or long, taking more than one minute). The different types of stimuli are intermixed within each page, but the number of brief items decreases progressively within each stack. The main goal of the task was to win as many points as possible, considering that large items scored 0 points and small items scored 100 points each. Nonetheless, points were used in the instructions only to see whether participants would respond accordingly, but the dependent variable in this task is the number of items and not points. In order to complete more items, given the limited time, the most efficient strategy (which the participant must discover as they perform the task) is to complete brief items to the exclusion of lengthy items. This requires the inhibition of a tendency to complete all of the items in sequence, which is established on the early pages of each stack, where all of the items are brief. Therefore, the main dependent variable from the R-SAT was the proportion of brief items completed (not including the first page of each stack) with regards to the total number of items attempted.

Procedure

Participants were assessed individually between April 2003 and November 2007 in a single session that lasted approximately 3 h and 45 min (including breaks) or on two consecutive days, depending on the rehabilitation centre availability. Participants did not consume food, caffeine or nicotine during tests administration, although smoking (a maximum of one cigarette) was allowed during the breaks to avoid nicotine withdrawal effects. SDIs and HCIs were not tested at a fixed time of the day, but to the best of the authors' knowledge there is no consistent evidence of biasing effects of this variable on neuropsychological performance

in this population. The tests included in the study were part of a more comprehensive battery aimed at examining neuropsychological functions in SDIs. Test administration was blocked for all participants and arranged to alternate between verbal and non-verbal tasks and between more- and less-demanding tasks. The order of administration was: FAS, RFFT, LNS, Stroop, Similarities, Category Test, R-SAT, OTM, Spatial Span, 5DT and IGT.

All of the participants in the study were informed about the objectives, benefits and possible inconveniences associated with the research protocol. Likewise, all of the participants signed an informed consent form certifying their voluntary participation. The SDIs and HCIs participants who requested it received a neuropsychological report about their performance on the tests. In addition, the control participants were paid €18 for their participation to ensure motivation.

Data analysis

First, in order to characterize neuropsychological performance differences between SDIs and HCIs, we conducted independent-samples *t*-tests (for those dependent variables unrelated to age and education: 5DT shifting score, 5DT interference score and R-SAT) or univariate analyses of covariance (ANCOVAs; for those dependent variables significantly associated with age, education or both: FAS, RFFT, LNS, Spatial span, Similarities, Category test total errors, OTM shifting score, Stroop interference score and IGT) using group (SDIs versus HCIs) as a between-subjects factor and age and education as covariates. Next, we explored dependent variables to examine the possible presence of outliers (defined as atypical values by the Explore command of SPSS v.15). Two outliers were detected in the R-SAT proportion of brief items distribution, two outliers were detected in the 5DT–interference score distribution, and three outliers were detected in the 5DT–shifting score distribution. These subjects were removed from further analyses with the corresponding dependent variables; therefore SDIs sample size for R-SAT analyses, $N = 58$, for 5DT interference, $N = 58$ and for 5DT shifting, $N = 57$. Next, we performed a series of multiple regression models to examine the impact of demographic variables, alcohol use and illegal drugs use on executive performance. Since the three illegal drugs motivating treatment demand in this sample were the main focus of the study, we first conducted multiple regression models including only cannabis, cocaine and heroin (both quantity and duration) as predictor variables; these analyses were included to assess the variance attributable to drug use before inclusion of demographics and alcohol. Next, to test the main aim of the study (i.e. to disentangle specific effects of alcohol versus illegal drugs on different executive components and determine the impact of cannabis, cocaine and heroin after discounting the effect of demographics and alcohol abuse), we conducted hierarchical multiple regression analyses. These models were set on three stages: (i) demographic variables associated with executive performance (age and years of education); (ii) total consumption of alcohol, which is the main substance of co-abuse; and (iii) quantity and duration of consumption of cannabis, cocaine and heroin. We developed independent regression model series for the variables quantity and duration of consumption of the different substances, to determine the specific effects of both parameters and avoid collinearity effects. These separate models also allowed us to adjust the number of predictors as a function of sample size: we used a maximum of five predictor variables for a sample size of 90; ratio of 15 cases by predictor variable (a ratio of at least 10 cases by predictor is considered appropriate) (Hair et al., 2000). Therefore, for each analysis we introduced three differentiated blocks of predictor variables in a sequential manner: the first block included the variables of age and years of education, the second block included the total alcohol consumption (i.e. a combined quantity × duration measurement was calculated to avoid that alcohol consumption of healthy control individuals, similar to that of SDIs in duration, yet of quite lower intensity, could slant the contribution of this factor), and finally, the third block included the quantity or duration of consumption of cannabis, cocaine and heroin. The different performance indices of the executive function neuropsychological tests were included as dependent variables. For each new block of variables entered in the regression model, we estimated the R^2 of the prediction change associated with that block and its statistical significance, with the aim of determining the differential contribution of each of the blocks to the regression model. To facilitate reading, in text we only present results from hierarchical models showing significant effects of alcohol or drug use after discounting the effects of demographic variables. Data from regression models including only drug use variables are presented in Tables (two first columns), along with hierarchical models.

Results

Group differences

SDIs performed significantly poorer than controls on all of the executive indices assessed, with effect sizes ranging from 0.6 (e.g. shifting) to 2.3 (analogical reasoning); see Table 3. All executive indices (with the exception of OTM shifting) yielded effect sizes circa or superior to 0.8 for differences between SDIs and HCIs, which are considered large effects according to Cohen (Zakzanis, 2001).

Regression models

The coefficients obtained with the hierarchical regression analyses are represented in Table 4, for the models including quantity of consumption, and in Table 5, for the models including duration of consumption. The impact of the entry of each block in each of the steps of the regression model is represented by means of the determination coefficient values (R^2). The results of multiple regressions including only drug measures (quantity or duration) are also included in the first two columns of Tables 4 and 5, respectively.

Quantity of consumption

Fluency: In the FAS test, after controlling for the effects of demographics, the block of total alcohol consumption was a significant predictor of performance. However, the entry of the block of quantity of consumption of other drugs

Table 3. Descriptive scores, independent group *t*-tests/univariate analyses of covariance (ANCOVAs), and effect sizes on the neuropsychological measures for substance-dependent individuals (SDIs) and healthy control individuals (HCIs)

		SDIs		HCIs				
Domain	Task	Mean	SD	Mean	SD	*F/t*	*p*-value	Cohen's delta
Fluency	FAS	33.81	10.55	51.43	9.80	46.52[a]	0.000	−1.71
	RFFT	82.86	23.72	110.33	19.94	20.11[a]	0.000	−1.21
Working memory	LNS	9.33	2.40	15.13	2.33	93.50[a]	0.000	−1.57
	Spatial Span	14.89	3.36	19.90	4.35	24.55[a]	0.000	−1.35
Reasoning	Similarities	18.11	4.51	27.76	3.01	90.55[a]	0.000	−2.37
	CT_tot_errors	66.89	24.01	31.80	25.32	30.86[a]	0.000	1.41
Shifting	5DT_shift	25.47	9.38	20.10	5.45	2.89[b]	0.005	0.64
	OTM_shift	21.89	15.32	14.13	7.57	2.18[a]	0.143	0.58
Interference	5DT_interf	15.74	6.46	11.10	3.77	4.28[b]	0.000	0.81
	Strp_interf	−1.67	6.07	4.15	7.24	9.63[a]	0.003	−0.89
Decision-making	IGT	−2.21	22.60	37.20	26.15	47.84[a]	0.000	−1.65
Self-regulation	R-SAT	82.95	16.46	93.98	5.70	−3.55[b]	0.001	−0.79

[a]*F*-value.
[b]Student's *t* value.
FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test.

significantly increased the predictive value of demographics and alcohol. The global model revealed that the quantity of cannabis was the most predictive variable of performance on this test. In the RFFT, neither the block of total alcohol consumption nor the block of illegal drugs consumption were predictors of performance on this task.

Working memory: In the LNS test, the block of total alcohol consumption showed a trend to significant effects ($p = 0.057$), but the entry of the block of quantity of consumption of drugs significantly improved the prediction of the former blocks. In the global model we observed that the quantity of cocaine and cannabis use had the highest predictive value of performance. In the Spatial Span task, we observed that the block of total alcohol consumption failed to predict performance on this task. Nevertheless, inclusion of the quantity of consumption of other drugs significantly improved the prediction of demographics and alcohol. The analysis of the global model coefficients showed that the quantity of cocaine use had the highest predictive value of performance on this task.

Reasoning: In the Similarities test, we observed that, after controlling for demographics and alcohol, the block of quantity of consumption of drugs was a significant predictor of performance. The analysis of the global model coefficients showed that the quantity of consumption of cannabis and cocaine were the variables with the highest predictive value of performance on this task. Similarly, in the Category test, the block of quantity of consumption of drugs showed a trend to significantly increase prediction of performance ($p = 0.062$), and the analysis of global model coefficients revealed that the quantity of cocaine was the most predictive variable of performance on this task.

Interference and shifting: In the 5DT (both interference and shifting scores) and the Stroop tests, neither the block of total alcohol consumption nor the block of other drugs had predictive capability of performance on these measures. In the OTM test, the entry of the block of quantity of consumption of drugs improved the prediction of previous blocks significantly, and quantity of heroin consumption was the most predictive variable.

Decision-making: In the IGT we observed that both the block of total alcohol consumption and the block of other drugs significantly predicted performance on this task. When analysing the global model, we observed that total alcohol consumption, quantity of cannabis and quantity of cocaine were the most predictive variables of performance on this task.

Self-regulation: In the R-SAT we observed that only the block of total alcohol consumption showed a trend to significantly predict performance on this task ($p = 0.077$). The inclusion of the block of drug measures failed to increase the prediction of the global model significantly.

Duration of consumption: In this section we only refer to the predictive value of the variables of cannabis, cocaine and heroin consumption, since the predictive value of the blocks of total alcohol consumption variable is the same as that of the previously described models.

Fluency: In the FAS test we observed that the block of consumption of drugs (cannabis, cocaine and heroin) improved the predictive value of demographics and alcohol significantly, with duration of cocaine consumption being the

Table 4. Multiple hierarchical regression models of the association between demographic variables, alcohol total consumption and quantity of cannabis, cocaine and heroin use and neuropsychological performance

		Model including only cannabis, cocaine and heroin		Hierarchical three-stage model including demographics, alcohol and drugs use				
Domain	Test	R^2 adjusted (p-value)	Significant contributors	Demographics R^2 change (p-value)	Alcohol R^2 change (p-value)	Cannabis/cocaine/heroin Quantity R^2 change (p-value)	Full model R^2 adjusted (p-value)	Significant contributors
Fluency	FAS	0.297 (0.000)	Cann Quant (0.000); Coc Quant (0.027); Heroin Quant (0.039)	0.096 (0.013)	0.086 (0.003)	0.177 (0.000)	0.313 (0.000)	Cann Quant (0.001)
	RFFT	0.061 (0.038)	Cann Quant (0.066)	0.133 (0.002)	0.017 (0.199)	0.034 (0.399)	0.124 (0.009)	Educ (0.005)
WM	LNS	0.286 (0.000)	Cann Quant (0.035); Coc Quant (0.000)	0.171 (0.000)	0.034 (0.057)	0.180 (0.000)	0.341 (0.000)	Educ (0.014); Cann Quant (0.032); Coc Quant (0.001)
	Spatial Span	0.096 (0.009)	Coc Quant (0.015)	0.109 (0.007)	0.006 (0.443)	0.081 (0.049)	0.137 (0.006)	Coc Quant(0.032)
Reasoning	Similarities	0.207 (0.000)	Cann Quant (0.022); Coc Quant (0.004)	0.173 (0.000)	0.030 (0.075)	0.118 (0.004)	0.272 (0.000)	Educ (0.005); Cann Quant (0.026); Coc Quant (0.032)
	CT_tot_errors	0.085 (0.016)	Coc Quant (0.027)	0.074 (0.039)	0.012 (0.308)	0.079 (0.062)	0.103 (0.022)	Coc Quant (0.047)
Shifting	5DT_shift	0.058 (0.047)		0.014 (0.556)	0.004 (0.558)	0.079 (0.080)	0.029 (0.213)	
	OTM_shift	0.130 (0.002)	Coc Quant (0.037); Heroin Quant (0.018)	0.105 (0.008)	0.008 (0.375)	0.092 (0.028)	0.148 (0.004)	Heroin Quant (0.047)
Interference	5DT_interf	0.058 (0.046)		0.005 (0.814)	0.011 (0.330)	0.078 (0.081)	0.027 (0.225)	
	Strp_interf	0.021 (0.191)		0.087 (0.020)	0.002 (0.667)	0.036 (0.347)	0.061 (0.083)	Age (0.073)
DM	IGT	0.260 (0.000)	Cann Quant (0.003); Coc Quant (0.011)	0.049 (0.111)	0.127 (0.000)	0.160 (0.000)	0.288 (0.000)	Alcoh tot cons (0.037); Cann Quant (0.004); Coc Quant (0.067)
Self-regulation	R-SAT	0.030 (0.136)	Cann Quant (0.084)	0.011 (0.619)	0.036 (0.077)	0.057 (0.168)	0.038 (0.164)	

Note: WM, Working Memory; DM, Decision-making; FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test; Cann, Cannabis; Quant, Quantity; Educ, Years of education; Coc, Cocaine; Alcoh tot cons, Alcohol total consumption.

