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COMPLICACIONES NEUROPSICOLÓGICAS ASOCIADAS A LA COMORBILIDAD ENTRE TRASTORNOS DE PERSONALIDAD Y CONSUMO DE COCAÍNA

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EL HOMBRE QUE SE LEVANTA ES AÚN

MÁS FUERTE QUE EL QUE NO HA CAÍDO

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ÍNDICE

ÍNDICE

PARTE I –MARCO CONCEPTUAL

CAPÍTULO 1: CONCOMITANCIA ENTRE CONSUMO DE COCAÍNA Y TRASTORNOS DE LA PERSONALIDAD

1.1. Introducción: Relevancia de la comorbilidad entre trastornos por uso de sustancias y trastornos de personalidad.

Diversos estudios epidemiológicos han puesto de manifiesto la alta comorbilidad entre los trastornos por uso de sustancias y otros trastornos psicopatológicos del Eje I del Manual Diagnóstico y Estadístico para los Trastornos Mentales (DSM-IV), destacando entre los más prevalentes los trastornos del estado de ánimo y los trastornos de ansiedad (Herrero et al., 2008). No obstante, la co-existencia de estos trastornos está en numerosas ocasiones vinculada a los efectos directos o residuales de las drogas de abuso sobre el sistema nervioso central, por lo que se ha distinguido entre trastornos independientes (que anteceden, se solapan o no están directamente relacionados con los efectos del consumo) vs. inducidos (los directamente relacionados con los efectos del consumo) (Torrens et al., 2011); por ejemplo, con frecuencia se describen trastornos del estado de ánimo o psicosis inducidos por el efecto de sustancias como el cannabis o la cocaína (Large et al., 2011; Torrens et al., 2004).

En cambio, también existe un alto grado de solapamiento entre los trastornos por uso de sustancias y trastornos psicopatológicos del Eje II, los trastornos de personalidad. El interés añadido de la co-existencia entre los trastornos por uso de sustancias y estos trastornos de la personalidad viene dado por la presencia de varios factores que son indicativos de una etiopatogenia común entre ambos tipos de trastornos. En primer lugar, si analizamos su curso epidemiológico, observamos que ambos emergen y se desarrollan dentro de los límites del periodo evolutivo correspondiente a la adolescencia (entre los 13 y los 20 años); mientras que los trastornos del Eje I pueden comenzar antes (p.e., trastornos de ansiedad, esquizofrenia) o después (p.e., trastornos del estado de ánimo) de este periodo (Paus et al., 2008). En segundo lugar, a diferencia de lo que

habitualmente ocurre con los trastornos del Eje I, las alteraciones de la personalidad normalmente preceden el inicio del consumo (Nees et al., 2011). Finalmente, la comorbilidad entre ambos tipos de trastornos está asociada con una persistencia significativamente superior de los problemas de consumo a lo largo del tiempo, un fenómeno congruente con la existencia de rasgos estables compartidos por ambas patologías (Fenton et al., 2011).

Teniendo en cuenta que la adolescencia es un intenso periodo neuromadurativo, caracterizado por el desarrollo progresivo y la consolidación de los sistemas cerebrales implicados en la motivación, el control ejecutivo y la cognición social (una extensa red frontal-parietal-límbica-estriada), es muy probable que la etiopatogenia común de ambos trastornos descanse en estos sistemas neurobiológicos (Paus et al., 2008). Las características neuropsicológicas y psicosociales que experimentan un mayor ajuste en relación con la maduración de estos sistemas fronto-parietales-límbico-estriados son el control inhibitorio, la regulación emocional y la toma de decisiones en contextos socio-afectivos (Schneider et al., 2011; Shaw et al., 2011; Whittle et al., 2006). Por tanto, estas características deberían co-existir en los trastornos por uso de sustancias y los trastornos de personalidad. Por otro lado, la evidencia neurocientífica indica que las diferencias individuales en estas características están estrechamente vinculadas con variaciones polimórficas en genes relacionados con el funcionamiento de los sistemas neurobiológicos citados (Hyde et al., 2011), por lo que ambos tipos de trastornos deberían presentar vulnerabilidades genéticas compartidas y relacionadas con la función de estos sistemas (Loth et al., 2012). Parece claro que un mejor conocimiento de estos factores puede contribuir a entender, prevenir y abordar mejor la co-existencia entre trastornos por uso de sustancias y trastornos de personalidad. El objetivo de este

apartado es revisar brevemente la relevancia de estos factores en la comorbilidad entre los trastornos por uso de cocaína y los trastornos de personalidad límite, antisocial/psicopático y obsesivo compulsivo, que suelen ser los más prevalentes entre este perfil de consumidores.

1.2. Características neuropsicológicas, neurobiológicas y genéticas compartidas por los trastornos por uso de cocaína y los trastornos de personalidad.

De acuerdo con las propuestas formuladas con objeto de la próxima (quinta) edición del Manual Diagnóstico y Estadístico para los Trastornos Mentales (APA, 2010) los trastornos de personalidad reflejarían la falta de capacidad para desarrollar un sentido de identidad propia (con déficits en el autoconcepto y la autodirección) y de establecer relaciones interpersonales adaptativas en el contexto de las normas culturales del individuo y de las expectativas que éstas generan. Estas dificultades generarían alteraciones específicas en características psicológicas claves para la adaptabilidad al medio, como la empatía o la intimidad. Estas dificultades son estables en el tiempo y de origen temprano (APA, 2010). La actual estructura categorial de los trastornos de personalidad, recogida en las versiones más recientes del Manual, daría paso a una clasificación dimensional de los mismos. Se prescindiría de los clústeres (A, B y C) como método de agrupación y se conservarían sólo seis trastornos de personalidad; el esquizotípico, antisocial/psicopático, límite, narcisista, evitativo y obsesivo compulsivo, definidos a partir de la predominancia de uno o varios rasgos dimensionales. Por tanto, la nueva clasificación delimitaría la entidad de los distintos trastornos en función de la presencia e intensidad de uno o más de los siguientes rasgos: afectividad negativa, desapego/introversión, antagonismo, desinhibición, compulsividad y psicoticismo/

esquizotipia. Asimismo a cada dominio le corresponderían distintas facetas o características descriptivas, tales como labilidad emocional, retraimiento social, insensibilidad, impulsividad, perfeccionismo, percepciones inusuales, etc (APA, 2010). Así pues, para ejemplificar lo descrito anteriormente, el trastorno límite de la personalidad podría tener asociados los siguientes rasgos y facetas: afectividad negativa y labilidad emocional, antagonismo y hostilidad o desinhibición e impulsividad.

Desde esta nueva aproximación dimensional, algunos de los rasgos, facetas y síntomas característicos en los trastornos de personalidad se solapan con déficits en dimensiones o componentes específicos de las funciones ejecutivas. Las funciones ejecutivas son un conjunto de habilidades encargadas de la generación y supervisión de conductas dirigidas a metas socialmente adaptativas e incluyen componentes específicos como la inhibición de respuestas/pensamientos/emociones inadecuados al contexto, la reversión de aprendizajes cognitivos o afectivos inapropiados y la toma de decisiones adaptativas (Verdejo-García y Bechara, 2010). Todos estos componentes ejecutivos, que dependen del funcionamiento de circuitos neuroanatómicos relativamente disociables (Robbins y Roberts, 2007), están severamente afectados en consumidores de cocaína (Fernández-Serrano, 2010). Paralelamente, los trastornos de personalidad que presentan mayor prevalencia en consumidores de cocaína son los trastornos límite, antisocial y obsesivo compulsivo (Herrero et al., 2008; Martínez-González y Trujillo-Mendoza, 2003), caracterizados predominantemente por los problemas de emocionalidad negativa y desinhibición, toma de decisiones y flexibilidad respectivamente (Ruocco et al., 2009). Por tanto, existe una importante correspondencia entre los rasgos y facetas que definen clínicamente los trastornos y los déficits neuropsicológicos que presentan.

No obstante, como se propone en relación con el nuevo DSM-V, distintos trastornos compartirían –aunque en distinta intensidad– rasgos y facetas dimensionales solapadas. Por ejemplo, el trastorno límite de la personalidad compartiría con el trastorno antisocial/psicopático la alta implicación en actividades potencialmente negativas, la reincidencia en conductas inapropiadas y desadaptativas, o los comportamientos hostiles y agresivos. Estos síntomas se corresponden con alteraciones en las dimensiones neuropsicológicas de inhibición, regulación emocional o toma de decisiones (Bouchard et al., 2010; Dell´Osso et al., 2010; Ruocco et al., 2009). No obstante, mientras que en el límite predominarían las alteraciones de inhibición, en el antisocial predominarían las alteraciones de toma de decisiones y ambos compartirían las de regulación emocional. Por otra parte el trastorno de la personalidad obsesivo compulsivo tiene asociado déficits neuropsicológicos en planificación, flexibilidad cognitiva, falta de definición en los procesos de toma de decisiones y memoria de trabajo (Aycicegi-Dinn et al., 2009; Ruocco et al., 2009). Estas alteraciones podrían dar lugar a un comportamiento rígido y poco espontáneo, al perfeccionismo como estrategia para evitar cometer errores así como a la paralización ante determinadas conductas por la indecisión y la excesiva necesidad de sopesar alternativas que le llevan, en numerosas ocasiones, a no completar las tareas –un rasgo compartido, por ejemplo, por el trastorno evitativo (Arntz et al., 2011; Esbec y Echeburúa, 2011).

En relación con las bases neuroanatómicas que subyacen a los rasgos y déficits compartidos por la dependencia de cocaína y los trastornos de personalidad, las técnicas de neuroimagen estructural y funcional se emplean cada vez con más frecuencia para determinar las alteraciones fisiológicas de distintas regiones del cerebro y los patrones disfuncionales de conectividad entre estas regiones. Estos mapas estructurales o de

activación pueden ser posteriormente correlacionados con rasgos y síntomas que definen y ayudan a clasificar clínicamente estos trastornos. Los resultados obtenidos con estas técnicas demuestran que las personas con dependencia de cocaína muestran reducciones estructurales en la corteza orbitofrontal, el cíngulo, la ínsula, o el cuerpo estriado (Barrós-Loscertales et al., 2011; Ersche et al., 2011; Godstein y Volkow, 2011) y alteraciones de la conectividad funcional entre todas estas regiones (Gu et al., 2010). Paralelamente, trastornos de personalidad –como el trastorno límite– se caracterizan por disfunciones de la actividad cerebral en regiones muy similares: orbitofrontal y cingulada, ínsula o estriado ventral (Dziobek et al., 2011; Enzi et al., 2011; Ruocco et al., 2010; Schulze et al., 2011). En el caso del trastorno antisocial se han observado reducciones estructurales y en las conexiones entre la corteza prefrontal ventromedial y la amígdala (Craig et al., 2009). El funcionamiento de estos sistemas está fuertemente ligado a las variaciones individuales en rasgos que definen sendos trastornos, como la impulsividad o la regulación emocional, como demuestran las correlaciones significativas entre los circuitos cerebrales y los dominios conductuales detectadas en múltiples estudios realizados en los respectivos trastornos (Goldstein et al, 2009; Wolf et al., 2011; Sheng et al., 2010).

Teniendo en cuenta el importante solapamiento cronológico en la emergencia de la adicción y los trastornos de personalidad durante la neuromaduración adolescente, y la correspondencia entre sus bases neuroanatómicas y rasgos característicos, es plausible proponer que ambos comparten una etiopatogenia común, probablemente cimentada en factores genéticos. En este contexto cobran especial relevancia los estudios de asociación genética, en los que se examina la asociación entre las variaciones funcionales –polimorfismos– en genes candidatos (p.e., los que determinan la

funcionalidad de los sistemas dopaminérgico y serotonérgico) y endofenotipos compartidos por la adicción y los trastornos de personalidad (p.e., la desinhibición o la desregulación emocional). Por ejemplo, en consumidores de cocaína portadores del genotipo MAOA- L del gen de la monoamino oxidasa A (relacionado con la función serotonérgica) se ha observado una mayor reducción estructural de la corteza prefrontal ventromedial, implicada en las funciones neuropsicológicas de inhibición y regulación afectiva (Alia-Klein et al., 2011). Este mismo genotipo es más frecuente en personas con trastorno límite y antisocial de la personalidad (Fergusson et al., 2011; Ni et al., 2009; Philibert et al., 2011) en los que se ha asociado con dificultades en la cognición social, conductas impulsivas y con el riesgo de llevar a cabo comportamientos violentos (Tikkanen et al., 2009, 2011). Otro ejemplo es el del polimorfismo 5HTTLPR, del gen del transportador de serotonina (SLC6A4), cuyo genotipo s/s se ha relacionado con mayor vulnerabilidad a desarrollar adicciones y con rasgos como la impulsividad y la desregulación emocional (Verdejo-García et al., 2008). El genotipo s/s y sus endofenotipos neuropsicológicos parecen converger en alteraciones neurofuncionales de la conectividad entre la corteza cingulada y la amígdala (Pezawas et al., 2005, 2008). Ambas alteraciones, en rasgos y funcionalidad anatómica, son compartidas por la adicción y los trastornos de personalidad límite y antisocial/psicopático (Douglas et al., 2011; Gu et al., 2010; Lyons-Ruth et al., 2007; Maurex et al., 2010; Wagner et al., 2009). Otro polimorfismo, en este caso relevante para la correspondencia entre la adicción y el trastorno obsesivo compulsivo, es el Taq 1 A del receptor D2 de dopamina (DRD2). Específicamente, el genotipo Taq1A1 está relacionado con mayor susceptibilidad a la adicción, pero también con una mayor dificultad para aprender de los errores y revertir aprendizajes previos (el rasgo de inflexibilidad que comparten dependientes de cocaína y obsesivo-compulsivos) (Denys et al., 2006; Jocham et al.,

2009). En realidad, el genotipo parece repercutir negativamente sobre la conectividad del cíngulo y el hipocampo (Klein et al., 2007), favoreciendo la formación de pensamientos y hábitos recurrentes que podrían derivar en uno de los trastornos, o en ambos, en función de otras múltiples influencias neuroevolutivas y ambientales.

Por lo tanto podemos concluir que existen evidencias científicas que apuntan directamente sobre las similitudes entre el consumo de cocaína y los trastornos de personalidad. Esto se basa en que ambos trastornos comparten características neuropsicológicas, de estructura y conectividad cerebral y genéticas que darían como resultado una manifestación clínica común basada en comportamientos, en muchas ocasiones, disfuncionales. Dado que en numerosos individuos se dan ambos trastornos de manera concomitante consideramos de gran relevancia profundizar en la comprensión de estos déficits con el objetivo de abordar con rigurosidad esta comorbilidad psicopatológica en el ámbito terapéutico.

CAPÍTULO 2: IMPULSIVIDAD, NEUROPSICOLOGÍA Y NEUROIMAGEN EN CONSUMIDORES DE COCAÍNA

2.1. Introducción

Después de presentar y discutir brevemente los correlatos neuropsicológicos, neurobiológicos y genéticos compartidos por los trastornos por uso de cocaína y los trastornos de personalidad, los siguientes apartados describirán resultados específicos sobre los déficits de impulsividad, rendimiento neuropsicológico y estructura y funcionamiento cerebral asociados con ambos trastornos.

Con el objetivo de facilitar la lectura y resumir el texto de los Capítulos 2 (centrado en los hallazgos de personalidad, neuropsicológicos y de neuroimagen en consumidores de cocaína) y 3 (centrado en los hallazgos de personalidad, neuropsicológicos y de neuroimagen en trastornos de personalidad), en los cuadros 1, 2 y 3 se presentan las principales dimensiones de impulsividad (Cuadro 1), principales componentes neuropsicológicos (Cuadro 2) y principales regiones neuroanatómicas asociadas de manera independiente con ambos tipos de trastornos (Cuadro 3).

Cuadro 1. Dimensiones de impulsividad-rasgo asociadas al consumo de cocaína y los trastornos de personalidad.

Dimensiones de impulsividad	Descripción
Urgencia Negativa	Tendencia a realizar actos impulsivos bajo condiciones de afecto negativo, como estrés, frustración o ira.
Urgencia Positiva	Tendencia a realizar actos impulsivos bajo condiciones de afecto positivo.
Falta de Perseverancia/ Impulsividad Atencional	Tendencia a la fluctuación de los recursos atencionales cuando las tareas u objetivos propuestos son largos o no permiten una solución rápida y sencilla.
Falta de Premeditación/ Impulsividad No-planeada	Tendencia a involucrarse en comportamientos rápidos sin plena consideración de sus posibles consecuencias.
Impulsividad Motora	Tendencia a disparar (o dificultad para inhibir) respuestas motoras inadecuadas para las circunstancias ambientales del momento.
Búsqueda de Sensaciones	Tendencia a involucrarse en conductas novedosas y excitantes que pueden resultar arriesgadas.

Cuadro 2. Dominios neuropsicológicos asociados con el consumo de cocaína y los trastornos de personalidad.

Dominios Neuropsicológicos	Descripción
Atención	Atención sostenida: capacidad para mantener una determinada respuesta durante una actividad continua
	Atención selectiva: focalización de los mecanismos de percepción sobre un estímulo particular omitiendo los estímulos irrelevantes
	Atención dividida: capacidad para responder simultáneamente a múltiples demandas
Inhibición	Capacidad de inhibir de manera controlada la producción de respuestas inmediatas, automáticas o impulsivas cuando el contexto lo requiere
Memoria de trabajo	Sistema de almacenamiento y gestión temporal de la información necesaria para llevar a cabo tareas complejas
Flexibilidad cognitiva	Capacidad de cambiar de respuesta o criterio en función de los cambios de contexto o de reglas o las modificaciones de los patrones de reforzamiento
Planificación/organización/secuenciación	Proceso de creación de metas, estrategias de desarrollo y subtareas necesarias para alcanzar una meta
Toma de decisiones	Capacidad para elegir la opción u opciones más favorables y adaptativas en el medio y largo plazo cuando se presentan distintas alternativas con diversas posibles consecuencias

Cuadro 3. Principales regiones cerebrales asociadas con el consumo de cocaína y los trastornos de personalidad.

Regiones	Funciones	Conexión con los constructos neuropsicológicos y de personalidad
Corteza Prefrontal Dorsolateral	Implicada en la mayoría de las funciones ejecutivas, con carácter esencial en la actualización de información.	• Impulsividad atencional • Memoria de Trabajo • Atención y esfuerzo cognitivo
Giro Frontal Inferior	Esencial para los procesos de inhibición de respuesta, ya sean éstas de carácter motor o emocional.	• Urgencia Negativa • Inhibición • Regulación emocional
Corteza Orbitofrontal	La sección medial es esencial en los procesos de asignación de valor emocional a los contenidos cognitivos. La sección lateral ha sido implicada en funciones de inhibición y flexibilidad.	• Urgencia Negativa • Inhibición • Flexibilidad • Toma de decisiones • Regulación emocional
Corteza Cingulada Anterior	La sección inferior al genu del cuerpo calloso (subgenual) es esencial para la experimentación y regulación de las emociones (especialmente las negativas). Las secciones anteriores y mediales son fundamentales para los procesos de resolución de conflicto.	• Impulsividad Motora • Urgencia negativa • Inhibición • Afectividad negativa • Regulación emocional
Ínsula	Esencial en la traducción de información interoceptiva en representaciones afectivas. Asociada con la percepción del arousal, la sensibilidad al castigo o la aversión al riesgo.	• Falta de premeditación • Inhibición • Toma de decisiones
Amígdala	Esencial en los procesos de asignación del valor emocional de estímulos apetitivos y aversivos y, por tanto, en el aprendizaje afectivo.	• Toma de decisiones
Estriado	La sección anterior es clave en la asignación de relevancia motivacional a estímulos. La sección posterior es clave en la regulación del output motor.	• Búsqueda de sensaciones • Impulsividad • Toma de decisiones • Regulación emocional

2.2. Impulsividad en consumidores de cocaína

Existe una amplia evidencia sobre la asociación entre el consumo de cocaína y la impulsividad (Verdejo-García et al., 2008). El constructo de impulsividad puede ser definido, a modo general, como la tendencia a actuar o a tomar decisiones sin la previsión adecuada aumentando así las posibilidades de obtener consecuencias negativas (Winstanley, 2011). Además, la impulsividad se define como un rasgo que permanece estable a lo largo del tiempo y como un factor asociado directamente con la vulnerabilidad para desarrollar una adicción (Ersche et al., 2012). No obstante, cabe reseñar que a pesar de considerarse un rasgo de personalidad, también puede verse modulado por los efectos derivados del consumo.

La impulsividad rasgo puede medirse a través de diversos cuestionarios que recogen información sobre predisposiciones generales de acción ante distintas situaciones. Entre los más destacados y utilizados en la investigación se encuentran el *Barratt Impulsiveness Scale* (BIS; Patton et al., 1995) y la escala UPPS-P *Impulsive Behavior Scale* (Smith et al., 2007; Whiteside and Lynam 2001). El primer instrumento es un recurso clásico para la medición de la presencia de un patrón de conducta impulsiva y mantenida a largo plazo y está compuesto por tres subescalas: Atencional, que evalúa la capacidad de focalización en las tareas y de resistencia a los pensamientos intrusivos; Motora, que evalúa la tendencia a actuar de manera impetuosa o repentina; y la No Planeada; que evalúa la capacidad para prestar suficiente consideración a las situaciones de decisión y de disfrutar con retos cognitivos aunque sean largos y complejos. Más recientemente, se desarrolló la escala UPPS-P que es un instrumento multidimensional que evalúa cinco facetas de personalidad que pueden predisponer al comportamiento impulsivo: Búsqueda de sensaciones, falta de perseverancia, falta de premeditación,

urgencia negativa y urgencia positiva. Las cuatro primeras dimensiones se incluyeron en la versión original de la escala UPPS, la quinta dimensión (de urgencia positiva) se incluyó a partir de estudios recientes que demostraron que el comportamiento impulsivo puede ser facilitado tanto por afectos negativos como positivos, prediciendo éstos distintos tipos de conductas disfuncionales y psicopatologías (Smith et al., 2007). La dimensión búsqueda de sensaciones incluye dos aspectos:1) la tendencia a divertirse y a realizar actividades excitantes/emocionantes y 2) a abrirse a nuevas experiencias que pueden o no ser arriesgadas. La falta de perseverancia se refiere a la capacidad de una persona para permanecer concentrada en una tarea que puede ser aburrida o difícil. La falta de premeditación se refiere a la tendencia a pensar y reflexionar sobre las consecuencias de una acción antes de participar en la misma. Por último, las dimensiones de urgencia hacen referencias a las tendencias a actuar de manera impulsiva en condiciones de emoción negativa (urgencia negativa) o positiva (urgencia positiva).

La incorporación de estos instrumentos u otros similares puede servirnos como herramienta eficaz para detectar de manera temprana el riesgo que presentan ciertos individuos para desarrollar problemas de adicción, o bien para caracterizar rasgos estables de personalidad que contribuyen a definir las actuaciones del individuo en un amplio rango de situaciones. Específicamente, la medición de los niveles de impulsividad en consumidores de cocaína nos permite determinar con precisión los tipos de situaciones en los que los sujetos tienden a actuar de manera impulsiva y definir mejor así nuestras estrategias de intervención. Por ejemplo, se ha demostrado que en el caso de consumidores dependientes de cocaína la dimensión urgencia negativa es la que mejor predice los problemas asociados al consumo de sustancias, tales como problemas

médicos, laborales, sociales y familiares, legales o psiquiátricos (Verdejo-García et al., 2007). No obstante, los individuos consumidores de cocaína también presentan puntuaciones significativamente elevadas en las escalas de falta de premeditación y falta de perseverancia (Fernández-Serrano et al., 2012). Asimismo, estudios recientes han demostrado elevaciones significativas de la búsqueda de sensaciones (Ersche et al., 2010). En lo referente a la escala BIS, también se han hallado elevadas puntuaciones en impulsividad en sujetos con dependencia a la cocaína (Coffey et al., 2003; Moeller et al., 2004) y, por otro lado, elevadas puntuaciones en el cuestionario han correlacionado negativamente con la edad de inicio del consumo, confirmando la hipótesis que vincula altos niveles de impulsividad-rasgo con el inicio temprano en el consumo de esta sustancia (Moeller et al., 2002).

Las investigaciones en sujetos con dependencia a la cocaína también demuestran que éstos presentan puntuaciones elevadas en cuestionarios de descuento asociado a la demora (Coffey et al., 2003; Kirby and Petry, 2004; Moeller et al., 2002). Uno de los cuestionarios más utilizados es el "Delay discounting questionnaire" o Test de descuento asociado a la demora (Kirby et al., 1999). Se trata de un cuestionario en el que el participante debe realizar elecciones hipotéticas entre distintas cantidades de dinero en función de si su entrega es inmediata o demorada en el tiempo (p.e., prefiere 5 Euros ahora o 12 Euros dentro de 13 días). Cada ítem varía en relación a los valores económicos ofrecidos (pequeños, medianos o grandes) y al tiempo a esperar para recibir la recompensa monetaria, de modo que es posible trazar –para cada individuo– una curva representativa del descuento que éste aplica al valor de un reforzador en función de la demora hasta obtenerlo. La variable dependiente derivada de esta prueba es el área bajo la curva (conocida habitualmente por sus iniciales en inglés, AUC) (Myerson et al.,

2001): cuanto menor es el valor de AUC mayor es el descuento aplicado al reforzador en función de la demora, es decir, mayor es la impulsividad o preferencia por recompensas inmediatas en la toma de decisiones. En este sentido, los consumidores de cocaína también parecen caracterizarse por una tendencia a preferir recompensas entregables de manera inmediata incluso frente a otras de mayor magnitud para cuya entrega tendrían que esperar más tiempo (Kirby and Petry, 2004; Moeller et al., 2002).

Para evaluar el proceso de cambio, tanto en las dimensiones de impulsividad como en otros dominios relacionados con los circuitos fronto-estriados del cerebro, se han utilizado escalas como la "Frontal Systems Behavior Scale" (FrSBe; Grace and Malloy, 2001). Se trata de un cuestionario compuesto por tres subescalas que evalúan síntomas de apatía, desinhibición y disfunción ejecutiva. En este caso, consideramos que la desinhibición es el concepto neuropsicológico más equivalente a la noción de personalidad impulsiva. En el contexto de la FrSBe la desinhibición se define como la dificultad para regular o suprimir respuestas automáticas o impulsivas cuando esta regulación es necesaria atender a las exigencias actuales del entorno; esta definición incluye las habilidades de regulación de comportamientos socialmente inadecuados o molestos y las habilidades de regulación de la labilidad emocional o las emociones desagradables de ira o frustración. En un estudio llevado a cabo en sujetos policonsumidores con dependencia al alcohol, cocaína y metanfetaminas se demostró que éstos presentaban elevaciones significativas de los síntomas de desinhibición, apatía y disfunción ejecutiva comparándolos con un grupo control (Verdejo-García, Bechara et al., 2006), mientras que un estudio posterior demostró que la severidad del consumo de cocaína estaba significativamente y específicamente correlacionada con la intensidad de

los síntomas de desinhibición de pacientes policonsumidores (Verdejo-García, Rivas-Pérez et al., 2006).

Como conclusión de este apartado se postula que existe una relación directa entre el consumo continuado de cocaína y elevados niveles de impulsividad. Por una parte, sabemos que la impulsividad es un rasgo característico que predispone al individuo a exponerse a situaciones de riesgo, como la adicción, y que por otra parte la exposición a la sustancia a lo largo del tiempo así como la intensidad en el consumo pueden también producir incrementos en las medidas dimensionales de impulsividad-rasgo.

2.3. Neuropsicología de la dependencia a la cocaína

Al igual que en el caso de la personalidad impulsiva, las variables neuropsicológicas pueden funcionar como factores de vulnerabilidad o como variables de resultado de la exposición al consumo. No obstante, ya que las pruebas intentan captar el funcionamiento cognitivo en el momento actual (frente a los cuestionarios de personalidad que miden rasgos estables), se asume que son mejores indicadores de los resultados del consumo crónicos. Por un lado sabemos que la cocaína produce efectos neuroadaptativos a través de diversos sistemas de neurotransmisión, como por ejemplo alterando los circuitos naturales de neurotransmisión de la dopamina y serotonina (Camí y Farré, 2003). Además se ha demostrado en modelos animales que su administración en dosis repetidas produce déficits de memoria de trabajo y reversión de aprendizajes asociados con neuroadaptaciones de la corteza prefrontal y regiones límbicas así como con una disminución del proceso de neurogénesis en neuronas del hipocampo (Canales, 2010; George et al., 2008; Porter et al., 2011; Sudai et al., 2011). No obstante, también

existe evidencia de vulnerabilidades cognitivas que predisponen al inicio del consumo, especialmente reseñable es el constructo de impulsividad, descrito en el apartado anterior, que en el campo de la neuropsicología se identifica con el concepto de inhibición o capacidad para cancelar o demorar respuestas que no son adecuadas en las circunstancias actuales (Verdejo-García et al., 2008). Con propósitos descriptivos en esta sección se repasarán los déficits neuropsicológicos asociados al consumo crónico de cocaína en humanos.

Con el objetivo de sintetizar la información nuestra revisión se basará en los hallazgos y conclusiones de dos estudios recientes de revisión cuantitativa y meta análisis que abordan directamente la problemática de la adicción a la cocaína y la consecuente afectación neuropsicológica (Fernández-Serrano et al., 2011; Jovanovski et al., 2005). A continuación se describirán los resultados de estudios posteriores a estos dos meta-análisis, con objeto de recoger las investigaciones más recientes.

