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MECANISMOS CEREBRALES Y TRATAMIENTO DE LA OBESIDAD EN ADOLESCENTES (BRAINOBE)

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ÍNDICE

PRESENTACIÓN

La Organización Mundial de la Salud (OMS, 1997) ha declarado la obesidad como una epidemia global que actualmente ocupa el quinto puesto en el ranking mundial de los problemas de salud (OMS, 2009). Wang y Lobstein (2006), utilizando los datos más recientes facilitados por la Internacional Obesity Task Force (IOTF), pronosticaron que en 2010 la prevalencia de sobrepeso y obesidad en niños y adolescentes con edad escolar sería del 46,4% en las Américas, del 41,7% en los países del este del Mediterráneo, del 38,2% en Europa, del 27,2% para los países del Pacífico Occidental y del 22,9% en el sudeste de Asia. Actualmente, la evidencia empírica señala que las complicaciones relacionadas con el sobrepeso y la obesidad están aumentando, no solo por el incremento de la prevalencia sino también por el aumento de la severidad (Lobstein, Baur, & Uauy, 2004). Por tanto, a día de hoy, los problemas de exceso de peso constituyen un importante problema tanto para la salud como para el ámbito social y económico (Gortmaker et al., 2011).

En los últimos años, la relevancia de este fenómeno ha suscitado un creciente interés científico que ha dado lugar a importantes aportaciones. Debido a que la obesidad constituye un problema complejo y multifactorial donde componentes de diversa índole (genéticos, biológicos, psicológicos y socioculturales) parecen estar implicados, la evidencia empírica surge desde diferentes perspectivas. Desde la perspectiva neuropsicológica, las investigaciones señalan que factores como la sensibilidad a la recompensa, la impulsividad o las funciones ejecutivas podrían ser claves para entender el desarrollo y mantenimiento de los problemas de exceso de peso. En consonancia con estos hallazgos, la realización de esta tesis tiene por objetivo explorar factores de personalidad y neuropsicológicos así como sus correlatos neuroanatómicos en adolescentes con exceso de peso. Asimismo, se examinará la anatomía de las regiones

cerebrales y los mecanismos cerebrales que subyacen durante el proceso de toma de decisiones en adolescentes con exceso de peso.

RESUMEN

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

La sección de introducción consta del Capítulo 1 donde expondremos la relevancia clínica de los problemas de exceso de peso, perspectivas neuropsicológicas para abordar la obesidad y algunas consideraciones sobre las singularidades neuropsicológicas de la adolescencia y aspectos de tratamiento para la obesidad en esta etapa.

La segunda sección contiene el Capítulo 2 en el que aportamos la justificación de la realización de este trabajo así como el objetivo principal y los objetivos específicos e hipótesis que se pretenden con el mismo.

La tercera sección consta de cuatro capítulos en el que se recogen un conjunto de cuatro estudios de investigación de carácter empírico. El capítulo 3 consiste en un estudio sobre la relación entre los factores de personalidad (sensibilidad a la recompensa y al castigo), el Índice de Masa Corporal (IMC) y las medidas neuropsicológicas de impulsividad y flexibilidad. Los resultados de esta investigación mostraron que los incrementos de adiposidad se asocian con mayores niveles de impulsividad ante emociones intensas y déficits cognitivos de flexibilidad.

El capítulo 4 está formado por un estudio sobre la eficacia de un tratamiento multi-componente para adolescentes con exceso de peso. Los resultados obtenidos indicaron que la intervención multi-componente produjo una reducción significativa del IMC, mostrando un tamaño del efecto medio. Además, se comprobó que la recuperación de las habilidades neuropsicológicas mejoraba la capacidad del tratamiento para reducir el IMC. Concretamente, encontramos que los adolescentes que a lo largo del tratamiento redujeron sus niveles de impulsividad bajo estados emocionales negativos intensos

(urgencia negativa) y mejoraron su respuesta de inhibición y cambio fueron los que perdieron más peso tras el tratamiento mientras que otras habilidades como la memoria de trabajo o la toma de decisiones no predecían mejoras tras la intervención.