Table 5. Multiple hierarchical regression models of the association between demographic variables, alcohol total consumption and duration of cannabis, cocaine and heroin use and neuropsychological performance

		Model including only cannabis, cocaine and heroin		Hierarchical three-stage model including demographics, alcohol and drugs use				
Domain	Test	R^2 adjusted (p-value)	Significant contributors	Demographics R^2 change (p-value)	Alcohol R^2 change (p-value)	Cannabis/cocaine/ heroin Duration R^2 change (p-value)	Full model R^2 adjusted (p-value)	Significant contributors
Fluency	FAS	0.160 (0.000)	Coc Durat (0.012)	0.096 (0.013)	0.086 (0.003)	0.130 (0.002)	0.262 (0.000)	Age (0.002); Educ (0.026); Coc Durat (0.012)
	RFFT	0.093 (0.010)	Coc Durat (0.007)	0.133 (0.002)	0.017 (0.199)	0.179 (0.033)	0.179 (0.001)	Educ (0.003); Coc Durat (0.015)
WM	LNS	0.179 (0.000)	Coc Durat (0.020)	0.171 (0.000)	0.034 (0.057)	0.113 (0.005)	0.269 (0.000)	Educ (0.001); Coc Durat (0.069)
	Spatial Span	0.098 (0.008)	Cann Durat (0.025)	0.109 (0.007)	0.006 (0.443)	0.080 (0.050)	0.137 (0.006)	Educ (0.012); Cann Durat (0.014)
Reasoning	Similarities	0.193 (0.000)	Coc Durat (0.004)	0.173 (0.000)	0.030 (0.075)	0.144 (0.001)	0.300 (0.000)	Educ (0.000); Coc Durat (0.009)
	CT_tot_errors	0.106 (0.006)	Cann Durat (0.090)	0.074 (0.039)	0.012 (0.308)	0.073 (0.084)	0.096 (0.028)	
Shifting	5DT_shift	−0.003 (0.432)		0.014 (0.556)	0.004 (0.558)	0.052 (0.224)	0.000 (0.430)	Coc Durat (0.074)
	OTM_shift	0.223 (0.000)	Coc Durat (0.002); Heroin Durat (0.002)	0.105 (0.008)	0.008 (0.375)	0.167 (0.001)	0.228 (0.000)	Educ (0.062); Coc Durat (0.016); Heroin Durat (0.003)
Interference	5DT_interf	0.064 (0.035)	Coc Durat (0.066)	0.005(0.814)	0.011(0.330)	0.098(0.036)	0.048(0.124)	Coc Durat (0.036)
	Strp_interf	0.102 (0.007)	Coc Durat (0.089)	0.087(0.020)	0.002(0.667)	0.076(0.065)	0.104(0.019)	Educ (0.065)
DM	IGT	0.125 (0.002)	Coc Durat (0.076)	0.049 (0.111)	0.127 (0.000)	0.060 (0.099)	0.181 (0.001)	Alcoh tot cons (0.013)
Self-regulation	R-SAT	−0.019 (0.710)		0.011 (0.619)	0.036 (0.077)	0.006 (0.916)	−0.017 (0.602)	

Note: WM, Working Memory; DM, Decision Making; FAS, Verbal fluency; RFFT, Ruff figural fluency test; LNS, Letter number sequencing; CT_tot errors, total number of errors on Category test; 5DT_shift, Five digit test shifting score; OTM_shift, Oral trail making shifting score; 5DT_interf, Five digit test interference score; Strp_interf, Stroop interference score; IGT, Iowa gambling task; R-SAT, Revised strategy application test; Cann, Cannabis; Durat, Duration; Educ, Years of education; Coc, Cocaine; Alcoh tot cons, Alcohol total consumption.

variable with the highest predictive value. In the RFFT the block of duration of drug consumption improved prediction of previous blocks significantly, and duration of cocaine consumption was the variable with the highest predictive value.

Working memory: In the LNS test, the block of duration of drug consumption improved the predictive value of demographics and alcohol significantly. Duration of cocaine consumption was the best predictor variable of performance on this task. In the Spatial span task, the block of duration of drug consumption improved prediction of demographics and alcohol significantly, but in this case the variable with the highest predictive value was duration of cannabis consumption.

Reasoning: In the Similarities task, the block of duration of drug consumption improved the predictive value of demographics and alcohol significantly, and duration of cocaine consumption was the best predictor of performance on this task. In the Category test, we observed that the block of durations of drugs consumption failed to significantly predict performance on this measure.

Interference and shifting: In the Stroop test, the block of duration of drug consumption was only marginally significant for prediction of performance on this task, and none of the individual drug variables (cannabis, cocaine or heroin) showed significant β-coefficients. In the 5DT, we observed that, for the interference score, the block of duration of drugs consumption produced a significant improvement in prediction, being the duration of cocaine consumption the best predictor of performance. As for the shifting score, the block of duration of drugs use failed to significantly predict performance, and only duration of cocaine use had a marginally significant effect ($p = 0.074$). In the OTM test, we observed that the block of drugs produced a significant improvement in prediction, with duration of heroin and cocaine being the variables with the highest prediction of performance.

Decision-making: In the IGT, we observed that the block of duration of drug consumption did not improve prediction of performance on this task, as compared with the block of alcohol consumption.

Self-regulation: In the R-SAT, we observed that the block of duration of drug consumption did not improve prediction of performance on this task, as compared with the block of alcohol consumption.

Summary

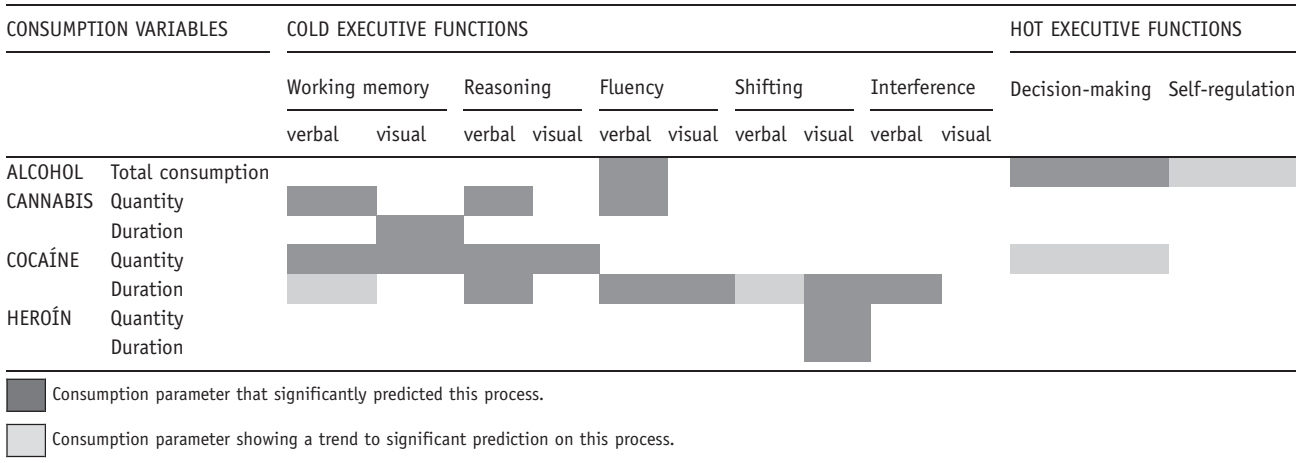
Group comparisons showed that SDIs performed significantly poorer than controls on all of the executive indices assessed, showing large effect sizes for differences on tests of fluency, working memory, reasoning, inhibition and decision-making. The hierarchical regression models showed a significant contribution of total alcohol consumption on verbal fluency and decision-making. As for quantity of consumption of the drugs that motivated treatment, we observed that: (i) the quantity of cannabis consumption predicts performance on verbal working memory, verbal reasoning, verbal fluency and decision-making; (ii) the quantity of cocaine consumption predicts performance on verbal and visual–spatial working memory, verbal and visual reasoning, and decision-making; and (iii) the quantity of heroin consumption predicts performance on visual–spatial shifting. As for duration, we observed that: (i) the duration of cannabis consumption predicts performance on visual working memory only; (ii) the duration of cocaine consumption predicts performance on verbal working memory and reasoning, both verbal and non-verbal fluency and shifting, and interference-based inhibition; and (iii) the duration of heroin consumption predicts performance on visual-spatial shifting (Table 6).

Discussion

Results showed that SDIs have a broad range of executive impairments, including fluency, working memory, reasoning, inhibition, shifting and decision-making deficits, of moderate to large magnitude according to effect sizes (Cohen's *d* range: 0.6–2.4). Importantly, these decrements are observed in SDIs with a median abstinence duration of 8 months, and therefore they should be regarded as long-term effects with relevant implications for the notion of addiction as a chronic brain disorder associated with frontal systems dysfunction (Goldstein and Volkow, 2002). Previous studies had obtained similar results (see the review by Verdejo-García et al., 2004), but the fact that virtually all SDIs are polysubstance abusers complicates the attribution of specific or generalized executive deficits to the effects of alcohol or any given drug. In this respect, the results from regression models revealed that severity of alcohol use is robustly associated with verbal fluency and decision-making decrements. As for the main drugs motivating treatment (cannabis, cocaine and heroin), results showed that quantity of cannabis and cocaine use have common detrimental effects on verbal working memory, analogical reasoning and decision-making measures, and that duration of cocaine and heroin use have common detrimental effects of visual–spatial shifting measures. On the other hand, we found specific effects of duration of cannabis use on visual–spatial working memory, and of duration of cocaine use on response inhibition.

Our first aim was to separate the effects of alcohol versus drugs use on different components of executive functions. Severity of alcohol use showed significant detrimental effects on verbal fluency and decision-making (on the IGT), and a trend to significant effects on working memory, but not on other executive components. Previous studies had proposed that severity of alcohol abuse was significantly associated with decrements on executive components of planning and flexibility in psychostimulants and heroin abusers co-abusing alcohol (Bolla et al., 2000; Fishbein et al., 2007; Goldstein et al., 2004). However, these studies were conducted in short-term abstinent SDIs (range of 2–4 weeks),

Table 6. Summary of significant associations between the different substances analysed and the different components of cold and hot executive functions



whereas one of the few studies available in long-term abstinent alcoholics found that decision-making performance (measured with the IGT) was impaired pervasively in these individuals even after six years of sobriety; being the magnitude of disadvantageous decision-making associated with the duration of peak alcohol use (Fein et al., 2004). Moreover, the alcoholic individuals who had impaired IGT performance had significant grey matter reductions in the amygdala, a key region for the operation of decision-making processes (Bechara et al., 2003). A recent structural magnetic resonance study have also provided evidence of significant structural reductions of grey matter (up to 20% lower) in the bilateral dorsolateral prefrontal cortex of alcoholics (Chanraud et al., 2007). This region has been proposed to be involved in verbal fluency and other executive operations associated with the updating of information in working memory (D'Esposito and Postle, 2002; Gauthier et al., 2009). Functional imaging studies have also demonstrated dysfunctional frontotemporal activation during verbal fluency performance using functional spectroscopy (Schecklmann et al., 2007), and significant correlations between PET-indexed left dorsolateral prefrontal hypometabolism and reduced verbal fluency performance in abstinent alcoholics (Dao-Castellana et al., 1998). There is also evidence that acute ethanol administration decreases left dorsolateral prefrontal cortex activation and impairs verbal fluency performance in healthy individuals (Wendt and Risberg, 2001). Overall, these studies support our results showing a prominent association between severity of alcohol use and poorer fluency and decision-making skills. Although fluency and decision-making are independent executive components (Verdejo-García and Pérez-García, 2007) they have in common being complex multifaceted operations encompassing access to long-term memory, clustering, monitoring and switching of information (in the case of fluency) (Fisk and Sharp, 2004; Troyer et al., 1998), and episodic/working memory, motivation and feedback processing and reversal learning (in the case of decision-making) (Bechara et al., 2005; Busemeyer and Stout, 2002; Gupta et al., 2009). Therefore, we may speculate that alcohol severity specifically affects some of the component operations of fluency and/or decision-making (e.g. working memory updating), or alternatively affects in a broad sense to multi-component executive processes.