El primer estudio de meta-análisis fue llevado a cabo por Jovanovski et al. (2005) y en él se compilan 15 estudios que exploran los principales dominios neuropsicológicos en consumidores de cocaína: atención, memoria visual, planificación visual, memoria de trabajo, fluidez verbal, percepción sensorial, rendimiento psicomotor, planificación y flexibilidad cognitiva y razonamiento abstracto. El hallazgo principal del estudio estriba en la detección de que en todos aquellos tests neuropsicológicos con un fuerte componente atencional los consumidores de cocaína obtenían un rendimiento significativamente deteriorado, por lo que podemos deducir que el consumo continuado de cocaína produce un potencial deterioro de la capacidad atencional. Los resultados de las pruebas neurocognitivas se registraron en un total de 481 consumidores de cocaína y 586 individuos sanos. El método utilizado fueron los análisis del tamaño del efecto

junto con el procedimiento estándar meta-analítico teniendo como objetivo evaluar la magnitud y el patrón de disfunción neuropsicológica en consumidores de cocaína. Las conclusiones detalladas indican que los dominios más deteriorados en términos de tamaño del efecto fueron: la atención, la memoria visual, la memoria de trabajo y planificación visual. No obstante, los autores destacan que la capacidad atencional estaría implicada en todos los dominios deteriorados descritos previamente. Además la atención se configura como un constructo cognitivo que engloba distintos subcomponentes específicos como la velocidad de procesamiento, la atención selectiva, la atención sostenida y la dividida. Dichos subcomponentes son requeridos en mayor o menor medida en tareas de memoria y planificación visual, pudiendo ser por tanto los responsables de la peor ejecución obtenida en consumidores de cocaína. En segundo lugar, los tamaños del efecto que se situaron por debajo de la media se observaron en pruebas de fluidez verbal y de otras funciones lingüísticas así como en tareas perceptivo-sensoriales. Por último, la mayoría de las tareas que evalúan el rendimiento motor mostraron tamaños del efecto mínimos, exceptuando el caso de una tarea que evalúa destreza manipulativa y requiere coordinación motora-visual compleja, además de detectar y discriminar daños cerebrales lateralizados hemisféricamente. Respecto a las pruebas que miden función ejecutiva se observó que los consumidores de cocaína obtuvieron un peor rendimiento en tareas de formación de conceptos, razonamiento abstracto y flexibilidad cognitiva, y que además mostraron dificultades en la capacidad de planificar y en la resolución de problemas, aunque en este caso los tamaños del efecto fueron de magnitud media.

El segundo estudio, de revisión cuantitativa basada en los tamaños del efecto de estudios caso-control (Fernández-Serrano et al., 2011), se centra en explorar los efectos

subagudos vs. crónicos de distintas sustancias (cannabis, psicoestimulantes, opiáceos y alcohol) sobre el rendimiento neuropsicológico. Su mayor punto de interés reside en la categorización entre el consumo de distintos tipos de sustancias y sus consecuentes dominios neuropsicológicos alterados, así como explorar cuáles son los déficits neurocognitivos específicos para cada una de las sustancias. La revisión se llevó a cabo desde una aproximación multidimensional, incluyendo el máximo número de dominios neuropsicológicos presentes en la literatura hasta el momento. Entre los mecanismos esenciales vinculados a la función ejecutiva se identificaron: el componente de memoria de trabajo y actualización de información, el componente inhibitorio incluyendo pruebas que evaluaron la acción impulsiva, como la inhibición de respuesta y la auto-regulación, y por otro lado las decisiones impulsivas, medidas con las tareas de apuestas y juego. También se evalúo el componente de flexibilidad teniendo en cuenta las tareas atencionales/cambio de set y los test de reversión probabilística.

Las conclusiones del estudio en relación al consumo de cocaína destacan elevados niveles de acción impulsiva en esta población clínica medidos a través de pruebas de inhibición de respuesta, como la Stop-Signal Task, así como altos niveles de decisión impulsiva medida a través de tareas de toma de decisiones. Por otro lado, también se detectó un bajo rendimiento en tareas de memoria de trabajo y episódica así como en tareas que medían atención selectiva. Además se observan dificultades en la ejecución de tareas de reconocimiento facial de expresiones emocionales y en pruebas de funcionamiento psicomotor. El análisis cuantitativo de los tamaños del efecto concluye que los efectos más robustos hallados en consumidores de cocaína, considerando que sean resultados coincidentes en más de una metodología aplicada, son las alteraciones

neuropsicológicas en los dominios de memoria de trabajo, acción y decisión impulsiva, procesamiento emocional y toma de decisiones.

Con posterioridad a estas dos revisiones cuantitativas se han publicado algunos estudios que aportan nuevos hallazgos al campo de la neuropsicología del consumo de cocaína. Las últimas investigaciones sobre el proceso adictivo tratan de estudiar este fenómeno desde una perspectiva de integración, interrelacionando los factores genéticos con rasgos de personalidad y destrezas cognitivas (endofenotipos) que pueden intervenir en la vulnerabilidad a la adicción y, a su vez, explorando las posibles neuroadaptaciones resultantes del consumo continuado de diversas sustancias. En este sentido, un estudio llevado a cabo por Ersche et al. (2012), compara tres grupos: sujetos con dependencia a psicoestimulantes, hermanos de estos sujetos sin historia previa o actual de consumo y, por último, voluntarios sanos. Las mediciones consistieron en la administración de una batería de tests neuropsicológicos (CANTAB), junto con una serie de cuestionarios que midieron funcionamiento psicosocial y emocional, rasgos de impulsividad-compulsividad y componentes de autoevaluación personal. Los resultados indican que los dos primeros grupos, el grupo de consumidores y sus hermanos, presentaron peor rendimiento que los controles en tests de control de respuesta (inhibición) y funciones ejecutivas. No obstante, el grupo de consumidores presentó puntuaciones significativamente más deterioradas que las del grupo de familiares en los dominios relacionados con las funciones ejecutivas. Por otra parte, ambos grupos también mostraron puntuaciones elevadas en medidas de impulsividad-compulsividad, funcionamiento emocional y autoevaluación. Los datos sugieren que diversas alteraciones neuropsicológicas pueden ser anteriores a la exposición de la sustancia y

que pueden ser un factor de riesgo predisponente para el desarrollo de un trastorno adictivo.

En el ámbito de las posibles neuroadaptaciones, aproximadas desde estudios correlacionales donde se desvelan los dominios neuropsicológicos más frecuentemente deteriorados y asociados con los patrones de consumo de cocaína, las investigaciones continúan coincidiendo en que los consumidores de cocaína presentan déficits en memoria de trabajo (Bustamante et al., 2011), inhibición de respuesta (Fernández-Serrano et al., 2010), flexibilidad cognitiva y perseveración (Woicik et al., 2011) y toma de decisiones afectivas (Kjome et al., 2010).

A la vista de los resultados obtenidos, podemos concluir que el consumo continuado de cocaína lleva asociado un deterioro significativo en diversos dominios neuropsicológicos, incluyendo los de atención, memoria de trabajo, inhibición de respuesta y procesamiento emocional, que en la mayoría de los casos predicen peores resultados del tratamiento e impactan negativamente en el ámbito, personal, social y laboral del individuo (Verdejo-García, Bechara et al., 2007; Lubman et al., 2009; Streeter et al., 2008). Por ello es importante definir y concretar desde la investigación los múltiples factores implicados en el proceso adictivo e integrarlos de una manera eficaz en el tratamiento psicológico.

2.4. Neuroimagen estructural y funcional en consumidores de cocaína

Como se ha comentado brevemente en los apartados anteriores, el consumo de cocaína provoca cambios neuroadaptativos en los circuitos fronto-estriados del cerebro (George et al., 2008). Estas modificaciones en los sustratos neurobiológicos pueden ser

cuantificadas a través de técnicas de neuroimagen como la resonancia magnética estructural. Las técnicas estructurales informan sobre la localización, forma y tamaño de algunas regiones cerebrales y permiten cuantificar los cambios volumétricos o de densidad de la sustancia gris y la sustancia blanca cerebral.

2.4.1. *Resonancia magnética estructural*

Siguiendo en la misma línea de los estudios conductuales, se ha propuesto que la impulsividad rasgo puede estar asociada con alteraciones de la densidad de la materia gris y la materia blanca en los circuitos cerebrales implicados en el consumo de cocaína y otros estimulantes (Ersche et al., 2011; Moreno-López et al., 2012; Verdejo-García et al., 2008). En este sentido, diversos estudios han detectado reducciones del volumen de materia gris en consumidores crónicos de cocaína en la corteza orbitofrontal, en el cíngulo anterior, en el giro frontal inferior, ínsula, amígdala, giro temporal y caudado (Ersche et al., 2011; Makris et al., 2004; Matochik et al., 2003; Moreno-López et al., 2012), regiones principalmente relacionadas con el aprendizaje de reforzadores (amígdala y corteza orbitofrontal) y con el control inhibitorio (cíngulo anterior, giro frontal inferior, ínsula y caudado) (ver Cuadro 3).

Por otro lado, en lo referente a las neuroadaptaciones derivadas de la interacción entre los rasgos de impulsividad y el consumo de cocaína, se ha demostrado que los cambios en la materia gris en las regiones del giro frontal inferior izquierdo, ínsula y putamen, están asociados con altas puntuaciones en la dimensión falta de premeditación, y que por otro lado las reducciones de materia gris en el giro frontal inferior correlacionan positivamente con altas puntuaciones en la subescala de urgencia negativa. (Moreno-López et al., 2012).

Por otra parte, se han estudiado los cambios estructurales producidos como consecuencia de la severidad del consumo, a este respecto las regiones del estriado y la corteza orbitofrontal están relacionados con la duración en el consumo de cocaína, es decir, cuanto más tiempo se ha estado consumiendo la sustancia mayor pérdida de volumen de materia gris en las áreas descritas (Ersche et al., 2011).

2.4.2. *Resonancia magnética funcional*

El segundo método de neuroimagen, la resonancia magnética funcional, permite la detección e identificación de áreas del cerebro durante su actividad asociada a fenómenos psicológicos, lo que la diferencia de las imágenes tradicionales de resonancia magnética que solo aportan una visión anatómica del cerebro. Las técnicas funcionales miden los cambios en la actividad, el metabolismo cerebral o en ciertos parámetros neurofarmacológicos como la densidad de receptores o los niveles de neurotransmisores y metabolitos.

Como explicamos en las secciones previas, existe evidencia consistente sobre cuáles son los dominios neuropsicológicos más afectados en sujetos con dependencia a la cocaína, por lo que en este apartado de neuroimagen funcional nos centraremos en los resultados de hipoactivación o hiperactivación funcional relacionados con los procesos cognitivos de atención/memoria de trabajo, inhibición y regulación emocional. En el caso de los procesos de atención y memoria de trabajo los estudios de neuroimagen han revelado reducciones de la activación de la corteza prefrontal dorsolateral y parietal inferior en sujetos con dependencia a la cocaína durante la realización de tareas de memoria de trabajo (Bustamante et al., 2011; Tomasi et al., 2007) y de un amplio espectro de regiones pertenecientes a los sistemas de focalización y control ejecutivo de la atención (mesencéfalo, tálamo y cíngulo anterior) durante paradigmas de atención

sostenida (Tomasi et al., 2007; 2010). Estos hallazgos reflejan la capacidad limitada de la red neuronal de los procesos de memoria de trabajo en consumidores de cocaína (Tomasi et al., 2005) y, por otro lado, puesto que la corteza parietal está implicada en los procesos de orientar respuestas de atención (Corbeta y Shulman, 2002), la hipoactivación de esta región estaría asociada con los potenciales problemas atencionales descritos en los individuos con dependencia de cocaína.

En el caso del control inhibitorio se ha demostrado que los sujetos con dependencia de cocaína hipoactivan el cíngulo anterior, el giro frontal medial derecho y la ínsula izquierda durante la ejecución de tareas que evalúan habilidades de control inhibitorio (Kaufman et al., 2003; Fillmore et al., 2002). Una insuficiente respuesta anticipatoria probablemente proveniente de la ínsula izquierda contribuiría a la capacidad de inhibir respuestas de manera satisfactoria, por otro lado el cíngulo anterior jugaría un papel fundamental en la inhibición de respuestas urgentes (Garavan et al., 2002).

En relación a los mecanismos de regulación emocional, son pocos los estudios que abordan esta cuestión en consumidores de psicoestimulantes. Por un lado se sabe que los consumidores de cocaína muestran alteraciones en los sistemas fronto-límbicos cuando se exponen a una tarea que implica un fuerte componente emocional (Verdejo-García et al., 2012). Por otro lado, en relación con lo anterior, un estudio llevado a cabo en consumidores de metanfetaminas demostró reducciones de la activación del giro frontal inferior durante distintos tipos de tareas de control cognitivo, tanto de inhibición de respuestas motoras como de regulación de emociones y respuestas de deseo de consumo (craving) (Tabibnia et al., 2011). Por tanto, asumimos que ésta es una de las regiones centrales especializadas en la inhibición de respuestas impulsivas o emociones negativas, dos importantes características clínicas de los consumidores de estimulantes.

Como conclusión de este apartado cabe recalcar la importancia de las técnicas de neuroimagen para continuar descifrando los sustratos cerebrales de los déficits neuropsicológicos presentados en consumidores de cocaína. Esto es posible gracias a los métodos que nos ayudan a identificar las distintas conexiones entre regiones cerebrales, detectando hiper o hipoactivaciones mientras que el sujeto realiza la tarea pertinente, y por otro lado, el conocimiento del nivel de densidad de materia gris o sustancia blanca. Todo ello nos ayuda a delinear las redes cerebrales afectadas en consumidores de cocaína y poder así intervenir de manera más precisa y eficaz en los procesos neuropsicológicos afectados.

CAPÍTULO 3: IMPULSIVIDAD, NEUROPSICOLOGÍA Y NEUROIMAGEN EN TRASTORNOS DE PERSONALIDAD DEL CLÚSTER B

3.1. Introducción

Para un repaso de los constructos de personalidad, dominios neuropsicológicos y regiones y circuitos neuroanatómicos el lector puede volver a consultar los cuadros 1-3 del Capítulo 2.

3.2. Impulsividad en los trastornos de personalidad del Clúster B

El trastorno por dependencia a la cocaína está frecuentemente asociado con otros trastornos psiquiátricos. Esta comorbilidad está asociada con una menor adherencia al tratamiento, mayor número de recaídas y con un incremento de los problemas de consumo a lo largo del tiempo (Fenton et al., 2011). En este sentido, los trastornos de personalidad se sitúan como uno de los trastornos duales más prevalentes en consumidores de cocaína (Chen et al., 2011; Martínez-González, 2011). Los trastornos de personalidad están caracterizados, según el DSM-IV por alteraciones en el plano cognitivo, afectivo e interpersonal que dan como resultado patrones desadaptativos e inflexibles de comportamiento que afectan de manera sustancial al funcionamiento global del individuo. En muchos casos esta patología dual puede desembocar en complicaciones que potencian características de personalidad implicadas en la vulnerabilidad (impulsividad) y además, intensificar los efectos adversos de las sustancias consumidas sobre los sistemas neuropsicológicos. Los trastornos de personalidad más prevalentes en consumidores de cocaína y sobre los que existe más base científica son el trastorno de personalidad antisocial y el trastorno de personalidad límite, trastornos pertenecientes al clúster B, según la clasificación del DSM-IV.

Los trastornos de personalidad del Clúster B se caracterizan por un patrón de conducta disfuncional/errática, una mala regulación de los procesos emocionales, y por un

comportamiento impulsivo y tendente al dramatismo. Los trastornos clasificados en este clúster son: i) Trastorno antisocial de la personalidad, caracterizado por un patrón general de desprecio y violación de los derechos de los demás; ii) Trastorno límite de la personalidad, definido por un patrón general de inestabilidad en las relaciones interpersonales, la autoimagen y la efectividad, además de una notable impulsividad; iii) Trastorno histriónico de la personalidad, se caracteriza por un patrón general de excesiva emotividad y búsqueda de atención; y, por último, iv) Trastorno narcisista de la personalidad, caracterizado por un patrón general de grandiosidad (en la imaginación o en el comportamiento), necesidad de admiración y falta de empatía.

Uno de los síntomas más característicos de los trastornos límite y antisocial de la personalidad son los elevados niveles de impulsividad rasgo. En el caso del trastorno límite, la intensidad de los síntomas de impulsividad está relacionada con la baja adherencia y los peores resultados en el tratamiento (Bornovalova et al., 2005; Forman et al., 2004; Henry et al., 2001; Koenigsberg et al., 2001; Lejuez et al., 2003; Morey et al., 2003). Por ejemplo, cuando se evalúan los niveles de impulsividad con la escala BIS de Barrat, (1995) se encuentra que los individuos con trastorno límite de la personalidad presentan mayores niveles de impulsividad cuando se comparan con otros grupos psicopatológicos como los individuos con trastorno bipolar (Henry et al., 2001). Por otro lado, utilizando el mismo instrumento, diversos estudios han observado que los individuos con trastorno límite obtienen mayores puntuaciones en los ítems relacionados con la falta de atención y con la tendencia hacia la acción sin anticipación de las consecuencias (Van Reekum et al., 1994, 1996).

Respecto a la escala de impulsividad UPPS-P, en varios estudios se han correlacionado síntomas característicos del trastorno límite de la personalidad con las diferentes

subescalas de la UPPS-P: Búsqueda de sensaciones, falta de perseverancia, falta de premeditación, urgencia negativa y urgencia positiva. En este sentido uno de los hallazgos más robustos encontrados es la relación entre la urgencia negativa y los síntomas autolesivos presentes en el trastorno límite (Chapman et al., 2006; Peters et al., 2012). Asimismo, en una muestra comunitaria, Tragessor y Robinson (2009) encontraron correlaciones significativas entre las dimensiones de urgencia negativa y falta de perseverancia y varios rasgos específicos del trastorno límite de la personalidad, como la inestabilidad afectiva, los problemas de identidad, la implicación en relaciones interpersonales negativas y las autolesiones. Estudios similares en muestras clínicas han resaltado asimismo la correlación significativa entre los síntomas del trastorno límite y las elevaciones de las dimensiones de urgencia negativa y falta de perseverancia (Jacob et al., 2010; Whiteside et al., 2005).

Las tareas de descuento asociado a la demora, relacionadas con la elección de recompensas o gratificaciones inmediatas a expensas de otras opciones más favorables pero demoradas en el tiempo, se han asociado con varios síntomas nucleares y desadaptativos del trastorno límite de la personalidad. Así pues, se ha observado que los síntomas autolesivos podrían ser conceptualizados como un comportamiento impulsivo elegido por los beneficios inmediatos de la distracción emocional y el alivio intenso de afecto negativo, a pesar de las consecuencias negativas que estas tendencias de acción conllevan a largo plazo (Linehan, 1993; Wagner y Linehan, 1999).

Los estudios de impulsividad rasgo en sujetos con trastorno de personalidad antisocial son más escasos en la literatura. Los resultados con las escala BIS en este grupo clínico indican elevadas puntuaciones en las dimensiones de impulsividad motora y no planeada (Swann et al., 2009). En otro estudio utilizando la misma escala de

impulsividad de Barrat también se demostró que la dimensión de impulsividad motora predecía de manera significativa la intensidad de los síntomas propios del trastorno de la personalidad antisocial (Fossati et al., 2004).

En relación con el cuestionario de descuento asociado a la demora (DDT; Kirby et al., 1999), el estudio de Petry et al., (2002) comparó tres grupos clínicos con potenciales déficits de hipersensibilidad a la recompensa inmediata: sujetos con un diagnóstico de dependencia de sustancias y trastorno de la personalidad antisocial, sujetos con dependencia a sustancias sin comorbilidad psiquiátrica e individuos sanos. Sus resultados mostraron que los sujetos con dependencia de sustancias y trastorno antisocial de la personalidad mostraron curvas de descuento más pronunciadas, lo que indica mayores niveles de impulsividad o preferencia por recompensas inmediatas en la toma de decisiones en los pacientes comórbidos.

Apenas existen en la literatura científica estudios que evalúen la impulsividad en los trastornos de la personalidad histriónico o narcisista. Sólo en el caso de una muestra comunitaria –no clínica– se detectaron correlaciones entre niveles elevados de impulsividad y conductas de consumo de sustancias y síntomas de los trastornos de la personalidad histriónico y antisocial (James y Taylor, 2007).

Estos resultados ponen de manifiesto el hecho que los elevados niveles de impulsividad rasgo forman parte del cuadro clínico de los trastornos de personalidad del clúster B, y que estos rasgos parecen similares a los revisados en el caso de los grupos de consumidores de cocaína. Por otro lado, el solapamiento entre ambos trastornos puede exacerbar síntomas relacionados con los procesos de impulsividad e incrementar la sintomatología propia de los trastornos pudiendo derivar en mayores complicaciones clínicas durante el proceso de intervención psicológica.

3.3. Neuropsicología de los trastornos de personalidad del Clúster B

Los síntomas de los distintos trastornos de personalidad presentan un importante solapamiento conceptual con las funciones ejecutivas, definidas como habilidades de actualización e integración de información cognitiva y afectiva necesarias para seleccionar, promover, y supervisar conductas socialmente adaptativas, inhibir respuestas inadecuadas, y detectar y corregir errores de ejecución promoviendo respuestas alternativas (ver Verdejo-García y Pérez-García, 2007). Este solapamiento indica que los distintos componentes de las funciones ejecutivas pueden estar significativamente dañados en los trastornos de personalidad del mismo modo que se ha demostrado en la adicción a la cocaína. De hecho, se ha propuesto que los trastornos de personalidad constituyen manifestaciones psicológicas de déficits en las funciones ejecutivas, una idea apoyada por la evidencia de que comparten bases genéticas (Coolidge et al., 2004; Friedman et al., 2008). Asimismo, numerosas investigaciones coinciden en que algunos componentes ejecutivos pueden estar dañados de manera común en todos los trastornos de personalidad, mientras que otros componentes ejecutivos pueden estar dañados de manera selectiva o más prominente en distintos grupos de trastornos de personalidad.

En este sentido, los trastornos de personalidad más estudiados en cuanto a alteraciones neuropsicológicas, han sido de nuevo, el trastorno de la personalidad límite y el antisocial.

En el caso del trastorno límite de la personalidad diversos estudios han detectado alteraciones significativas en distintos componentes neuropsicológicos. Los resultados de un meta-análisis reciente centrado en la neuropsicología de este trastorno indican que las tareas donde los tamaños del efecto de las diferencias entre los grupos clínicos y

controles fueron más robustos estaban relacionadas con la atención, la flexibilidad cognitiva y la velocidad de procesamiento (Ruocco, 2005). Los déficits en estos dominios neuropsicológicos son indicativos de la existencia de alteraciones en los sistemas fronto-estriados en sujetos con trastorno de la personalidad límite. Por otro lado, en el mismo meta-análisis también se detectó que los individuos con trastorno límite obtienen un peor rendimiento en planificación y en aprendizaje y memoria de trabajo, dominios relacionados con posibles disfunciones en áreas fronto-parietales y fronto-temporales respectivamente.

Estudios más recientes, con controles mejor ajustados de variables confusoras como el cociente intelectual, destacan como déficits principales del trastorno límite los relacionados con los componentes ejecutivos de inhibición de respuesta, flexibilidad, fluidez verbal y toma de decisiones (Fertuck et al., 2005; Haaland et al., 2009). En cuanto a otros dominios neuropsicológicos se observa también un bajo rendimiento en la capacidad atencional (Haaland et al., 2009), resultado que coincide con la investigación realizada por Posner el at. (2002), que identificó deficiencias específicas en la red atencional implicada en la resolución de conflictos y el control cognitivo. Por último, con el objetivo de medir el control inhibitorio en individuos con trastorno límite de la personalidad, el estudio llevado a cabo por Domes et al. (2006) concluyó que las personas con trastorno límite tienen dificultades para reprimir activamente la información relevante cuando ésta es de carácter aversivo, lo que indica que la capacidad inhibitoria de los pacientes con trastorno límite está relacionada con variables estado-rasgo del afecto inestable.

En la literatura científica existen muy pocos estudios que exploren las alteraciones neuropsicológicas en individuos con trastorno de la personalidad antisocial. La mayoría

de estudios realizados se han centrado, por un lado, en los rasgos de psicopatía (que pueden o no estar presentes en el trastorno de la personalidad antisocial) y, por otro lado, en el trastorno de conducta disocial diagnosticado en la niñez y en la adolescencia que se considera un precedente del trastorno antisocial de la personalidad en adultos. En ambos casos los estudios coinciden en señalar como principales alteraciones neuropsicológicas, las de procesamiento emocional, toma de decisiones (Fairchild et al., 2009) y control inhibitorio (Dolan, 2012).

Hasta la fecha no existen estudios específicos que evalúen dominios neuropsicológicos en el trastorno de la personalidad histriónico y narcisista.

Podemos concluir que los déficits neuropsicológicos en los trastornos de personalidad del clúster B no han sido suficientemente estudiados a día de hoy. De acuerdo con las investigaciones revisadas el trastorno de la personalidad límite está asociado con déficits significativos de las habilidades atencionales y de control ejecutivo, mientras que el antisocial se relaciona con déficits de procesamiento emocional y toma de decisiones. No obstante, no todos los estudios abordan todos los dominios, por lo que los resultados no pueden aún ser concluyentes.

3.4. Neuroimagen de los trastornos de personalidad del clúster B

3.4.1. Neuroimagen estructural de los trastornos de personalidad del clúster B

Diversos estudios han demostrado reducciones del volumen de materia gris en distintas regiones cerebrales de grupos de individuos con trastornos de personalidad límite (Nunes et al., 2009; Ruocco et al., 2012). En un reciente estudio de meta-análisis (Ruocco et al., 2012) donde se comparan un total de 205 sujetos con trastorno límite de

la personalidad frente a 222 controles sanos procedentes de 11 estudios, se demostraron reducciones volumétricas significativas y bilaterales en la amígdala (13%) y en el hipocampo (11%). Dada la magnitud de las diferencias, los autores exponen que las disminuciones volumétricas pueden servir como importantes marcadores biológicos para el trastorno de la personalidad límite. Asimismo, los datos parecen consistentes con la magnitud de los tamaños del efecto en los déficits de memoria verbal y visual hallados en estudios neuropsicológicos en sujetos con el mismo trastorno (Ruocco, 2005), lo que podría sugerir un posible correlato cognitivo de las disminuciones estructurales presentes.

Del mismo modo en el trastorno de la personalidad antisocial se han hallado reducciones estructurales en la corteza orbitofrontal derecha, en la corteza prefrontal dorsolateral izquierda y en la corteza cingulada anterior derecha (ver meta-análisis en Yang y Raine, 2009). En este sentido, las reducciones volumétricas en la corteza orbitofrontal derecha se asocian con alteraciones en la conducta social, en la toma de decisiones y en el procesamiento emocional (Tranel et al., 2002), las reducciones en la corteza cingulada anterior están vinculadas con alteraciones en el control inhibitorio y el procesamiento emocional (Danckert et al, 2000; Hornak et al, 2003) y, por último, las reducciones estructurales en la corteza prefrontal dorsolateral izquierda están asociadas con alteraciones cognitivas en atención, flexibilidad y con problemas de control de impulsos (Grattan y Eslinger, 1992; Hornak et al, 2004;. Stuss et al, 2001).

3.4.2. Neuroimagen funcional de los trastornos de personalidad del Clúster B

El estudio en técnicas de neuroimagen funcional en el trastorno de personalidad límite se ha centrado especialmente en el estudio del funcionamiento de los mecanismos de regulación emocional. A este respecto, los sujetos con trastorno límite se caracterizan por disfunciones, tanto incrementos como reducciones, de la actividad cerebral en regiones de la corteza cingulada anterior y el estriado ventral (Enzi et al., 2011), corteza orbitofrontal lateral derecha (Ruocco et al., 2010) e ínsula (Dziobek et al., 2011).

En lo referente al trastorno antisocial de la personalidad, los estudios de neuroimagen funcional destacan especialmente las reducciones en la activación de distintas regiones de la corteza prefrontal, incluyendo la corteza prefrontal ventromedial, la corteza prefrontal dorsolateral y la corteza cingulada de acuerdo con el meta-análisis de Yung y Raine (2009). Apenas existen estudios en trastorno narcisista; de hecho, el único estudio disponible se llevó a cabo en individuos con rasgos subclínicos del trastorno, que mostraron déficits de activación de la ínsula en un paradigma orientado a generar respuestas de empatía (Fan et al., 2001). Asimismo, no se han explorado hasta la fecha las bases neurofuncionales del trastorno histriónico.

PARTE II –ESTUDIOS EMPÍRICOS

CAPÍTULO 4: OBJETIVOS E HIPÓTESIS

El **Objetivo General** de esta tesis doctoral es el de caracterizar los rasgos de personalidad impulsiva, las funciones ejecutivas y la estructura y funcionamiento cerebral asociados con la comorbilidad entre la adicción a la cocaína y los trastornos de personalidad. A continuación desarrollamos los Objetivos específicos, que se asientan en un conjunto de asunciones derivadas de la investigación científica en personalidad, cognición y neuroimagen en cada uno de estos trastornos:

Ya que la impulsividad y las funciones ejecutivas se asocian tanto con la vulnerabilidad a la adicción como con sus consecuencias neuroadaptativas, nuestro primer Objetivo (**Objetivo 1 –Estudio 1**) fue el de determinar qué dimensiones de impulsividad y qué disfunciones ejecutivas son compartidas por la adicción a la cocaína y el juego patológico (una adicción conductual que comparte mecanismos de vulnerabilidad pero está libre de los efectos neuroadaptativos de las drogas) y cuáles son específicos de la dependencia a la cocaína y, por tanto, reflejan los resultados de la exposición a esta sustancia.

Ya que la adicción a la cocaína presenta altas tasas de comorbilidad con los trastornos de personalidad (especialmente con los del Clúster B) y comparten con éstos rasgos impulsivos y de desregulación afectiva y déficits cognitivos y cerebrales, nuestro segundo Objetivo (**Objetivo 2 –Estudio 2**) fue el de caracterizar las dimensiones de impulsividad, las disfunciones cognitivas y ejecutivas y las alteraciones neuroanatómicas que definen la comorbilidad entre los trastornos de personalidad del Clúster B y la dependencia a la cocaína.

Ya que una de las principales características cognitivas y de personalidad compartida por la adicción a la cocaína y los trastornos de personalidad son los déficits de

inhibición o regulación emocional, en especial en relación con afectos negativos, nuestro tercer Objetivo (**Objetivo 3 –Estudio 3**) fue el de investigar los patrones de activación y conectividad cerebral en consumidores de cocaína expuestos a un paradigma de experimentación y regulación de emociones negativas durante un escáner de resonancia magnética funcional (RMf).