El capítulo 5 lo constituye un estudio sobre las asociaciones entre la estructura cerebral y medidas de personalidad (evaluadas a través del cuestionario de Sensibilidad a la Recompensa y al Castigo y la escala UPPS-P) y cognitivas (valoradas por la tarea Stroop) en adolescentes con exceso de peso frente a adolescentes con peso normal. Además, examinamos la anatomía de las regiones cerebrales entre los adolescentes de ambos grupos. Por un lado, los resultados indicaron correlaciones significativas solo en los adolescentes con peso normal. Concretamente, la sensibilidad a la recompensa y la urgencia positiva se asociaron negativamente con el volumen de materia gris en el cortex somatosensorial secundario izquierdo y la respuesta de inhibición correlacionó positivamente con el volumen del cortex prefrontal dorsolateral izquierdo. Por otro lado, los resultados mostraron que los adolescentes con exceso de peso presentaban un mayor volumen de materia gris en el hipocampo derecho en comparación con los adolescentes de peso normal.

El capítulo 6 consistió en un estudio sobre los sustratos neurofuncionales de la toma de decisiones bajo condiciones de recompensa y riesgo. Los resultados revelaron que durante el proceso de toma de decisiones los adolescentes con exceso de peso, en comparación con los de peso normal, mostraban una menor activación en la ínsula izquierda y una mayor activación en el mesencéfalo. Por otro lado, durante los momentos posteriores a la recepción de la recompensa los adolescentes con exceso de peso exhibían una mayor activación en el giro frontal inferior. Estas diferencias en activación cerebral se observaron en ausencia de diferencias significativas a nivel conductual entre ambos grupos.

La cuarta y última sección contiene el Capítulo 7 en el llevamos a cabo una discusión conjunta de los hallazgos obtenidos a través de los distintos estudios haciendo especial énfasis en sus implicaciones teóricas y clínicas. Asimismo presentamos un apartado de conclusiones y perspectivas futuras de investigación.

I. INTRODUCCIÓN

CAPÍTULO 1

1. Epidemiología y relevancia clínica del problema

La prevalencia de sobrepeso y obesidad adolescente ha aumentado considerablemente en las últimas décadas (Lee, Lee, Guo, & Harris, 2011; Ogden, Carroll, Kit, & Flegal, 2012). Las tasas más altas de prevalencia se corresponden con los países de ingresos más altos, sin embargo, este problema no se restringe a dichos países, el incremento también existe en los países con ingresos medios y bajos. Esto supone un importante problema ya que la creciente evidencia relaciona los problemas de exceso de peso con consecuencias negativas tanto para la salud, a corto y largo plazo, como para el ámbito social y económico (Gortmaker et al., 2011). Tanto es así que, la Organización Mundial de la Salud (OMS, 1997) ha declarado la obesidad como una epidemia global que actualmente ocupa el quinto puesto en el ranking mundial de los problemas de salud (OMS, 2009). Como consecuencia, en los últimos años, se han realizado muchos estudios con el objetivo de determinar cuál es la prevalencia actual y su tendencia, qué consecuencias se relacionan con dicha problemática y cuáles son los factores que predisponen y mantienen los problemas de exceso de peso en adolescentes.

1.1. Prevalencia de sobrepeso y obesidad en adolescentes

La diversidad de criterios y de metodologías utilizadas por los diferentes países y autores hace difícil consensuar cuál es la magnitud actual de obesidad en la población adolescente (Pérez-Rodrigo, Aranceta-Bartrina, Serra-Majem, Moreno, & Delgado Rubio, 2006). Generalmente, la obesidad es definida como un exceso de grasa corporal. Sin embargo, no existe una distinción clara entre la cantidad de grasa que es normal y la que no lo es y además, cuando se trabaja con grandes tamaños muestrales la medición directa de la grasa corporal es difícil y costosa (Flegal & Ogden, 2011; Spruijt-Metz, 2011). La OMS, la International Obesity Task Force (IOTF) y otras organizaciones