Our second aim was to determine the contribution of quantity and duration of consumption of the main drugs that motivated treatment to decrements on executive components functioning. In this regard, we found common detrimental effects of quantity of cannabis use and cocaine use on measures of verbal updating of working memory, analogical reasoning and decision-making. A principal component analysis performed on a comprehensive battery of executive functions tests concluded that measures of working memory and analogical reasoning (along with fluency measures) load together on a factor that we and others have labelled 'updating' (Verdejo-García and Pérez-García, 2007); which consists of continuous refreshing/updating of working memory contents in order to set task demands and optimize performance (Miyake et al., 2000; Stuss and Alexander, 2007; Verdejo-García and Pérez García, 2007). These results are consistent with several sources of evidence, including animal studies showing cocaine and cannabinoid dose-related modulation of working memory performance (Deadwyler et al., 2007; Egerton et al., 2006; George et al., 2008), human studies showing dose-related negative effects of severity of cannabis and cocaine use on updating measures in polydrug abusers (Medina et al., 2007; Verdejo-García et al., 2007a), and the conclusions of a recent meta-analysis of neuropsychological studies in cocaine abusers showing moderate effect sizes for updating indices, which are durable across abstinence (Jovanovski et al., 2005). Functional imaging studies have linked these updating deficits to prefrontal cortex, cingulate cortex and superior parietal cortex dysfunctions (Jager et al., 2006; Kübler et al., 2005). Nonetheless, there is also intriguing evidence showing that cannabis users have abnormally increased hippocampal activation in response to executive tasks demands (Eldreth et al., 2004; Nestor et al., 2008). Moreover, a recent structural magnetic resonance imaging study has revealed significant volumetric reductions (circa 12%) in the hippocampus of long-term cannabis users (Yücel et al., 2008). Therefore, hippocampal dysfunction may also play a prominent role on cannabis-induced updating deficits. In fact, duration of cannabis was also linked to

poorer spatial working memory, a process that has been associated with the hippocampal endocannabinoid system activation in animal models (Deadwyler et al., 2007). Similarly, for decision-making, very recent studies have shown that both cannabis and cocaine abuse have dose-related detrimental effects on IGT performance (Bolla et al., 2003, 2005; Verdejo-García et al., 2007a). However, results from functional imaging and cognitive models studies suggest that both groups may fail to make advantageous decisions for different reasons: cannabis abusers display PET-indexed prominent activation in non-specialized areas (e.g. cerebellum and occipital cortex) during IGT performance (Bolla et al., 2005), whereas cocaine abusers exposed to the same paradigm show dysfunctional activation of regions typically involved in reward processing and decision-making (e.g. striatum and orbitofrontal cortex) (Bolla et al., 2003). Moreover, cognitive decision models of the IGT have shown that cannabis abusers fail the task because they place more attention on recent than distal outcomes, whereas cocaine abusers fail because they place more attention on gains than on losses (Busemeyer and Stout, 2002).

Regression models have also shown common effects of cocaine and heroin duration of use on cognitive shifting. Animal models have shown that repeated administration of cocaine produces impairments in cognitive flexibility, specifically in perseveration and reversal learning linked to orbitofrontal cortex functioning (Jentsch et al., 2002; Schoenbaum et al., 2004; Stalnaker et al., 2006, 2009). These findings have been nicely translated to humans by several studies showing relatively specific effects of cocaine abuse on cognitive shifting (Ersche et al., 2008; Verdejo-García and Pérez-García, 2007) and electrophysiological indices of decreased error-related processing and impaired behavioural correction of errors in cocaine abusers (Franken et al., 2007). Although there is no equivalent body of animal research on the opioid modulation of cognitive shifting, a number of human neuropsychological studies have shown that heroin abusers have significant impairments in intradimensional set-shifting, perseveration, risk-taking and decision-making tasks (Fishbein et al., 2007; Lyvers and Yakimoff, 2003; Ornstein et al., 2000; Verdejo-Garcia et al., 2005a; see also the review by Gruber et al., 2007), which have been attributed to grey matter decrements in the medial and inferior prefrontal cortex, insula and temporal cortex (Lyoo et al., 2006) and dysfunctional activation of the rostral anterior cingulate cortex in response to error feedback (Forman et al., 2004). Therefore, abnormal error processing and subsequent failure of 'quality control' executive mechanisms may underlie flexibility deficits in both cocaine and heroin abusers.

Finally, we found specific effects of duration of cocaine abuse on one inhibition measure, the 5DT interference index. Previous results from our lab and others have supported relatively specific deleterious effects of psychostimulants on a number of neuropsychological indices of response inhibition, including the Stroop test, the Go–No Go, the Continuous Performance test or the Stop-Signal task (Bolla et al., 2004; Colzato et al., 2007; Li et al., 2008; Verdejo-García et al., 2007c). Furthermore, these deficits have been linked to patterns of severity of drug use (Bolla et al., 2004; Verdejo-García et al., 2005b) and to brain measures of reduced activation of the anterior cingulate and lateral prefrontal cortices during inhibition trials (using PET or fMRI) (Bolla et al., 2004; Li et al., 2008), and white matter decrements in the genu of the corpus callosum (using diffusion tensor imaging) (Moeller et al., 2005). These effects may be explained by a more intense neuromodulatory effect of psychostimulants on the cingulate cortex-striatal system (Bolla et al., 2003; Paulus et al., 2002, 2003, 2005; see also the review by Li and Sinha, 2008). However, this result may be interpreted with caution for several reasons. First, there is growing evidence that disinhibition deficits may predate initiation of drug use and constitute a liability marker for substance use disorders (see Dalley et al., 2007 and Belin et al., 2008 for animal evidence; see Verdejo-García et al., 2008 for a review of human evidence); therefore, we cannot draw conclusions on the causality of inhibition deficits. Second, there is no consistency between our findings on the 5DT and the results of other inhibition tests, such as the Stroop. We think this may be due to the fact that Stroop performance is more influenced by age and educational factors (Kaplan et al., 2009), making it harder to establish a drug-related effect. However, more research is warranted to investigate the specific effects of cocaine and other psychostimulants on inhibitory control processes.

Overall, these results obtained in mid-term abstinent substance abusers may have important implications for their quality of life and their ability to take advantage of cognitive behavioural therapy-based treatment programs. Deficits in working memory, reasoning, fluency and cognitive flexibility may be associated with difficulties in retaining complex instructions, selecting relevant information from clinical sessions or group interactions, and generalizing specific learning to other familiar and social interactive activities. On the other hand, treatment headways require that addicted individuals reverse strong habits and over-rehearsed decision patterns. Cognitive deficits have been associated with poorer clinical progression levels (Leber et al., 1985), a lower level of participation and implication in the treatment (Fals-Stewart and Lucente, 1994) and higher rates of treatment dropout and drug relapse (Aharonovich et al., 2003, 2006, 2008; Passetti et al., 2008; Streeter et al., 2008; Teichner et al., 2002). In this respect, our results stress the need to promote rehabilitation programs targeted to restore or compensate executive dysfunction in SDIs.

Finally, several limitations of this study should be mentioned. First, there is evidence of age-related cognitive decline from the thirties onwards (Herndon et al., 1997; Salthouse, 2009), and therefore some of the executive declines in our sample may be related to normal aging. However, our regression models adequately controlled for the effects of age and education, and all of the drug effects reported were obtained after removing the effect of these variables. Second, due to a lower prevalence of female inpatients during recruitment, our sample was predominantly composed of males. Future studies should investigate how these findings may or may not generalize to a female population of SDI. Third, some executive indices that were impaired in SDI failed to show any association with alcohol or drug use (e.g. the R-SAT). It is possible that in these cases the relatively medium sample size (further limited after outliers exclusion) may have contributed to type

II error or, alternatively, that these deficits relate to different aspects of the addiction phenomenon (e.g. age of first use, personality patterns). Furthermore, there is an inherent limitation linked to the reliability of self-reports of drug use; nonetheless, when considering the limitations of other methods, such as toxicological analyses or structured interviews categorical approaches, to catch the time line, peak effects and dimensional aspects of drug history, self-reports end up as the approach with highest face validity (see Verdejo-García et al., 2004 for a discussion of this methodological challenge of drug abuse cognitive studies). Finally, as mentioned above, the current cross-sectional data do not allow us to determine whether these alterations preceded drug use and contributed to higher severity patterns, or if they occur as a consequence of persistent drug use. Longitudinal studies are warranted to address this relevant question.

Acknowledgements

This work is supported by the Spanish Ministry of Science and Innovation (MICINN), under the FPU national plan (grant reference AP 2005-1411) and Research Paper SEJ 2006-08278, and the Junta de Andalucía through the Research Project P07.HUM 03089. This study complies with the current laws of Spain and all international ethical guidelines for human studies.

References

Abi-Saab D, Beauvais J, Mehm J, Brody M, Gottschalk C, Kosten TR (2005) The effect of alcohol on the neuropsychological functioning of recently abstinent cocaine-dependent subjects. *Am J Addict* 14: 166–178.

Aharonovich E, Brooks AC, Nunes EV, Hasin DS (2008) Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioral therapy treatment outcome. *Drug Alcohol Depend* 95: 279–283.

Aharonovich E, Hasin DS, Brooks AC, Liu X, Bisaga A, Nunes EV (2006) Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug Alcohol Depend* 81: 313–322.

Aharonovich E, Nunes E, Hasin D (2003) Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug Alcohol Depend* 71: 207–211.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW (2003) Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci* 6: 115–116.

Bechara A, Damasio H, Damasio AR (2000) Emotion, decision making and the orbitofrontal cortex. *Cereb Cortex* 10: 295–307.

Bechara A, Damasio H, Damasio AR (2003) Role of the amygdala in decision-making. *Ann N Y Acad Sci* 985: 356–369.

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50: 7–15.

Bechara A, Damasio H, Tranel D, Damasio AR (2005) The Iowa Gambling Task and the somatic marker hypothesis: Some questions and answers. *Trends Cogn Sci* 9: 159–162.

Belin D, Mar AC, Dalley JW, Robbins TW, Everitt BJ (2008) High impulsivity predicts the switch to compulsive cocaine taking. *Science* 320: 1352–1355.

Beveridge TJR, Gill KE, Hanlon CA, Porrino LJ (2008) Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys. *Phil Trans R Soc B* 363: 3257–3266.

Bolla KI, Brown K, Eldreth BA, Tate K, Cadet BA, Cadet JL (2002) Dose-related neurocognitive effects of marijuana use. *Neurology* 59: 1337–1343.

Bolla KI, Eldreth DA, London ED, et al. (2003) Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. *NeuroImage* 19: 1085–1094.

Bolla KI, Eldreth DA, Matochik JA, Cadet JL (2005) Neural substrates of faulty decision-making in abstinent marijuana users. *NeuroImage* 26: 480–492.

Bolla K, Ernst M, Kiehl K, et al. (2004) Prefrontal cortical dysfunction in abstinent cocaine abusers. *J Neuropsychiatry Clin Neurosci* 16: 456–464.

Bolla KI, Funderburk FR, Cadet J (2000) Differential effects of cocaine and cocaine alcohol on neurocognitive performance. *Neurology* 54: 2285–2292.

Brand M, Roth-Bauer M, Driessen M, Markowitsch HJ (2008) Executive functions and risky decision-making in patients with opiate dependence. *Drug Alcohol Depend* 7: 64–72.

Busemeyer JR, Stout JC (2002) A contribution of cognitive decision models to clinical assessment: Decomposing performance on the Bechara gambling task. *Psychol Assess* 14: 253–262.

Chanraud S, Martelli C, Delain F, et al. (2007) Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology* 32: 429–438.

Collette F, Olivier L, Van der Linden M, et al. (2005) Involvement of both prefrontal and inferior parietal cortex in dual-task performance. *Cognitive Brain Res* 24: 237–251.

Colzato LS, Van den Wildenberg WPM, Hommel B (2007) Impaired inhibitory control in recreational cocaine users. *PLoS ONE* 2: e1143.

Cools R, Clark L, Owen AM, Robbins TW (2002) Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci* 22: 4563–4567.

Dalley JW, Fryer TD, Brichard L, et al. (2007) Nucleus accumbens d2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* 315: 1267–1270.

Dao-Castella MH, Samson Y, Legault F, et al. (1998) Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. *Psychol Med* 28: 1039–1048.

Deadwyler SA, Goonawardena AV, Hampson RE (2007) Short-term memory is modulated by the spontaneous release of endocannabinoids: evidence from hippocampal population codes. *Behav Pharmacol* 18: 571–580.

DeFilippis NA (2002) *Category Test: Computer Version Research Edition*. Lutz, FL: Psychological Assessment Resources.

Denckla MB, Reiss AL (1997) Prefrontal-subcortical circuits in developmental disorders. In: Krasnegor NA, Lyon GR, Goldman-Rakic PS (eds) *Development of the Prefrontal Cortex: Evolution, Neurobiology, and Behaviour*. Baltimore, MD: Brookes.

D'Esposito M, Postle B (2002) The organization of working memory function in lateral prefrontal cortex: evidence from event-related functional MRI. In: Stuss DT, Knight RT (eds) *Principles of Frontal Lobe Functioning*. New York: Oxford University Press.

D'Esposito M, Postle BR, Ballard D, Lease J (1999) Maintenance versus manipulation of information held in working memory: An event-related fMRI study. *Brain Cogn* 41: 66–86.

De Win MML, Reneman L, Jager G, et al. (2007) A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. *Neuropsychopharmacology* 32: 458–470.

Di Sclafani V, Tolou-Shams M, Price LJ, Fein G (2002) Neuropsychological performance of individuals dependent on crack-cocaine, or crack-cocaine and alcohol, at 6 weeks and 6 months of abstinence. *Drug Alcohol Depend* 66: 161–171.

Dreher JC, Koechlin E, Tierney M, Grafman J (2008) Damage to the fronto-polar cortex is associated with impaired multitasking. *PLoS ONE* 3: e3227.

Egerton A, Allison C, Brett RR, Pratt JA (2006) Cannabinoids and prefrontal cortical function: insights from preclinical studies. *Neurosci Biobehav Rev* 30: 680–695.