Finalmente, para investigar el impacto de la comorbilidad psicopatológica en el funcionamiento cerebral asociado a la regulación emocional de individuos dependientes de cocaína, nuestro cuarto Objetivo (**Objetivo 4 –Estudio 4**) fue el de investigar los patrones diferenciales de activación y conectividad cerebral en consumidores de cocaína con y sin trastornos de personalidad del Clúster B expuestos a un paradigma de experimentación y regulación de emociones negativas durante un escáner de RMf.

Las principales Hipótesis que se derivan de estos Objetivos y que se detallan más minuciosamente en cada uno de los estudios que siguen, serían las siguientes:

Hipótesis 1: Los pacientes con dependencia de cocaína, en comparación con los pacientes diagnosticados con juego patológico y los controles no-consumidores, presentarán elevaciones en las dimensiones de impulsividad relacionadas con el afecto negativo (urgencia negativa) y en diversos componentes de las funciones ejecutivas.

Hipótesis 2: Los pacientes con dependencia de cocaína y trastornos de personalidad del Clúster B, en comparación con los pacientes con dependencia de cocaína sin comorbilidades y los controles no-consumidores, presentarán elevaciones en las dimensiones de impulsividad relacionadas con el afecto negativo (urgencia negativa), déficits de atención e inhibición y reducciones anatómicas en regiones fronto-límbico-estriadas.

Hipótesis 3: Los pacientes con dependencia de cocaína, en comparación con los controles no-consumidores, presentarán incrementos de la activación corticolímbica en respuesta a estímulos afectivos negativos y menor eficiencia de la conectividad fronto-límbica durante la aplicación de estrategias de regulación emocional de estos afectos negativos.

Hipótesis 4: Los pacientes con dependencia de cocaína y trastornos de personalidad del Clúster B, en comparación con los pacientes con dependencia de cocaína sin comorbilidades y los controles no-consumidores, presentarán reducciones de la activación corticolímbica en respuesta a estímulos afectivos negativos y menor eficiencia de la conectividad fronto-límbica durante la aplicación de estrategias de regulación emocional de estos afectos negativos.

CAPÍTULO 5: ESTUDIO 1

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Comparison of impulsivity and working memory in cocaine addiction and pathological gambling: Implications for cocaine-induced neurotoxicity

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Abstract

Background: The aim of this study was to compare the cognitive performance of cocaine dependent individuals (CDI) with that of pathological gamblers (PG). Cocaine dependence and pathological gambling share neurobiological vulnerabilities related to addiction, but PG are relatively free of the toxic consequences, such that any additional deficits observed in CDI may be interpreted as pertaining to specific drug effects.

Methods: We used a case-control observational design contrasting multiple measures of impulsivity (UPPS-P trait impulsivity, delay discounting) and executive measures of response inhibition (Stroop) and working memory performance (N-back) between groups of CDI (n=29), PG (n=23), and healthy controls (n=20). We conducted one-way ANOVAs, followed by planned pairwise tests and calculations of Cohen´s d to estimate significant differences between the groups.

Results: CDI, as compared to PG, had elevated scores on UPPS-P Negative Urgency and poorer performance on working memory (2-back). PG had steeper delay-discounting rates. Both groups had elevated Positive Urgency and poorer Stroop inhibition compared to controls. Peak amount of cocaine use was negatively correlated with working memory and response inhibition performance.

Conclusion: We found cocaine-related specific elevations in Negative Urgency and working memory deficits, putatively identified as cocaine neurotoxicity effects. Other aspects of impulsivity (Positive Urgency, Stroop inhibition) were increased across CDI and PG groups and may reflect vulnerability factors for addiction.

Key words: Cocaine, Pathological Gambling, Impulsivity, Working Memory, Neurotoxicity.

1. Introduction

Cocaine use is, after cannabis, the second most widely used illegal drug in Europe and the US, with one of the highest rates of substance dependence and treatment demand in the past year (EMCDDA Statistical bulletin, 2011; National Survey on Drug Use and Health, 2010). Cocaine addiction is characterized by rapid and intense hedonic effects and binging patterns of administration, followed by strong cravings, stress and negative affect during abstinence (Goldstein and Volkow, 2002). Chronic cocaine use is also associated with robust cognitive deficits, especially in the domains of working memory, response inhibition, and impulsive decision-making (see review in Fernández-Serrano et al., 2011). These cognitive-executive deficits have relevance for the etiology and treatment of cocaine use disorders: they may confer risk for drug use initiation, and facilitate transitions between recreational use and substance dependence (George and Koob, 2010; Verdejo-García et al., 2008); and they may also hinder cocaine use behavior change by buffering the beneficial effects of treatment interventions, or favoring poor compliance and relapse (Aharonovich et al., 2008; Streeter et al., 2008; Turner et al., 2009). To further understand these processes, it is important to dissociate the specific harmful effects of cocaine use on cognition, from the cognitive traits that predispose the initiation and escalation of drug-taking (Kreek et al., 2005).

The purpose of this study was to compare the cognitive performance of cocaine dependent individuals (CDI) with that of pathological gamblers (PG). Pathological gambling is increasingly viewed as a behavioral addiction, which shares core features with other substance addictions, including vulnerability mechanisms (e.g., genetics, impulsive personality), clinical features (e.g., craving, frequent relapses), and neurobiological alterations in frontostriatal systems (Bowden-Jones and Clark, 2011; Potenza, 2009). The direct comparison of CDI and PG may be informative for at least

two reasons. First, these two disorders have some notable similarities in terms of subjective effects, reinforcing schedules, and temporal patterns of consumption (characterized by intense episodes of repeated administration ["binges"] followed by periods of abstinence). In fact, the possibility to play a game of chance is an effective competitive option to decrease cocaine self-administration in humans (Vosburg et al., 2010). In these respects, cocaine addiction is arguably more similar to pathological gambling than other forms of drug dependence. Second, this comparison may increase our understanding about the extent of cognitive impairment occurring as a consequence of cocaine use. Cocaine dependence and pathological gambling share the neurobiological vulnerability that may confer higher risk for addictions, but one assumes that PG (without drug comorbidities) are spared from the toxic consequences, such that the additional deficits observed in cocaine addiction may be interpreted as pertaining to specific drug effects.

The neuropsychological literature in cocaine dependence highlight deficits related to impulsivity and executive functions. However, important differences emerge as a function of severity of cocaine dependence. For example, recreational cocaine users have deficits in inhibitory control, but not in working memory or set-shifting (Colzato et al., 2007, 2009). They also show relatively higher elevations of certain impulsivity dimensions, including Lack of Perseverance (akin to Barratt's attentional impulsivity) and Positive Urgency (the tendency to commit impulsive acts when under strong positive affect) (Verdejo-García et al., 2010). Conversely, cocaine dependence is associated with robust impairments in working memory, delay-discounting and reinforcement-learning/ perseveration (Fernández-Serrano et al., 2011; Woicik et al., 2011). These findings are in agreement with animal studies, which demonstrate that chronic administration of cocaine induces deficits in working memory and cognitive

flexibility, likely via neurotoxic effects on prefrontal cortex, hippocampus and basolateral amygdala (Porter et al., 2011; Stalnaker et al., 2007; Sudai et al., 2011). CDI also show prominent deficits in emotion regulation, which are associated with higher stress reactivity and diminished impulse control (Fox et al., 2011). Indeed, Negative Urgency –the tendency to commit impulsive acts when under intense negative affect, is the main predictor of the severity of addiction-related problems in stimulant-dependent individuals (Verdejo-García et al., 2007).

Previous neuropsychological studies in PG have also demonstrated robust deficits on several aspects of impulsivity –response inhibition, delay discounting and impulsive decision-making (Fuentes et al 2006; Goudriaan et al., 2006; Kertzman et al 2008; Lawrence et al., 2009; Michalczuk et al., 2011). As for trait impulsivity, the dimension of Positive Urgency is specifically associated with escalation of gambling behavior in community youths (Cyders and Smith, 2008), whereas PG show clinically significant increases both in Positive and Negative Urgency (Michalczuk et al., 2011). Conversely, the degree of executive dysfunction in PG is far from clear –studies reporting positive findings have been frequently conducted in small, unrepresentative samples (see review in Van Holst et al., 2010), and at least three studies have demonstrated a dissociation between cognitive impulsivity deficits, in the context of intact working memory or cognitive flexibility (Cavedini et al., 2002; Goudriaan et al., 2006; Lawrence et al 2009).

With these issues in mind, we compared the neuropsychological performance of CDI, PG, and healthy controls (HC) on probes of working memory and response inhibition/flexibility. We also employed the UPPS-P scale of impulsive behaviour to quantify the five dimensions pertaining to trait impulsivity, and the delay discounting questionnaire to assess relative preference for immediate vs. delayed rewards. We

hypothesized that CDI and PG would have similar cognitive deficits in domains associated with addiction liability, namely delay discounting and response inhibition. On the other hand, we predicted that CDI would have poorer performance than PG in domains associated with cocaine-induced neurotoxicity –working memory and flexibility. With regard to trait impulsivity, in accordance with previous evidence, we hypothesized that CDI and PG would share significant elevations in positive and negative urgency, with more robust effects of negative urgency on cocaine patients, due to the impact of the drug on emotion regulation systems.

2. Methods

2.1. Participants:

Twenty-nine CDI, 23 PG, and 20 non-drug using, non-gambling healthy controls (HC) participated in this study. CDI were recruited as they commenced treatment in the clinic "Centro Provincial de Drogodependencias (CPD)" in Granada (Spain). This public facility provides CBT-based treatment for substance use related disorders in an outpatient basis. PG were recruited as they commenced treatment in the outpatient center "Asociación Granadina de Jugadores en Rehabilitación (AGRAJER)" in Granada (Spain). This facility provides self-help oriented interventions for problem and pathological gambling, and is the only public-funded treatment service dedicated to these problems in the south of Spain. The inclusion criteria for these clinical groups included: (i) meeting DSM-IV criteria for cocaine dependence or pathological gambling –as assessed by the Structured Clinical Interview for DSM-IV Disorders –Clinician Version (SCID; First et al., 1996); (ii) having IQ levels above 80 –as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman, 1990); and (iii) having a minimum abstinence interval of 15 days –as determined by weekly urine

toxicological tests (CDI) or cross validated therapist- and self-reports (PG). Exclusion criteria were: (i) absence of any other Axis I or Axis II comorbid disorders –with the exception of alcohol abuse and nicotine dependence; (ii) absence of history of head injury and neurological, infectious, systemic or any other diseases affecting the Central Nervous System; (iii) having followed other treatments within the two years preceding the study onset; and (iv) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID, whereas Axis II disorders were assessed using the International Personality Disorders Examination (IPDE) (Loranger et al., 1994; Spanish version by López-Ibor et al., 1996). We also used the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners et al., 1999) to rule out the presence of adult ADHD symptoms. Healthy controls were recruited from local employment agencies taking care to match them to the clinical groups in the main demographic characteristics and IQ. In addition to the former exclusion criteria, healthy controls could not meet any diagnosis of substance use disorders –with the exception of nicotine dependence. Axis I and II disorders were also assessed in this group using the SCID, the IPDE and the CAAID. The three groups were matched on years of education and full IQ scores; however, they showed a trend to significant differences on age –PG were older than controls (Table 1). Age was not significantly correlated with any of the impulsivity or cognitive measures within the different groups; due to this lack of effects, and considering the low inter-quartile range of this variable [6-11] we did not use it as a covariate in subsequent analyses. Monthly amount of tobacco use was also significantly different between groups –as expected, both clinical groups had higher use than controls. Correlation analyses showed that tobacco use was only significantly associated with delay-discounting, such that we employed ANCOVA models to control for tobacco use in this measure. Monthly amount of alcohol use also showed a trend to

significant differences between the groups (p=0.049) –this was due to differences in alcohol use between CDI and HC, but not between CDI and PG. Correlation analyses showed that alcohol use was only significantly associated with Stroop Inhibition performance, and therefore we also employed ANCOVA models to control for alcohol use in this measure.

Table 1. Descriptive scores and between-group comparisons for sociodemographic and consumption patterns in cocaine dependent individuals (CDI), pathological gamblers (PG), and healthy controls (HC). Numbers represent means and standard deviations (in parentheses).

	CDI (n=29)	PG (n=23)	HC (n=20)	*p*
Demographic variables				
Age	33.2 (6.7)	35.6 (8.7)	28.6 (3.6)	0.005
Years of education	9.6 (1.6)	9.8 (2.2)	10.6 (1.8)	0.206
Total IQ	96.5 (9.9)	102.1 (20.3)	103.5 (7.9)	0.173
Patterns of drug use/gambling				
Quantity TMU cocaine (gr.)	17.26 (24.22)			
Quantity peak use cocaine (gr.)	60.32 (89.81)			
Age of onset cocaine use	22.33 (6.83)			
Duration of TMU cocaine (months)	53.08 (54.38)			
Quantity TMU alcohol (SDU)	36.1 (46.8)	12.6 (16.9)	9.4 (8.1)	0.049
Quantity peak use alcohol (SDU)	85.5 (76.3)	55.6 (69.6)	19.8 (16.2)	0.166
Quantity TMU tobacco (cig.)	605.2 (340.1)	570.0 (164.8)	181.6 (130.6)	0.006
Quantity peak use tobacco (cig.)	1120 (444.2)	1000 (173.2)	360 (216.3)	0.032
Quantity TMU gambling (episodes)		26.68 (19.24)		
Quantity peak use gambling (episodes)		87.15 (73.19)		
Age of onset gambling		22.68 (8.42)		
Duration of TMU gambling (months)		28.04 (23.06)		

Note. *TMU*, *typical monthly use; Peak Use*, monthly use during maximum use; *SDU*, standard drinking units; *gr.*, grams; *cig.*, cigarettes.

2.2. Instruments:

2.2.1. Questionnaire measures of impulsivity:

UPPS-P impulsive behavior scale (Smith et al., 2007; Whiteside and Lynam 2001; Spanish version by Verdejo-García et al., 2010): This is a 59-item inventory designed to measure five distinct personality pathways to impulsive behavior: Sensation Seeking, Lack of Perseverance, Lack of Premeditation, Negative Urgency, and Positive Urgency. The first 4 dimensions were included in the original version of the UPPS scale; the fifth dimension has been included based on recent work by Smith et al. (2007). Sensation Seeking (12 items) incorporates two aspects: 1) the tendency to enjoy and pursue activities that are exciting, and 2) an openness to trying new experiences that may or may not be dangerous; Lack of Perseverance (10 items) refers to an individual's ability to remain focused on a task that may be boring or difficult; Lack of Premeditation (11 items) refers to the tendency to think and reflect on the consequences of an act before engaging in that act; and finally urgency (26 items) refers to the tendency to experience strong impulses under conditions of negative affect (Negative Urgency –12 items) or positive affect (Positive Urgency –14 items). Each item on the UPPS is rated on a 4-point scale ranging from 1 (strongly agree) to 4 (strongly disagree). We obtained the total scores of each of these five UPPS–P dimensions for analyses.

Delay-discounting questionnaire (Kirby et al., 1999): This is a monetary-choice questionnaire asking for individual preferences between smaller, immediate rewards and larger, delayed rewards varying on their value and time to be delivered. The questionnaire is composed of a fixed set of 27 choices; the amounts of money and delays used in all 27 trials are reported in Kirby et al. (1999). The dependent measure was based on the area under the curve (AUC) methodology (Myerson et al., 2001), as

employed in recent studies investigating delay discounting in substance abusers (Field et al. 2006; Field et al. 2007). The AUC was calculated for the range of reward magnitudes included in the questionnaire (small, medium, and large), according to the formula (x2−x1)[(y1−y2)/2], where x1 and x2 are successive delays, and y1 and y2 are the subjective values associated with these delays. We also calculated the *k* parameter, which expresses the individual's sensitivity to delay, assuming a hyperbolic discounting function. The *k* parameter was calculated for each of the three reward magnitudes offered by the questionnaire: small, medium and large.

2.2.2. Cognitive measures of executive functions:

    Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (CWIT) (Delis et al., 2001)*:* This paper and pencil test is based on the Boston process approach (Milberg et al., 2009), which posits that there is a primary function that each test is designed to measure, but also component functions that contribute to performance on a particular task. Rather than a single test of executive control, the CWIT includes a series of four conditions that are administered to determine whether poor performance is due to specific impairment in the component functions of response speed (C1 + C2), response inhibition (C3 − C1), or response switching (C4 − C3). The first condition (C1) presents patches of colors and participants have to name them as quickly and accurately as they can. The second condition (C2) presents the words "red", "blue" and "green" printed in black ink and participants are asked to read aloud the words written. The third condition (C3) introduces the inhibition demand: the words "red", "blue" and "green" are printed in incongruent colors ink and participants have to name the color and ignore the word. In the fourth condition (C4) the items are similar to condition three but participants have to switch their response between naming the color

of the ink and ignoring the word or reading the word (when the item is inside a little box). Based on our study aims, we used as performance indices the time measures of response inhibition (C3 – C1), and response switching (C4 – C3), and the two error measures: inadvertent and self-corrected errors committed in C3 (inhibition errors) and C4 (shifting errors).

N-back (Watter et al., 2001): the N-back is a well-validated measure for assessment of working memory. The task consists of a continuous stream of letters that appeared on the computer screen one at a time at a constant rate. Participants were instructed to press two different buttons of the keyboard to indicate if each letter presented was (Y) or not (N) repeated with regard to the preceding letter (1-back block) or two preceding letters (2-back block) of the stream. Each block (1-back, 2-back) started with a practice row of 10 letters, followed by a continuous row of 100 letters. Each letter for the n-back trials was presented for 2 seconds. This task requires participants to temporarily maintain in memory and continuously update information about the identity and order of the letters appearing on the screen. We used the number of hits from the 1-back and 2-back conditions as the main dependent measures from this test. We also analyzed the number of false alarms of both conditions.

2.3. Statistical analysis:

All analyses were conducted in SPSS v. 17. We first explored the data in order to detect missing data points and potential outliers. In the DDT, we excluded one individual from the PG group who uniformly selected the delayed options across the 27 items, such that the pre-specified amounts and delays in the questionnaire failed to isolate indifference points. In the Stroop test, one healthy control showed inhibition scores more than 2 SD above the mean of the group, and was excluded from the Stroop analyses. To test the

main hypotheses, we conducted one-way ANOVAs. Post-hoc comparisons used the Least Significant Difference, which is appropriate for deconstructing between-groups differences in 3-group designs (Cardinal and Aitken, 2006). Cohen´s d values were calculated for each of the between-groups contrasts to index effect sizes. We used Pearson correlation analyses to examine the association between patterns of drug use (typical dose and peak use) on performance measures.

3. Results

3.1. Differences between CDI, PG and HC on Impulsivity measures:

UPPS: We found significant differences between the groups in the dimensions of Positive Urgency, $F_{(2,64)}=10.92$, $p<0.001$, and Negative Urgency, $F_{(2,64)}=19.48$, $p<0.001$. Pairwise tests showed that in the case of Positive Urgency both CDI and PG scored higher than HC ($p<0.001$, and $p=0.004$ respectively), but the CDI and PG groups did not differ significantly ($p=0.108$). In the case of Negative Urgency, CDI scored significantly higher than both PG ($p=0.01$) and HC ($p<0.001$); PG also scored higher than HC ($p=0.001$) (see Table 2). The other UPPS subscales did not display significant between-group differences: Lack of Premeditation $F_{(2,64)}=2.79$, $p=0.069$; Lack of Perseverance $F_{(2,64)}=1.82$, $p=0.17$; Sensation Seeking $F_{(2,64)}=1.07$, $p=0.349$.

DDT: We found significant differences between the groups in the AUC index, $F_{(2,67)}=4.26$, $p=0.018$. Pairwise tests showed that PG had significantly smaller AUC than both CDI and HC ($p=0.024$, and $p=0.008$ respectively). CDI and HC did not differ significantly in AUC ($p=0.52$) (Figure 1). The 3 (Group) * 3 (Reward Magnitude) mixed-design ANOVA on log-transformed k scores showed significant main effects of Magnitude, $F_{(2,67)}=37.65$, $p<0.001$, and Group, $F_{(2,68)}=3.28$, $p=0.04$, but no effects of the interaction (Figure 1). The one-way ANOVA on the log-transformed average k

scores showed significant differences between the groups, $F_{(2,67)}=3.99$, p=0.02. Pairwise tests showed that PG had significantly higher k values than both CDI (p=0.03) and HC (p=0.01); there were no significant differences between CDI and HC (p=0.62). ANCOVA models accounting for tobacco use did not alter results.

3.2. Differences between CDI, PG and HC on cognitive measures of executive functions:

Stroop: We found significant differences between the groups in the inhibition index (C3 − C1), $F_{(2,68)}=4.04$, p=0.022, but not in the shifting index (C4 − C3), $F_{(2,68)}=0.5$, p=0.607. Pairwise tests on inhibition scores showed that CDI performed poorer than HC (p=0.006). PG also performed poorer than controls at a trend level (p=0.056). There were no significant differences between CDI and PG (p=0.418). We also conducted non-parametric analyses on the number of inhibition errors. Results showed significant differences between groups, due to higher number of errors in both CDI and PG as compared to controls. ANCOVA models accounting for alcohol use did not alter results.

N-back: We found no significant differences between the groups in the main index of number of hits of the 1-back condition, $F_{(2.69)}=2.060$, p=0.135. Conversely, we found significant differences between the groups in the main index of number of hits of the 2-back condition, $F_{(2,69)}=3.37$, p=0.04. Pairwise tests showed that CDI performed significantly poorer than both PG (p=0.03), and HC (p=0.033). There were no significant differences between PG and HC (p=0.967). There were no significant differences between the groups on false alarms in the 1-back, $F_{(2,69)}=2.06$, p=0.086, or 2-back, $F_{(2,69)}=1.88$, p=0.16.

Table 2. Descriptive scores, significant results from group comparisons and effect sizes (Cohen's d) between cocaine dependent individuals (CDI), pathological gamblers (PG), and healthy controls (HC). Numbers represent means and standard deviations (in parentheses).

	CDI (n=24)	PG (n=23)	HC (n=20)	F test	CDI vs. PG	CDI vs. HC	PG vs. HC
UPPS subscales							
Negative urgency	31.9 (6.2)*+	27.7 (4.2)*	21.8 (5.2)	$F(2, 64)=19.48, p=0.000$	$d=0.77$	$d=1.72$	$d=1.23$
(Lack of) premeditation	24.5 (4.3)*	24.8 (3.2)*	22.4 (2.9)	$F(2, 64)=2.79, p=0.069$	$d=0.07$	$d=0.51$	$d=0.69$
(Lack of) perseverance	20.5 (4.4)	21.2 (4.9)	18.8 (3.0)	$F(2, 64)=1.82, p=0.170$	$d=0.14$	$d=0.43$	$d=0.58$
Sensation seeking	28.3 (7.3)	29.8 (5.7)	31.5 (8.2)	$F(2, 64)=1.07, p=0.349$	$d=0.21$	$d=0.40$	$d=0.23$
Possitive urgency	31.7 (8.7)*	28.1 (7.0)*	21.1 (6.3)	$F(2, 64)=10.919, p=0.000$	$d=0.45$	$d=1.31$	$d=0.98$
Delay discounting test							
AUC- Total	0.47 (0.2)	0.32 (0.1)+	0.52 (0.2)	$F(2, 67)=4.266, p=0.018$	$d=0.75$	$d=0.20$	$d=0.95$
Cognitive measures							
Stroop inhibition index	23.1 (13.3)*	20.4 (12.7)	13.4 (6.1)	$F(2, 68)=4.044, p=0.022$	$d=0.20$	$d=0.66$	$d=0.46$
Stroop shifting index	12.9 (10.8)	13.7 (10.0)	10.84 (6.3)	$F(2, 67)=0.504, p=0.607$	$d=0.07$	$d=0.23$	$d=0.45$
1n-back number of hits	26.8 (2.6)	27.8 (1.6)	28 (1.8)	$F(2.69)=2.060, p=0.135$	$d=0.44$	$d=0.53$	$d=0.14$
1n-back false alarms	0.96 (1.1)	0.73 (0.1)	0.3 (0.7)	$F(2.69)=2.542, p=0.086$	$d=0.20$	$d=0.66$	$d=0.46$
2n- back number of hits	23.3 (5.1)*+	26.0 (4.41)	26.1 (3.0)	$F(2, 69)=3.374, p=0.040$	$d=0.56$	$d=0.63$	$d=0.17$
2n- back false alarms	4.68 (4.65)	2.78 (2.41)	3.25 (3.36)	$F(2.69)=1.881, p=0.160$	$d=0.49$	$d=0.34$	$d=0.16$

* p<0.05 between CDI and PG vs Controls;
+ P<0.05 between CDI vs PG
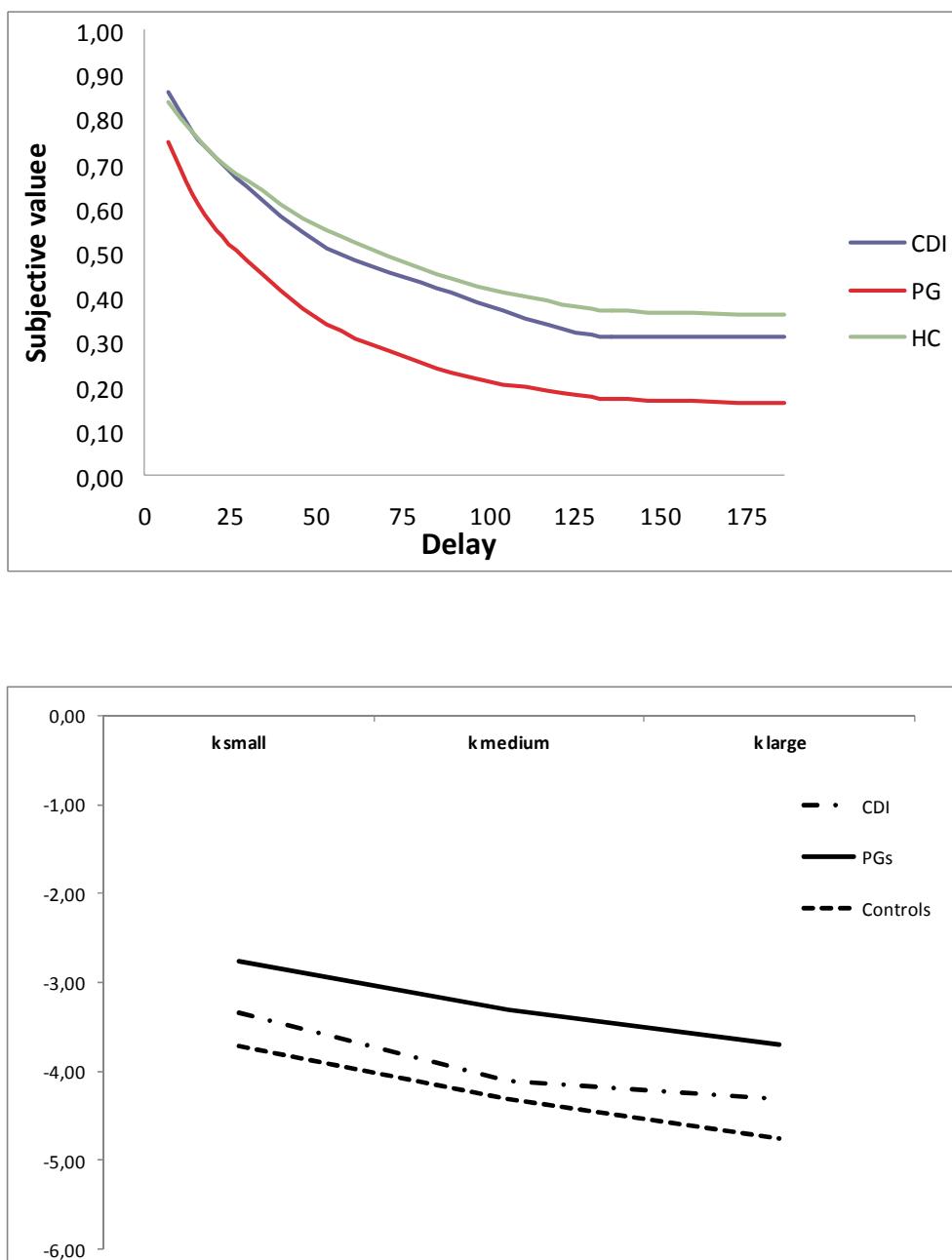
Figure 1. Area under the Curve (Upper panel) and k values (Bottom panel) as a function of reward magnitude in cocaine dependent individuals (CDI), pathological gamblers (PG), and healthy controls (HC).

3.3. Correlations with patterns of drug use:

We display the inter-correlations between the different measures in Table 3. DDT AUC was significantly negatively correlated with regular cocaine use, r=-0.36, p=0.044, and regular tobacco use, r=-0.33, p=0.05. Stroop-inhibition performance was significantly correlated with peak cocaine use, r=0.48, p=0.014, and regular alcohol use, r=0.36, p=0.01 –in both cases greater use correlated with larger inhibition time or worse performance. N-back performance was significantly negatively correlated with both regular cocaine use, r=-0.43, p=0.014, and peak cocaine use, r=-0.49, p=0.01.

4. Discussion

We found that CDI, as compared to PG, had elevated scores on Negative Urgency and poorer performance on working memory (2-back). Conversely, compared to the cocaine group, pathological gamblers had steeper delay-discounting rates. Both cocaine dependent individuals and pathological gamblers, when compared to healthy controls, had elevated Positive Urgency and poorer response inhibition. Correlation analyses showed significant negative associations between the peak amount of cocaine use and performance on the working memory and response inhibition tasks. Typical monthly use of cocaine was also negatively associated with delay-discounting. These results support our initial hypotheses, by showing common correlates of substance and behavioral addictions on response inhibition and Positive Urgency, and additional cocaine-related effects on working memory and Negative Urgency.