recomiendan el uso del Índice de Masa Corporal (IMC; peso (kg)/ altura^2 (m^2)), basado en mediciones antropométricas, como un indicador estándar para estimar la prevalencia de la obesidad en los estudios de población (Pérez-Rodrigo et al., 2006). En la etapa adulta, los puntos de corte para clasificar el estatus del IMC están bien establecidos, ya que en esta etapa, el IMC parece tener una alta correlación tanto con la adiposidad como con las complicaciones clínicas o riesgos para la salud que conlleva el exceso de grasa (Flegal & Ogden, 2011). Sin embargo, en la etapa adolescente y a pesar de que el IMC también es considerado como un buen indicador indirecto del grado de adiposidad (Rolland-Cachera, 2011), la determinación adecuada del estatus del IMC es más complicada. Por un lado, al ser la adolescencia una etapa de desarrollo, el IMC debe ajustarse a los valores de sexo y edad, por otro lado, no existe un consenso uniforme a nivel internacional sobre cuáles son los puntos de corte o los criterios que deben usase para definir el sobrepeso y la obesidad a lo largo de la etapa infanto-juvenil (Pérez-Rodrigo et al., 2006; Rolland-Cachera, 2011). Para abordar esta cuestión, la IOTF (Cole, Bellizzi, Flegal, & Dietz, 2000) desarrollaron diferentes puntos de corte para el sobrepeso y la obesidad basándose en datos de muestras internacionales. Las referencias están establecidas para el intervalo de edad que oscila desde los 2 a los 18 años y tienen varias ventajas con respecto a otras clasificaciones (Rolland-Cachera, 2011). Así, en las últimas décadas, los puntos de corte de la IOTF han sido usados en muchos estudios de prevalencia de Europa y otros continentes.

Los datos disponibles muestran que la obesidad infanto-juvenil en España es un problema de salud pública por su magnitud y su creciente tendencia. Según los datos de los tres últimos estudios epidemiológicos sobre obesidad realizados en España, el IMC a los 13 años ha pasado de 18,4 en 1984, a 20,4 en 1992 y a 21,1 en el período 1998-2000 (Serra-Majem et al., 2003). La tendencia indica un incremento en la prevalencia de

sobrepeso y obesidad infanto-juvenil de la población española. Los datos más actuales se derivan del Estudio enKid (Serra-Majem et al., 2003). Dicho estudio fue realizado entre 1998 – 2000. Durante este periodo se evaluaron a 3.534 personas de entre 2 – 24 años. Usando los criterios de Cole et al. (2000), la estimación de la prevalencia de obesidad fue de 6,3%. Conjuntamente, el sobrepeso y la obesidad afectan a un 24,4% de la muestra. La obesidad fue significativamente más alta en chicos (7,9%) que en chicas (4,6%) y los valores más altos se observan entre los 6 y 13 años (Serra-Majem, Aranceta-Bartrina, Pérez-Rodrigo, Ribas-Barba, & Delgado-Rubio, 2006). Con respecto a Europa, siguiendo los criterios de Cole et al. (2000) y teniendo en cuenta solo el intervalo de edad de entre 14 - 17 años, España ocupa el segundo lugar con mayores tasas de prevalencia en chicos, por detrás de Chipre y seguido de Reino Unido. En el caso de las chicas, los países con mayores tasas de prevalencia son, en el siguiente orden: Reino Unido, Irlanda, Hungría e Italia (Aranceta, Moreno, Moya, & Anadón, 2009). Wang y Lobstein (2006) utilizando los datos más recientes facilitados por la IOTF, pronosticaron que en 2010 la prevalencia de sobrepeso y obesidad en niños y adolescentes con edad escolar sería del 46,4% en las Américas, del 41,7% en los países del este del Mediterráneo, del 38,2% en Europa, del 27,2% para los países del Pacífico Occidental y del 22,9% en el sudeste de Asia. Los autores indican que no existen datos suficientes para realizar una previsión fiable de prevalencia para los países de África.