Eldreth DA, Matochik JA, Cadet JL, Bolla K (2004) Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *NeuroImage* 23: 914–920.

Ersche KD, Roiser JP, Robbins TW, Sahakian BJ (2008) Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans. *Psychopharmacology* 197: 421–431.

EMCDDA (2008) *Annual Report 2008: the State of the Drugs Problem in the European Union*. Available at http://www.emcdda.eu. Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

Fals-Stewart W, Lucente S (1994) The effect of neurocognitive status and personality functioning on length of stay in residential substance abuse treatment: An integrative study. *Psychol Addict Behav* 8: 1–12.

Fein G, Klein L, Finn P (2004) Impairment on a simulated gambling task in long-term abstinent alcoholics. *Alcohol Clin Exp Res* 28: 1487–1491.

Fillmore MT, Rush CR (2002) Impaired inhibitory control of behavior in chronic cocaine users. *Drug Alcohol Depend* 66: 265–273.

Fillmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug Alcohol Depend* 67: 157–167.

Fishbein DH, Krupitsky E, Flannery BA, et al. (2007) Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use. *Drug Alcohol Depend* 90: 25–38.

Fisk JE, Sharp CA (2004) Age-related impairments in executive functioning: Updating, inhibition, shifting and access. *J Clin Exp Neuropsychol* 26: 874–890.

Forman SD, Dougherty GG, Casey BJ, et al. (2004) Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol Psychiatry* 55: 531–537.

Franken IHA, Nijs IMT, Muris P, Van Strien JW (2007) Alcohol selectively reduces brain activity during the affective processing of negative information. *Alcohol Clin Exp Res* 31: 919–927.

Gauthier CT, Duyme M, Zanca M, Capron C (2009) Sex and performance level effects on brain activation during a verbal fluency task: A functional magnetic resonance imaging study. *Cortex* 45: 164–176.

George O, Mandyam CD, Wee S, Koob GF (2008) Extended access to cocaine self-administration produces long-lasting prefrontal cortex-dependent working memory impairments. *Neuropsychopharmacology* 33: 2474–2482.

Gilbert SJ, Spengler S, Simons JS, Frith CD, Burgess PW (2006) Differential functions of lateral and medial rostral prefrontal cortex (area 10) revealed by brain–behavior associations. *Cereb Cortex* 16: 1783–1789.

Glass JM, Buu A, Adams KM, et al. (2009) Effects of alcoholism severity and smoking on executive neurocognitive function. *Addiction* 104: 38–48.

Golden CJ (1978) *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*. Wood Dale, IL: Stoelting Co.

Goldstein RZ, Volkow ND (2002) Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry* 159: 1642–1652.

Goldstein RZ, Leskovjan AC, Hoff AL, et al. (2004) Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. *Neuropsychologia* 42: 1447–1458.

Gruber SA, Silveri MM, Yurgelun-Todd DA (2007) Neuropsychological consequences of opiate use. *Neuropsychol Rev* 17: 299–315.

Gupta R, Duff MC, Denburg NL, Cohen NJ, Bechara A, Tranel D (2009) Declarative memory is critical for sustained advantageous complex decision-making. *Neuropsychologia* 47: 1686–1693.

Hair JF, Jr, Anderson RE, Tatham RL, Black WC (2000) *Análisis Multivariante*, Quinta edición (in Spanish). Prentice Hall.

Herndon JG, Moss MB, Rosene DL, Killiany RJ (1997) Patterns of cognitive decline in aged rhesus monkeys. *Behav Brain Res* 87: 25–34.

Jager G, Kahn RS, Van Den Brink W, Van Ree JM, Ramsey NF (2006) Long-term effects of frequent cannabis use on working memory and attention: An fMRI study. *Psychopharmacology* 185: 358–368.

Jentsch JD, Olausson P, De la Garza R, Taylor JR (2002) Impairments of reversal learning and response perseveration after repeated, intermittent cocaine administrations to monkeys. *Neuropsychopharmacology* 26: 183–190.

Jovanovski D, Erb S, Zakzanis K (2005) Neurocognitive deficits in cocaine users: A quantitative review of the evidence. *J Clin Exp Neuropsychol* 27: 189–204.

Kaplan RF, Cohen RA, Moscufo N, et al. (2009) Demographic and biological influences on cognitive reserve. *J Clin Exp Neuropsychol* 31: 1–9.

Koechlin E, Summerfield C (2007) An information theoretical approach to prefrontal executive function. *Trends Cogn Sci* 11: 229–235.

Kübler A, Murphy K, Garavan H (2005) Cocaine dependence and attention switching within and between verbal and visuospatial working memory. *Eur J Neurosci* 21: 1984–1992.

Leber WR, Parsons OA, Nichols N (1985) Neuropsychological test results are related to ratings of men alcoholics' therapeutic progress: A replicated study. *J Stud Alcohol* 46: 116–121.

Lee TM, Pau CW (2002) Impulse control differences between abstinent heroin users and matched controls. *Brain Inj* 16: 885–889.

Leland DS, Paulus MP (2005) Increased risk-taking decision-making but not altered response to punishment in stimulant-using young adults. *Drug Alcohol Depend* 78: 83–90.

Levine B, Dawson D, Boutet I, Schwartz ML, Stuss DT (2000) Assessment of strategic self-regulation in traumatic brain injury: Its relationship to injury severity and psychosocial outcome. *Neuropsychology* 14: 491–500.

Lezak MD (2004) *Neuropsychological Assessment*, 4th edn. New York: Oxford University Press.

Li CS, Huang C, Yan P, Bhagwagar Z, Milivojevic V, Sinha R (2008) Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology* 33: 1798–1806.

Li CS, Sinha R (2008) Inhibitory control and emotional stress regulation: Neuroimaging evidence for frontal–limbic dysfunction in psycho-stimulant addiction. *Neurosci Biobehav Rev* 32: 581–597.

Loeber S, Duka T, Welzel H, et al. (2009) Impairment of cognitive abilities and decision making after chronic use of alcohol: The impact of multiple detoxifications. *Alcohol Alcohol* 44: 372–381.

López-Torrecillas F, Godoy JF, Pérez-García M, Godoy D, Sánchez-Barrera M (2001) Variables modulating stress and coping that discriminate drug consumers from low or not drug consumers. *Addict Behav* 25: 161–165.

Lubman DI, Yucel M, Pantelis C (2004) Addiction, a condition of compulsive behaviour? Neuroimaging and neuropsychological evidence of inhibitory dysregulation. *Addiction* 99: 1491–1502.

Lyoo K, Pollack MH, Silvery MM, et al. (2006) Prefrontal and temporal gray matter density decreases in opiate dependence. *Psychopharmacology* 184: 139–144.

Lyvers M, Yakimoff M (2003) Neuropsychological correlates of opioid dependence and withdrawal. *Addict Behav* 28: 605–611.

Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF (2007) Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence. *J Int Neuropsychol Soc* 13: 807–820.

Miyake A, Friedman NP, Emerson MJ, Witzky AH, Howerther A (2000) The unity and diversity of executive function and their contribution to complex frontal lobe tasks: A latent variable analysis. *Cogn Psychol* 41: 49–100.

Moeller FG, Hasan KM, Steinberg JL, et al. (2005) Reduced anterior corpus callosum white matter integrity is related to increased impulsivity and reduced discriminability in cocaine-dependent subjects: diffusion tensor imaging. *Neuropsychopharmacology* 30: 610–617.

Nestor L, Roberts G, Garavan H, Hester R (2008) Deficits in learning and memory: Parahippocampal hyperactivity and frontocortical hypoactivity in cannabis users. *NeuroImage* 40: 1328–1339.

Ornstein TJ, Iddon JL, Baldacchino AM, et al. (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. *Neuropsychopharmacology* 23: 113–126.

Passetti F, Clark L, Mehta MA, Joyce E, King M (2008) Neuropsychological predictors of clinical outcome in opiate addiction. *Drug Alcohol Depend* 94: 82–91.

Pau CWH, Lee TMC, Chan SF (2002) The impact of heroin on frontal executive functions. *Arch Clin Neuropsychol* 17: 663–670.

Paulus MP, Hozack N, Frank L, Brown GB, Schuckit MA (2003) Decision-making by methamphetamine-dependent subjects is associated with error-rate independent decrease in prefrontal and parietal activation. *Biol Psychiatry* 53: 65–74.

Paulus MP, Hozack N, Zauscher BE, et al. (2002) Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology* 26: 53–63.

Paulus MP, Tapert SF, Schuckit MA (2005) Neural activation patterns of methamphetamine-dependent subjects during decision-making predicts relapse. *Arch Gen Psychiatry* 62: 761–768.

Picton TW, Stuss DT, Alexander MP, Shallice T, Binns MA, Gillingham S (2007) Effects of focal frontal lesions on response inhibition. *Cereb Cortex* 17: 826–838.

Pitel AL, Rivier J, Beaunieux H, Vabret F, Desgranges B, Eustache F (2009) Changes in the episodic memory and executive functions of abstinent and relapsed. Alcoholics over a 6-month period. *Alcohol Clin Exp Res* 33: 490–498.

Robinson JE, Heaton RK, O'Malley SS (1999) Neuropsychological functioning in cocaine abusers with and without alcohol dependence. *J Int Neuropsychol Soc* 5: 10–19.

Roselli M, Ardila A (1996) Cognitive effects of cocaine and polydrug abuse. *J Clin Exp Neuropsychol* 18: 122–135.

Ruff RM (1996) *Ruff Figural Fluency Test: Professional Manual*. Lutz, FL: Psychological Assessment Resources.

Salthouse TA (2009) When does age-related cognitive decline begin? *Neurobiol Aging* 30: 507–514.

Schecklmann M, Ehlis AC, Plichta MM, Boutter HK, Mezger FG, Fallgatter AJ (2007) Altered frontal brain oxygenation in detoxified alcohol dependent patients with unaffected verbal fluency performance. *Psychiatry Res Neuroimaging* 156: 129–138.

Schoenbaum G, Saddoris MP, Ramus SJ, Shaham Y, Setlow B (2004) Cocaine-experienced rats exhibit learning deficits in a task sensitive to orbitofrontal cortex lesions. *Eur J Neurosci* 19: 1997–2002.

Sedó M, Levenson R, Leonard A (1995) Reading-free Stroop Interference Tests: automatic and effortful processing. In *Proceedings of the 17th Midyear Conference of the International Neuropsychological Society*, Angers, France.

Sedó M (2005) *Test de los Cinco Dígitos: Five Digit Test*. Madrid: TEA Ediciones.

Stalnaker TA, Roesch MR, Franz TM, Burke KA, Schoenbaum G (2006) Abnormal associative encoding in orbitofrontal neurons in cocaine-experienced rats during decision-making. *Eur J Neurosci* 24: 2643–2653.

Stalnaker TA, Takahashi Y, Roesch MR, Schoenbaum G (2009) Neural substrates of cognitive inflexibility after chronic cocaine exposure. *Neuropharmacology* 56: 63–72.

Streeter CC, Terhune DB, Whitfield TH, et al. (2008) Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology* 33: 827–836.

Stuss DT, Alexander MP (2007) Is there a dysexecutive syndrome? *Philos Trans R Soc Lond B Biol Sci* 29: 901–915.

Swan GE, Lessov-Schlaggar CN (2007) The effects of tobacco smoke and nicotine on cognition and the brain. *Neuropsychol Rev* 17: 259–273.

Tarter RE, Kirisci L, Mezzich A, et al. (2003) Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Am J Psychiatry* 160: 1078–1085.

Teichner G, Horner MD, Roitzsch JC, Herron J, Thevos A (2002) Substance abuse treatment outcomes for cognitively impaired and intact outpatients. *Addict Behav* 27: 751–763.

Troyer AK, Moscovitch M, Winocur G, Alexander MP, Stuss D (1998) Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia* 36: 499–504.

UNODC (2008) *United Nations World Drug Report 2008*. United Nations Office of Drugs and Crime.

Van der Elst W, Van Boxtel MPJ, Van Breukelen GJP, Jolles J (2006) The Stroop color-word test. Influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 13: 62–79.

Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI (2007a) The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug Alcohol Depend* 90: 2–11.

Verdejo-García A, Lawrence AJ, Clark L (2008) Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. *Neurosci Biobehav Rev* 32: 777–810.

Verdejo-García A, López Torrecillas F, Aguilar de Arcos F, Pérez García M (2005b) Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: A multiple regression analysis. *Addict Behav* 30: 89–101.

Verdejo-García A, López-Torrecillas F, Orozco C, Pérez-García M (2004) Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant and opioid abuse. *Neuropsychol Rev* 14: 1–41.

Verdejo-García A, Perales JC, Pérez-García M (2007c) Cognitive impulsivity in cocaine and heroin polysubstance abusers. *Addict Behav* 32: 950–966.

Verdejo-García A, Pérez-García M (2007) Profile of executive deficits in cocaine and heroin polysubstance users: common and differential effects on separate executive components. *Psychopharmacology* 190: 517–530.

Verdejo-García A, Rivas-Pérez C, Vilar-López R, Pérez García M (2007b) Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. *Drug Alcohol Depend* 86: 139–146.