The finding that cocaine dependence is specifically associated with working memory deficits is in agreement with findings from animal models showing cocaine-induced neurotoxicity in prefrontal and hippocampal neurons which result in working memory impairments (Canales, 2010; George et al., 2008; Porter et al., 2011; Sudai et

al., 2011). Our findings are also consistent with results from previous neuropsychological studies, which consistently point to this function as robustly impaired in chronic cocaine users compared to healthy controls (Fernández-Serrano et al., 2011); interestingly, these deficits are not observed in recreational cocaine users (Colzato et al., 2009). Neuroimaging studies have also demonstrated that CDI have reduced dorsolateral prefrontal and inferior parietal cortex activations in response to working memory loads similar to the ones used in our behavioural task (Bustamante et al., 2011; Tomasi et al., 2007). Notably, performance differences were observed in the 2-back condition, which is particularly sensitive to dorsolateral prefrontal and parietal cortex dysfunction with regard to the 1-back condition (Carlson et al., 1998), in which we failed to find significant effects. Critically, the main novelty of our findings is the use of a control group of PG –who constitute a model of 'drug free' addiction without neurotoxicity (Bechara 2003, Verdejo-Garcia et al 2008). Because pathological gambling is mainly associated with neurobiological abnormalities in ventral frontostriatal circuitry (Potenza et al., 2003, Reuter et al., 2005), our finding may indicate that chronic cocaine use, on top of addiction-related neurobiological vulnerabilities, may induce additional neuroadaptations in more extensive prefrontal and parietal regions. A second relevant difference between CDI and PG was that the former had elevated Negative Urgency scores. Previous results had shown that both CDI and PG have increased Negative Urgency scores with regard to healthy controls (Fernández-Serrano et al., 2011b, Michalczuk et al., 2011). The increased levels found in the cocaine group may indicate that cocaine exerts stronger neuroadaptations in two other neural systems: the paralimbic network (medial orbitofrontal-anterior cingulate-insula), which has been associated with urgency scores in an fMRI study (Joseph et al., 2009), and the HPA-stress regulation system, which is sensitive to cocaine-induced

neuroadaptations in animal models (Koob and Volkow, 2010), and is sensitized in chronic cocaine dependent individuals (Sinha et al., 2003).

In terms of resemblances vs. differences between these two forms of addiction, we found that both cocaine and gambling pathologies share problems with Positive Urgency and response inhibition. The finding that both groups have elevations in Positive Urgency in fitting with evidence showing that this dimension of impulsivity is longitudinally predictive of gambling behavior among community youths (Cyders et al., 2008). Positive Urgency is also elevated in non-treatment seeker recreational users not meeting criteria for psychostimulant dependence (Verdejo-García et al., 2010). Together, these findings suggest that Positive Urgency may act as a vulnerability marker for the development of different forms of addiction. As for response inhibition, although we did not find substantial performance differences between CDI and PG, correlational analyses indicated that the peak amount of cocaine use was negatively associated with inhibitory control performance (see also Bolla et al., 2004), suggesting that persistent cocaine binge use patterns may further exacerbate inhibition deficits – which are arguably present before addiction onset and predispose to both behavioral and substance addictions (Verdejo-García et al., 2008). An unexpected finding was the fact that PG had steeper delay discounting rates than both CDI and healthy controls. Previous studies had shown that both PG and cocaine users have increased discounting rates (see review in Reynolds, 2008), and we did in fact detect a significant association between monthly amount of cocaine use and steeper discounting curves in that group. Therefore, the discrepancy between ours and previous results may stem from two sources: (i) as a group, the CDI included in this study had overly less severe consumption patterns than those in studies showing positive findings, and (ii) some of the previous studies have used less stringent exclusion criteria. For example, we

specifically excluded patients having comorbid ADHD or Axis II disorders (e.g., antisocial personality disorder), which are neatly characterized by increased sensitivity to reward and impulsivity (Hurst et al., 2011; Petry, 2002).

In conclusion, we found cocaine-related specific elevations in Negative Urgency and working memory deficits (putatively identified as cocaine neurotoxicity effects), whereas CDI shared increased Positive Urgency and impaired response inhibition with PG (regarded as vulnerability traits conferring risk for addiction). This study presents a number of strengths, including the careful recruitment of CDI and PG who were commencing treatment and the rigorous control of potential confounders: IQ, comorbid Axis I and II psychopathology, and active drug use in the CDI and the PG groups. Some relevant not-fully controlled potentially contributing confounders are amount of nicotine use, which was increased in both clinical groups with respect to controls, and amount of alcohol use, which was increased in CDI with respect to controls –but not with respect to PG. However, tobacco use was only significantly correlated with delay discounting, and alcohol use was only significantly with Stroop Inhibition performance; in both cases, covariate analyses accounting for these effects did not alter results. In addition, we should note some other relevant limitations, such as the limited sample size –which was nonetheless sufficient to detect robust effect sizes – and the lack of correlation between gambling-severity measures and impulsivity and cognitive indices; such that more refined measures of gambling patterns should be incorporated in future studies.

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CAPÍTULO 6: ESTUDIO 2

(Enviado a la Revista Drug and Alcohol Dependence)

Negative urgency, disinhibition and reduced temporal pole gray matter characterize the comorbidity of cocaine dependence and personality disorders

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Abstract

Background: Individuals with cocaine dependence and co-occurring personality disorders are more likely to have increased impulsivity, dysfunctional beliefs, executive dysfunction and brain structural abnormalities by virtue of the conjoint impact of both pathologies.

Methods: We recruited 32 cocaine dependent patients with comorbid Cluster B personality disorders, 44 cocaine dependent patients without comorbidities and 34 non-drug-using controls. They completed the UPPS-P impulsivity scale, the Personality Belief Questionnaire, and executive function tests of working memory, attention/response inhibition and shifting. A subsample (n=61) was also scanned using Magnetic Resonance Imaging. We used univariate ANOVAs for group comparisons, and tested the predictive capacity of cognitive measures on personality diagnoses with multivariate logistic regression.

Results: Cocaine dependent patients with personality disorders had elevated negative urgency and borderline beliefs, decreased inhibition and attention regulation, and reduced temporal pole gray matter with respect to the rest of the sample. Trait and cognitive measures correctly classified 73% of comorbid patients (60% sensitivity and 82% specificity).

Conclusion: The co-occurrence of cocaine dependence and personality disorders is associated with negative-mood impulsivity and beliefs, executive dysfunction and temporal pole attrition.

Key words: Cocaine, Personality Disorders, Impulsivity, Executive Functions, Volumetric Based Morphometry, Temporal Pole.

1. Introduction

Cocaine dependence is frequently associated with comorbid psychiatric disorders, being the highest rates for mood, anxiety and personality disorders –especially Cluster B antisocial and borderline diagnoses (Chen et al., 2011). The co-occurrence of personality disorders is particularly influential for cocaine addiction severity and treatment outcomes; for example, the presence of comorbid personality disorders is associated with heavier cocaine intake, lower rates of treatment request, and decreased likelihood of cocaine dependence remission (Ford et al., 2009; López-Quintero et al., 2011). However, little is known about the trait, cognitive and neurobiological characteristics that define the comorbidity between cocaine dependence and personality disorders. The upcoming classification approaches to psychiatric diagnosis have posited that the quest for these characteristics should rest upon dimensional traits and neurocognitive endophenotypes linked to the addiction and personality disorders clinical phenotypes (Livesley, 2011; Robbins et al., 2012). In accordance to existing evidence, these characteristics may include impulsivity and executive dysfunction (including disinhibition), which are associated with deficits in frontostriatal regions (Robbins et al., 2012).

Several studies have underscored the impact of impulsivity on both cocaine addiction and personality pathology (Verdejo-García et al., 2008). More recently, multidimensional approaches to impulsive behavior have revealed that distinct facets of impulsivity are associated with particular forms of psychopathology (Whiteside and Lynam, 2003). In particular, the facet of negative urgency (i.e., the tendency to act impulsively when under negative affect) is specifically increased in cocaine dependent patients compared to pathological gamblers (Albein-Urios et al., 2012). This facet,

which is conceptually linked to the trait of negative affectivity, is also a significant predictor of externalizing and borderline psychopathology (Settles et al., 2012). With regard to executive control, factorial models describe at least three independent components, namely updating, inhibition and switching (Miyake et al., 2000), which are further assisted by fluent energization and allocation of attentional resources (Stuss, 2011). Both patients with cocaine dependence and patients with Cluster B personality disorders exhibit lower performance on cognitive tests of each of these components compared to healthy controls (Haaland et al., 2009; Verdejo-García and Pérez-García, 2007). Both impulsivity and executive control are associated with gray matter deficits in frontostriatal, temporal and limbic brain regions among cocaine dependent patients (Moreno-López et al., 2012). In the case of personality disorders, gray matter reductions have been observed in frontal, hippocampal and amygdala regions (Ruocco et al., 2012; Soloff et al., 2008).

The overlap between impulsive facet traits, executive control deficits and lower frontal, temporal and limbic gray matter in patients with cocaine dependence and patients with personality disorders suggests that the co-occurrence of both disorders may be associated with additive or synergistic deterioration of these neurocognitive characteristics. In addition, patients with personality disorders also exhibit marked dysfunctional beliefs associated with their disorders (Beck et al., 2001). These dysfunctional beliefs would foster a narrowed set of overused emotional and behavioral dispositions that allegedly form the core clinical phenotype of personality disorders (Fournier et al., 2012). Because these beliefs promote recurrent unpleasant emotions and prepotent actions schemas they should be positively correlated with impulsivity and negatively correlated with executive control.

To address these unresolved questions, the aims of this study were: (i) to compare impulsivity, executive control and gray matter volumes in cocaine dependent patients with vs. without Cluster B personality disorders, (ii) to explore the association between dysfunctional beliefs and neurocognitive characteristics in cocaine dependent patients with vs. without Cluster B personality disorders, and (iii) to explore if the combination of neurocognitive characteristics and cognitive beliefs predicts the presence of Cluster B personality diagnosis. We hypothesized that: (i) cocaine dependent patients with comorbid personality disorders would have increased negative urgency, decreased executive control, and reduced gray matter volumes in frontal, temporal and limbic regions; (ii) dysfunctional beliefs will be positively correlated with impulsivity and negatively correlated with executive control; and (iii) the neurocognitive characteristics and the dysfunctional beliefs would significantly predict the presence of comorbid personality pathologies.

2. Methods

2.1. Participants:

Seventy-six cocaine users and 34 non-drug-using controls statistically matched for age and education distributions were recruited for study purposes (see Table 1). Cocaine users were classified in two groups based on personality disorders diagnosis: 32 participants met criteria for cocaine dependence and personality disorders (13 with histrionic diagnosis, 12 with borderline diagnosis, 6 with antisocial diagnosis and 1 with narcissistic diagnosis) and 44 participants met criteria for cocaine dependence without comorbidities.

Cocaine users were recruited as they started treatment in the clinic "Centro Provincial de Drogodependencias (CPD)" in Granada (Spain), which provides

behavioral treatment for substance-related disorders in an outpatient setting. The inclusion criteria for the cocaine groups were defined as follows: (i) age range between 18 and 45 years old; (ii) IQ levels above 80 –as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman, 2001); (iii) meeting DSM-IV criteria for cocaine dependence –as assessed by the Structured Clinical Interview for DSM-IV Disorders –Clinician Version (SCID) (First et al., 1997); (iv) being treatment commencers; and (v) abstinence duration >15 days. Abstinence was confirmed by twice weekly urine tests plus an ad hoc test on the testing days. Inclusion criteria for cocaine dependent patients with comorbid personality disorders were restricted to diagnoses pertaining to Cluster B, which are the more prevalent among cocaine users (1). Axis II disorders were assessed using the International Personality Disorders Examination (Loranger et al., 1994). The exclusion criteria were: (i) the presence of any other Axis I disorders –with the exceptions of alcohol abuse, nicotine dependence and attention deficit and hyperactivity disorder (ADHD) –as measured by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners, 1999); (ii) history of head injury or neurological, infectious, systemic or any other diseases affecting the central nervous system; (iii) having followed other treatments within the two years preceding the study onset; and (iv) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID.

Healthy controls were recruited from local employment agencies taking care to match them to the clinical groups in the main demographic characteristics. In addition to the former exclusion criteria, healthy controls could not meet any diagnosis of substance-related disorders –with the exception of nicotine dependence. Axis I and II disorders were also assessed in this group using the SCID, the IPDE and the CAAID.

All the diagnoses were conducted by a board clinical psychologist, whereas all subsequent tests were administered by an independent (blind to diagnosis) evaluator.

86

Table 1. Demographic and alcohol and drug use characteristics of the participants.

	CDI PDB (n=32)		CDI (n=44)		Controls (n=34)		Statistic	
	M	SD	M	SD	M	SD	F	p
Demographics								
Age	33.13	7.7	31.28	6.5	30.5	4.3	1.462	0.236
Years of education	10.63	2.2	10.28	1.7	10.47	1.7	0.309	0.730
Verbal IQ	100.16	10.23	99.21	8.3	106.14	8.4	6.197	0.003
Performance IQ	95.87	11.75	96.61	9.84	103.52	9.04	5.800	0.004
Total IQ	95.7	11.04	95.02	8.09	103.02	7.8	8.546	0.000
Patterns of drug use								
Cocaine use age at onset	21.29	6.33	20.89	6.06	--	--	0.074	0.786
Cocaine grams per month	16.35	21.38	15.57	20.85	--	--	0.024	0.877
Cocaine duration of use (months)	50.09	44.07	44.71	49.97	--	--	0.001	0.973
Cocaine duration of abstinence (months)	4.47	7.60	2.36	3.86	--	--	2.366	0.128
Alcohol use age at onset	19.17	3.47	17.44	4.23	18.50	4.45	1.289	0.282
Alcohol standard units per month	42.28	55.96	35.60	53.56	10	8.71	3.058	0.053
Alcohol duration of use (months)	73.54	74.13	85.20	75.35	82.20	52.22	0.200	0.819
Tobacco use age at onset	17.33	5.79	16.33	3.64	18.60	5.39	0.904	0.411
Tobacco cigarettes per month	470.90	279.69	583.33	307.94	271	203.75	4.626	0.014
Tobacco duration of use (months)	133.71	105.00	100.83	96.05	77.10	93.87	1.276	0.287

2.2. Instruments

Trait Impulsivity: UPPS-P impulsive behavior scale (Whiteside and Lynam, 2001): This is a 59-item inventory designed to measure five personality pathways to impulsive behavior: Sensation Seeking, Lack of Perseverance, Lack of Premeditation, Negative Urgency, and Positive Urgency. The reliability of the different subscales (Cronbach's α) ranged from 0.75 (lack of perseverance) to 0.93 (positive urgency). We obtained the total scores of each of these UPPS-P dimensions for analyses.

Dysfunctional beliefs: Personality Belief Questionnaire; *PBQ* (Beck and Beck, 1991). The PBQ is a self-report questionnaire that consists of nine scales that measure specific beliefs and assumptions associated with the different personality disorders. Here we only used the four scales corresponding to Cluster B personality disorders: antisocial, borderline, histrionic and narcissistic. The Spanish version of the scale holds appropriate psychometric characteristics and the reliability of the different scales (Cronbach's α) in this sample ranged from 0.71 (narcissistic) to 0.88 (borderline).

Executive Function Tests: We used a cognitive battery designed to measure the three executive components plus attention allocation skills though well-validated tests:

Updating: *Letter Number Sequencing* (Wechsler, 2008) and *2-back task* (Watter *et al.*, 2001). The performance indices obtained from these tests were the number of hits.

Inhibition: *Stroop Color-Word Interference Test* (Delis et al., 2001). The performance index was the inhibition score (color-word interference time minus color-naming time).

Shifting: *Category Test* (DeFilippis, 1993). We used the computerized abbreviated version of this test (124 stimuli). The performance index was the total number of errors.

Attention: *d2 Cancellation Test* (Brickenkamp, 2002). This test includes 14 different lines of letters including targets (d's with two dashes) and distracters (e.g., d's with less than two dashes, p's, etc). Performance indices were: efficiency (total number of trials minus total number of errors), concentration (number of correct items minus commission errors), and fluctuation (maximum total items processed in a trial minus minimum total items processed in a trial). These indices measure selective attention, concentration and fluctuation of attentional resources respectively.

2.3. MRI acquisition and pre-processing:

Participants were scanned on a 3T whole body MRI scanner (Phillips Achieva X-series) operating with an eight-channel phased array head coil. For each participant, a 3D volume was acquired using a T1-weighted turbo-gradient-echo sequence (3D-TFE) in the sagittal plane, with a 0.94x0.94x1.0 mm resolution (160 slices, FOV=240x240 mm2, matrix 256 x 256), TR=8.3 ms, TE=3.8 ms, TI = 1022.6264 ms, and flip angle=8°. This sequence was optimal for reducing motion sensitivity, susceptibility artifacts and field inhomogeneities. Structural imaging data were pre-processed and analyzed using statistical parametric mapping 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab R2007b (MathWorks, Natick, MA, USA). We used the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) to segment raw images and extract probabilistic maps of gray matter, white matter and cerebrospinal fluid; normalize the gray matter segments (using DARTEL normalization) to a gray matter template in MNI space; modulate normalized gray

matter images with the Jacobian determinants (from the flow-fields derived from the normalization step) to restore volumetric information; and finally smooth images with a 3-D Gaussian filter of 8mm full width at half maximum (FWHM).

2.4. Statistical Analyses:

2.4.1. Behavioral analyses:

These analyses were conducted in SPSS v. 19 and Stata v. 11. We first explored the data to detect missing data points and potential outliers. All the data missing points pertained to the questionnaire measures (incomplete questionnaires), such that in the UPPS-P analyses the groups sizes were n=25 (comorbid), n=35 (non-comorbid) and n=34 (controls), and in the PBQ analyses the groups sizes were n=23 (comorbid), n=32 (non-comorbid) and n=30 (controls). Cognitive tests were completed by all participants. After accounting for questionnaire data misses, the sample power still yielded an adequate estimated value of 0.88 (Erdfelder et al., 1996). We next checked the normality of the distribution for the main dependent variables using Kolgomorov-Smirnov tests. All measures met normality assumptions with the exceptions of PBQ borderline scale, Stroop inhibition and d2 fluctuation scores. Once taken into account their initial distributions we proceeded to log-transform the first two variables and to square-root-transform the latter one, after which all of them fitted with normality assumptions. To test the first hypotheses, we conducted one-way ANOVAs. Post hoc comparisons used the least significant difference, which is appropriate for deconstructing between-groups differences in 3-group designs (Cardinal and Aitken, 2006). Cohen's *d* values were calculated for each of the between-groups contrasts to index effect sizes. To test the second hypothesis, we conducted Pearson correlation analyses to examine the association between PBQ-indexed dysfunctional beliefs and executive performance. To

test the third hypothesis, we performed a multivariate logistic regression model including the variables showing significant differences between cocaine users with and without comorbidities as predictors and the actual clinical diagnoses as dependent measure.

2.4.2. Imaging analyses:

These analyses were performed in a subsample of 61 participants: 20 cocaine dependent individuals with Cluster B personality disorder (11 with borderline diagnosis, 6 with histrionic diagnosis and 3 with antisocial diagnosis), 20 cocaine dependent individuals without comorbidities, and 21 controls. This subsample did not diverge from the main sample in any of the demographic or clinical characteristics.

We first analyzed gray matter differences between cocaine dependent individuals with comorbid personality disorders, cocaine dependent individuals without comorbidities, and non-drug-using controls. The general linear model was used to conduct voxel-wise comparisons between the three groups (i.e. controls>cocaine without comorbidities>cocaine with Cluster B diagnoses) using an ANCOVA model with total gray matter volume as a covariate. We additionally explored the associations between gray matter and UPPS-P, PBQ and executive tests with the aim of detecting brain regions showing differential correlations as a function of group (controls vs. cocaine without comorbidities vs. cocaine with Cluster B diagnoses).

The statistical significance threshold for comparisons was established combining voxel significance and cluster extent thresholds. For all comparisons, spatial extent thresholds were determined by 1000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox (individual voxel threshold probability of 0.001, cluster connection radius of 5mm, FWHM smoothness of 8 mm, whole brain

mask volume of 103900 voxels). The Wake Forrest University PickAtlas (Maldjian et al., 2003) was used to create a mask that encompassed the brain regions showing significant gray matter reductions in cocaine users as found in our previous VBM study (Moreno-López et al., 2012). These regions included the medial and inferior frontal gyrus, the cingulate gyrus, the caudate head, the amygdala/hippocampus, the insula and the middle/inferior temporal gyrus. The minimum spatial cluster extent (K_E) resulted to satisfy a family-wise error rate correction of $P_{FWE}<0.05$ was 188 voxels, although this resulting cluster extent threshold was spatially adjusted to account for the non-isotropic smoothness of VBM images using the approach proposed by (Raftery, 1996).

3. Results

3.1. Background and clinical characteristics:

Both groups of cocaine users had lower IQ levels than controls but they did not differ between each other. Sex was also unbalanced between the groups due to a higher number of women in the cocaine personality disorder group (10 vs. 2 in the non-comorbid and control groups). Both unbalances have been described by epidemiological studies as inherent to the populations addressed (Chen et al., 2011). Therefore, we reasoned that these differences do not reflect sampling mismatches, such that they were not further controlled for. Seven cocaine patients of the cocaine comorbid group (22%) and four patients of the non-comorbid group (9%) met criteria for ADHD diagnosis; however, these proportions were not different between the groups (p>0.05). With respect to drug use, both groups of cocaine users had similar distributions for age at onset, monthly use and duration of cocaine and alcohol use. Tobacco use was greater in both cocaine groups compared to controls, but patterns of use did not differ in the cocaine groups.

3.2. Cognitive and brain structural characteristics of cocaine dependent patients with vs. without comorbidities:

3.2.1. Trait Impulsivity:

The two groups of cocaine users had significantly higher scores than controls on the dimensions of positive and negative urgency, lack of premeditation and lack of perseverance. The cocaine personality disorder group, compared to the cocaine non-comorbid group, showed significantly higher scores on negative urgency (Table 2, upper panel).

3.2.2. Dysfunctional beliefs:

The two groups of cocaine users had significantly increased levels of dysfunctional beliefs than controls with respect to the four dimensions of interest: antisocial, borderline, histrionic, and narcissistic. The cocaine personality disorder group, compared to the cocaine non-comorbid group, only showed significantly higher scores in the borderline dimension (Table 2, middle panel).

3.2.3. Executive functions:

The two groups of cocaine users had significantly worse performance than controls in all the executive domains and tests: updating (Letter Number Sequencing and 2-back), inhibition (Stroop), rule shifting (Category test), and attention (d2). The cocaine personality disorder group, compared to the cocaine non-comorbid group, showed significantly poorer performance on Stroop inhibition and d2 fluctuation scores (Table 2, lower panel).

Table 2. Descriptive scores, statistics and effect sizes for between-group differences on trait impulsivity (UPPS-P), cognitive beliefs (PBQ) and neurocognitive measures of executive function.

	CDI PDB		CDI		Controls		Statistics		Effect Sizes (Cohen's *d*)		
	M	SD	M	SD	M	SD	F	p	CDI PDB vs. CDI	CDI PDB vs. HC	CDI vs. HC
UPPS-P											
Negative urgency	35.64	5.09	31.37	6.65	22.23	5.82	39.96	0.000	0.70	2.42	1.46
(Lack of) premeditation	26.36	6.73	24.97	5.02	22.82	3.80	3.55	0.033	0.24	0.67	0.48
(Lack of) perseverance	23.16	5.24	20.62	4.51	19.91	3.52	4.16	0.019	0.52	0.75	0.17
Sensation seeking	30.58	7.51	28.88	8.07	30.14	8.08	0.38	0.684	0.21	0.06	0.15
Positive urgency	34.64	9.67	30.68	10.09	21.85	6.40	16.80	0.000	0.45	1.61	1.04
PBQ											
Antisocial	29.60	9.47	24.53	11.03	18.13	7.34	9.60	0.000	0.48	1.37	0.67
Borderline	19.17	9.31	12.28	9.47	6.93	6.07	13.87	0.000	0.73	1.60	0.66
Histrionic	18.6	10.04	15.09	7.17	11.93	8.48	4.03	0.021	0.41	0.72	0.40
Narcissistic	19.47	9.03	15.84	8.12	12.76	6.93	4.59	0.013	0.42	0.84	0.40
Cognitive measures											
LNS (Hits)	9.12	3.24	8.97	2.58	11.64	2.41	10.54	0.000	0.05	0.88	1.06
2-back (Hits)	23.12	4.51	23.34	5.04	26.17	3.43	5.10	0.008	0.05	0.76	0.64
d2 (Total Responses)	410.21	85.01	417.58	80.08	490.70	72.97	10.85	0.000	0.09	1.01	0.94
d2 (Concentration)	150.62	41.51	161.60	37.95	198.76	35.99	14.60	0.000	0.27	1.24	1.00
d2 (Fluctuation)	17.21	9.26	12.88	3.99	11.58	3.19	12.27	0.000	0.79	1.05	0.35
Stoop inhibition (Time s.)	27.93	17.11	20.79	11.71	17.11	9.26	5.98	0.003	0.50	0.79	0.34
Category test (Errors)	46.29	17.7	41.28	16.96	30.64	18.97	6.59	0.002	0.28	0.85	0.59

3.2.4. Volumetric brain differences:

Results showed a linear decrease in the volume of the right middle temporal pole, with controls having more gray matter density than cocaine users without comorbidities, who in turn exhibited larger gray matter density than cocaine users with personality disorders (Figure 1).
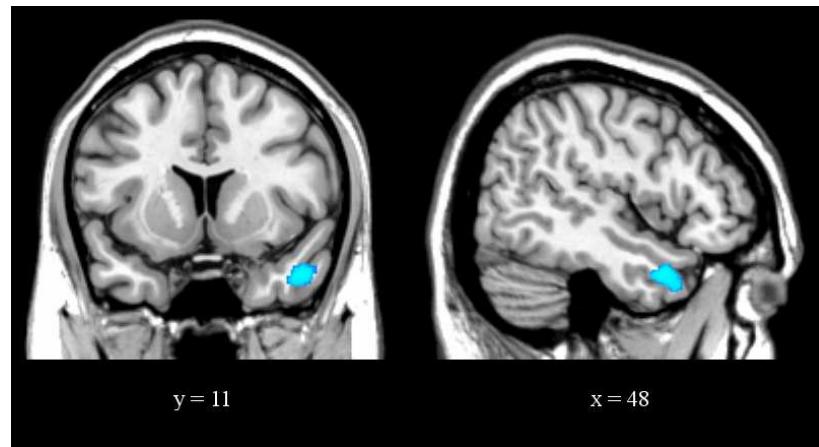
Figure 1. Cluster with significant between-group differences (controls > CDI > CDI PDB) located in the right middle temporal pole (peak at x, y, z = 48, 11, -30, t=4.22; *p*<0.05). Results are overlaid on coronal (left) and sagittal (right) sections of a normalized brain and the numbers correspond to the 'y' and 'x' coordinates in MNI space.

3.2.5. Associations between cognitive beliefs, neurocognitive characteristics and brain structure:

In these analyses we only included those variables showing significant differences between cocaine patients with vs. without personality disorders. We found a positive correlation between borderline beliefs and negative urgency (r=0.56, p<0.01), and a negative correlation between borderline beliefs and Stroop inhibition (r=0.3, p<0.05). Subsequent correlations parsing out the cocaine groups showed that this association was mainly driven by the cocaine patients without comorbid diagnoses (Figure 2).
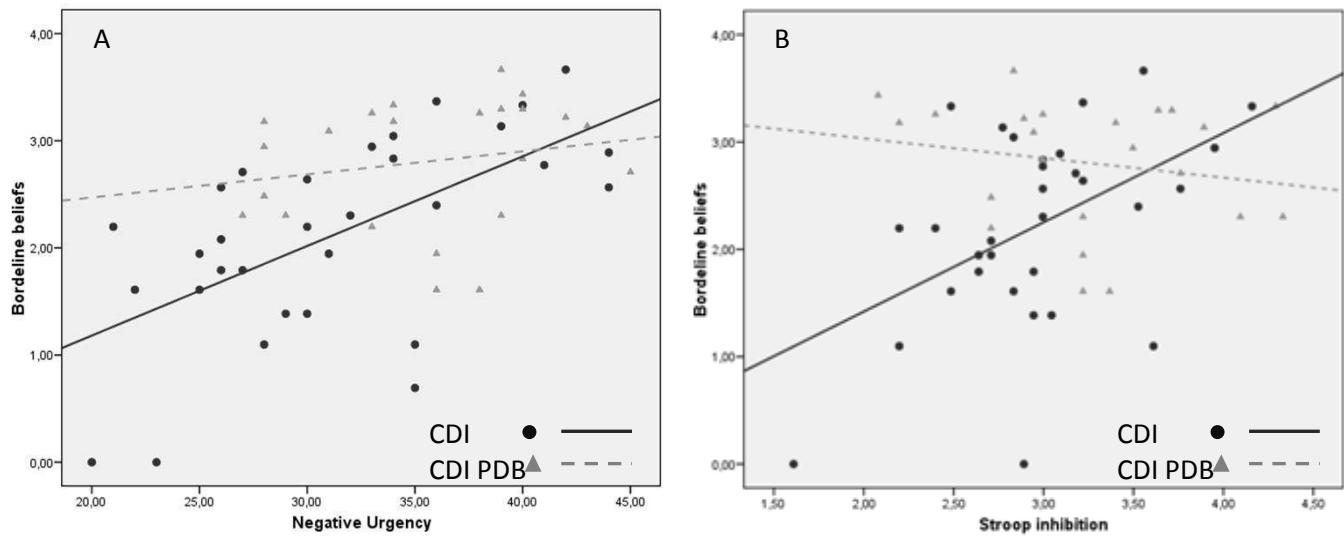
Figure 2. Correlations between PBQ borderline dysfunctional beliefs and UPPS-P Negative urgency (Panel A: r=0.488; p<0.01 for cocaine patients without comorbidities and r=-0.190; p>0.05 for cocaine patients with personality disorders) and Stroop inhibition (Panel B: r=0.611; p<0.01 for cocaine patients without comorbidities and r=0.192; p>0.05 for cocaine patients with personality disorders).