1.2. Consecuencias asociadas a la obesidad y factores predisponentes

Dada la alta y creciente prevalencia de sobrepeso y obesidad adolescente en la mayor parte de los países del mundo, es importante conocer qué costes conlleva el exceso de peso en la adolescencia y qué factores pueden predisponer o mantener dicho problema. Hasta hace poco tiempo, las consecuencias de la obesidad adolescente no eran muy evidentes porque dicho problema no estaba tan extendido. Sin embargo, las

complicaciones relacionadas con el sobrepeso y la obesidad están aumentando, no solo por el incremento de la prevalencia sino también por el aumento de la severidad (Lobstein et al., 2004). A nivel de salud física, los estudios clínicos sugieren que los adolescentes con sobrepeso u obesidad tienen un mayor riesgo de complicaciones médicas, siendo el síndrome metabólico uno de los más informados (Acosta, Manubay, & Levin, 2008). A nivel psicosocial, la obesidad adolescente ha sido asociada con baja autoestima, estigmatización y síntomas depresivos (Chaiton et al., 2009). Además, un estudio realizado por Whitaker, Wright, Pepe, Seidel, y Dietz (1997) muestra que si se es obeso en la etapa infanto-juvenil existe una mayor probabilidad de ser obeso en la etapa adulta y que dicha probabilidad aumenta con la edad. Una revisión más reciente (Singh, Mulder, Twisk, van Mechelen, & Chinapaw, 2008) confirma que el exceso de peso en la etapa infanto-juvenil es un fuerte predictor de la obesidad adulta. Por tanto, podría decirse que la obesidad en la adolescencia no es un fenómeno transitorio y que si no se corrige, puede convertirse en un problema crónico, con graves efectos negativos sobre la salud. Como consecuencia, la obesidad en la adolescencia no sólo es perjudicial para la salud individual, sino que también supondría un aumento del gasto público. Durante la adolescencia, la obesidad se relaciona con un mayor gasto económico tanto de forma directa (tratamiento de complicaciones médicas) como indirecta (visitas al médico, ausencia escolar, etc.), además de los gastos intangibles que no pueden ser estimados (deterioro de la calidad de vida, bienestar social, etc.) (Lobstein et al., 2004). Durante la etapa adulta, los costes sanitarios asociados a la obesidad parecen superar a los provocados por el consumo de tabaco o por los problemas con el alcohol (Sturm, 2002).

Debido a que la obesidad constituye un gran problema, cada vez hay más estudios que intentan esclarecer cuáles son las causas o los factores que predisponen o mantienen

esta epidemia. La evidencia empírica surge desde diferentes perspectivas y factores de diversa índole (genéticos, biológicos, psicológicos y socioculturales) parecen estar implicados. Una revisión detallada de los diferentes factores que podrían influir en la predisposición y/o mantenimiento de la obesidad excedería los propósitos de este trabajo, por tanto, nos centraremos en los factores neuropsicológicos que parecen subyacer bajo esta problemática. En las últimas décadas, los drásticos cambios producidos en el entorno y el estilo de vida han modificado la forma en la que percibimos los alimentos y regulamos su ingesta (Zheng, Lenard, Shin, & Berthoud, 2009). El circuito hipotalámico es crucial para regular la conducta homeostática de la ingesta y en los últimos años, se ha avanzado mucho en la identificación de estos mecanismos. Sin embargo, cada vez existen más estudios que sugieren que otros circuitos cerebrales distintos a los que regulan el balance energético están involucrados en el consumo de alimentos y la obesidad (Berthoud & Morrison, 2008). Basándose en los paralelismos que parecen existir entre la obesidad y la adicción (Acosta et al., 2008), recientemente se ha propuesto que la sobrealimentación podría reflejar un desequilibrio entre los circuitos motivacionales (por su implicación en los procesos de recompensa y condicionamiento) y los circuitos que controlan e inhiben las respuestas preponderantes (Volkow, Wang, Fowler, & Telang, 2008). Más concretamente, este modelo plantea la obesidad como un problema de adicción a la comida (Volkow & O'Brien, 2007; Volkow & Wise, 2005), en el que estarían principalmente implicados cuatro circuitos: (i) elevación de la recompensa, (ii) motivación/impulso, (iii) aprendizaje/condicionamiento y (iv) control inhibitorio/regulación emocional/función ejecutiva. Desde esta perspectiva, se argumenta que en personas vulnerables, el consumo de grandes cantidades de alimento apetitoso (aquel que tiene un alto contenido de azúcar o altas combinaciones de azúcar y grasa) podría provocar un desequilibrio en