Verdejo-Garcia A, Toribio C, Orozco K, Puente K, Pérez García M (2005a) Neuropsychological functioning in methadone

maintenance patients versus abstinent heroin abusers. *Drug Alcohol Depend* 78: 283–288.

Verhaeghen P, Cerella J (2002) Aging, executive control, and attention: a review of meta-analyses. *Neurosci Biobehav Rev* 26: 849–857.

Verrico CD, Jentsch JD, Roth RH, Taylor JR (2004) Repeated, intermittent Δ^9-tetrahydrocannabinol administration to rats impairs acquisition and performance of a test of visuospatial divided attention. *Neuropsychopharmacology* 29: 522–529.

Wadsworth EJK, Moss SC, Simpson SA, Smith AP (2006) Cannabis use, cognitive performance and mood in a sample of workers. *J Psychopharmacol* 20: 14–23.

Wechsler D (1997a) *Wechsler Adult Intelligence Scale*, 3rd edn.

Wechsler D (1997b) *Wechsler Memory scale*, 3rd edn.

Wendt PE, Risberg J (2001) Ethanol reduces rCFB activation of left dorsolateral prefrontal cortex during a verbal fluency task. *Brain Lang* 77: 197–215.

Whitlow CT, Liguori A, Livengood LB, Hart SL, Mussat-Whitlow BJ, Lamborn CM (2004) Long-term heavy marijuana users make costly decisions on a gambling task. *Drug Alcohol Depend* 76: 107–111.

Yang L, Sun ZS, Zhu YP (2007) Proteomic analysis of rat prefrontal cortex in three phases of morphine-induced conditioned place preference. *J Proteome Res* 6: 2239–2247.

Yücel M, Solowij N, Respondek C, et al. (2008) Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 65: 694–701.

Zakzanis KK (2001) Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effects size analyses for neuropsychological researchers. *Arch Clin Neuropsychol* 16: 653–677.

Zelazo PD, Carter A, Reznick JS, Frye D (1997) Early development of executive function: A problem-solving framework. *Rev Gen Psychol* 1: 198–226.

Anexo IV

Drug and Alcohol Dependence xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Impact of severity of drug use on discrete emotions recognition in polysubstance abusers

María José Fernández-Serrano[a], Óscar Lozano[b], Miguel Pérez-García[a,c], Antonio Verdejo-García[a,c,*]

[a] Dept. Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Granada, 18071 Granada, Spain
[b] Dept. Psicología, Universidad de Huelva, 21004 Huelva, Spain
[c] Institute of Neuroscience F. Olóriz, Universidad de Granada, 18071 Granada, Spain

ARTICLE INFO

Article history:
Received 7 May 2009
Received in revised form
26 November 2009
Accepted 1 December 2009
Available online xxx

Keywords:
Anger
Disgust
Fear
Sadness
Emotion recognition
Polysubstance use

ABSTRACT

Neuropsychological studies support the association between severity of drug intake and alterations in specific cognitive domains and neural systems, but there is disproportionately less research on the neuropsychology of emotional alterations associated with addiction. One of the key aspects of adaptive emotional functioning potentially relevant to addiction progression and treatment is the ability to recognize basic emotions in the faces of others. Therefore, the aims of this study were: (i) to examine facial emotion recognition in abstinent polysubstance abusers, and (ii) to explore the association between patterns of quantity and duration of use of several drugs co-abused (including alcohol, cannabis, cocaine, heroin and MDMA) and the ability to identify discrete facial emotional expressions portraying basic emotions. We compared accuracy of emotion recognition of facial expressions portraying six basic emotions (measured with the Ekman Faces Test) between polysubstance abusers (PSA, $n = 65$) and non-drug using comparison individuals (NDCI, $n = 30$), and used regression models to explore the association between quantity and duration of use of the different drugs co-abused and indices of recognition of each of the six emotions, while controlling for relevant socio-demographic and affect-related confounders. Results showed: (i) that PSA had significantly poorer recognition than NDCI for facial expressions of anger, disgust, fear and sadness; (ii) that measures of quantity and duration of drugs used significantly predicted poorer discrete emotions recognition: quantity of cocaine use predicted poorer anger recognition, and duration of cocaine use predicted both poorer anger and fear recognition. Severity of cocaine use also significantly predicted overall recognition accuracy.

1. Introduction

Addiction is a chronic relapsing disorder characterized by persistent brain alterations associated with cognitive, motivational and emotional alterations (Goldstein and Volkow, 2002; Verdejo-Garcia et al., 2004). Neuropsychological studies have demonstrated extensive mid- and long-term cognitive alterations in individuals with substance use disorders (see Ersche and Sahakian, 2007; Verdejo-Garcia et al., 2004 for reviews), but there is disproportionately less research on the neuropsychology of emotional alterations associated with addiction. One of the key aspects of adaptive emotional functioning is the ability to decode emotional cues and recognize emotions in the faces of others, especially in relation to the six basic emotions: anger, disgust, fear, happiness, sadness and surprise (Adolphs, 2002). Emotion recognition is relevant to addiction in several regards. On the one hand, emotion recognition is fundamental for prosocial behavior, normal socialization and interaction (Blair, 2003), which is typically impaired in addiction (Reay et al., 2006; Roselli and Ardila, 1996; Homer et al., 2008). Moreover, simulation theories argue that the emotional states of others are understood and recognized by generating similar states in oneself (Goldman and Sripada, 2005), and evidence supports the link between altered emotion recognition and parallel alterations in emotion experience and behavioral manifestations (Calder and Young, 2005). These notions are particularly relevant to addiction according to the somatic marker theory, which posits that substance addiction is associated with abnormal activation and integration of emotional states involved in the experience of subjective urges (e.g., craving) and in the guidance of decision-making (Verdejo-Garcia and Bechara, 2009). Furthermore, the neural substrates of emotion recognition overlap with neural systems strongly involved in the escalation and maintenance of addiction, including the orbitofrontal cortex, the cingulate gyrus, the insula, and the ventral striatum (Verdejo-Garcia and Bechara,

* Corresponding author at: Facultad de Psicología, Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Universidad de Granada, Campus de Cartuja S/N, 18071 Granada, Spain. Tel.: +34 958 242 948; fax: +34 958 243 749.
E-mail address: averdejo@ugr.es (A. Verdejo-García).

0376-8716/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2009.12.007

2009); and there is evidence of relative specificity in the neural systems supporting recognition of discrete emotions, with reliable and specific association between fear and the amygdala, disgust and the insula/basal ganglia, and anger and the lateral orbitofrontal cortex and the ventral striatum (Calder et al., 2001, 2004; Murphy et al., 2003). Therefore, it is reasonable to assume that drug use can be selectively associated with poorer recognition of discrete emotions as much as it is selectively associated with decreased functioning of particular cognitive and neural systems.

Available studies about the chronic (non-acute) deficits of discrete emotions recognition in addiction have mainly focused on alcohol dependence, and most studies have chosen to index the ability to estimate the intensity of the emotions displayed (but not accuracy of recognition). Studies on alcohol have shown that alcoholics tend to overestimate the intensity of the emotion displayed by facial expressions of happiness, anger and disgust (Foisy et al., 2007a; Kornreich et al., 2001; Townshend and Duka, 2003). Studies measuring recognition accuracy have shown that alcoholics have poorer recognition of expressions of sadness (Frigerio et al., 2002) and difficulties to discriminate anger and disgust (Townshend and Duka, 2003); although other studies have failed to find differences in emotion recognition accuracy between alcoholics and non-drug comparison individuals (Foisy et al., 2007b; Salloum et al., 2007). A comparison between alcohol and opiate dependents showed that alcoholics had overall poorer emotion recognition (across several emotions) than abstinent and methadone-maintained opiate dependents (Kornreich et al., 2003). A recent study comparing abstinent vs. methadone-maintained opiate users showed that methadone patients were overall slower but more accurate in the recognition of expressions of disgust; being accuracy positively correlated with lifetime use of methadone (Martin et al., 2006). Studies on cocaine and polysubstance psycho-stimulants abusers have shown relatively specific alterations in the recognition of expressions of fear (Kemmis et al., 2007; Verdejo-Garcia et al., 2007); however, the psycho-stimulant groups from both studies markedly differed on severity of drug exposure and patterns of other drugs co-abuse. Moreover, a more recent study did not find significant differences on emotion recognition between cocaine abusers and controls (Woicik et al., 2009). To our knowledge, no studies have been performed about the chronic effects of MDMA or cannabis use on emotion recognition, although there is suggestive evidence of acute and sub-acute effects of these drugs on facial emotional processing (Fusar-Poli et al., 2009; Hoshi et al., 2004). Overall, the evidence on chronic deficits of emotion recognition in addiction is scarce and has yielded considerably mixed results.

In addition, most studies have neglected the potential relevance of patterns of quantity and duration of drug use in relation to chronic emotion recognition deficits in the context of polysubstance abuse. Cognitive neuropsychological studies have successfully established an association between estimates of amount and duration of drug use and alterations in specific cognitive domains and neural systems (see Bolla et al., 1999, 2000, 2002, 2004; Fernández-Serrano et al., 2009; Goldstein et al., 2004; Verdejo-Garcia et al., 2005). Similarly, we expect that severity of use of different drugs can contribute to explain differential alterations in discrete emotions recognition, since all the brain areas involved in emotion recognition are related to the motivational brain circuitry implicated in addiction. Therefore, the aims of this study are: (i) to replicate previous findings showing poorer facial emotion recognition in polysubstance abusers (Verdejo-Garcia et al., 2007) using a larger sample and (ii) to explore the association between patterns of quantity and duration of use of several drugs co-abused (including alcohol, cannabis, cocaine, heroin and MDMA) and the ability to identify discrete facial emotional expressions portraying basic emotions in polysubstance abusers.

Table 1
Descriptive scores for the socio-demographic characteristics of polysubstance abusers (PSA) and non-drug using comparison individuals (NDCI).

Socio-demographic variables	PSA	NDCI	t/χ^2	p value
	Mean (SD)/ frequency	Mean (SD)/ frequency		
Age	31.78 (8.05)	26.40 (8.03)	3.03[a]	.003
Educational level (%)				
Primary	6.2	3.3		
Secondary	76.9	56.7	6.02[b]	.05
Superior	16.9	40		
Gender (%)				
Men	84.6	80	.312[b]	.58
Women	15.4	20		

[a] Value of Student's t.
[b] Value of Chi-square χ^2.

2. Methods

2.1. Participants

Sixty-five polysubstance abusers (PSA) aged 21–53 years (10 women), and 30 non-drug using comparison individuals (NDCI) aged 18–49 years (6 women), participated in this study; socio-demographic characteristics from both groups are displayed in Table 1. PSA and NDCI groups had similar distributions for gender and educational level but differed significantly on age; all these variables were explored in subsequent analyses. PSA were recruited during residential treatment at one therapeutic community ("Proyecto Hombre") in the city of Granada, Spain. This center provides psychological treatment and educational/occupational counseling in a controlled environment during an extended period of time. The PSA sample was composed of polysubstance users of several drugs, including cannabis, cocaine, heroin, alcohol, ecstasy (MDMA), amphetamines and benzodiazepines. Selection criteria for participants in the PSA group were: (i) meeting the DSM-IV criteria for substance dependence, (ii) absence of documented comorbid mood or personality disorders as assessed by clinical reports, (iii) absence of documented head injury or neurological disorders, (iv) not being currently enrolled in opioid substitution treatment or taking prescription drugs affecting Central Nervous System (CNS), and (v) minimum abstinence duration of 15 days before testing, although the mean duration of abstinence in the group was 33.10 weeks (SD = 12.38, range 12–80 weeks), so that it was possible to rule out alterations related to the acute or short term effects of the drugs used. Urine analyses for cannabis, benzodiazepines, cocaine, amphetamines, and heroin metabolites were conducted routinely at the treatment setting to confirm abstinence. NDCI were selected by means of local advertisements and snowball communication among adult people from the community. Selection criteria for these comparison participants were: (i) absence of current or past substance abuse, excluding past or current social drinking (less than ten drinks per week), (ii) absence of documented major psychiatric disorders, (iii) absence of documented head injury or neurological disorder, and (iv) not being on any medication affecting CNS. The mean amount of alcohol use in control participants was 8.85 units/month (SD = 20.66) and the mean duration of alcohol consumption was 6.70 years (SD = 7.29).

2.2. Instruments

2.2.1. Information on patterns of quantity and duration of drug use. Data regarding lifetime amount and duration of use of the different drugs was self-reported by participants and collected using the Interview for Research on Addictive Behavior (IRAB; Verdejo-Garcia et al., 2005). This interview provides an estimation of: (i) average lifetime monthly use of each substance (quantity per month) and (ii) total duration of use of each substance (duration in years). Descriptive scores for these variables in the present sample are presented in Table 2.