Prediction of clinical diagnosis:

Due to the strong collinearity between negative urgency and borderline beliefs we conducted two parallel multivariate logistic regression models including UPPS-P negative urgency, Stroop inhibition and d2 fluctuation (Model 1) or PBQ borderline beliefs, Stroop inhibition and d2 fluctuation (Model 2) as predictors. Both models showed an appropriate fit to the data (Hosmer-Lemeshow test). Model 1 explained a 24% of variance, and Model 2 explained a 19% of variance. The contributing variables holding statistically significant coefficients in the final model were UPPS-P negative urgency and d2 fluctuation in Model 1, and PBQ borderline and d2 fluctuation in Model 2. Both models yielded sound percentages of correctly classified subjects (73% and 69% respectively). However, a direct contrast using the Bayesian Information Criterion (34) showed that Model 1 was significantly superior (Table 3).

Table 3. Multivariate regression models predicting the existence of comorbid personality disorders (upper panel) and proportions of correct classifications of the models (lower panel).

	Model 1				Model 2			
	OR	SE	P	CI	OR	SE	P	CI
Negative urgency	1.127	0.062	0.03	1.011 – 1.255				
d2 fluctuation	5.162	3.077	0.006	1.605 – 16.603	3.246	1.853	0.039	1.06 – 9.94
Stroop inhibition	2.797	1.613	0.074	0.904 – 8.659	1.95	1.114	0.242	0.637 – 5.975
Borderline beliefs					2.581	1.188	0.039	1.047 – 6.364

	Diagnosis for Model 1	Diagnosis for Model 2
R^2	0.241	0.191
Chi^2	19.395 (p<0.01)	14.065 (p<0.01)
Hosmer-Lemeshow	9.19 (p>0.05)	8.53 (p>0.05)
BIC	-7.163	-2.098
Sensitivity	60%	56.52%
Specificity	82.35%	77.42%
Correctly classified	72.88%	68.52%

4. Discussion

This study yields three main findings: (i) cocaine dependent individuals with comorbid personality disorders, compared to cocaine dependent individuals without comorbidities, have elevated negative urgency, higher intensity of borderline beliefs, worse performance on tests of response inhibition and attention regulation, and comparatively less gray matter in the right temporal pole; (ii) the intensity of borderline beliefs was significantly associated with greater negative urgency and worse response inhibition within the non-comorbid cocaine users, whereas these correlations are diluted in the comorbid patients; and (iii) the combination of facet traits (negative urgency or borderline beliefs) and cognitive indices (attentional fluctuation) significantly predict the presence of comorbid personality disorders in cocaine dependent patients.

These findings indicate that, on top of the impulsive traits and executive control deficits associated with cocaine dependence (Verdejo-García et al., 2008), patients with comorbid personality disorders exhibit increased negative urgency and worse executive control. The elevations in negative urgency illustrate that comorbid patients are more prone to engage in impulsive acts when under strong negative emotions. Although this is a hallmark of some of the specific personality disorders (e.g., borderline) we should emphasize that these elevations were observed against a control group of cocaine users without comorbidities, in whom increased negative urgency symptoms are manifest (Albein-Urios et al., 2012). In terms of cognitive performance, the higher d2 fluctuation indicates that cocaine patients with personality disorders exhibit more irregular allocation of attentional resources into the tasks at hand. Future studies should explore if this deficit is associated with conceptually related DSM 5 diagnostic features, such as lack of self-direction –defined as instability in goals or plans. Moreover, the decreased response inhibition performance fits with the proposed role of the disinhibition trait in

DSM 5 borderline and antisocial diagnoses, and with previous evidence showing that alcohol dependent patients with comorbid Cluster B personality disorders have poorer inhibition than non-comorbid alcoholics (Dom et al., 2006). Moreover, the imaging results showed that cocaine dependent patients with comorbid personality disorders had lower gray matter volumes in the right medial temporal pole. This region, which is richly connected with medial frontal regions through the uncinate fasciculus, has been involved in self-referential and social-emotional processes (Olson et al., 2007), two of the key drawbacks characterizing personality pathology.

In agreement with our initial assumptions the cocaine dependent patients with personality disorders showed higher levels of dysfunctional beliefs associated with the Cluster B spectrum. However, only borderline beliefs showed significant elevations in the cocaine patients with comorbid psychopathologies compared to patients without comorbidities. This elevation may reflect the notion that these distortions are especially salient and disturbing (Baer et al., 2012), and the fact that they are frequently endorsed by borderline patients but also by patients with other personality disorders (Beck et al., 2001). The finding that the remaining dimensions were significantly increased in cocaine patients without any comorbidities is in agreement with dimensional approaches to personality psychopathology (Bhar et al., 2012; Bornovalova et al., 2010), by suggesting that the core dysfunctional beliefs that characterize different personality disorders are to some extent manifest in cocaine users that do not meet formal diagnostic criteria. Along the same lines we found a stronger association between borderline beliefs and negative urgency/response inhibition in the non-comorbid patients, whereas this association was diluted in the comorbid patients. Finally, we found that the combination of dimensional traits and executive indices, especially negative urgency, borderline beliefs and attentional fluctuation, can

powerfully predict the presence of comorbid personality disorders in cocaine users, with particularly high levels of specificity. These results support and give precise content to upcoming diagnostic criteria based on dimensional facet traits such as negative affectivity and disinhibition.

This study holds important strengths and worth noting limitations. Strengths include the careful selection and clinical characterization of cocaine dependent patients, the close matching of drug use characteristics between the two groups of cocaine patients (both in cocaine, alcohol and tobacco use patterns), and the specificity provided by the control group of non-comorbid cocaine patients to the impulsivity and cognitive findings in Cluster B comorbid patients. Among the limitations, we should cite the questionnaire data missing, the IQ mismatch between cocaine users and controls, and the heterogeneous diagnoses forming the comorbid group. The data missing was addressed by post-hoc power analyses that supported the sufficiency of the sample size. The impact of IQ mismatch is minimal since our aims pertained to the comparisons between cocaine patients with and without comorbidities, which were indeed well matched in this variable. Finally, both lower IQs and heterogeneous clinical presentation are inherent features of cocaine patients which cannot be sorted out without impacting the generalizability of clinical research.

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CAPÍTULO 7: ESTUDIO 3

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Reappraisal of negative emotions in cocaine dependence: Dysfunctional corticolimbic activation and connectivity.

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Abstract

Cocaine dependence is associated with pronounced elevations of negative affect and deficient regulation of negative emotions. We aimed to investigate the neural substrates of negative emotion regulation in cocaine dependent individuals, as compared to non-drug-using controls, using functional resonance imaging (fMRI) during a reappraisal task. Seventeen cocaine dependent individuals abstinent for at least 15 days and without other psychiatric comorbidities, and 18 IQ-matched non-drug using controls participated in the study. Participants performed the reappraisal task during fMRI scanning: they were exposed to 24 blocks of negative affective or neutral pictures that they should Observe (neutral pictures), Maintain (sustain the emotion elicited by negative pictures) or Suppress (regulate the emotion elicited by negative pictures through previously trained reappraisal techniques). Task-related activations during two conditions of interest (Maintain>Observe and Suppress>Maintain) were analyzed using the general linear model in SPM8 software. We also performed psychophysiological interaction (PPI) seed-based analyses based on one region from each condition: the dorsolateral prefrontal cortex (dlPFC –Maintain>Observe) and the inferior frontal gyrus (IFG –Suppress>Maintain). Results showed that cocaine users had increased right dlPFC and bilateral temporoparietal junction activations during Maintain>Observe, whereas they showed decreased right IFG, posterior cingulate cortex, insula and fusiform gyrus activations during Suppress>Maintain. PPI analyses showed that cocaine users increased functional coupling between the dlPFC and emotion-related regions during Maintain>Observe, whereas they showed decreased functional coupling between the right IFG and the amygdala during Suppress>Maintain. These findings indicate that cocaine dependent individuals have dysfunctional corticolimbic activation and connectivity during negative emotion experience and reappraisal.

Introduction

Cocaine addiction is associated with pronounced elevations of negative affect and decreased inhibitory control (Koob & Volkow 2010). These cognitive-affective deficits seem to play a major distressing role during cocaine abstinence: patients frequently experience strong negative moods (Epstein & Preston 2010), which may trigger drug-seeking responses by virtue of negative reinforcement mechanisms (Baker et al. 2004; Uslaner et al. 1999). In accordance with this notion, stress-induced cocaine craving is a robust determinant of upcoming drug relapse (Sinha et al. 2006).

These deficits may stem from a breakdown of the brain systems that support adequate emotion experience and regulation, namely an enhanced reactivity of the corticolimbic regions involved in the processing of negative affect, coupled with deficient regulation of this emotional input by the cognitive control network (Cheetham et al., 2010). Cortical structures seem to play a key role in regulating emotions. Specifically, significant activations of the right dorsolateral prefrontal cortex have been observed during efforts to sustain negative affective responses in healthy volunteers (Phan et al., 2005), and during attended vs. unexpected negative affective images in major depression patients (Grimm et al., 2008). With respect to cognitive reappraisal (the cognitive control directed to reduce the negative affective experience), meta-analytic evidence highlights the role of both the ventromedial prefrontal cortex and the right inferior frontal gyrus (Diekhof et al., 2011). Nonetheless, the ventromedial prefrontal cortex stands as a domain-general node for multiple forms of emotion regulation (including fear extinction or placebo effects), whereas the right inferior frontal gyrus is preferentially involved in cognitive emotion regulation in healthy subjects (Diekhof et al., 2011) and in stimulant (methamphetamine) users (Tabibnia et al., 2011). Both

during cognitive maintenance and during regulation of negative emotion, the activation of cortical structures is accompanied by a concordant augmentation (appraisal) or reduction (reappraisal) of activation in the amygdala (Curcic-Blake, Swart & Aleman, 2012; Phan et al., 2005). Previous functional magnetic resonance imaging (fMRI) studies in cocaine users have shown that these networks may be dysfunctional; for example, cocaine users compared to controls display heightened activation of limbic regions like the amygdala and hypoactivation of cortical cognitive control regions (especially the right inferior frontal gyrus) during the induction of anger (Drexler et al. 2000) or the experimentation of sad emotions (Wexler el al. 2001). Likewise, structural imaging studies have revealed that cocaine users present volumetric abnormalities in brain regions relevant for negative emotion experimentation and regulation, such as the amygdala or the inferior frontal gyrus (Moreno-López et al. 2012).

These neuroadaptations may actually intrude into (or stem from) more stable personality traits linked to emotional dysregulation, such as negative urgency –the tendency to act impulsively when under strong negative affects (Whiteside & Lynam 2001). In healthy individuals, negative urgency is negatively correlated with activation of cognitive control regions (e.g., anterior cingulate cortex) during emotional arousal (Joseph et al. 2009). Furthermore, the related construct of punishment sensitivity is positively associated with the activity of the right dorsolateral prefrontal cortex (Shackman et al., 2009). In cocaine users, negative urgency scores are increased compared to those of pathological gamblers (who share addictive mechanisms but are relatively free of neuroadaptive drug effects), and these scores correlates with volumetric measures of dorsolateral prefrontal cortex attrition (Moreno-López et al. 2012; Albein-Urios et al. 2012). Therefore, it is arguable that the cocaine-induced neuroadaptations that impact

emotion regulation systems are also associated with negative urgency traits, contributing to explain the stability of these deficits across abstinence.

The aims of this study are: (i) to investigate the neural substrates of negative emotion regulation in cocaine dependent patients, as compared to non-drug using controls, using fMRI during a reappraisal task; and (ii) to explore the link between the brain systems supporting emotion regulation and the trait of negative urgency in both groups. We hypothesized that: (i) cocaine users would display increased right dorsolateral prefrontal and amygdala activation during negative emotion experimentation, and decreased inferior frontal gyrus and other prefrontal regions activation during cognitive reappraisal; and (ii) negative urgency would positively correlate with corticolimbic activations during experimentation, and negatively correlate with prefrontal activations during reappraisal. To further explore the interaction between bottom-up and top-down systems, we also performed connectivity analyses that stemmed from empirically derived regions of interest: the right dorsolateral prefrontal cortex and the right inferior frontal gyrus.

Materials and methods

Participants

Seventeen cocaine dependent individuals and 18 non-drug using controls participated in the study. Cocaine dependent individuals were recruited as they commenced treatment in the clinic "Centro Provincial de Drogodependencias (CPD)" in Granada (Spain). This public facility provides cognitive behavioral treatment for substance use related disorders in an outpatient setting. The inclusion criteria for the cocaine dependent group were defined as follows: (i) age range between 18 and 45 years old; (ii) meeting DSM-

IV criteria for cocaine dependence –as assessed by the Structured Clinical Interview for DSM-IV Disorders – Clinician Version (SCID) (First *el al.* 1997); (iii) having IQ levels above 80 – as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman & Kaufman 1990); and (iv) having a minimum abstinence interval of 15 days. This abstinence period was confirmed by twice weekly urine toxicological tests plus an additional test on the scanner day. Exclusion criteria were: (i) the presence of any other Axis I or Axis II comorbid disorders –with the exceptions of alcohol abuse and nicotine dependence; (ii) the presence of history of head injury and neurological, infectious, systemic or any other diseases affecting the central nervous system; (iii) having followed other treatments within the 2 years preceding the study onset; and (iv) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID, whereas Axis II disorders were assessed using the International Personality Disorders Examination (Loranger *et al.* 1994; López-Ibor 1999). We also used the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners 1999) to rule out the presence of adult ADHD symptoms (American Psychiatric Association 1994). Healthy controls were recruited from local employment agencies taking care to match them to the clinical groups in the main demographic characteristics and IQ. In addition to the former exclusion criteria, healthy controls could not meet any diagnosis of substance use disorders –with the exception of nicotine dependence. Axis I and II disorders were also assessed in this group using the SCID, the IPDE and the CAAID. The demographical data of participants is summarized in Table 1.

Table 1. Demographic and clinical characteristics of Cocaine Dependent Individuals (CDI) and Healthy Controls (HC).

	CDI n=17 Mean (SD)	HC n=18 Mean (SD)	*p* value
Demographic variables			
Age	36.41 (5.99)	30.50 (4.64)	*p*=0.002
Gender	16 (M)/1 (F)	17 (M)/1 (F)	
Laterality	14 (R)/3 (L)	17 (R)/1 (L)	
Years of education	9.76 (1.71)	10.56 (1.91)	*p*=0.208
Verbal IQ	100.82 (8.62)	105.77 (7.94)	*p*=0.090
Clinical variables			
Monthly cocaine use (gr.)	18.79 (27.53)		
Duration cocaine (months)	56.55 (59.02)		
Abstinence cocaine (months)	2.50 (5.59)		
Monthly alcohol use (SDU)	30.18 (30.64)	8.91 (8.44)	*p*=0.016
Duration alcohol (months)	91.15 (94.79)	91.70 (56.77)	*p*=0.986

SD, standard deviation; (M), male; (F), female; (R), right; (L), left; IQ, intelligence quotient; gr., grams; SDU, standard drinking units.

fMRI Task: Cognitive Reappraisal Task

We used a modified version of the original cognitive reappraisal task designed by (Phan *et al*. 2005). The task consists on the presentation of series of blocks showing neutral or negative picture stimuli that participants must (i) Observe (to passively observe neutral pictures), (ii) Maintain (to actively focus on the emotions elicited by negative emotional pictures, sustaining them over time), or (iii) Suppress (to reappraise the emotions induced by the negative emotional pictures by virtue of cognitive reappraisal techniques previously trained).

We used 24 stimuli that were extracted from the International Affective Picture System (Lang, Bradley & Cuthbert 2001): eight neutral pictures (e.g., household objects), which were presented in the Observe condition and 16 highly unpleasant arousing pictures (e.g., mutilations) that were presented in the Maintain and Suppress conditions. The images were selected according to IAPS Spanish normative values for valence and arousal (Moltó *et al.*, 1999); mean valence values were 2.50 (0.94), 2.50 (0.82) and 5.53 (0.82) for images included in the Maintain, Suppress and Observe conditions respectively, whereas arousal values were 6.44 (0.46), 6.40 (0.60) and 4.28 (0.73) for images included in the Maintain, Suppress and Observe conditions respectively. Pairwise comparisons showed that Maintain and Suppress values did not differ between them in valence or arousal ($p > 0.9$), whereas both differed from the Observe values in valence and arousal ($p < 0.001$). The task consisted of 12 blocks: four blocks for each of the three conditions. Instructions (Observe vs. Maintain vs. Suppress) were pseudo-randomized along the task to avoid the induction of sustained mood states. Each block began with the instruction prompt ("Observe" or "Maintain" or "Suppress") presented in the middle of the screen during 4 seconds. After the prompt, participants viewed two

different pictures of equal valence for 10-sec each. Each block was followed by 10 seconds of baseline during which a cross fixation is presented on the screen to minimize carryover effects.

Inside scanner behavioral measures:

Immediately after the second picture of each block, the intensity of the negative emotion experienced was self-rated on a 1-5 number scale that appeared for five seconds (where 1 is "neutral" and 5 is "extremely negative").

Outside scanner behavioral measures:

The UPPS-P scale (Whiteside & Lynam 2001) is a 59-item inventory designed to measure five independent personality pathways to impulsive behavior. In this case, due to the focus on negative emotion regulation, we were specifically interested in the dimension of Negative Urgency, which refers to the tendency to experience strong impulses under conditions of negative affect.

Procedures

Participants were scheduled 60 minutes ahead of the scanner session to be debriefed about task instructions and trained to decrease the intensity of their negative emotions through cognitive reappraisal techniques (Gross 1999). Debriefing and training was conducted by a Master degree clinical psychologist (NAU). After the general training on the reappraisal techniques, all participants performed a supervised rehearsal of the maintenance and reappraisal strategies using five different trial images, and they subsequently completed a verbal yes/no questionnaire about the perceived sufficiency of the training and their perceived competency to perform the task. Only after successful

rehearsal and positive responses to both questions the participants were entered into the scanner. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology, Northridge, California, USA). Behavioral responses were recorded through a five-button box, Evoke Response Pad System (Resonance Technology Inc., Northridge, California, USA). The UPPS-P scale was administered in an independent session, along with a battery of cognitive tests that will be reported elsewhere.

Imaging data acquisition and preprocessing

We used a 3.0 Tesla clinical MRI scanner, equipped with an eight-channel phased-array head coil (Intera Achieva, Philips Medical Systems, Eindhoven, The Netherlands). During acquisition, a T2*-weighted echo-planar imaging (EPI) was obtained (TR = 2000 ms, TE = 35 ms, FOV = 230 x 230 mm, 96 x 96 matrix, flip angle = 90º, 21 4 mm axial slices, 1 mm gap, 234 scans). A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (3D-TFE) (160 slices, TR = 8.3 ms, TE = 3.8 ms, flip angle = 8°, FOV = 240 x 240, 1 mm^3 voxels) was obtained in the same experimental session for anatomical reference.

The functional images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks, Natick, MA, USA). Preprocessing included slice timing correction, reslicing to the first image of the time series, normalization, using affine and smoothly nonlinear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm).

Statistical analyses

Behavioral Analyses: Behavioral data was analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We conducted independent-sample t-tests to compare the two groups on relevant socio-demographic variables, negative urgency scores and self-reported ratings of emotional intensity inside the scanner. Prior to image analysis, the effect of task condition on self-reported emotion was calculated to assure that the participants had followed the instructions during the task (e.g, Suppress scores lower than Maintain). Intra-subject effect of the three conditions analysis was performed also with SPSS.

fMRI, main task effects: In agreement with the main aims of the study two contrasts of interest were defined at the first-level (single-subject) analysis: (1) "Maintain>Observe" and (2) "Suppress>Maintain". The first contrast indexes brain activations associated with negative emotion experimentation, whereas the second contrast indexes brain activations associated with reappraisal of negative emotions. Conditions were modeled for the 20 seconds that the images were on the screen and did not include instruction and rating periods. The BOLD response at each voxel was convolved with the SPM8 canonical hemodynamic response function (using a 128-s high-pass filter). One-sample t-tests were conducted to assess intra-group activation in each of the contrasts. In these tests the statistical threshold was set at $p<0.05$ False Discovery Rate (FDR) whole-brain corrected, with a minimum cluster size extent (KE) of 10 contiguous voxels. Between-group comparisons were conducted with two-sample t-tests on the resulting first-level contrast images. In these tests, in which we include group as an additional source of variance, the significance threshold was set at $p<0.005$

(uncorrected; KE = 10 voxels), which is optimal to achieve an appropriate balance between the risk of error Type I and II (Lieberman & Cunningham 2009).

Psychophysiological interactions analysis: To explore the effective connectivity between the brain regions activated during the task, we conducted a PsychoPhysiological Interactions (PPI) analysis using SPM8 (Friston *et al*. 1997). Here we explored the impact of the two contrasts of interest (the "psychological" factor) on the strength of time-course correlations between two empirically obtained regions of interest (ROIs) with all the other regions of the brain (the "physiological" factor). To perform the first level analysis (subject-level), the ROIs were drawn from the set of regions showing group-differences in the two contrasts performed on task activation analyses (Maintain>Observe and Suppress>Maintain). Based on the combination of our initial theoretical predictions and the results obtained in the fMRI main task effects, we selected one region from each contrast: the right dorsolateral prefrontal cortex (Maintain>Observe) and the right inferior frontal gyrus (Suppress>Maintain). These regions have previously shown to be relevant for negative emotion experimentation and reappraisal, respectively (Grimm *et al*. 2008; Curcic-Blake *et al*. 2012). Hence, we extracted the first eigenvariate time series from a 7 mm radial sphere: the dorsolateral prefrontal cortex (dlPFC) (x=54, y=12, z=42) –in the case of Maintain>Observe, and the inferior frontal gyrus (IFG) (x=56, y=24, z=16) –in the case of Suppress>Maintain. Intra-group analysis threshold (one sample t-test) was set at $p<0.001$ (uncorrected; KE = 10 voxels), and between-group differences (two sample t-test) at $p<0.005$ (uncorrected; KE = 10 voxels).

Correlation analyses: Two sets of correlation analyses were performed in SPSS using the peak activations derived from the two main fMRI contrasts (Maintain>Observe and Suppress>Maintain) and the PPI maps. For both analyses, the beta eigenvalues corresponding to each region of interest were extracted for each participant, and then correlated with inside- and outside-scanner behavioral measures; that is, with self-reported ratings of intensity of negative emotion and the Negative Urgency scores from the UPPS-P scale, respectively.

Results

Behavioral results:

Independent-sample t-tests showed no differences between the groups in the Observe, Maintain or Suppress ratings (p>0.1 in all cases). Related-samples t-tests showed significant differences between Maintain and Observe (p<0.05), and between Suppress and Maintain (p<0.05); as expected, the intensity of negative emotion was greater in Maintain vs. Observe, and smaller in Suppress vs. Maintain (Table 2). With respect to the UPPS-P, the scores of Negative Urgency significantly differed between the groups, with CDI subjects showing higher scores than healthy controls (Table 2).

Table 2. Self- reports of the intensity of negative emotions induced on each task condition and negative urgency scores in cocaine dependent individuals (CDI) and healthy controls (HC).

Inside scanner ratings	CDI n=17 Mean (SD)	HC n=18 Mean (SD)	*p* value
Maintain	3.68 (0.93)	3.13 (0.97)	*p*=0.103
Suppress	3.24 (0.82)	2.76 (1.04)	*p*=0.154
Observe	1.86 (0.86)	1.64 (0.67)	*p*=0.439
Outside scanner UPPS scale			
Negative Urgency	33.17 (6.51)	22.22 (5.01)	*p*=0.000

Imaging results:

Maintain > Observe:

Task activations:

Similar to previous studies using the reappraisal task, both groups commonly activated bilateral posterior sensory regions, the thalamus, and the medial frontal and right inferior frontal gyrus. In addition, controls activated the midbrain, the bilateral amygdala, the left anterior cingulate cortex and the right orbitofrontal cortex, whereas cocaine users activated the right dlPFC and the supplementary motor area.

Group differences:

Compared to controls, cocaine users showed significantly increased activations in the bilateral dlPFC, the temporoparietal junction, and the left IFG. No regions showed significantly increased activation in controls vs. cocaine users.
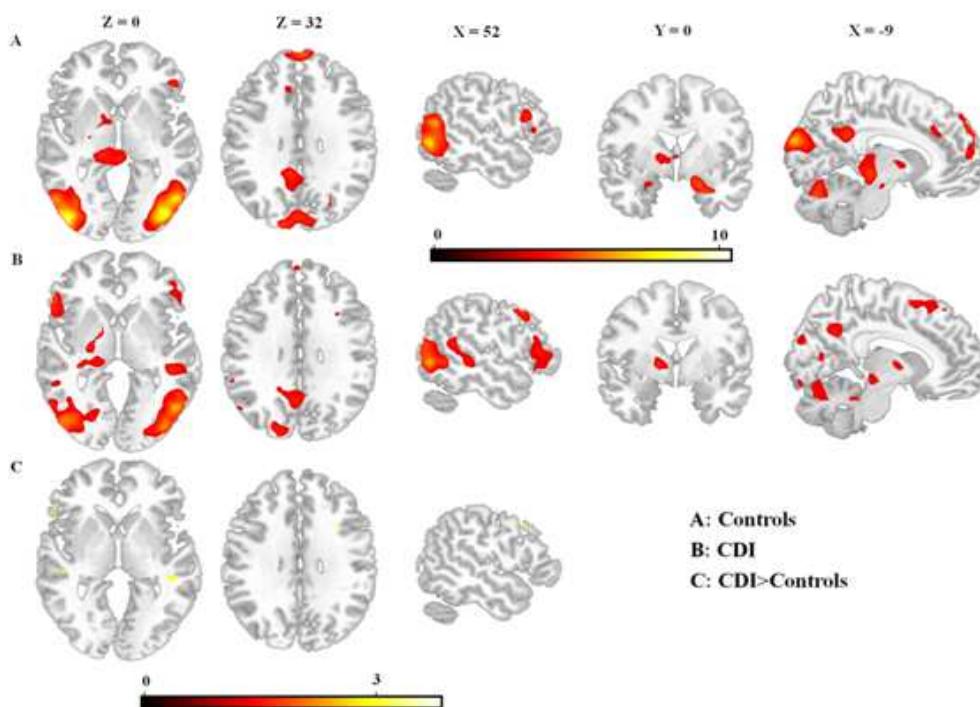

Figure 1. Within-group activations and between-group differences in response to negative emotion experimentation (Maintain>Observe): Cocaine dependent individuals (CDI), controls, and CDI>Controls.

Table 3. Regions showing significant activations during Maintain>Observe: One-sample t-tests for Controls and Cocaine Dependent Individuals (CDI), and independent-sample t-tests showing significant differences between the groups (CDI>Controls).

	BA	Side	MNI Coordinates			Volume (mm^3)	t
			X	Y	Z		
Controls							
Occipitotemporal Cortex	18/19/37	L	-44	-88	0	31.552	10.31
Occipitotemporal Cortex	18/19/37	R	42	-80	0	39.416	8.53
Cerebellum		L/R	-18	-74	-26	23.480	5.71
Medial Frontal Gyrus	9/10	L/R	6	60	26	5.264	5.60
Amygdala	34	R	20	-4	-22	1.888	5.37
Amygdala / Hippocampus	34	L	-22	0	-20	1.360	3.54
IFG	44/45	R	50	14	20	1.248	5.07
IFG	47	R	48	34	-2	224	4.35
Post. Thalamus / Tectum		L/R	-8	-28	-8	5.872	4.97
Ant. Thalamus		L/R	-12	0	0	1.112	4.45
Precuneus	31	L/R	-6	-48	28	3.056	4.74
OFC	47	R	34	32	-22	368	4.26
Midbrain		L/R	-4	-18	-18	240	4.14
ACC	32	L	-8	28	32	312	4.03
CDI							
Occipitotemporal Cortex	18/19/37	R	40	-52	-24	19.120	7.10
Occipitotemporal Cortex	18/19/37	L	-46	-78	2	20.920	6.86
IFG	45/47	R	58	28	8	2.992	5.38
IFG	45/47	L	-52	28	-2	4.880	4.99
Cerebellum		L/R	-18	-72	-26	12.184	4.70
Post. Thalamus / Tectum		L	-12	-24	-8	2.960	4.70
Precuneus	7/31	L/R	-4	-62	34	3.384	4.43
Ant. Thalamus		L	-14	-2	2	1.152	4.41
Supplementary Motor Area	6/8	L/R	-6	8	60	2.192	4.34
dlPFC	10	R	36	56	20	400	4.11
Medial Frontal Gyrus	9	L/R	0	56	34	784	3.89
CDI > Controls							
dlPFC		R	32	14	30	160	3.82
dlPFC	9	R	54	12	42	176	3.54
Temporoparietal	21	R	46	-32	-6	592	3.65
Temporoparietal	22	L	-46	-30	-2	200	3.14
IFG	47	L	-52	30	-2	160	3.04

Suppress >Maintain:

Task activations:

Controls had significant activations in posterior sensory regions, the posterior cingulate cortex, the right medial frontal gyrus and the bilateral IFG and dlPFC (see Supplementary Table). No regions showed significant activations in the cocaine users group at the selected threshold.