la interacción de estos circuitos, que resultaría en un aumento del valor reforzante del alimento apetitoso y un debilitamiento de los circuitos que ejercen el control. Dicha alteración se produciría como consecuencia de un proceso de aprendizaje condicionado y un restablecimiento de los umbrales de recompensa, debidos al consumo de grandes cantidades de alimentos apetitosos. El debilitamiento de las redes corticales descendentes que regulan las respuestas preponderantes llevarían a una ingesta impulsiva y compulsiva de alimentos apetitosos y como consecuencia, al desarrollo y mantenimiento de la obesidad (Volkow, Wang, & Baler, 2011). En resumen, podría decirse que los factores neuropsicológicos implicados en el desarrollo y mantenimiento de la obesidad apuntan hacia sensibilidad de la recompensa, comportamientos impulsivos y/o compulsivos y pobre funcionamiento ejecutivo.

2. Modelos neuropsicológicos de la obesidad

En los últimos años, el modelo de adicción a la comida está experimentando un rápido y creciente apoyo, debido en parte a una mejor comprensión de la neurobiología de la adicción. En conjunto, los datos aportados parecen apoyar ciertos solapamientos entre la adicción a las drogas y la obesidad y esto podría permitir el desarrollo de nuevas intervenciones para tratar la obesidad. Sin embargo, este planteamiento es relativamente reciente y son necesarios más datos para poder superar las limitaciones pendientes (Avena, Gold, Kroll, & Gold, 2012). Basándose en los criterios del Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) para el abuso de sustancia, este modelo plantea que los fenotipos conductuales de la adicción parecen asemejarse a los comportamientos y desequilibrios cerebrales que se dan en la obesidad (Volkow & O'Brien, 2007). Sin embargo, estos fenotipos parecen asemejarse más a las personas que padecen trastorno por atracón que a las personas que padecen obesidad y una cuestión importante es que no todas las personas que padecen dicho trastorno son

obesas, ni todas las personas con exceso de peso padecen trastorno por atracón (Ziauddeen, Farooqi, & Fletcher, 2012). Por ello, desde la neuropsicología surgen diferentes modelos que intentan explicar los problemas de exceso de peso.

2.1. Sensibilidad hacia la recompensa

La sensibilidad a la recompensa es un constructo que se deriva de las investigaciones llevadas a cabo en el campo de la adicción y que actualmente, se está utilizando cada vez más en los estudios relacionados con la conducta de comer. La sensibilidad a la recompensa está vinculada a un aumento de la disponibilidad de dopamina en las vías mesocorticolímbicas (Davis, Strachan, & Berkson, 2004). Las personas que son sensibles a la recompensa parecen detectar más fácilmente los estímulos gratificantes que hay en el ambiente y además, parecen ser más propensas para acercarse a ellos (Davis, Strachan, et al., 2004). Los cambios acontecidos en las últimas décadas en el sistema alimentario mundial (mayor palatabilidad de la comida, extensa variedad de alimentos, alimentos baratos de fácil y rápido acceso, continua presencia de estímulos alimentarios, mayor densidad de energía en los alimentos, mayor tamaño de las porciones, etc.) podrían estar propiciando la obesidad (Swinburn et al., 2011), ya que cuando individuos vulnerables son expuestos a estos ambientes, las señales de hambre pueden ser impulsadas por las señales hedónicas del ambiente, en ausencia de necesidades metabólicas (Zheng et al., 2009). De hecho, la sensibilidad a la recompensa se asocia positivamente con el IMC y predispone a las personas a comer más allá de los requerimientos nutricionales (Davis, Strachan, et al., 2004; Loxton & Dawe, 2001). Así, la conducta de ingesta puede verse influenciada por las condiciones ambientales y las predisposiciones individuales.