2.2.2. Test of emotion recognition: Ekman Faces Test (EFT). The Ekman Faces Test (EFT) is a computer task that assesses recognition of facial emotional expressions. The task uses stimuli from the Facial Expressions of Emotion: Stimuli and Tests (FEEST; Young et al., 2002). A series of 60 stimuli featuring faces portraying basic emotions were presented. Faces depicted expressions of anger, disgust, fear, happiness, sadness and surprise (6 emotions, 10 faces each). Photographs were posed by each of 10 models (six female, four male). Each face was presented on a computer monitor for a maximum of 5 s and individuals were asked to select one of the six expression labels (listed above) that best described the emotion expressed. The labels were visible throughout testing, thus minimizing working memory demands, and individuals were given as much time as they required to respond. No feedback was given regarding the appropriateness of their responses. For this study we were especially interested in measures of number of correct identifications for each of the six emotions displayed (discrete emotions recognition scores, ranging 0–10).

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007

Table 2
Descriptive scores for patterns of quantity and duration of drug use in the group of polysubstance abusers (PSA).

Substances used	Percentage users	Drug use variables	Mean	SD
Cannabis	53.1	Quantity (joints/month)	141.90	175.88
		Duration (years)	7.89	7.86
Cocaine	63.5	Quantity (g/month)	45.95	42.54
		Duration (years)	7.36	5.83
Heroin	24	Quantity (g/month)	9.60	23.17
		Duration (years)	1.67	3.95
Methadone	7.3	Quantity (mg/month)	112.64	557.47
		Duration (years)	0.17	0.80
Ecstasy	31.2	Quantity (pills/month)	11.76	22.63
		Duration (years)	1.70	3.92
Alcohol	87.5	Quantity (units/month)	552.21	473.31
		Duration (years)	11.06	7.48
Amphetamines	13.5	Quantity (g/month)	1.69	5.24
		Duration (years)	0.83	2.06
Benzodiazepines	9.8	Quantity (units/month)	13.07	40.80
		Duration (years)	0.66	2.90

We also obtained the sum score of total correct identifications (total recognition, ranging 0–60).

2.2.3. Apathy subscale from the Frontal Systems Behavioral Scale (Grace and Malloy, 2001). The full scale contains 46 items that assess behavioral problems linked to prefrontal systems dysfunction. The instrument is divided in three independent subscales: apathy (linked to anterior cingulate and medial frontal dysfunctions), disinhibition (linked to orbitofrontal dysfunction), and executive dysfunction (linked to dorsolateral prefrontal cortex dysfunction). For this study we only used the scores from the apathy subscale in order to control for possible effects of blunted affect and lack of initiative on emotion recognition. Factor analyses of the FrSBe in several neurological populations have supported the validity of these subscales (Stout et al., 2003). Furthermore, there is evidence in support of the reliability and utility of the FrSBe subscales in the detection of frontal behavioral symptoms in neuropsychiatric populations such as schizophrenia (Velligan et al., 2002), and substance use disorders (Verdejo-Garcia et al., 2006).

2.3. Procedure

Participants were assessed individually as part of a 3 h session aimed to thoroughly examine neuropsychological functioning in PSA. The duration of the EFT was on average approximately 10 min. All of the participants in the study were informed about the objectives, benefits, and possible inconveniences associated with the research protocol. Likewise, all the participants signed an informed consent form certifying their voluntary participation. The NDCI participants were paid €18 for their collaboration to ensure motivation; PSA were not compensated due to internal rules of the treatment program.

2.4. Data analysis

The main dependent variables (e.g., discrete emotions recognition) were not normally distributed; therefore, we conducted non-parametric analyses (Mann–Whitney *U* tests) to examine differences between PSA and NDCI on emotion recognition performance.

To address the main aim of the study, we first conducted non-parametric Spearman correlations between measures of quantity and duration of use of the different drugs (cannabis, cocaine, heroin, alcohol, ecstasy, amphetamines and benzodiazepines) and the discrete emotions recognition scores (anger, disgust, fear, happiness, sadness and surprise) in order to select relevant drug use variables to include in multivariate analyses (we selected those variables that were significantly correlated with emotion recognition). We also explored the correlations between other potentially confounding variables (i.e., sex, age, education, apathy) and the dependent variables. Next, we included the selected drug measures and confounding variables (all variables with significant correlations) as independent variables using Tobit regression models (Tobit, 1958); the dependent variables were the six discrete emotions recognition scales. Therefore, correlation analyses were conducted for exploratory purposes and thus non-corrected for multiple comparisons. On the other hand, we used Bonferroni adjustments to correct for multiple comparisons in multivariate Tobit regression models. The Tobit regression technique allowed us to counteract the influence of the non-normal distribution of the dependent variables that exhibited a ceiling effect. With this technique, the maximum score on the discrete emotions recognition scales can be handled as censored data (between 10.5% and 21% of data were right censured observations). Independent variables (quantity and duration of the different drugs) were categorized as dummy variables. Each of the independent variables was categorized into two sets of two variables. In the first set the first variable took a "1" value when participants had used the drug, and a "0" value when they had not used the drug. In the second set the first variable took a "1" value when participants had scores equal to or superior to the mean of the sample (indicating heavy quantity or duration of use), whereas the remaining scores took a "0" value. This approach allowed us to independently examine the influence of any use of each of the drugs, and of heavy (above the mean) use of each of the drugs. These four dummy coded variables were entered as predictors in the regression models conducted for each of the discrete emotion recognition scores and for the total recognition score. We conducted two separate models, one for quantity and one for duration of use of the different drugs. Model coefficients were estimated using maximum-likelihood methods. Variables with *p*-values greater 0.05 were then progressively eliminated, in a backward-step process. Nonetheless, because there were significant correlations between the drug use predictor variables to be included in the model we conducted a multicollinearity test using the analysis of variance inflation factors (VIF) for the independent variables. In all the models subsequently reported the predictor variables yielded VIF values lower to 10 (the threshold for detection of multicollinearity); the higher values were obtained in the regression model of duration of drugs used on anger recognition (values ranging 4.46–4.27). Therefore, we can rule out that multicollinearity problems are biasing the results obtained in the regression models.

3. Results

3.1. Comparisons between PSA and NDCI

Table 3 shows comparisons between discrete emotions recognition scores of PSA and NDCI. PSA showed significantly poorer recognition of expressions of anger ($U = 585$; $p < 0.01$), disgust ($U = 610$; $p < 0.01$), fear ($U = 591$; $p < 0.01$), sadness ($U = 645$;

Table 3
Comparison between polysubstance users (PSA) and non-drug using comparison individuals (NDCI) on emotion recognition performance.

Discrete emotions recognition scores	PSA mean (SD)	NDCI mean (SD)	Cohen's *d*
Anger	7.77 (1.69)	8.83 (1.44)	0.66*
Disgust	7.68 (1.70)	8.73 (1.36)	0.66*
Fear	6.37 (2.15)	7.80 (2.06)	0.67*
Happiness	9.86 (0.43)	9.87 (0.43)	0.023
Sadness	7.61 (1.83)	8.60 (1.38)	0.58*
Surprise	8.46 (1.66)	9.17 (1.02)	0.48
Total recognition score	47.75 (4.46)	53.00 (4.61)	1.16*

* Cohen's $d \geq 0.5$ indicating greater than medium effect sizes.

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007

Table 4
Spearman's correlations between drug use parameters (quantity and duration) and recognition of discrete emotions and total emotion recognition.

	Anger	Disgust	Fear	Happiness	Sadness	Surprise	Total
Cannabis quantity	−0.351**	−0.125	−0.229*	0.059	−0.207	−0.151	−0.341**
Cannabis duration	−0.246*	−0.170	−0.249*	0.099	−0.175	−0.156	−0.334**
Cocaine quantity	−0.319**	−0.224*	−0.268*	0.106	−0.334**	−0.079	−0.389**
Cocaine duration	−0.335**	−0.242*	−0.339**	0.111	−0.301**	−0.125	−0.461**
Heroin quantity	−0.239*	−0.116	−0.269*	0.166	−0.114	−0.189	−0.3**
Heroin duration	−0.229*	−0.123	−0.273*	0.155	−0.106	−0.131	−0.279*
Methadone quantity	−0.197	−0.161	−0.239*	0.093	−0.147	−0.246*	−0.316**
Methadone duration	−0.275*	−0.113	−0.206	0.086	−0.108	−0.186	−0.276*
Ecstasy quantity	−0.195	−0.125	−0.143	0.017	−0.197	−0.152	−0.219*
Ecstasy duration	−0.257*	−0.039	−0.058	−0.089	−0.099	−0.085	−0.123
Alcohol quantity	−0.248*	−0.245*	−0.344**	0.038	−0.211	−0.102	−0.414**
Alcohol duration	0.021	−0.127	−0.081	−0.053	−0.008	−0.084	−0.124
Amph quantity	−0.054	−0.043	−0.222*	−0.039	−0.009	0.009	−0.146
Amph duration	−0.062	−0.035	−0.182	−0.052	−0.031	0.014	−0.125
Bzd quantity	−0.103	0.009	−0.052	0.100	−0.119	−0.054	−0.099
Bzd duration	−0.101	−0.006	−0.056	0.100	−0.121	−0.046	−0.010

Note: Amph, amphetamines, Bzd, benzodiazepines.
* $p < 0.05$.
** $p < 0.01$.

Table 5
Tobit regression models using parameters of quantity of the different drugs used and confounding variables as independent variables and recognition of discrete emotions as dependent variables.

Emotions	Quantity of use	Coef	95% Coef interval	*p* value
Anger	Cocaine quantity	−1.555	(−2.557, −0.553)	0.003*
	Cons	9.324	(8.515, 10.133)	0.000
Fear	Alcohol quantity > Avg	−1.255	(−2.342, −0.167)	0.024
	Years of education	0.277	(0.075, 0.479)	0.08
	Cons	4.493	(2.193, 6.793)	0.000
Sadness	Years of education	0.245	(0.067, 0.422)	0.007
	Cons	5.545	(3.652, 7.439)	0.000
Total	Cocaine quantity	−4.04	(−6.213, −1.864)	0.000*
	Years of education	0.484	(0.079, 0.889)	0.020
	Apathy	−0.159	(−0.277, −0.041)	0.009
	Cons	51.356	(44.727, 57.986)	0.000

Note: Avg, average, Coef, coefficients, Cons, constant.
* Significant results after correction for multiple testing, resulting in a significance levels of $p = 0.05/14 = 0.0035$.

$p < 0.01$), and total recognition score ($U = 403$; $p < 0.01$). We found no significant differences for recognition of expressions of happiness and surprise.

3.2. Correlations

Table 4 shows the correlations between measures of quantity and duration of the drugs used and discrete emotions and total recognition scores. Cocaine was the substance used that showed a greater number of significant correlations with emotion recognition scores. Duration of alcohol and amphetamines use, and measures of quantity and duration of benzodiazepines use failed to show significant correlations with the emotions recognition scores. None of the drugs measures was significantly correlated with recognition of expressions of happiness. Those drug measures that showed significant correlations with the dependent variables were selected and included in subsequent multivariate regression models.

For potentially confounding variables, results showed that sex and age had non-significant correlations with the dependent variables. On the other hand, years of education were significantly associated with recognition scores for anger ($r = 0.247$; $p < 0.05$), disgust ($r = 0.256$; $p < 0.05$), fear ($r = 0.415$; $p < 0.01$), and total emotion recognition ($r = 0.378$; $p < 0.01$) when using the whole sample, and only with recognition scores for fear within the PSA group. In addition, apathy scores were not significantly correlated with the dependent variables when using the whole sample, but they were significantly correlated with recognition scores for fear ($r = -0.420$; $p < 0.05$), sadness ($r = -0.623$; $p < 0.01$) and total emotion recognition ($r = -0.465$; $p < 0.05$) within the PSA group. Therefore, we included years of education and apathy (but not sex or age) on subsequent regression models.

3.3. Tobit regression models

Tables 5 and 6 show the results of Tobit regression models. For quantity measures, regression models showed that quantity of cocaine use significantly predicted poorer recognition of expressions of anger; heavy (above the mean) quantity of alcohol use significantly predicted poorer recognition of expressions of fear although its effect turned non-significant after multiple testing corrections (Table 5). For duration measures, regression models showed that duration of cocaine use significantly predicted poorer recognition of expressions of anger and fear. Apathy scores and duration of ecstasy use were also significant predictors of the recognition of expressions of fear, although they did not survive Bonferroni adjustments for multiple comparisons (Table 6).

The results from the global model using total recognition as the dependent variable indicated that quantity and duration of cocaine use, apathy scores and years of education were the variables that impacted more significantly negatively on emotion recognition. However, cocaine use parameters were the only significant predictor variables after Bonferroni adjustments for multiple comparisons.

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007

Table 6
Tobit regression models using parameters of duration (years) of the different drugs used and confounding variables as independent variables and recognition of discrete emotions as dependent variables.

Emotions	Duration of use	Coef	95% Coef Interval	*p* value
Anger	Cocaine duration	−1.563	(−2.587, −0.539)	0.003*
	Cons	9.321	(8.513, 10.129)	0.000
Fear	Cocaine duration	−2.159	(−3.252, −1.066)	0.000*
	Ecstasy duration	−2.04	(−0.086, −3.994)	0.041
	Apathy	−0.075	(−0.135, −0.015)	0.015
	Cons	10.169	(8.162, 12.176)	0.000
Sadness	Years of education	0.245	(0.067, 0.422)	0.007
	Cons	5.545	(3.652, 7.439)	0.000
Total	Cocaine duration	−4.841	(−6.874, −2.808)	0.000*
	Apathy	−0.160	(−0.280, −0.039)	0.010
	Cons	56.984	(52.997, 60.969)	0.000

Note: Avg, average, Coef, coefficients, Cons, constant.
* Significant results after correction for multiple testing, resulting in a significance levels of $p = 0.05/14 = 0.0035$.