Group differences:

The direct between-groups comparison showed that most of the above mentioned regions had significantly decreased activation in cocaine users relative to controls (Table 4). More specifically, these findings were located in the cerebellum, the posterior sensory regions, the right thalamus, the left insula, the posterior cingulate cortex, the left dlPFC and the bilateral IFG (Figure 2). No regions showed significantly increased activation in cocaine users vs. controls.
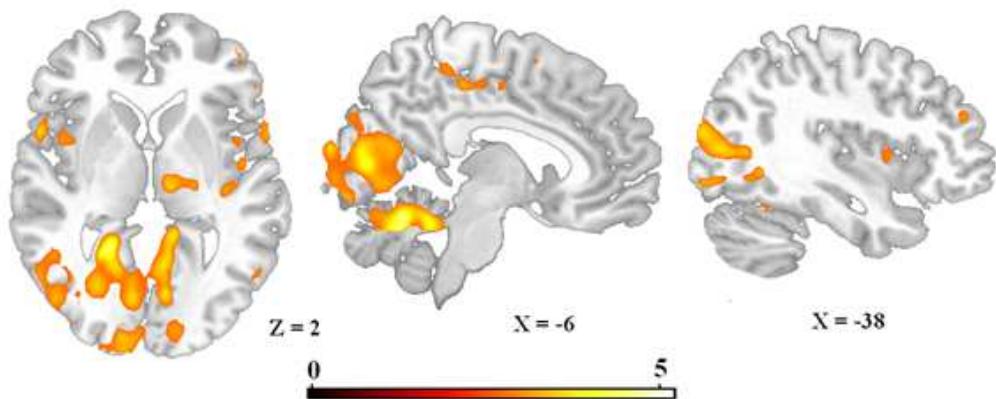

Figure 2. Between-group differences during reappraisal of negative emotions (Suppress>Maintain): Regions showing increased activation in cocaine dependent individuals (CDI) vs. controls.

Table 4. Brain regions showing significantly increased activation in Controls vs. Cocaine Dependent Individuals (CDI) during reappraisal (Suppress>Maintain).

	BA	Side	MNI Coordinates			Volume (mm³)	*t*
			X	Y	Z		
Controls > CDI							
Fusiform Gyrus	30	L	-18	-50	-2	79.008	5.18
Fusiform Gyrus	19	R	16	-58	-12		4.41
Cerebellum		L/R	-12	-66	-28		5.13
Occipitotemporal Cortex	37/39	L	-42	-66	8		4.49
Occipitotemporal Cortex	18	R	38	-86	-12		4.23
Parieto-Occipital	7/19	L	-14	-86	34		4.43
Cuneus	17/31	L	-6	-80	6		4.14
Cuneus	18	R	10	-76	-2		3.86
Posterior Cingulate Cortex	31	L/R	-6	-30	46	2.040	3.45
Thalamus		R	14	-18	-2	2.312	3.67
IFG	44	L	-56	8	6	1.176	4.04
IFG	6	R	64	2	8	1.016	3.76
IFG		R	60	26	14	320	3.36
OFC	10	R	50	44	-4	232	3.40
dlPFC		L	-36	44	22	152	3.18
Insula	13	L	-40	6	0	472	3.16

Note. CDI, cocaine dependent individuals; IFG, inferior frontal gyrus; OFC, orbitofrontal cortex; dlPFC, dorsolateral prefrontal cortex.

PPI Analyses on Maintain > Observe and Suppress > Maintain:

Seed selection:

Functional connectivity analyses were performed to explore whether specific regions showing significant between-group differences in the main task contrasts were abnormally connected with other regions of the emotion regulation system during the task in the group of cocaine users. Among the clusters showing significant between-group differences, we selected the right dlPFC (which showed greater activation in cocaine vs. controls during Maintain>Observe; MNI coordinates x= 54, y= 12, z= 42, see Table 3 and Figure 1), and the right IFG (hypoactivated in cocaine users during Suppress>Maintain; MNI coordinates x= 56, y= 24, z= 16, see Table 4 and Figure 2).

Group differences in Maintain > Observe:

In cocaine users, as compared to controls, the right *dlPFC seed* showed increased functional coupling with the bilateral posterior sensory regions, the bilateral fusiform gyrus, the bilateral medial frontal gyrus, the right amygdala, the inferior temporal and orbitofrontal cortices, and the right insula/putamen region in cocaine users vs. controls (see Table 5 and Figure 3). No regions showed significantly greater right *DLPFC* connectivity in controls vs. cocaine users.

Group differences in Suppress > Maintain:

In control participants, as compared to cocaine users, the right *IFG seed* showed increased functional coupling with the bilateral amygdala, the left superior temporal and orbitofrontal cortices, the right fusiform gyrus and the bilateral anterior thalamus in controls vs. cocaine users (see Table 6 and Figure 3). No regions showed significantly greater right IFG connectivity in cocaine users vs. controls.
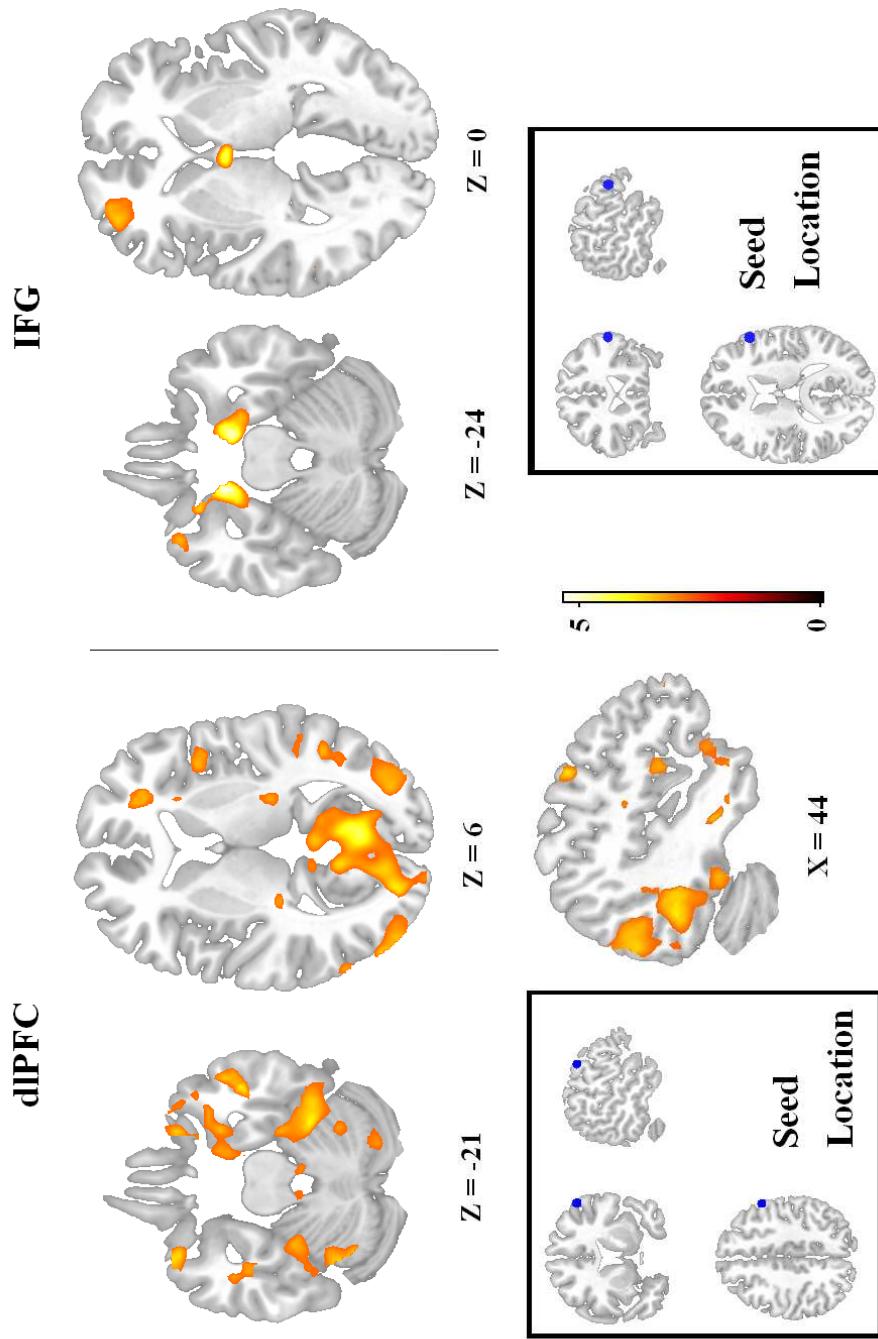
Figure 3. Regions showing different patterns of functional connectivity in cocaine dependent individuals (CDI) *vs.* controls stemming from the seeds of the right dorsolateral prefrontal cortex (dlPFC) and the right inferior frontal gyrus (IFG) during negative emotion experimentation (Maintain>Observe) and reappraisal (Suppress>Maintain).

Table 5. Brain regions showing increased functional connectivity with the right dorsolateral prefrontal cortex seed in Cocaine Dependent Individuals (CDI) vs. Controls during experimentation of negative emotions (Maintain>Observe).

	BA	Side	MNI Coordinates			Volume (mm³)	t
			X	Y	Z		
CDI > Controls							
Cuneus/Fusiform	18/19/30/37	L/R	10	-68	2	82.824	4.78
Inferior Temporal Gyrus	20/21	R	48	-14	-22	1.104	4.30
OFC	47	L	-34	24	-24	848	3.81
dlPFC	8	R	46	8	50	488	3.75
Medial Frontal Gyrus	10	R	12	54	10	360	3.55
Medial Frontal Gyrus	10	L	-8	56	4	1.072	3.49
Temporal/Amygdala/OFC	28/38/47	R	28	22	-26	3.664	3.54
Insula	13	R	44	12	6	544	3.41
Putamen		R	30	14	0	456	3.35
Precuneus	7	L/R	6	-56	46	408	3.18

Table 6. Brain regions showing increased functional connectivity with the right inferior frontal gyrus seed in Controls vs. Cocaine Dependent Individuals (CDI) during reappraisal (Suppress>Maintain).

	BA	Side	MNI Coordinates			Volume (mm³)	t
			X	Y	Z		
Controls> CDI							
Amygdala	28/34	R	14	-6	-26	1.760	5.03
Amygdala	28/34	L	-14	-4	-26	1.248	5.19
Ant. Thalamus		L/R	0	-2	0	576	4.50
OFC	10	L	-30	52	-2	1.208	3.71
Superior Temporal Gyrus	38	L	-38	20	-26	416	3.47
Fusiform Gyrus	20	R	56	-4	-30	336	3.36

Correlations with behavioral measures:

For inside-scanner behavioral measures, the intensity of self-reported negative emotion during Maintain>Observe was negatively correlated to left insula activity in whole-sample analyses ($r=-0.53$, $p<0.05$). More specifically, this correlation was stronger in cocaine users ($r=-0.76$, $p<0.05$) than in control subjects ($r=-0.23$, $p>0.05$).

For outside-scanner measures, in the whole sample analyses negative urgency positively correlated with right dlPFC activation during Maintain>Observe ($r=0.58$, $p<0.005$). In addition, the functional connectivity between the right dlPFC and the right insula/orbitofrontal cortex during Maintain>Observe was more strongly correlated with negative urgency in cocaine users than in control subjects ($r=0.53$, $p<0.05$, and $r=0.25$, $p>0.05$, respectively) (see Figure 4A). During Suppress>Maintain, negative urgency was negatively correlated with the functional connectivity between the right IFG and the amygdala in controls ($r=-0.53$, $p<0.05$), whereas this association was non-significant in CDI subjects ($r=0.30$, $p>0.05$) (see Figure 4B).

Confounders' effects: Both groups were well matched for most potentially confounding variables but in spite of recruitment efforts they significantly differed on the age distribution. Because our selection criteria only allowed age ranges between 18 and 45 years old, and age was not expected to impact on the conditions of interest, we have reported the results obtained without covariating for this variable. Nonetheless, in a conservative approach we subsequently replicated all analyses using age as a confounder and, as expected, results were unchanged.
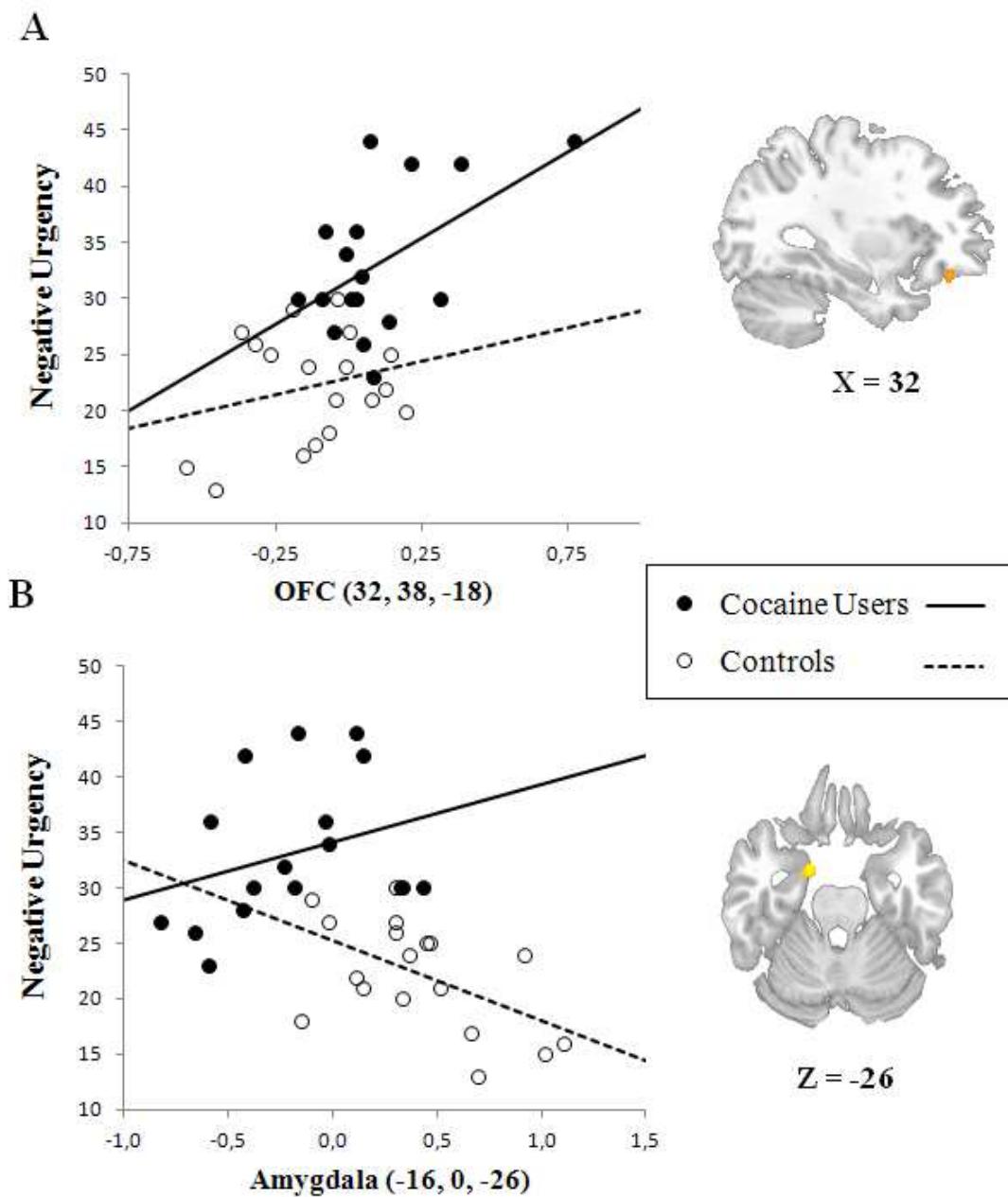
Figure 4. Correlations between regions functionally connected with the dlPFC (Maintain>Observe) (Panel A) and the IFG (Suppress>Maintain) (Panel B) seeds and outside-scanner scores of negative urgency.

Discussion

Our main findings show that cocaine dependent individuals have increased activations in the right dlPFC, the temporoparietal regions bilaterally, and the left IFG during experimentation of negative emotions, whereas they show decreased activation in the bilateral IFG, the posterior cingulate, the insula, the thalamus and the posterior sensory regions during cognitive reappraisal of these negative emotions. In agreement with our initial hypotheses, connectivity analyses showed that cocaine users had increased connectivity between right dlPFC and limbic (amygdala) and extra-limbic emotional regions (orbitofrontal cortex, insula) during negative emotion experimentation. On the other hand, they show reduced connectivity between the right IFG and these emotional regions (amygdala, OFC) during reappraisal. Finally, scores of negative urgency positively correlated with right dlPFC activation during negative emotion experimentation, and negatively correlated with right IFG connectivity during reappraisal. These results biologically substantiate increased sensitization towards negative emotion, coupled with abnormal regulation of these emotional states in cocaine dependent individuals without other psychiatric comorbidities.

Between-group differences in brain activations observed during negative emotion experimentation are in agreement with our initial predictions. Cocaine users showed increased activation of the right dlPFC, which has been associated with negative emotional appraisal and depression severity (Grimm *et al*. 2008; Phan *et al*., 2005). The right dlPFC is also involved in the cognitive operations supporting drug craving (Hester & Garavan 2009), implying that cocaine users may appraise negative emotional states "as if" they were actually drug cravings (Fox *et al*. 2008). Along with the right dlPFC, the bilateral temporoparietal regions and the left inferior frontal gyrus showed

significantly increased activations in cocaine users compared to controls. These regions are importantly involved in successful memory encoding, autobiographical memory, and self vs. others representations (Kim & Hamann 2012; Svoboda, McKinnon & Levine 2006), such that increased activation might represent heightened recollection of autobiographical memories during negative emotion experimentation in the cocaine group. This enhanced reactivity to negative stimuli may be associated with the patterns of task-related functional connectivity, since cocaine users showed increased connectivity between the right dlPFC and regions involved in visual-attentional processing, emotion perception and subjective appraisal (McRae *et al*. 2010), which overall indicate that cocaine users display greater reactivity of brain emotional systems during experimentation of negative emotion. Importantly, this heightened reactivity was associated with trait variations in negative urgency. This is in agreement with previous studies showing that dispositional variations in traits associated with punishment sensitivity can modulate right dlPFC tonic activity (Shackman *et al*. 2009) as well as its phasic impact on HPA-axis neuroendocrine responses (Baeken *et al*. 2011). Also in accordance with initial hypotheses, negative urgency correlated with the connectivity between the dlPFC and the orbitofrontal cortex, supporting the association between this personality dimension and the brain dynamics involved in the processing of negative affect (Joseph *et al*. 2009). There was also a negative correlation between intensity of negative affect and insula activation, which might be explained by distorted interoceptive mechanisms leading to excessive appraisal of negative emotion (Verdejo-García, Clark & Dunn 2012). Overall, the data drawn from this contrast fit well with the notion that cocaine addiction is linked to sensitization of the brain systems involved in the processing of negative affect and stress (Koob & Volkow 2010).

Analyses of activations during reappraisal showed that cocaine users have reduced activations in a broad set of brain regions involved in cognitive control (IFG, left dlPFC) (Goldstein & Volkow 2011), down-regulation of heightened emotional states (posterior cingulate, insula and medial prefrontal cortex) (Grecucci *et al*. 2012), and attention (the thalamus and posterior visual-perceptual stream). This pattern indicates that cocaine users may be less able to engage the optimal brain circuitry to exert down-regulation of strong negative emotional states. Within this brain network, the right IFG has shown to be a critical piece to exert appropriate cognitive control of different response modalities (motor or emotional), and specifically the cognitive control of drug cravings (Tabibnia *et al*. 2011; Volkow *et al*. 2010). The analyses of right IFG connectivity showed that the activation of this region during reappraisal is temporally synchronized with activations in bilateral amygdala in controls but not in patients. Furthermore, the connectivity between the IFG and the amygdala was associated with the trait of negative urgency specifically within controls; participants with higher urgency scores showed diminished connectivity. Basic neuroimaging findings indicate that the connections between these regions are actually bidirectional, such that the amygdala may initially update the IFG, and then the IFG may exert top-down regulation of the amygdala input (Curcic-Blake *et al*. 2012). Other regions associated with this network were the orbitofrontal cortex and the anterior thalamus, which are part of the emotional salience network (Seeley *et al*. 2007) that the right IFG purportedly works to inhibit. Cocaine users seem to have significantly impaired functioning of this emotion regulation system, which may contribute to explain a range of relevant clinical phenomena, such as persistent negative affect, emotional lability, poor anger management or intolerance to frustration. Overall, the data from this contrast fit well with the notion that cocaine addiction is associated with poor regulation of negative

emotional states and high risk of negative-reinforcement based relapse episodes (Sinha *et al*. 2006). They also support the pertinence of developing and testing novel treatment interventions aimed to target emotion perception and appraisal mechanisms (Verdejo-García *et al*. 2012).

This study holds important strengths and also worth noting limitations. Among the first, we should number: the careful selection of cocaine dependent patients without other substance related disorders or related comorbidities, the duration of abstinence (always superior to 15 days, allowing us to rule out acute or residual drug effects), and the good match between the cocaine and control groups in terms of relevant socio-demographic variables not often controlled for (e.g., IQ). Although the groups significantly differed on age, our selection criteria stringently restricted the age range for inclusion (18-45 years old) in order to minimize the potential impact of ageing on the patterns of brain functioning. Furthermore, covariate analyses including age as a confounder did not change the results that we present here. It is also worth noting that cocaine users and controls did not differ on their subjective ratings of the images. The lack of behavioral differences supports the validity of the reappraisal training, although we cannot fully discard subtle individual differences in the application of the reappraisal techniques. Future studies should also explore if the lack of behavioral differences are replicated in behavioral studies specifically designed for this aim. However, for the purpose of the current imaging study, the equivalence in behavioral output strengthens our specificity in investigating differences in brain activations in the absence of obvious differential performances. Other potential limitations include the relatively small sample size and the inclusion of patients with nicotine dependence and alcohol abuse. Nonetheless, in each case we should stress the difficulty of recruiting large clinical samples meeting our

strict inclusion criteria, and the virtual impossibility of finding cocaine users without substantial nicotine and alcohol use.

Authors contribution

AVG designed the study. NAU and JMM conducted the recruitment and clinical characterization of participants. JVR, SA and CSM conducted neuroimaging analyses. NAU and AVG developed a first draft of the manuscript, later revised by all authors.

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CAPÍTULO 8: ESTUDIO 4

(Enviado a la Revista Psychological Medicine)

Cocaine users with comorbid Cluster B personality disorders show dysfunctional brain activation and connectivity of the emotional salience and regulation networks during negative emotion maintenance and reappraisal

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Abstract

Background: Cocaine dependence often co-occurs with Cluster B personality disorders. Since both disorders are characterized by emotion regulation deficits, we predicted that cocaine comorbid patients would exhibit dysfunctional patterns of brain activation and connectivity during reappraisal of negative emotions.

Methods: 18 cocaine users with comorbid Cluster B personality disorders, 17 cocaine users without comorbidities and 21 controls participated in this functional magnetic resonance study. Participants were scanned during performance of a reappraisal task in which they had to maintain or suppress the emotion induced by negative affective pictorial stimuli. We followed region of interest (ROI) and whole-brain approaches to investigate brain activations and connectivity associated with negative emotion experience and reappraisal.

Results: Cocaine users with comorbid personality disorders showed reduced activation of the subgenual anterior cingulate cortex during negative emotion maintenance and increased activation of the lateral orbitofrontal cortex and the amygdala during reappraisal. Amygdala activation correlated with impulsivity and antisocial beliefs in the comorbid group. Connectivity analyses showed that in the cocaine comorbid group the subgenual cingulate was less efficiently connected with the amygdala and the fusiform gyri and more efficiently connected with the anterior insula during maintenance, whereas during reappraisal the left orbitofrontal cortex was more efficiently connected with the amygdala and the right orbitofrontal cortex was less efficiently connected with the dorsal striatum.

Conclusions: Cocaine users with comorbid Cluster B personality disorders have distinctive patterns of brain activation and connectivity during maintenance and

reappraisal of negative emotions. Abnormal activations during reappraisal correlate with impulsivity and dysfunctional beliefs.

Introduction

Cocaine dependence is frequently associated with comorbid psychiatric disorders, being the highest rates for mood, anxiety and personality disorders –especially Cluster B diagnoses (Chen et al., 2011). The co-occurrence of personality disorders is particularly influential for cocaine addiction severity and treatment outcomes; for example, the presence of comorbid personality disorders is associated with heavier cocaine intake, lower rates of treatment request, and decreased likelihood of cocaine dependence remission (Ford et al., 2009; López-Quintero et al., 2011). In terms of cognitive-affective functioning cocaine dependent patients with comorbid personality disorders, compared to non-comorbid cocaine users, exhibit higher levels of negative emotion-driven impulsivity (negative urgency), more intense dysfunctional beliefs associated with personality pathology, poorer cognitive control skills, and reduced gray matter in brain regions relevant for social-emotional cognition (Albein-Urios et al., in submission). This profile, together with previous evidence (Fox et al., 2007), is indicative of greater difficulties in cognitive-emotion regulation skills among cocaine users with comorbid personality disorders. However, little is known about the functioning of the brain systems involved in cognitive-emotion regulation among comorbid patients.

We recently demonstrated that cocaine dependent individuals without comorbid psychopathologies have dysfunctional activation of the frontal-limbic networks involved in negative emotion experience and reappraisal: they showed increased right dorsolateral prefrontal activation during negative emotion maintenance and decreased right inferior frontal gyrus-limbic connectivity during cognitive reappraisal (Albein-Urios et al., 2012). Although no studies up to now have investigated the brain

functioning of cocaine users with concurrent Axis II disorders, the neuroimaging findings in non-substance dependent individuals with Cluster B personality disorders demonstrate that they also show significant deficits in the emotion regulation networks (Ruocco et al., 2012; Yang and Raine, 2009). Specifically, they exhibit consistent reductions in subgenual anterior cingulate cortex activation during negative emotion experience (Ruocco et al., 2012) and increased insula and decreased orbitofrontal cortex activation during reappraisal (Schulze et al., 2010). The subgenual cingulate cortex and the anterior insula are primarily involved in the emotional salience network (Taylor et al., 2009), whereas the lateral orbitofrontal cortex connects with two different pathways involved in negative emotion regulation: the striatum pathway, associated with better reappraisal success, and the amygdala pathway, associated with poorer reappraisal success (Wager et al., 2008). Since both cocaine dependence and Cluster B personality disorders are associated with dysfunctions in the brain regions and networks supporting emotion regulation, the co-occurrence of both diagnoses may presumably convey more profound deficits in these regions and networks.

Here we used the cognitive reappraisal paradigm (Phan et al., 2005) to investigate potential differences in the patterns of functional activation and connectivity of these regions of interest (anterior cingulate cortex, insula, orbitofrontal cortex, striatum and amygdala) between cocaine users with vs. without comorbid personality disorders compared to normal controls. In agreement with previous evidence, we hypothesized that the cocaine dependent patients with comorbid personality disorders –compared to non-comorbid users and controls– would show differential patterns of brain activation in the subgenual anterior cingulate cortex during negative emotion maintenance and in the lateral orbitofrontal cortex-amygdala pathway during negative emotion reappraisal.

We also predicted that the personality traits and beliefs that characterize cocaine comorbid patients (negative urgency and dysfunctional beliefs) would correlate with the brain substrates of negative emotion maintenance and regulation.

Methods

Participants:

Thirty-five cocaine users and 21 non-drug-using controls statistically matched for education and IQ distributions were recruited for study purposes (see Table 1). Cocaine users were classified in two groups based on personality disorders diagnosis: 18 participants met criteria for cocaine dependence and Cluster B personality disorders (9 with borderline diagnosis, 7 with histrionic diagnosis and 2 with antisocial diagnosis) and 17 participants met criteria for cocaine dependence without comorbidities.

Cocaine users were recruited as they started treatment in the clinic "Centro Provincial de Drogodependencias (CPD)" in Granada (Spain), which provides behavioral treatment for substance-related disorders in an outpatient setting. The inclusion criteria for the cocaine groups were defined as follows: (i) age range between 18 and 45 years old; (ii) IQ levels above 80 –as measured by the Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman, 2001); (iii) meeting DSM-IV criteria for cocaine dependence – as assessed by the Structured Clinical Interview for DSM-IV Disorders –Clinician Version (SCID) (First et al., 1997); (iv) being treatment commencers; and (v) abstinence duration >15 days. Abstinence was confirmed by twice weekly urine tests plus an ad hoc test on the testing days. Inclusion criteria for cocaine dependent patients with comorbid personality disorders were restricted to diagnoses pertaining to Cluster B, which are the more prevalent among cocaine users. Axis II disorders were assessed

using the International Personality Disorders Examination (Loranger et al., 1994). The exclusion criteria were: (i) the presence of any other Axis I disorders –with the exceptions of alcohol abuse, nicotine dependence and attention deficit and hyperactivity disorder (ADHD) –as measured by the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Conners, 1999); (ii) history of head injury or neurological, infectious, systemic or any other diseases affecting the central nervous system; (iii) having followed other treatments within the two years preceding the study onset; and (iv) having entered treatment by court request. Comorbid Axis I disorders were assessed with the SCID.

Healthy controls were recruited from local employment agencies. In addition to the former exclusion criteria, healthy controls could not meet any diagnosis of substance-related disorders –with the exception of nicotine dependence. Axis I and II disorders were also assessed in this group using the SCID, the IPDE and the CAAID.

All the diagnoses were conducted by a board clinical psychologist, whereas all subsequent tests were administered by an independent (blind to diagnosis) evaluator.

Table 1: Demographic and clinical characteristic of the three study groups: Cocaine users without comorbidities (Cocaine), Cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

	Cocaine n=17 Mean (SD)	Cocaine+PD n=18 Mean (SD)	Controls n=21 Mean (SD)	P-value
Demographic variables				
Age	36.41 (5.99)	35.83 (7.88)	31.00 (4.60)	0.016
Gender	16 (M) / 1 (F)	12 (M) / 6 (F)	20 (M) / 1 (F)	
Laterality	14 (R) / 3 (L)	16 (R) / 2 (L)	20 (R) / 1 (L)	
Years of education	9.76 (1.71)	11.11 (2.08)	10.38 (1.96)	0.128
Verbal IQ	100.82 (8.62)	102.33 (10.64)	105.76 (8.75)	0.253
Clinical variables				
Monthly cocaine use (g)	18.79 (27.53)	21.33 (26.71)		0.784
Duration cocaine (months)	56.55 (59.02)	54.33 (47.96)		0.903
Abstinence cocaine (months)	2.50 (5.59)	6.38 (9.68)		0.158
Age of onset cocaine use (years)	23.00 (7.70)	22.77 (7.10)		0.930
Monthly alcohol use (SDU)	30.18 (30.64)	42.60 (51.30)	10.07 (9.74)	0.054
Duration alcohol (months)	91.15 (94.79)	93.00 (85.04)	83.75 (56.20)	0.950
Age of onset alcohol use (years)	18.33 (4.46)	19.71 (4.10)	19.14 (5.53)	0.733
Monthly tobacco use (cig.)	608.33 (415.88)	458.69 (314.39)	286.25 (458.69)	0.125
Duration tobacco (months)	141.50 (132.13)	151.87 (112.64)	76.37 (104.25)	0.327
Age of onset tobacco use (years)	16.16 (2.88)	17.93 (6.46)	17.75 (5.23)	0.663

SD, standard deviation; (M), male; (F), female; (R), right; (L), left; IQ, intelligence quotient; gr., grams; SDU, standard drinking units; cig., cigarettes.

fMRI task: cognitive reappraisal task:

We used a cognitive reappraisal task described in Albein-Urios et al. (2012), which adapted the original version designed by Phan et al. (2005). The task consists of the presentation of series of blocks showing neutral or negative picture stimuli that participants must (1) Observe (to passively observe neutral pictures); (2) Maintain (to

actively focus on the emotions elicited by negative emotional pictures, sustaining them over time); or (3) Suppress (to re-appraise the emotions induced by the negative emotional pictures by virtue of cognitive reappraisal techniques previously trained).

We used 24 stimuli that were extracted from the International Affective Picture System (Lang, Bradley & Cuthbert 2001): eight neutral pictures (e.g. household objects), which were presented in the Observe condition and 16 highly unpleasant arousing pictures (e.g. mutilations) that were presented in the Maintain and Suppress conditions. The images were selected according to IAPS Spanish normative values for valence and arousal (Moltó et al. 1999); mean valence values were 2.50 (0.94), 2.50 (0.82) and 5.53 (0.82) for images included in the Maintain, Suppress and Observe conditions, respectively, whereas arousal values were 6.44 (0.46), 6.40 (0.60) and 4.28 (0.73) for images included in the Maintain, Suppress and Observe conditions, respectively. Pairwise comparisons showed that Maintain and Suppress values did not differ between them in valence or arousal ($P > 0.9$), whereas both differed from the Observe values in valence and arousal ($P < 0.001$).

The task consisted of 12 blocks: four blocks for each of the three conditions. Instructions (Observe versus Maintain versus Suppress) were pseudo-randomized along the task to avoid the induction of sustained mood states. Each block began with the instruction prompt ('Observe' or 'Maintain' or 'Suppress') presented in the middle of the screen during 4 seconds. After the prompt, participants viewed two different pictures of equal valence for 10 seconds each. Each block was followed by 10 seconds of baseline during which a cross fixation is presented on the screen to minimize carryover effects.

Inside scanner behavioral measures:

Immediately after the second picture of each block, the intensity of the negative emotion experienced was self-rated on a 1–5 number scale that appeared for 5 seconds (where 1 is 'neutral' and 5 is 'extremely negative').

Outside scanner behavioral measures:

The *UPPS-P* scale (Whiteside and Lynam 2001) is a 59-item inventory designed to measure five independent personality pathways to impulsive behavior. In this case, due to the focus on negative emotion regulation, we were specifically interested in the dimension of negative urgency, which refers to the tendency to experience strong impulses under conditions of negative affect.

The *Personality Belief Questionnaire –PBQ* (Beck and Beck, 1991) is a self-report questionnaire that consists of nine scales that measure specific beliefs and assumptions associated with the different personality disorders. Here we only used the four scales corresponding to Cluster B personality disorders: antisocial, borderline, histrionic and narcissistic. The Spanish version of the scale (Albein-Urios et al., 2011) holds appropriate psychometric characteristics and the reliability of the different scales (Cronbach's α) in this sample ranged from 0.71 (narcissistic) to 0.88 (borderline).

Procedures:

Participants were scheduled 60 minutes ahead of the scanner session to be debriefed about task instructions and trained to decrease the intensity of their negative emotions through cognitive reappraisal techniques (Gross, 1999). Debriefing and training was

conducted by a master's degree clinical psychologist (NAU). After the general training on the reappraisal techniques, all participants performed a supervised rehearsal of the maintenance and reappraisal strategies using five different trial images, and they subsequently completed a verbal yes/no questionnaire about the perceived sufficiency of the training and their perceived competency to perform the task. Only after successful rehearsal and positive responses to both questions were the participants entered into the scanner. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology, Northridge, CA, USA). Behavioral responses were recorded through a five-button box, Evoke Response Pad System (Resonance Technology Inc.). The UPPS-P and PBQ scales were administered in an independent session, along with a battery of cognitive tests that will be reported elsewhere.

Imaging data acquisition and preprocessing:

We used a 3.0 Tesla clinical MRI scanner, equipped with an eight-channel phased-array head coil (Intera Achieva, Philips Medical Systems, Eindhoven, The Netherlands). During acquisition, a T2*-weighted echo-planar imaging (EPI) was obtained (TR = 2000 ms, TE = 35 ms, FOV = 230 x 230 mm, 96 x 96 matrix, flip angle = 90°, 21 4-mm axial slices, 1-mm gap, 234 scans). A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (3D-TFE) (160 slices, TR = 8.3 ms, TE = 3.8 ms, flip angle = 8°, FOV = 240 x 240, 1 mm3 voxels) was obtained in the same experimental session for anatomical reference.

The functional images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks, Natick, MA, USA).

Preprocessing included slice timing correction, re-slicing to the first image of the time series, normalization, using affine and smoothly non-linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm).

Statistical analyses:

Behavioral analyses:

Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We conducted one-way ANOVAs followed by Tukey tests to compare the three groups on relevant socio-demographic variables. Although age showed a significant between-group difference (cocaine users with and without comorbidities older than controls), subsequent analyses showed that it was not correlated with brain activations in any of the contrasts of interest, and therefore it was not further considered. We also used ANOVAs and subsequent Tukey tests to explore potential differences on self-reported ratings of emotional intensity inside the scanner and on personality measures of impulsivity and dysfunctional beliefs. Prior to image analysis, the effect of task condition on self-reported emotion was calculated to assure that the participants had followed the instructions during the task (e.g. Suppress scores lower than Maintain). Intra-subject effect of the three conditions analysis was performed also with SPSS.

fMRI, main task effects:

Two contrasts of interest were defined at the first-level (single-subject) analysis: (1) 'Maintain>Observe' and (2) 'Suppress>Maintain'. The first contrast indexes brain activations associated with negative emotion experimentation, whereas the second

contrast indexes brain activations associated with reappraisal of negative emotions. Conditions were modeled for the 20 seconds that the images were on the screen and did not include instruction and rating periods. The BOLD response at each voxel was convolved with the SPM8 canonical hemodynamic response function (using a 128-s high-pass filter). Between-group comparisons were conducted with an ANOVA on the resulting first-level contrast images.

Psychophysiological interactions analysis:

To explore the effective connectivity between the brain regions activated during the task, we conducted a psychophysiological interactions (PPI) analysis using SPM8 (Friston et al. 1997). Here, we explored the impact of the two contrasts of interest (the 'psychological' factor) on the strength of time-course correlations between two empirically obtained seed-regions of interest with all the other regions of the brain (the 'physiological' factor). To perform the first-level analysis (subject-level), the seeds were selected in accordance to two criteria: belonging to the predetermined set of regions of interest (ROIs, see below), and showing group differences in the two contrasts performed on task activation analyses (Maintain>Observe and Suppress>Maintain). Two regions met these criteria: the subgenual cingulate (for Maintain>Observe) and the orbitofrontal cortex (Suppress>Maintain). Hence, we extracted the first eigenvariate time series from a 7-mm radial sphere: the subgenual cingulate cortex (x = -14, y = 20, z = -16) –in the case of Maintain>Observe—and the left orbitofrontal cortex (x = -30, y = 30, z = -4) and right OFC (x = 52, y = 26, z = -12) –in the case of Suppress>Maintain.

Imaging analyses and Threshold:

To explore main task effects and PPI, we followed a region of interest (ROI) approach using the areas previously defined in the background section: anterior cingulate cortex, insula, orbitofrontal cortex, striatum and amygdala. In these tests, the statistical threshold was set at p<0.05 false discovery rate (FDR) corrected across the voxels of each ROI (i.e., using Small Volume Correction, or SVC, procedures). We also performed a whole-brain voxel-wise analysis in order to explore other brain areas where could be differences between the groups. In this case the results were corrected for multiple comparisons with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1,000 Monte Carlo simulations using AlphaSim (Ward et al., 2000) as implemented in the SPM REST toolbox (Song et al., 2011). The input parameters included brain mask of 156.444 voxels, an individual voxel threshold probability of 0.001 (0.005 for PPI analyses) and a cluster connection radius of 5 mm, at 8 mm FWHM smoothness. A minimum cluster extent (KE) of 121 voxels (312 for PPI analyses) was estimated to satisfy a P_{FWE} <.05.

Correlation analyses:

Two sets of correlation analyses were performed in SPSS using the peak activations derived from the two main fMRI contrasts (Maintain>Observe and Suppress>Maintain) and the PPI maps. For both analyses, the beta eigenvalues corresponding to each ROI were extracted for each participant, and then correlated with inside- and outside-scanner behavioral measures, that is, with self-reported ratings of intensity of negative emotion and with the negative urgency scores of the UPPS-P scale and subscales scores from the PBQ.

Results

Behavioral results

Results are displayed in Table 2. ANOVAs showed no differences between the groups in the Observe, Maintain or Suppress ratings (P > 0.1 in all cases). Related-samples t-tests showed significant differences between Maintain and Observe (P < 0.05), and between Suppress and Maintain (P < 0.05); as expected, the intensity of negative emotion was greater in Maintain versus Observe, and smaller in Suppress versus Maintain (Table 2). With respect to the UPPS-P, the scores of negative urgency significantly differed between the groups, with cocaine users with and without comorbidities scoring higher than controls (P<0.001). The PBQ borderline and antisocial scales also showed differences between the groups (P<0.05). In the borderline scale both cocaine users with and without comorbidities scored higher than controls (P<0.05). In the antisocial scale the cocaine users with concurrent personality disorders scored higher than cocaine users without comorbidities and controls (P<0.05).

Table 2. Self- reports of the intensity of the negative emotions induced by each of the task conditions (inside-scanner) and scores of the UPPS-P negative urgency subscale and of the Personality Belief Questionnaire Cluster B subscales (outside-scanner).

	Cocaine Mean (SD)	Cocaine+PD Mean (SD)	Controls Mean (SD)	P- value
Inside scanner ratings				
Maintain	3.68 (0.93)	3.54 (0.70)	3.12 (0.97)	0.101
Suppress	3.24 (0.82)	2.70 (0.63)	2.69 (1.00)	0.130
Observe	1.86 (0.86)	2.03 (1.08)	1.68 (0.71)	0.483
UPPS-P scale				
Negative Urgency	33.17 (6.51)	36.59 (4.76)	23.48 (5.71)	0.000
Personality Belief Questionnaire				
Borderline	13.36 (10.04)	18.44 (10.31)	7.62 (7.54)	0.008
Antisocial	23.71 (11.63)	29.56(9.92)	19.44 (7.51)	0.019
Narcissistic	14.79 (8.84)	16.81 (7.54)	14.43 (7.39)	0.663
Histrionic	15.36 (8.11)	16.81 (10.92)	12.94 (9.44)	0.521

SD = standard deviation; UPPS = impulsive behavior scale; PBQ = Personality Belief Questionnaire.

Imaging results:

For the sake of brevity, we only present in the main text and Figures the findings from group comparisons in the main contrasts of interest (Maintain>Observe and Suppress>Maintain), with special emphasis on the ROI results. For a detailed account of the one-sample task activations results and the between-group whole-brain comparisons please see Supplementary Tables S1 to S7.

Maintain>Observe:

Cocaine users with concurrent personality disorders showed decreased activation of the subgenual anterior cingulate cortex compared to cocaine users without comorbidities and controls. In addition, according to the whole-brain analyses, cocaine users with concurrent personality disorders also showed decreased activation of the left dorsolateral prefrontal cortex, left lateral orbitofrontal cortex and left supplementary motor area with respect to cocaine users without comorbidities but not with respect to controls (Figure 1).
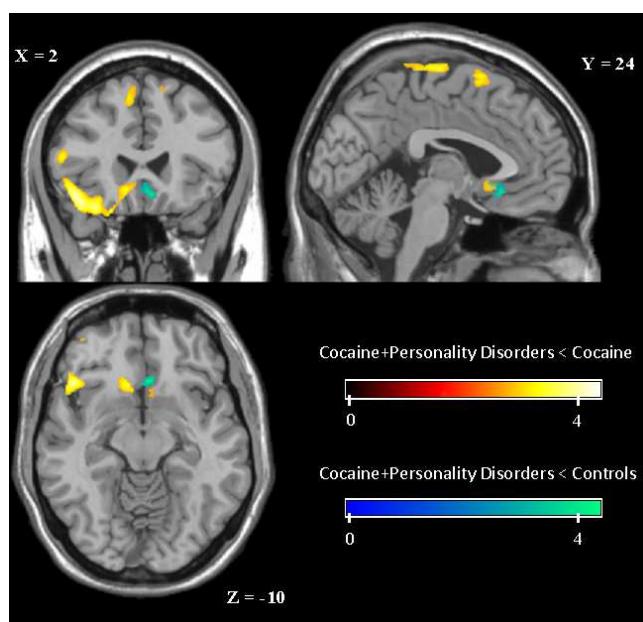
Figure 1: Brain regions showing significantly reduced activation during Maintain>Observe in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities (in yellow) and controls (in blue).

Suppress>Maintain:

In comparison to cocaine users without comorbidities, cocaine users with concurrent personality disorders showed increased activation of the amygdala and the lateral orbitofrontal cortex (bilaterally), as well as the inferior frontal and subcallosal gyri of the left hemisphere. The behavioral scores of negative urgency and antisocial beliefs positively correlated with amygdala activation in the cocaine comorbid group, but not in cocaine users without comorbidities or controls (Figure 2).
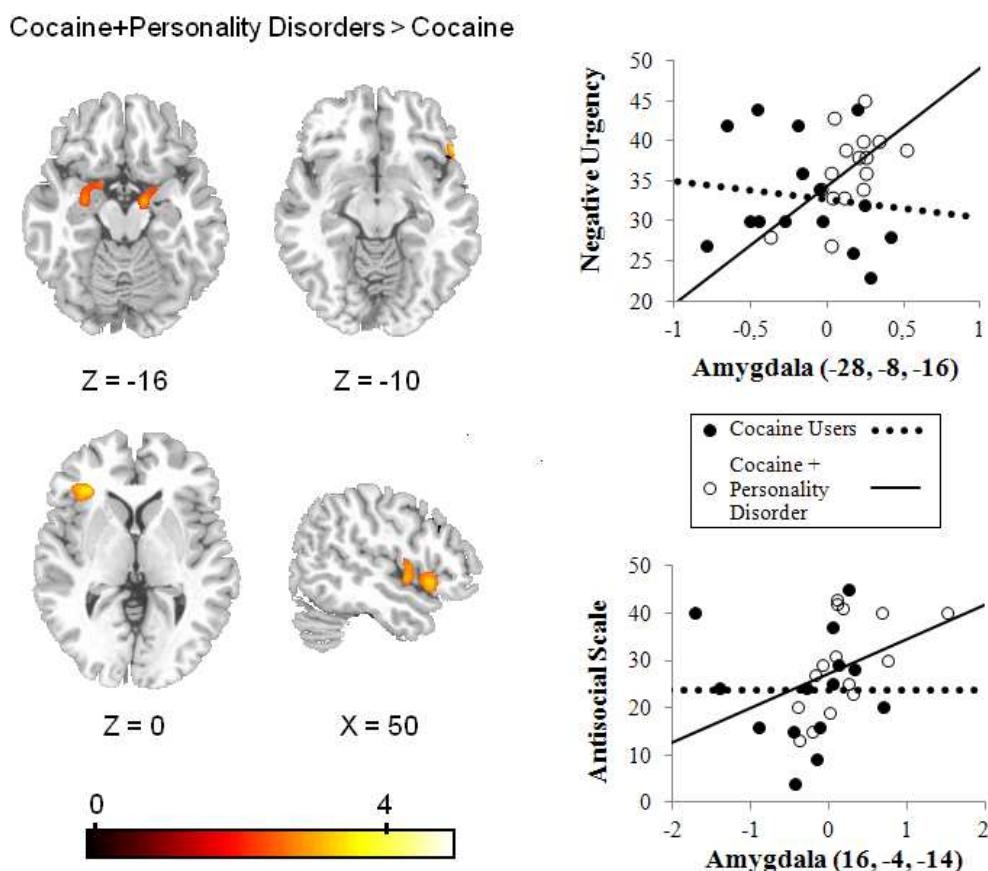

Figure 2: Brain regions showing significantly increased activation during Suppress>Maintain in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities and correlations between these regions and personality scores of negative urgency and antisocial dysfunctional beliefs.

PPI Analyses:

Group differences in Maintain>Observe:

Cocaine users with concurrent personality disorders, in comparison to cocaine users without comorbidities, showed *decreased* functional coupling between the subgenual cingulate cortex and left amygdala and bilateral fusiform gyri in comparison to cocaine users without comorbidities (see Figure 3, left top panel). In addition, they showed *increased* functional coupling between the subgenual cingulate cortex and the right anterior insula in comparison to cocaine users without comorbidities and controls (see Figure 3, left bottom panel).

Group differences in Suppress>Maintain:

In comparison with cocaine users without comorbidities, cocaine users with concurrent personality disorders showed *increased* functional coupling between the left orbitofrontal cortex and the left amygdala, thalamus, and tempo-occipital cortex (see Figure 3, right top panel). Conversely, also in comparison to cocaine users without comorbidities, cocaine users with concurrent personality disorders showed *decreased* functional coupling between the right orbitofrontal cortex and the left lenticular nucleus (putamen and globus pallidus), extending to the adjacent posterior insular cortex (see Figure 3, right bottom panel). We found no significant differences in connectivity between the cocaine groups and controls.
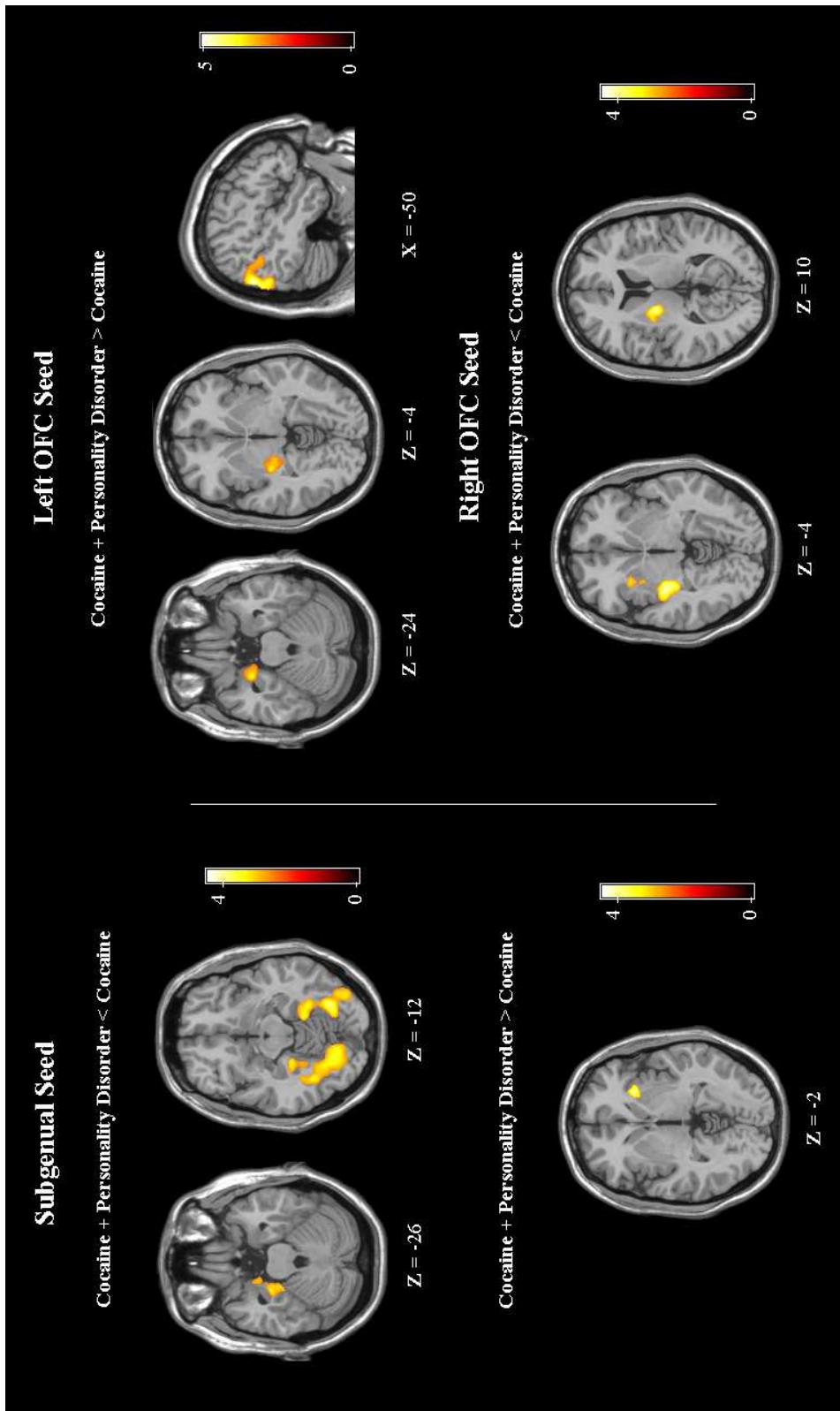
Figure 3: Left panel displays the regions showing significantly reduced (top) and increased (bottom) functional connectivity with the subgenual anterior cingulate cortex seed in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities during Maintain>Observe. Right panel displays the regions showing significantly increased (top) and decreased (bottom) functional connectivity with the lateral orbitofrontal cortex seed in cocaine users with comorbid personality disorders compared to cocaine users without comorbidities during Suppress>Maintain.

Discussion

In agreement with initial hypotheses, cocaine users with concurrent Cluster B personality disorders showed reduced subgenual anterior cingulate cortex activation during negative emotion maintenance, and increased lateral orbitofrontal cortex (BA 47) and amygdala activations during cognitive reappraisal. The personality scores of negative urgency and antisocial beliefs were significantly elevated in the cocaine comorbid group, and both scores positively correlated with the reappraisal-related amygdala activation exclusively within this group. Connectivity analyses further showed that within the cocaine comorbid group the subgenual cingulate was less efficiently connected with the left amygdala and fusiform gyri and more efficiently connected with the right anterior insula during maintenance, whilst during reappraisal the left orbitofrontal cortex was more efficiently connected with the left amygdala and the right orbitofrontal cortex was less efficiently connected with the dorsal striatum.

According to these findings, cocaine users with concurrent Cluster B personality disorders are specifically characterized by reduced subgenual anterior cingulate cortex activation during active maintenance of negative emotions. The subgenual anterior cingulate cortex is normally engaged during recall of aversive states, and its activation correlates with the appraisal of negative emotions (Kross et al., 2009). Conversely, brain lesions encompassing the subgenual anterior cingulate cortex result in insensitivity to punishment (relative to reward) in the guidance of decision-making (Bechara et al., 1994), which is a hallmark of the social behavior of individuals with personality disorders (Dadds and Salmon, 2003). Our connectivity results further showed that in the cocaine comorbid patients the subgenual anterior cingulate cortex was less efficiently connected with a broader network of regions (amygdala and

fusiform gyri) which are also importantly involved in moderating responses to aversive stimuli (Pujol et al., 2009). On the other hand, also in comorbid patients, the subgenual cingulate cortex was more efficiently connected with the anterior insula, which is part of a large-scale brain network associated with emotional salience (Taylor et al., 2009). All in all, the results from this contrast suggest that cocaine users with concurrent personality disorders have deficient functioning of the brain regions supporting experiential and appraisal aspects of negative emotion with respect to non-comorbid cocaine users and controls. There were also a number of regions in which non-comorbid cocaine users showed increased activation than comorbid users (left lateral orbitofrontal, dorsolateral prefrontal cortex and supplementary motor regions). Because these areas are involved in cognitive control (Cole and Schneider, 2007) and they did not significantly differ between cocaine users and controls, we interpret that this finding reflects higher cognitive effort to sustain negative emotion in the non-comorbid vs. the comorbid patients.

During reappraisal of negative emotions the cocaine users with concurrent Cluster B personality disorders showed increased lateral orbitofrontal cortex (BA 47) and amygdala activations compared to the non-comorbid cocaine users. Connectivity analyses further showed that comorbid patients exhibited increased functional coupling between the left lateral orbitofrontal cortex and the left amygdala, the thalamus and temporal-occipital regions. Noteworthy, the neural pathway connecting the lateral orbitofrontal cortex with the amygdala has been associated with reduced reappraisal success (Wager et al., 2008) and with predominantly distracting vs. reappraisal strategies of emotion regulation (McRae et al., 2010). In agreement with these notions, our correlation analyses showed that specifically within the comorbid group there was a

positive association between the reappraisal-related amygdala activation and the intensity of negative urgency (the tendency to act impulsively when under strong negative affect). We also found a significant correlation between reappraisal-related amygdala activation and the scores of antisocial-related cognitive beliefs, which is in fitting with evidence showing that amygdala activation during reappraisal is associated with the tendency to ruminate and focus on negative aspects of one's self (Ray et al., 2005). Therefore, these findings indicate that cocaine patients with comorbid personality disorders display enhanced engagement of neural networks conveying low efficiency to perform adequate emotion regulation strategies, and that this brain patterns are associated with negative beliefs and negative-emotion driven impulsive behavior. Conversely, the cocaine comorbid patients showed decreased functional connectivity between the right lateral orbitofrontal cortex and the dorsal striatum, a pathway purported to support successful cognitive reappraisal and behavioral restraint (Holmann et al., 2012).

In summary, cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities and healthy controls in terms of decreased activation and connectivity of the brain networks involved in moderating responses to aversive stimuli during negative emotion maintenance. In addition, cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities in terms of less efficient connectivity of the emotion regulation network during negative emotion reappraisal, being these abnormalities correlated with the impulsive trait of negative urgency, and with the intensity of Cluster-specific dysfunctional beliefs. This study holds important strengths and also worth noting limitations. Among the first, we

should number the careful selection of cocaine dependent patients with and without Cluster B disorders but not other comorbidities, the duration of supervised abstinence (always superior to 15 days, allowing us to rule out acute or residual drug effects), and the good match between the cocaine and control groups in terms of relevant socio-demographic variables not often controlled for (e.g., IQ). Although the groups significantly differed on age, our selection criteria stringently restricted the age range for inclusion (18-45 years old) and age was not significantly correlated with the patterns of brain functioning in any of the contrasts of interest. Other potential limitations include the relatively small sample size and the inclusion of patients with nicotine dependence and alcohol abuse. Nonetheless, in each case we should stress the difficulty of recruiting large clinical samples meeting our strict inclusion criteria, and the virtual impossibility of finding cocaine users without substantial nicotine and alcohol use.

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Supplementary Material from the Manuscript

Cocaine users with comorbid Cluster B personality disorders show dysfunctional brain activation and connectivity in the emotional salience and regulation networks during negative emotion maintenance and reappraisal

This section includes:

Table S1: Regions showing significant activations during Maintain>Observe: one-sample t-tests for cocaine users without comorbidities (Cocaine), cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

Table S2: Regions showing significant activations during Suppress>Maintain: one-sample t-tests for cocaine users without comorbidities (Cocaine), cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

Table S3: Regions showing significant differences during Maintain>Observe and Suppress>Maintain between the three groups: Cocaine users without comorbidities (Cocaine), Cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

Table S4: Brain regions showing increased functional connectivity with the subgenual cingulate cortex seed during Maintain>Observe: one sample t-test.

Table S5: Brain regions showing increased functional connectivity with the left OFC seed during Suppress>Maintain: one sample t-test.

Table S6: Brain regions showing increased functional connectivity with the right OFC seed during Suppress>Maintain: one sample t-test.

Table S7: Brain regions showing group differences in functional connectivity with the subgenual anterior cingulate seed during Maintain>Observe, and with the orbitofrontal cortex seed during Suppress>Maintain.