4. Discussion

The principal novel findings from this study are: (i) that mid- to long-term abstinent polysubstance abusers have poorer recognition of facial expressions portraying negative emotions, including anger, disgust, fear and sadness, but not positive or neutral emotions (e.g., happiness and surprise); (ii) that patterns of quantity and duration of use of certain drugs are able to predict emotion recognition performance in polysubstance abusers. Specifically, quantity of cocaine use was associated with poorer recognition of anger, and duration of cocaine use predicted poorer recognition of both anger and fear. Overall, lifetime quantity and duration of cocaine use were the variables that best predicted total emotion recognition.

The results of comparing emotion recognition performance between polysubstance abusers and controls were consistent with previous results showing altered recognition of negative emotions in abusers of different substances, including alcohol (Frigerio et al., 2002; Townshend and Duka, 2003), opiates (Kornreich et al., 2003), cocaine (Kemmis et al., 2007) and polysubstance users with a predominant history of alcohol (Foisy et al., 2005) or psychostimulants use (Verdejo-Garcia et al., 2007). With regard to our previous study, which showed that psycho-stimulants polysubstance abusers had prominent deficits in the recognition of fear, these results in a larger sample of similar clinical characteristics extend the range of discrete emotions affected by revealing additional deficits in anger, disgust and sadness recognition. However, our results stand in contrast with recent findings from Woicik et al. (2009), who did not find differences in emotion recognition between cocaine abusers and non-drug comparison individuals. As we show in our regression models, differences related to lifetime quantity or duration of cocaine and co-abused drugs usage (e.g., alcohol) may account for discrepancies between studies. Furthermore, the main thesis of the Woicik paper (i.e., that recent cocaine use could mask neuropsychological impairment) applies to their results on emotion recognition, since cocaine users with positive urine tests outperformed recently abstinent cocaine users with negative urine screens (75% vs. 59% of hits in the EFT, respectively). Moreover, our study provides additional evidence on the stability of emotion recognition deficits, which are still observable after an abstinence period ranging between 3 and 20 months, extending results from previous studies that described persistent emotion recognition deficits during mid-term abstinence (circa 3 months) in alcoholics (Foisy et al., 2007a). Interestingly, correlation analyses failed to detect a significant association between duration of abstinence and emotion recognition (data not shown), suggesting there is not straightforward improvement of emotion recognition across time of abstinence. This is particularly relevant because emotion recognition deficits are associated with the number of previous detoxifications (a proxy of previous treatment failures) (Townshend and Duka, 2003) and severity of interpersonal problems (Kornreich et al., 2002) in alcoholics, what may similarly apply to other substance use disorders groups. Therefore, emotion recognition deficits may constitute a risk factor for poorer treatment outcome and social readjustment in addiction.

The patterns of quantity and duration of use of the different drugs are able to significantly predict selective alterations in the recognition of discrete emotions, similar to previous findings on cognitive neuropsychological domains (Bolla et al., 1999, 2000, 2002, 2004; Fernández-Serrano et al., 2009; Goldstein et al., 2004; Verdejo-Garcia et al., 2005). Our results showed that lifetime quantity of cocaine use was negatively associated with recognition of facial expressions of anger. Converging evidence from neuropsychological and neuroimaging studies indicates that anger recognition relies importantly on the functioning of the lateral orbitofrontal cortex and the ventral striatum (Calder et al., 2004; Murphy et al., 2003). Anger recognition is also selectively modulated by dopamine functioning; disruption of the recognition of anger expressions has been observed after acute administration of a D2 receptor antagonist (Lawrence et al., 2002), and during withdrawal from dopamine replacement therapy in Parkinson disease patients (Lawrence et al., 2007). In view of this evidence, it has been proposed that anger recognition is encompassed within a broader neural system mainly involved in incentive motivation and reward pursuit (Lawrence et al., 2007). Accordingly, the neural and pharmacological systems that support anger recognition overlap with the persistent neuroadaptations that characterize psycho-stimulant addiction (Fuchs et al., 2004; Jentsch and Taylor, 1999; Robinson and Berridge, 2003). Furthermore, the association between cocaine use and anger recognition is clinically relevant in light of comparative research showing that the same systems involved in coding discrete emotions are implicated in the experience and behavioral responses related to these emotions (Calder and Young, 2005). Accordingly, a previous study in cocaine abusers found significant associations between self-reported symptoms of anger and decreased lateral orbitofrontal cortex metabolism (Goldstein et al., 2005). Furthermore, both cue- and stress-induced craving can specifically increase symptoms of anger and sadness in abstinent cocaine abusers but not social drinkers (Fox et al., 2008).

In addition, duration of cocaine use significantly predicted poorer fear recognition. These results partly replicate our previous finding of defective fear recognition in psycho-stimulant polysubstance users (Verdejo-Garcia et al., 2007), and the results of

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007

a previous study showing that regular cocaine use was specifically associated with poorer fear recognition (Kemmis et al., 2007). Nonetheless, it is worth noting that regression models also showed a trend to significant prediction of heavy quantity of use of alcohol and duration of ecstasy use on fear recognition. The ability to recognize fear has been selectively associated with the amygdala, and previous studies have revealed decreased amygdala volumes in both cocaine users (Makris et al., 2004) and alcohol users (Fein et al., 2006); in fact, a recent study showed that decreased amygdala volumes are related to greater subjective craving and higher risk of relapse in alcoholics (Wrase et al., 2008). Moreover, alcoholic individuals have a selectively blunted startle response to negatively but not positively valenced stimuli (Miranda et al., 2003), similar to amygdala lesioned patients (Angrilli et al., 1996), and reflecting insensitivity to threatening stimuli and impaired fear conditioning. Less specific startle reflex alterations have also been observed in abstinent cocaine users (Efferen et al., 2000), but animal studies have demonstrated that cocaine administration can impair amygdala-dependent fear conditioning (Burke et al., 2006; Wood et al., 2007).

It is worth noting that other socio-demographic and affect-related variables were also relevant predictors of both specific and global indices of emotion recognition although neither of them survived multiple testing corrections. More years of education were correlated with better recognition of expressions of sadness and overall better emotion recognition accuracy. Correlation analyses indicated that this pattern was mainly driven by the scores of the control group, and therefore this effect should be further explored in future research with clinical populations. In addition, apathy scores showed a trend to predict poorer recognition of fear and total emotion recognition. Although regression models showed that only cocaine use parameters were significantly associated with emotion recognition, the non-significant trends suggest that blunted affect and lack of initiative (proposed to relate to anterior cingulate cortex functioning) may also play a role in explaining the poorer ability of PSA to decode and recognize basic emotions in others' faces. It is also reasonable to expect that other affect-related variables (e.g., depression, irritability or alexythimia) can importantly modulate emotion recognition in substance abusers but we could not test this effect in the present study because we did not included specific measures of these constructs. Nonetheless, the potential contribution of depression could work to increase (but not to decrease) recognition of negative emotions; studies in clinical and high risk depression groups have revealed that these individuals display increased sensitivity to negative emotions measured by behavioral and electrophysiological indices, coupled with increased negative emotion-induced activation of the amygdala (Leppänen, 2006). Similarly, previous studies have failed to detect a significant influence of alexythimia on emotion recognition in substance abusers (Mann et al., 1995) although it has a significant effect on emotion recognition in healthy controls (Lane et al., 2000). The differential and combined contribution of these affect-related variables should be further explored by future studies.

We should note that our study have worth mentioning limitations, including the mixed pattern of polysubstance use that characterized the sample, the fact that we used a very selective, perhaps not entirely "normal" drug-free comparison group (with absence of drug use and minimal alcohol exposure—less than 9 units per month), and the use of only one index of emotion processing. The first limitation just reflects the typical pattern of use of individuals that demand and enter addiction treatment. Furthermore, we have attempted to address this polysubstance use pattern by means of regression models that targeted the selective influence of different substances while controlling for collinearity effects. A related issue is that that some drugs were rather infrequently used (methadone, amphetamine, benzodiazepines) and that subsequently the power of the analyses for the different drugs of abuse might be rather different and, therefore, these differences in frequency might be partly responsible for the differences in significant association between the various drug variables and emotional face recognition variables. Although this issue may have impacted the explanatory power of infrequently used variables it did not seem to affect the main results obtained for relatively frequently used drugs; for example, cannabis was the one of the most ubiquitously used drug but failed to predict emotion recognition, whereas MDMA, comparatively less frequently used, showed a trend to significantly predict fear recognition. With respect to the composition of the control group, our aim was to minimize any effect of drug exposure on emotion recognition in our comparison probands. However, we acknowledge the need to extend these findings by using other clinical comparison groups with mild patterns of alcohol and drug use or with emotion-related alterations (e.g., depression, dysthimia). These other comparison groups could improve our knowledge on the specificity of emotion recognition alterations in clinical groups of PSA. The latter limitation should be addressed in future studies using more comprehensive assessment of different emotion perception and experience modalities. In this regard, a key unresolved issue is that of if these deficits on emotion recognition have a neat parallel on emotion experience and behavioral symptoms. With regard to emotional experience, previous results from our lab indicate that polysubstance abusers have significant difficulties to experience arousal in response to negatively valenced images (Aguilar de Arcos et al., 2005). For behavioral responses, Lawrence et al. (2007) found that disruption of anger processing in Parkinson disease patients was linked to reduced levels of exploratory excitability, and in accordance, correlation and regression tests in our sample showed that both anger and fear recognition scores were linked to apathy symptoms measured by the Frontal Systems Behavioral Scale.

In spite of the above mentioned limitations these results have both important theoretical and clinical implications. The alterations of emotion perception in polysubstance abusers fit in with the formulations of the somatic marker theory (Verdejo-Garcia and Bechara, 2009), which posits a key role of emotion regulation in addiction. Furthermore, deficits of emotion recognition can be tightly linked to the clinical functioning and risk of relapse of substance abusers. Alterations in the recognition of anger and sadness are related to clinical symptoms of apathy, depression, aggression and hostility, which are enhanced during craving and serve as a proxy of relapse (Dodge et al., 2005). Similarly, alterations of fear processing can impair adequate categorization and recognition of risky scenarios (Redish et al., 2008), one of the main targets of relapse prevention treatment (Marlatt and Gordon, 1985). Moreover, alterations in disgust recognition can strongly bias interpretation of interoceptive signals of anxiety and discomfort (Calder et al., 2001), thus promoting automatic behaviors aimed to achieve immediate relieve, a mechanism that has been implicated in the severity of obsessive-compulsive disorder (Sprengelmeyer, 2007). Finally, overall defective emotion recognition has been proposed to affect adaptive decision-making (Verdejo-Garcia et al., 2007), a reliable marker of drug relapse (Passetti et al., 2008; Paulus et al., 2005).

Role of funding source

Funding for this study was provided by Spanish MICINN, under the FPU national plan (grant ref. AP 2005-1411) and SEJ 2006-08278, and with funds from the Junta de Andalucía from P07.HUM 03089; these sources had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007

Contributors

Authors Verdejo-García, Fernández-Serrano and Pérez-García designed the study and wrote the protocol. Authors Lozano and Verdejo-García undertook the statistical analysis, and authors Fernández-Serrano and Verdejo-García wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