Table S1: Regions showing significant activations during Maintain>Observe: one-sample t-tests for cocaine users without comorbidities (Cocaine), cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

	BA	Side	MNI Coordinates			Volume (mm³)	T-value
			X	Y	Z		
Cocaine + PD							
Occipitotemporal cortex	18, 19, 37, 39	R	44	-80	-2	27272	7.67
Occipitotemporal cortex	18, 19, 37, 39	L	-46	-58	-22	34472	6.25
Cerebellum		L/R	-6	-72	-26	10312	5.78
Superior Frontal Gyrus	8, 9, 10	L/R	-14	42	52	9176	5.25
Post. Thalamus		L	-20	-20	16	1992	4.71
Amygdala	34	L	-14	-6	-18	1368	4.61
Precuneus		L/R	8	-44	18	1168	4.54
Post. Thalamus		R	10	-22	-4	1000	4.20
OFC	47	L	-38	30	-10	208	4.15
SMA	6, 8	L/R	-2	20	60	232	3.70
Cocaine							
Occipitotemporal cortex	18, 19, 37, 39	R	40	-52	-24	40432	7.24
Occipitotemporal cortex	18, 19, 37, 39	L	-46	-76	2	38424	7.02
IFG	38, 45, 47	L	-50	20	-10	3600	5.06
Cerebellum		L/R	-14	-72	-22	8472	4.83
Thalamus		L	-14	-28	-4	2416	4.66
Temporal Lobe	21, 22	L	-56	-2	-26	320	4.52
IFG	38, 45, 47	R	58	28	12	4688	4.52
Precuneus	7	L/R	-2	-60	34	2824	4.49
Medial Frontal Gyrus	9, 10	L/R	-2	58	20	1632	4.41
SMA	6, 8	L/R	-2	10	62	2480	4.27
dlPFC	10	R	32	56	22	400	3.95
Thalamus		L/R	6	-18	8	2072	3.76
Controls							
Occipitotemporal cortex	18, 19, 37, 39	L	-42	-86	-2	43608	9.83
Occipitotemporal cortex	18, 19, 37, 39	R	42	-82	-2	35688	9.21
Cerebellum		L/R	-20	-78	-26	15096	6.67
Medial Frontal Gyrus	9, 10	L/R	6	58	26	6008	6.29
Post. Thalamus		L/R	-14	-30	-2	2416	5.19
Amygdala	34, 35	L	-20	-14	-12	4264	5.00
Ant. Thalamus		L/R	2	-6	6	1296	4.89
Superior Temporal Gyrus	38	L	-46	22	-16	1352	4.25
PCC	31	L/R	-2	-50	28	1880	4.20
Amygdala	34	R	20	-2	-20	896	4.12
IFG	44, 45	R	50	18	20	1032	4.12
OFC	47	R	34	32	-20	224	4.08
SMA	6, 8	L/R	-8	22	60	1576	4.06
ACC	32	L/R	-2	34	26	304	3.66
Caudate		L	-12	2	4	824	3.63

BA, Brodmann area; PD, personality disorder; IFG, inferior frontal gyurs; PCC, posterior cingulate cortex; OFC, orbitofrontal cortex; SMA, supplementary motor area; ACC, anterior cingulate cortex.

Table S2: Regions showing significant activations during Suppress>Maintain: one-sample t-tests for cocaine users without comorbidities (Cocaine), cocaine users with comorbid Personality Disorder (Cocaine + PD) and non-drug using Controls.

	BA	Side	MNI Coordinates			Volume (mm³)	T-value
			X	Y	Z		
Cocaine + PD							
Parieto-Occipital	7, 19	R	32	-84	24	4304	5.62
dlPFC	9, 46	R	50	12	26	1280	5.02
Occipital Lobe	18, 19	R	26	-68	-10	4928	4.51
dlPFC-Precentral Gyrus	6, 9	R	40	2	40	448	4.37
OFC	47	L	-32	30	-4	520	4.24
Occipital Lobe	19	L	-30	-88	22	360	4.07
Middle Frontal Gyrus	8	R	28	14	44	320	4.03
Controls							
Occipital Lobe	17, 18, 19	L	-10	-76	-4	11880	7.06
Occipital Lobe	17, 18, 19	R	10	-76	-4	14520	6.18
Parieto-Occipital	7, 19	L	-34	-90	16	8840	5.26
dlPFC-IFG	9, 46	R	36	8	44	17248	5.17
Parieto-Occipital	7, 19	R	32	-82	26	6808	5.06
dlPFC-Precentral Gyrus	6, 9	L	-40	2	34	6472	4.34
Superior Temporal Gyrus	22	L	-62	-48	12	1200	3.80
Supramarginal Gyrus	40	R	56	-52	24	744	3.69
Medial Frontal Gyrus	8, 9	R	10	40	40	1224	3.58
OFC	47	R	40	46	-2	1136	3.50
PCC	7	L/R	6	-44	46	360	3.16

BA, Brodmann area; PD, personality disorder; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyurs; PCC, posterior cingulate cortex; OFC, orbitofrontal cortex.

Table S3: Regions showing significant differences during Maintain>Observe and Suppress>Maintain between the three groups: Cocaine users without comorbidities (Cocaine), Cocaine users with comorbid Personality Disorder (Cocaine+PD) and non-drug using Controls.

	BA	Side	MNI Coordinates			Volume (mm^3)	T-value
			X	Y	Z		
Maintain > Observe							
Cocaine + PD < Cocaine							
Subgenual cingulate	25	L/R	-14	20	-16	1504	3.97
dlPFC	45, 46	L	-56	28	8	2184	4.30
OFC	47	L	-46	24	-14	2648	4.18
SMA	6	L/R	12	12	64	2712	3.93
Cocaine + PD < Controls							
Subgenual cingulate	25	L/R	6	22	-14	1024	4.27
Suppress > Maintain							
Cocaine + PD > Cocaine							
Inferior Frontal gyrus	22, 44	L	-56	10	6	1584	4.25
OFC	47	R	52	26	-12	1248	3.63
OFC	47	L	-30	30	-4	3640	3.63
Amygdala	34	L	-28	-8	-16	2416	3.05
Amygdala	34	R	16	-4	-14	1632	3.03
Subcallosal gyrus		L	-22	4	-14	352	2.61

BA, Brodmann area; PD, personality disorder; dlPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; SMA, supplementary motor area.

Table S4: Brain regions showing increased functional connectivity with the subgenual cingulate cortex seed during Maintain>Observe: one sample t-test.

	BA	Side	MNI Coordinates			Volume (mm^3)	T-value
			X	Y	Z		
Cocaine							
Superior Temporal Gyrus	21	L	-48	-8	-22	4856	4.25

BA, Brodmann area.

Table S5: Brain regions showing increased functional connectivity with the left OFC seed during Suppress>Maintain: one sample t-test.

	BA	Side	MNI Coordinates			Volume (mm³)	T-value
			X	Y	Z		
Cocaine + PD							
Fusiform Gyrus	19	L	-22	-60	-12	4128	3.75
Occipital Lobe	19	L	-30	-88	32	2.800	3.93
Amygdala	34	L	-24	-2	-24	4200	3.89
Amygdala		R	26	-4	-22	1944	2.95
Cocaine							
Inferior Parietal Lobule	40	R	54	-50	44	2744	3.95
Controls							
PCC	30	L/R	-2	-60	8	6584	4.48
ACC		L/R	-16	28	10	2552	3.82
Amygdala	34	L	-20	-8	-20	1208	3.66
Amygdala		R	24	-6	-28	232	2.37

BA, Brodmann area; PD, personality disorder; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex.

Table S6: Brain regions showing increased functional connectivity with the right OFC seed during reappraisal (Suppress>Maintain): one sample t-test.

	BA	Side	MNI Coordinates X	Y	Z	Volume (mm³)	T-value
Cocaine							
Amygdala		L	-32	-8	-12	400	2.83
Insula	13, 22	L	-40	-14	-2	12120	4.77
Postcentral Gyrus	2, 3, 4	L	-40	-24	42	5560	3.56
Inferior Parietal Lobule	40	R	36	-48	44	4824	4.41
Middle Frontal Gyrus	8	R	28	20	52	2480	4.25
Controls							
Fusiform Gyrus	37	R	32	-40	-12	6216	3.58
Fusiform Gyrus	37	L	-34	-36	-12	8536	3.63
Caudate		L/R	4	2	2	2968	3.50

BA, Brodmann area; PD, personality disorder; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex.

Table S7: Brain regions showing group differences in functional connectivity with the subgenual anterior cingulate seed during Maintain>Observe, and with the orbitofrontal cortex seed during Suppress>Maintain.

	BA	Side	MNI Coordinates			Volume (mm^3)	T-value
			X	Y	Z		
Maintain > Observe (Subgenual)							
Cocaine + PD < Cocaine							
Fusiform gyrus		L	-34	-58	-8	4072	4.43
Fusiform gyrus		R	28	-68	-12	3200	3.72
Amygdala	34	L	-18	-4	-26	1392	2.91
Cocaine + PD > Cocaine							
Anterior Insula	13, 47	R	28	20	-2	2448	4.07
Cocaine + PD > Controls							
Insula	13, 47	R	24	20	-2	3392	4.88
Suppress > Maintain (Left OFC)							
Cocaine + PD > Cocaine							
Tempo-occipital cortex	19, 39	L	-50	-76	18	12168	5.00
Thalamus	28, 35	L	-22	-22	-4	2944	3.86
Amygdala	34	L	-22	-4	-24	3064	3.81
Suppress > Maintain (Right OFC)							
Cocaine > Cocaine + PD							
Lenticular nucleus		L	-20	-6	10	2512	4.48
Insula	13	L	-38	-14	-4	5048	4.19

BA, Brodmann area; PD, personality disorder; OFC, orbitofrontal cortex.

CAPÍTULO 9: DISCUSIÓN GENERAL, CONCLUSIONES Y PERSPECTIVAS FUTURAS

4.1. Discusión general

Este apartado discutiremos de manera general nuestros hallazgos en relación con cada una de las hipótesis que planteamos al inicio de esta tesis.

En relación con nuestra primera Hipótesis, los resultados del primer estudio confirmaron que los pacientes con dependencia de cocaína comparten rasgos de urgencia positiva y déficits de inhibición de respuesta con el grupo de individuos con adicción sin sustancia (juego patológico), pero en cambio difieren de éstos por sus mayores niveles de urgencia negativa y su peor rendimiento en memoria de trabajo. Estos hallazgos sugieren que las elevaciones de la dimensión de urgencia negativa y los déficits en memoria de trabajo están específicamente asociados con el consumo crónico de cocaína, mientras que las elevaciones del rasgo de urgencia positiva y los déficits del control inhibitorio, presentes en ambos grupos, pueden constituir factores de riesgo para el desarrollo de las adicciones, o bien marcadores generalizados de las transiciones en el control del comportamiento que se producen en adicciones con y sin sustancia (Everitt y Robbins, 2005).

En resumen, nuestro primer estudio demuestra que la adicción con y sin sustancia está asociada con comportamientos impulsivos en situaciones emocionales positivas y a déficits del control inhibitorio, mientras que la adicción a la cocaína produce deterioros diferenciales de la capacidad para controlar comportamientos impulsivos bajo condiciones de afecto negativo y de la capacidad para organizar y actualizar información, necesaria para ajustar el comportamiento a los objetivos deseados (Verdejo-García y Bechara, 2010). En este sentido, nuestros resultados son coincidentes con los de un estudio reciente en el que se compara la personalidad y el rendimiento cognitivo de consumidores de cocaína y de sus familiares "no afectados" (Ersche et al.,

2012). Sus resultados mostraron que consumidores y familiares comparten rasgos de impulsividad-compulsividad y déficits del control inhibitorio, pero en cambio los consumidores rindieron significativamente por debajo de los controles en tests de memoria de trabajo y planificación de objetivos. Por tanto, la impulsividad rasgo (a excepción de la urgencia negativa) y el control inhibitorio se postulan como endofenotipos de la adicción, mientras que la regulación de los impulsos en situaciones de frustración, estrés o ira y los déficits de actualización de información en la memoria de trabajo se postulan como resultados de los efectos neuroadaptativos de la cocaína.

En cuanto a las implicaciones de nuestros resultados para el contexto clínico es importante destacar que las elevaciones del rasgo de urgencia negativa se han asociado con mayores niveles de severidad de problemas socio-familiares, laborales y legales asociados con la adicción (Verdejo-García et al., 2007), mientras que los déficits de memoria de trabajo se han asociado con la facilitación de respuestas de deseo ("craving") o recaídas y con peores resultados de retención y adherencia al tratamiento (Serper et al., 2000; Sofuoglu et al., 2012).

En relación con nuestra segunda Hipótesis los resultados del segundo estudio confirmaron que los pacientes con dependencia a la cocaína y comorbilidad con trastornos de personalidad del clúster B presentan mayores niveles de urgencia negativa y creencias disfuncionales y peor rendimiento en tareas de regulación atencional e inhibición de respuesta con respecto a sujetos con adicción a la cocaína sin trastornos comórbidos. Aunque en nuestras hipótesis planteábamos que los consumidores con trastornos comórbidos presentarían reducciones del volumen de materia gris en regiones fronto-límbico-estriadas, la única diferencia significativa se produjo en el polo temporal derecho. Pese a no ser una de las regiones de interés a priori, esta región está

densamente conectada con la corteza orbitofrontal y con la amígdala (encargadas de asignar valor emocional a estímulos apetitivos y aversivos) y tiene una fuerte implicación en funciones de procesamiento emocional y cognición social (Olson et al., 2007).

En resumen, nuestro segundo estudio demuestra que la comorbilidad entre la adicción a la cocaína y los trastornos de personalidad del Clúster B se relaciona con una exacerbación de aquellos rasgos y déficits cognitivos que comparten ambos trastornos. Por ejemplo, en individuos con trastornos de personalidad límite o rasgos antisociales/psicopáticos la urgencia negativa es un predictor robusto de la severidad de sus síntomas psicopatológicos (Peters et al., 2012; Whiteside y Lynam, 2003). En el caso de los consumidores de cocaína las dificultades de regulación del afecto negativo se habían detectado en consumidores no-comórbidos (Fernández-Serrano et al., 2012; Verdejo-García et al., 2007) y existían indicios preliminares de que estos déficits eran más pronunciados en pacientes con comorbilidad con Eje II (Fox et al., 2007). Resultados similares se han obtenido en el contexto de las funciones ejecutivas. Diversos estudios apuntan a que la atención y el control ejecutivo son los principales déficits de los pacientes con trastornos de personalidad límite y antisocial una vez ajustados confusores como el CI (Dolan et al., 2012; Haaland et al., 2009) como también indican los meta-análisis en consumidores de cocaína (Jovanovski et al., 2005; Fernández-Serrano et al., 2011). Por tanto, podemos concluir que la comorbilidad amplifica los déficits característicos de ambos trastornos, siendo la intensidad de las creencias disfuncionales y la severidad de los rasgos de urgencia negativa correlatos específicos del deterioro ejecutivo. Destaca también la afectación específica del polo

temporal, una región esencial para los procesos relacionados con la cognición social y la inteligencia emocional, que son déficits compartidos por ambos trastornos.

En relación con las posibles implicaciones de nuestros resultados para el contexto clínico, debemos destacar en primer lugar que la combinación de los índices de urgencia negativa, creencias disfuncionales y regulación atencional son capaces de predecir la presencia de comorbilidad entre ambos trastornos con índices de especificidad destacablemente altos, por lo que estas herramientas pueden contribuir a mejorar el diagnóstico diferencial de estos trastornos duales. En segundo lugar estos hallazgos apuntan a la importancia de implementar estrategias de intervención específicas para los pacientes con diagnóstico comórbido, haciendo especial hincapié en la posibilidad de romper el vínculo entre afectos negativos, creencias disfuncionales y actos impulsivos, y en la posibilidad de mejorar sus habilidades de cognición social mediante entrenamientos cognitivos (Alfonso et al., 2011) o fármacos de nueva generación (p.e,, oxitocina) (McGregor y Bowen, 2012).

En relación con nuestra tercera Hipótesis, los resultados del tercer estudio confirmaron que los pacientes con dependencia de cocaína presentaron mayor reactividad corticolímbica y reducciones de la conectividad fronto-límbica durante las tareas de experimentación y regulación emocional respectivamente. Los pacientes con dependencia de cocaína mostraron hiperactivaciones de la corteza prefrontal dorsolateral derecha y de la juntura temporo-parietal, bilateralmente, mientras se esforzaban por focalizar y mantener las emociones negativas. De acuerdo con estudios previos, este patrón parece reflejar una excesiva reactividad cortical en respuesta a la experimentación de afectos negativos y una mayor vinculación de estos afectos a experiencias personales (la corteza temporo-parietal es clave en procesos de

mentalización y memoria autobiográfica) (Spreng et al., 2009). Por otro lado, los consumidores mostraron hipoactivaciones del giro frontal inferior derecho y de la conectividad entre éste y la amígdala durante la condición de regulación de emociones negativas. En este caso, los consumidores muestran déficits en la activación y la conectividad de una región especializada en la inhibición y regulación de conductas y emociones, tanto emociones positivas y negativas como emociones de deseo o "craving" (Tabibnia et al., 2011). Concluimos, por tanto, que los consumidores de cocaína presentan una exacerbación de su respuesta cortical ante estímulos afectivos negativos, de acuerdo con el modelo de sensibilización al estrés (Koob y Volkow, 2010) y una reducción de la capacidad funcional de los sistemas especialistas en controlar o regular dichas emociones de una forma adaptativa.

En cuanto a las posibles implicaciones de estos hallazgos para el contexto clínico, destaca la conexión entre las dos estructuras afectadas en consumidores y fenómenos clínicos como el "craving" (Tabibnia et al., 2009). Enlazando con los resultados del primer estudio (déficits en urgencia negativa y memoria de trabajo) y basándonos en el papel central de la corteza prefrontal dorsolateral en la memoria de trabajo y en el "craving" por la cocaína (Camprodon et al., 2007) y la correlación entre urgencia negativa e hiperactivación de la red dorsolateral/hipoactivación de la red frontal inferior, es factible especular que la sobrecarga producida por contenidos afectivos negativos en dicha región puede facilitar los deseos de consumo y limitar la capacidad de regiones adyacentes (giro frontal inferior) para controlar respuestas impulsivas. La ruptura de este ciclo podría conseguirse mediante la reducción de los niveles de afecto negativo o mediante la estimulación de las capacidades de memoria de trabajo y, por tanto, de los

recursos gestores e inhibitorios de la corteza prefrontal dorsolateral, como indican estudios recientes en consumidores de alcohol (Houben et al., 2011).

En relación con nuestra última Hipótesis los resultados del cuarto estudio demostraron que los consumidores de cocaína con trastorno de personalidad del Clúster B presentaban un patrón de activación y conectividad cerebral sustancialmente diferenciado del de los consumidores sin comorbilidades. Bajo condiciones de experimentación de emociones negativas, donde los consumidores no comórbidos hiperactivaban la corteza dorsolateral, los pacientes con trastornos del Clúster B hipoactivan la corteza cingulada anterior subgenual, implicada en la moderación de la reactividad ante estímulos aversivos y en la percepción subjetiva ("appraisal") del afecto negativo. Por otro lado, durante la regulación de las emociones negativas los consumidores con trastornos comórbidos mostraron incrementos diferenciales de la activación y la conectividad funcional entre corteza orbitofrontal lateral y la amígdala, una red que ha sido asociada con menor eficiencia en la consecución de la regulación deseada.

Estos resultados son más coincidentes con los de los hallazgos de neuroimagen en los trastornos de personalidad límite o antisocial –que se caracterizan por defectos en la activación del cíngulo subgenual y la amígdala durante la experimentación y la baja eficiencia de la corteza orbitofrontal durante las estrategias de autorregulación (Ruocco et al., 2012; Schulze et al., 2011; Yang y Raine, 2009)– que con los obtenidos hasta la fecha en consumidores de cocaína u otros psicoestimulantes (Tabibnia et al., 2011). Por tanto, de acuerdo con los resultados conductuales del Estudio 2, podemos concluir que los pacientes con trastornos de personalidad comórbida realizan una mala gestión de los afectos negativos, que se relaciona con déficits primarios en la activación y

comunicación entre regiones clave para la experimentación y regulación de estos afectos.

En cuanto a la posible aplicación de los hallazgos al contexto clínico, destaca de nuevo la correlación significativa entre los patrones disfuncionales de activación cerebral durante la regulación afectiva y los rasgos de urgencia negativa y creencias disfuncionales. Asumimos por tanto que la ruptura del ciclo impasividad-creencias-desregulación afectiva y desinhibición conductual puede contribuir a normalizar estos sistemas cerebrales o, alternativamente, la estimulación de estas regiones (cíngulo subgenual o corteza orbitofrontal) puede contribuir a desvincular dichos procesos.

4.2. Conclusiones

Las conclusiones derivadas de los cuatro estudios que conforman el trabajo de esta tesis doctoral son:

1. Los individuos con dependencia de cocaína difieren de los jugadores patológicos y de los controles no-consumidores en la elevación de sus niveles de urgencia negativa y en su peor rendimiento en un test de actualización de información en la memoria de trabajo. A partir de estos resultados postulamos que los elevados niveles de impulsividad en situaciones de afecto negativo y los déficits en memoria de trabajo están específicamente asociados con las neuroadaptaciones generadas por el consumo de cocaína.

2. Los pacientes con dependencia de cocaína y trastornos de personalidad del Clúster B se diferencian de los pacientes con dependencia de cocaína sin comorbilidades y de los controles no-consumidores en sus niveles superiores de

urgencia negativa y creencias disfuncionales asociadas al trastorno límite, en su peor rendimiento en tests de regulación atencional y control inhibitorio, y en su menor volumen de materia gris en el polo temporal derecho. Por tanto, concluimos que la intensidad de los niveles de impulsividad en situaciones de afecto negativo y de las distorsiones cognitivas, los déficits de inhibición regulación atencional y las reducciones en el polo temporal están específicamente asociadas con la comorbilidad entre la dependencia de cocaína y los trastornos de personalidad del Clúster B.

3. Los individuos con dependencia de cocaína (sin comorbilidad asociada) se diferencias de los controles no-consumidores en el incremento de la activación de la corteza prefrontal dorsolateral derecha durante la experimentación de emociones negativas y en la disminución de la conectividad funcional entre el giro frontal inferior y la amígdala durante el ejercicio de control cognitivo de emociones negativas. Por tanto, concluimos que los pacientes con dependencia de cocaína presentan patrones disfuncionales de activación y conectividad corticolímbica durante el mantenimiento o la regulación de las emociones negativas. Estos déficits están asociados con elevaciones del rasgo de urgencia negativa.

4. Los pacientes con dependencia de cocaína y trastorno de personalidad del Clúster B se diferencian de los pacientes con dependencia de cocaína sin comorbilidades y de los controles no-consumidores en la disminución de la activación y la conectividad de las redes cerebrales implicadas en la experimentación y regulación eficiente de emociones negativas, que además

correlacionan con las elevaciones del rasgo de urgencia negativa y con la intensidad de las creencias disfuncionales específicas del Clúster B.

4.3. Perspectivas futuras

Tras el análisis de los resultados y conclusiones obtenidos y las preguntas de investigación que quedan irresueltas, las perspectivas de investigación futura derivadas de esta tesis son, entre otras, las siguientes:

1. Si bien los trastornos de personalidad del Clúster B son los más frecuentemente asociados a la adicción a la cocaína, en nuestra selección de pacientes hemos detectado un número considerable de consumidores con trastornos del Clúster C (característicamente ansiosos y temerosos). Aunque sus resultados no se incluyen en esta tesis nuestros análisis preliminares indican que éstos también presentan perfiles de deterioro neuropsicológico diferenciado (déficits más pronunciados en la memoria de trabajo) y disfunciones de la corteza cingulada anterior. Los estudios futuros deberán profundizar en las características neuropsicológicas y neurobiológicas de la comorbilidad con estos trastornos, así como en sus potenciales implicaciones clínicas.

2. Aunque nuestro estudio identifica características diferencialmente asociadas al consumo de cocaína (vs. adicciones conductuales) y a la comorbilidad con trastornos de personalidad (vs. diagnósticos no duales) son necesarios diseños longitudinales que identifiquen cuándo y cómo emergen (a nivel neuropsicológico y neurobiológico) estas características que predicen el desarrollo de adicciones y de adicciones con complicaciones psiquiátricas. Estas

investigaciones pueden contribuir asimismo a clarificar qué rasgos y destrezas se relacionan con la etiopatogenia común de ambos trastornos (surgen y se desarrollan simultáneamente) y cuáles se asocian preferentemente a uno u otro pero interactúan en último término en un diagnóstico dual.

3. Ya que hemos observado (Estudio 2) que las medidas de impulsividad, creencias y rendimiento atencional son predictoras específicas de la presencia de comorbilidad con trastornos de personalidad, es necesario investigar cómo estas medidas pueden combinarse con otras más tradicionales y con nuevas tecnologías con el objetivo de mejorar la detección temprana y el diagnóstico diferencial de la comorbilidad entre la adicción a la cocaína y trastornos de personalidad.

4. Asimismo sería interesante explorar si las medidas de impulsividad y atención/inhibición permiten capturar diferencias individuales dentro de la población clínica y que confieran una repercusión directa sobre las variables de resultado del tratamiento de la adicción a la cocaína. Nuestros resultados preliminares utilizando modelos de clases latentes indican que dentro de la población de pacientes adictos se pueden identificar subgrupos con perfiles diferenciales de impulsividad y rendimiento cognitivo, que a su vez resultan en diferencias significativas en sus niveles de craving, de ajuste psicosocial o de calidad de vida.

5. Ya que a lo largo de los 4 estudios hemos identificado rasgos y dominios cognitivos específicamente asociados con la adicción a la cocaína o con la comorbilidad entre uso de cocaína y trastornos de personalidad (urgencia negativa, fluctuación atencional, desinhibición y desregulación emocional), sería

pertinente diseñar un programa de ensayos clínicos dirigidos a estimular/entrenar específicamente estas habilidades o sus bases cerebrales y en comparación con los tratamientos usuales para valorar su posible valor añadido en la eficacia de los tratamientos contra la adicción.

6. Aunque en este estos estudios no hemos incluido variables genéticas somos conscientes del importante papel que éstas juegan, tanto en la vulnerabilidad compartida a ambos trastornos como en la expresión de los rasgos que los caracterizan. De hecho, en uno de los genes candidatos que hemos podido analizar hasta la fecha (gen MAOA) hemos detectado que los consumidores portadores de los polimorfismos asociados con baja actividad de la enzima los niveles de impulsividad y los déficits de procesamiento emocional están significativamente exacerbados.

CAPÍTULO 10: ENGLISH SUMMARY

The clinical presentation of patients with cocaine dependence patients is probably the result of a combination of pre-existent and current personality traits, addiction-related characteristics (e.g., impulsiveness or cognitive distortions, which are shared by substance and non-substance addictions), cocaine-related neuroadaptations, and comorbid psychopathologies. All these aspects have been theoretically associated with the personality construct of impulsivity, with the neuropsychological constructs of cognitive or executive control, and with the frontal-limbic-striatal networks supporting both personality traits and executive control skills.

Basing on these assumptions, the main aim of this doctoral thesis was to characterize impulsivity, executive control and frontal-limbic-striatal functioning in cocaine addiction (vs. non-substance addiction) and in cocaine addiction plus comorbid personality disorders (vs. non-comorbid cocaine addiction).

Because in terms of substance vs. non-substance addictions cocaine dependence and pathological gambling share substantial similarities, and because in terms of comorbidity the Cluster B personality disorders (i.e., borderline, antisocial, histrionic and narcissistic) are the most frequently associated with cocaine dependence in epidemiological studies, we focused our studies in the comparisons between:

- Cocaine dependent individuals vs. pathological gamblers, and
- Cocaine dependent individuals with comorbid Cluster B personality disorders vs. Cocaine dependent individuals without psychiatric comorbidities.

Studies 1 and 2 deal with trait and cognitive measures and brain anatomical measures. Specifically, Study 1 investigates differences in impulsive personality and executive

control performance between cocaine dependent patients and pathological gamblers. Study 2 investigates differences in impulsive personality, cognitive distortions, executive control performance and brain anatomy differences between cocaine users with comorbid Cluster B personality disorders and cocaine users without psychiatric comorbidities.

Studies 3 and 4 deal with functional resonance imaging (fMRI) measures of brain activation and connectivity. The frontal-limbic-striatal networks were challenged with an emotion regulation (reappraisal) task. Task selection was also motivated by the fact that both cocaine users and individuals with personality disorders share emotion regulation difficulties. Study 3 compares the patterns of activation and connectivity between cocaine users without psychiatric comorbities and non-drug using controls. Study 4 compares the patterns of activation and connectivity between cocaine users with comorbid Cluster B personality disorders, cocaine users without psychiatric comorbities and non-drug using controls.

Our main hypotheses (further detailed in each of the studies) were:

1. Cocaine dependent patients, compared to pathological gamblers, will have increased negative emotion-driven impulsivity and poorer executive control.
2. Cocaine dependent patients with comorbid Cluster B personality disorders, compared to cocaine dependent patients without comorbidities, will have increased negative emotion-driven impulsivity and dysfunctional beliefs, and greater deficits in executive control performance and frontal-limbic-striatal gray matter.

3. Cocaine dependent patients, compared to non-drug using controls, will have increased corticolimbic reactivity during negative emotion experience, and less efficient corticolimbic connectivity during negative emotion reappraisal.

4. Cocaine dependent patients with comorbid Cluster B personality disorders, compared to cocaine dependent patients without comorbidities, will have decreased corticolimbic reactivity during negative emotion experience, and less efficient corticolimbic connectivity during negative emotion reappraisal.

Based on the results from the 4 studies reported and discussed in the framework of this PhD proposal, we can conclude the following:

1. Cocaine dependent individuals differ from pathological gamblers and healthy controls in terms of increased levels of negative urgency and poorer performance in working memory. Therefore, we conclude that increases in negative emotion driven impulsivity and deficits in working memory are specifically associated with cocaine-related neuroadaptations.

2. Cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities and healthy controls in terms of increased levels of negative urgency and borderline-related dysfunctional beliefs, poorer performance in attention regulation and inhibition skills, and reduced gray matter in the right temporal pole. Therefore, we conclude that increases in negative emotion related impulsivity and cognitive distortions, decreased attention regulation and temporal pole attrition are specifically associated with the comorbidity between cocaine dependence and concurrent Cluster B personality disorders.

3. Cocaine dependent individuals (without comorbidities) differ from healthy controls in terms of increased right dorsolateral prefrontal activation during negative emotion maintenance and decreased functional coupling between the inferior frontal gyrus and the amygdala during negative emotion reappraisal. Therefore, we conclude that cocaine dependent individuals present dysfunctional corticolimbic activation and connectivity when asked to cognitively maintain and control negative emotions. These deficits are associated with the impulsive trait of negative urgency.

4. Cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities and healthy controls in terms of decreased activation and connectivity of the brain networks involved in moderating responses to aversive stimuli during negative emotion maintenance. In addition, cocaine dependent individuals with comorbid Cluster B personality disorders differ from cocaine dependent individuals without comorbidities in terms of less efficient connectivity of the emotion regulation network during negative emotion reappraisal, being these abnormalities correlated with the impulsive trait of negative urgency, and with the intensity of Cluster-specific dysfunctional beliefs.

CAPÍTULO 11: REFERENCIAS

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