References

Adolphs, R., 2002. Neural systems for recognizing emotion. Curr. Opin. Neurobiol. 12, 169–177.
Aguilar de Arcos, F., Verdejo-Garcia, A., Peralta-Ramirez, M.I., Sanchez-Barrera, M., Perez-Garcia, M., 2005. Experience of emotions in substance abusers exposed to images containing neutral, positive, and negative affective stimuli. Drug Alcohol Depend. 78, 159–167.
Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G., di Paola, F., 1996. Startle reflex and emotion modulation impairment after a right amygdala lesion. Brain 119 (Pt 6), 1991–2000.
Blair, R.J., 2003. Facial expressions, their communicatory functions and neuro-cognitive substrates. Philos. Trans. R. Soc. Lond. B Biol. Sci. 358, 561–572.
Bolla, K.I., Rothman, R., Cadet, J.L., 1999. Dose-related neurobehavioral effects of chronic cocaine use. J. Neuropsychiatry Clin. Neurosci. 11, 361–369.
Bolla, K.I., Funderburk, F.R., Cadet, J.L., 2000. Differential effects of cocaine and cocaine alcohol on neurocognitive performance. Neurology 54, 2285–2292.
Bolla, K.I., Brown, K., Eldreth, D., Tate, K., Cadet, J.L., 2002. Dose-related neurocognitive effects of marijuana use. Neurology 59, 1337–1343.
Bolla, K., Ernst, M., Kiehl, K., Mouratidis, M., Eldreth, D., Contoreggi, C., Matochik, J., Kurian, V., Cadet, J., Kimes, A., Funderburk, F., London, E., 2004. Prefrontal cortical dysfunction in abstinent cocaine abusers. J. Neuropsychiatry Clin. Neurosci. 16, 456–464.
Burke, K.A., Franz, T.M., Gugsa, N., Schoenbaum, G., 2006. Prior cocaine exposure disrupts extinction of fear conditioning. Learn. Mem. 13, 416–421.
Calder, A.J., Keane, J., Lawrence, A.D., Manes, F., 2004. Impaired recognition of anger following damage to the ventral striatum. Brain 127, 1958–1969.
Calder, A.J., Young, A.W., 2005. Understanding the recognition of facial identity and facial expression. Nat. Rev. Neurosci. 6, 641–651.
Calder, A.J., Lawrence, A.D., Young, A.W., 2001. Neuropsychology of fear and loathing. Nat. Rev. Neurosci. 2, 352–363.
Dodge, R., Sindelar, J., Sinha, R., 2005. The role of depression symptoms in predicting drug abstinence in outpatient substance abuse treatment. J. Subst. Abuse Treat. 28, 189–196.
Efferen, T.R., Duncan, E.J., Szilagyi, S., Chakravorty, S., Adams, J.U., Gonzenbach, S., Angrist, B., Butler, P.D., Rotrosen, J., 2000. Diminished acoustic startle in chronic cocaine users. Neuropsychopharmacology 22, 89–96.
Ersche, K.D., Sahakian, B.J., 2007. The neuropsychology of amphetamine and opiate dependence: implications for treatment. Neuropsychol. Rev. 17, 317–336.
Fein, G., Torres, J., Price, L.J., Di Sclafani, V., 2006. Cognitive performance in long-term abstinent alcoholic individuals. Alcohol. Clin. Exp. Res. 30, 1538–1544.
Fernández-Serrano, M.J., Pérez-García, M., Schmidt Río-Valle, J., Verdejo-García, A., 2009. Neuropsychological consequences of alcohol and drug abuse on different components of executive functions. J Psychopharmacol, in press, doi:10.1177/0269881109349841.
Foisy, M.L., Philippot, P., Verbanck, P., Pelc, I., van der Straten, G., Kornreich, C., 2005. Emotional facial expression decoding impairment in persons dependent on multiple substances: impact of a history of alcohol dependence. J. Stud. Alcohol 66, 673–681.
Foisy, M.L., Kornreich, C., Fobe, A., D'Hondt, L., Pelc, I., Hanak, C., Verbanck, P., Philippot, P., 2007a. Impaired emotional facial expression recognition in alcohol dependence: do these deficits persist with midterm abstinence? Alcohol. Clin. Exp. Res. 31, 404–410.
Foisy, M.L., Kornreich, C., Petiau, C., Parez, A., Hanak, C., Verbanck, P., Pelc, I., Philippot, P., 2007b. Impaired emotional facial expression recognition in alcoholics: are these deficits specific to emotional cues? Psychiatry Res. 150, 33–41.
Fox, H.C., Hong, K.I., Siedlarz, K., Sinha, R., 2008. Enhanced sensitivity to stress and drug/alcohol craving in abstinent cocaine-dependent individuals compared to social drinkers. Neuropsychopharmacology 33, 796–805.
Frigerio, E., Burt, D.M., Montagne, B., Murray, L.K., Perrett, D.I., 2002. Facial affect perception in alcoholics. Psychiatry Res. 113, 161–171.
Fuchs, R.A., Evans, K.A., Parker, M.P., See, R.E., 2004. Differential involvement of orbitofrontal cortex subregions in conditioned cue-induced and cocaine-primed reinstatement of cocaine seeking in rats. J. Neurosci. 24, 6600–6610.
Fusar-Poli, P., Landi, P., O'Connor, C., 2009. Neurophysiological response to emotional faces with increasing intensity of fear: a skin conductance response study. J. Clin. Neurosci. 16 (7), 981–982.
Goldman, A.I., Sripada, C.S., 2005. Simulationist models of face-based emotion recognition. Cognition 94, 193–213.
Goldstein, R.Z., Volkow, N.D., 2002. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am. J. Psychiatry 159, 1642–1652.
Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G.J., Fowler, J.S., Volkow, N.D., 2004. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 42, 1447–1458.
Goldstein, R.Z., Alia-Klein, N., Leskovjan, A.C., Fowler, J.S., Wang, G.J., Gur, R.C., Hitzemann, R., Volkow, N.D., 2005. Anger and depression in cocaine addiction: association with the orbitofrontal cortex. Psychiatry Res. 138, 13–22.
Grace, J., Malloy, P.F., 2001. FrSBe. Frontal Systems Behavior Scale. Psychological Assessment Resources Inc., Lutz, FL.
Homer, B.D., Solomon, T.M., Moeller, R.W., Mascia, A., DeRaleau, L., Halkitis, P.N., 2008. Methamphetamine abuse and impairment of social functioning: a review of the underlying neurophysiological causes and behavioral implications. Psychol. Bull. 134, 301–310.
Hoshi, R., Bisla, J., Curran, H.V., 2004. The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expressions: preliminary findings. Drug Alcohol Depend. 76, 297–304.
Jentsch, J.D., Taylor, J.R., 1999. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology (Berl.) 146, 373–390.
Kemmis, L., Hall, J.K., Kingston, R., Morgan, M.J., 2007. Impaired fear recognition in regular recreational cocaine users. Psychopharmacology (Berl.) 194, 151–159.
Kornreich, C., Blairy, S., Philippot, P., Hess, U., Noel, X., Streel, E., Le Bon, O., Dan, B., Pelc, I., Verbanck, P., 2001. Deficits in recognition of emotional facial expression are still present in alcoholics after mid- to long-term abstinence. J. Stud. Alcohol 62, 533–542.
Kornreich, C., Philippot, P., Foisy, M.L., Blairy, S., Raynaud, E., Dan, B., Hess, U., Noel, X., Pelc, I., Verbanck, P., 2002. Impaired emotional facial expression recognition is associated with interpersonal problems in alcoholism. Alcohol Alcohol. 37, 394–400.
Kornreich, C., Foisy, M.L., Philippot, P., Dan, B., Tecco, J., Noel, X., Hess, U., Pelc, I., Verbanck, P., 2003. Impaired emotional facial expression recognition in alcoholics, opiate dependence subjects, methadone maintained subjects and mixed alcohol-opiate antecedents subjects compared with normal controls. Psychiatry Res. 119, 251–260.
Lane, R.D., Sechrest, L., Riedel, R., Shapiro, D.E., Kaszniak, A.W., 2000. Pervasive emotion recognition deficit common to alexythimia and the repressive coping style. Psychosom. Med. 62, 492–501.
Lawrence, A.D., Calder, A.J., McGowan, S.W., Grasby, P.M., 2002. Selective disruption of the recognition of facial expressions of anger. Neuroreport 13, 881–884.
Lawrence, A.D., Goerendt, I.K., Brooks, D.J., 2007. Impaired recognition of facial expressions of anger in Parkinson's disease patients acutely withdrawn from dopamine replacement therapy. Neuropsychologia 45, 65–74.
Leppänen, J.M., 2006. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. Curr. Opin. Psychiatry 19, 34–39.
Mann, L.S., Wise, T.N., Trinidad, A., Kohanski, R., 1995. Alexythimia, affect recognition, and five factors of personality in substance abusers. Percept. Motor Skills 81, 35–40.
Makris, N., Gasic, G.P., Seidman, L.J., Goldstein, J.M., Gastfriend, D.R., Elman, I., Albaugh, M.D., Hodge, S.M., Ziegler, D.A., Sheahan, F.S., Caviness Jr., V.S., Tsuang, M.T., Kennedy, D.N., Hyman, S.E., Rosen, B.R., Breiter, H.C., 2004. Decreased absolute amygdala volume in cocaine addicts. Neuron 44, 729–740.
Marlatt, G.A., Gordon, J.R. (Eds.), 1985. Relapse Prevention: Maintenance Strategies in Addictive Behavior Change. Guilford, New York.
Martin, L., Clair, J., Davis, P., O'Ryan, D., Hoshi, R., Curran, H.V., 2006. Enhanced recognition of facial expressions of disgust in opiate users receiving maintenance treatment. Addiction 101, 1598–1605.
Miranda Jr., R., Meyerson, L.A., Myers, R.R., Lovallo, W.R., 2003. Altered affective modulation of the startle reflex in alcoholics with antisocial personality disorder. Alcohol. Clin. Exp. Res. 27, 1901–1911.
Murphy, F.C., Nimmo-Smith, I., Lawrence, A.D., 2003. Functional neuroanatomy of emotions: a meta-analysis. Cogn. Affect. Behav. Neurosci. 3, 207–233.
Passetti, F., Clark, L., Mehta, M.A., Joyce, E., King, M., 2008. Neuropsychological predictors of clinical outcome in opiate addiction. Drug Alcohol Depend. 94, 82–91.
Paulus, M.P., Tapert, S.F., Schuckit, M.A., 2005. Neural activation patterns of methamphetamine-dependent subjects during decision-making predict relapse. Arch. Gen. Psychiatry 62, 761–768.
Reay, J.L., Hamilton, C., Kennedy, D.O., Scholey, A.B., 2006. MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgement processes. J. Psychopharmacol. 20, 385–388.
Redish, A.D., Jensen, S., Johnson, A., 2008. A unified framework for addiction: vulnerabilities in the decision process. Behav. Brain Sci. 31, 415–437, discussion 437–487.
Robinson, T.E., Berridge, K.C., 2003. Addiction. Annu. Rev. Psychol. 54, 25–53.
Roselli, M., Ardila, A., 1996. Cognitive effects of cocaine and polydrug abuse. J. Clin. Exp. Neuropsychol. 18, 122–135.
Salloum, J.B., Ramchandani, V.A., Bodurka, J., Rawlings, R., Momenan, R., George, D., Hommer, D.W., 2007. Blunted rostral anterior cingulate response during a simplified decoding task of negative emotional facial expressions in alcoholic patients. Alcohol. Clin. Exp. Res. 31, 1490–1504.
Sprengelmeyer, R., 2007. The neurology of disgust. Brain 130, 1715–1717.

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007

Stout, J.C., Ready, R.E., Grace, J., Malloy, P.F., Paulsen, J.S., 2003. Factor analysis of the Frontal Systems Behavior Scale (FrSBe). Assessment 10, 79–85.
Tobit, J., 1958. Estimation of relationship for limited dependent variables. Econometrica 26 (1), 24–36.
Townshend, J.M., Duka, T., 2003. Mixed emotions: alcoholics' impairments in the recognition of specific emotional facial expressions. Neuropsychologia 41, 773–782.
Velligan, D.I., Ritch, J.L., Sui, D., DiCocco, M., Huntzinger, C.D., 2002. Frontal systems behavior scale in schizophrenia: relationships with psychiatric symptomatology, cognition and adaptive function. Psychiatry Res. 113, 227–236.
Verdejo-Garcia, A., Lopez-Torrecillas, F., Gimenez, C.O., Perez-Garcia, M., 2004. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. Neuropsychol. Rev. 14, 1–41.
Verdejo-Garcia, A.J., Lopez-Torrecillas, F., Aguilar de Arcos, F., Perez-Garcia, M., 2005. Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict. Behav. 30, 89–101.
Verdejo-Garcia, A., Rivas-Perez, C., Lopez-Torrecillas, F., Perez-Garcia, M., 2006. Differential impact of severity of drug use on frontal behavioral symptoms. Addict. Behav. 31, 1373–1382.
Verdejo-Garcia, A., Rivas-Perez, C., Vilar-Lopez, R., Perez-Garcia, M., 2007. Strategic self-regulation, decision-making and emotion processing in poly-substance abusers in their first year of abstinence. Drug Alcohol Depend. 86, 139–146.
Verdejo-Garcia, A., Bechara, A., 2009. A somatic marker theory of addiction. Neuropharmacology 56 (Suppl. 1), 48–62.
Wood, S.C., Fay, J., Sage, J.R., Anagnostaras, S.G., 2007. Cocaine and Pavlovian fear conditioning: dose-effect analysis. Behav Brain Res. 176, 244–250.
Woicik, P.A., Moeller, S.J., Alia-Klein, N., Maloney, T., Lukasik, T.M., Yeliosof, O., Wang, G.J., Volkow, N.D., Goldstein, R.Z., 2009. The neuropsychology of cocaine addiction: recent cocaine use masks impairment. Neuropsychopharmacology 34, 1112–1122.
Wrase, J., Makris, N., Braus, D.F., Mann, K., Smolka, M.N., Kennedy, D.N., Caviness, V.S., Hodge, S.M., Tang, L., Albaugh, M., Ziegler, D.A., Davis, O.C., Kissling, C., Schumann, G., Breiter, H.C., Heinz, A., 2008. Amygdala volume associated with alcohol abuse relapse and craving. Am. J. Psychiatry 165, 1179–1184.
Young, A.W., Perrett, D.I., Calder, A.J., Sprengelmeyer, R., Ekman, P., 2002. Facial Expressions of Emotion: Stimuli and Tests (FEEST). Thames Valley Test Company, Bury, St. Edmunds.

Please cite this article in press as: Fernández-Serrano, M.J., et al., Impact of severity of drug use on discrete emotions recognition in polysubstance abusers. Drug Alcohol Depend. (2010), doi:10.1016/j.drugalcdep.2009.12.007