Uno de los instrumentos que permite medir la sensibilidad a la recompensa es el cuestionario de Sensibilidad a la Recompensa y al Castigo (Torrubia, Ávila, Moltó, & Caseras, 2001). Los resultados de un estudio llevado a cabo por Loxton y Dawe (2006), donde aplicaron dicho instrumento, indican que tanto la sensibilidad a la recompensa como la sensibilidad al castigo parecen asociarse con comportamientos alimenticios disfuncionales. Sin embargo, la mayoría de los estudios desarrollados en las últimas décadas se han centrado en los aspectos de la sensibilidad a la recompensa, quizá guiados por los paralelismos entre la obesidad y la adicción. Los resultados de los estudios indican que la alta sensibilidad a la recompensa se relaciona con la conducta de comer en exceso y una mayor preferencia por los alimentos dulces y grasos, ambos factores han sido relacionados positivamente con el IMC (Davis et al., 2007). La preferencia por alimentos ricos en grasa ha sido asociada con la subestimación del tamaño de las porciones y esta subestimación parece ser mayor en personas con exceso de peso y alta sensibilidad a la recompensa (Davis, Curtis, Tweed, & Patte, 2007). Además, cuando la comida es variada, la sensibilidad a la recompensa aumenta de manera significativa la ingesta calórica tanto en niños (Guerrieri, Nederkoorn, & Jansen, 2008a) como en adultos (Guerrieri et al., 2007). Los estudios llevados a cabo en neuroimagen confirman las relaciones entre este rasgo motivacional y la activación cerebral. Así, una mayor sensibilidad a la recompensa se relaciona con una mayor activación en el estriado ventral, amígdala, mesencéfalo, cortex orbitofrontal y regiones del pálido ventral ante imágenes de alimentos apetitosos (Beaver et al., 2006). Stoeckel et al. (2008) encuentran que ante imágenes de alimentos con alto valor calórico, las personas con exceso de peso, en comparación con personas de peso normal, muestran una mayor activación en un gran número de regiones cerebrales que hipotéticamente median las respuestas motivacionales y emocionales relacionadas con los estímulos

alimenticios. En resumen, podríamos decir que las diferencias individuales en la sensibilidad a la recompensa, o la tendencia a ser atraídos por los estímulos gratificantes que hay en el entorno, podría ser uno de los factores que contribuyeran a la vulnerabilidad de comer en exceso y/o desarrollar problemas de exceso de peso (Small, 2009).

En los últimos años, se han propuesto diferentes teorías que intentan explicar la etiología de la obesidad basándose en una desregulación de la actividad dopaminérgica en el sistema de recompensa. En comparación con los mecanismos homeostáticos de la alimentación, el conocimiento acerca de cómo el sistema de recompensa del cerebro influye en la regulación de la ingesta de alimentos es mucho más escaso. No obstante, se han identificado algunas áreas y circuitos cerebrales que parecen estar implicados en la recepción de comida apetitosa o con los estímulos que se relacionan con ésta (Kenny, 2011). El hipotálamo lateral podría regular la respuesta de recompensa de alimentos apetitosos e impulsar los comportamientos de búsqueda de comida. El cuerpo estriado, el cual recibe estimulación dopaminérgica desde el área tegmental ventral y la sustancia negra, regularía las propiedades motivacionales y de incentivos de los alimentos. La ínsula procesaría la información visceroceptiva y del gusto, así como su valoración hedónica. La amígdala parece ser esencial para el aprendizaje de las representaciones que vinculan las propiedades incentivas con los resultados, pero no para el mantenimiento de tales representaciones. Por el contrario, la cortex orbitofrontal parece ser crucial para el mantenimiento dichas representaciones, manteniéndolas en la memoria y actualizándolas con la nueva información, para así, poder utilizarlas guiando la conducta apetitiva (Berthoud & Morrison, 2008; Kenny, 2011).

En general, la evidencia empírica sugiere que un desequilibrio del funcionamiento de dopamina en el sistema de recompensa podría explicar la etiología de la obesidad.

Recientemente, la hipótesis más aceptada es la visión a favor del hiper-funcionamiento dopaminérgico. Los proponentes de esta teoría (Davis et al., 2007; Loxton & Dawe, 2001, 2006; Guerrieri et al., 2007, 2008) argumentan que los individuos con riesgo de desarrollar obesidad inicialmente experimentan una mayor recompensa cuando ingieren alimentos, lo cual les lleva a comer en exceso y como consecuencia, se produce una reducción de la señal de dopamina ante la ingesta y una mayor actividad de dopamina en las regiones que codifican el valor de la recompensa ante la presencia de señales de alimentos apetitosos. Sin embargo, otros autores (Wang et al., 2001; Wang, Volkow, Thanos, & Fowler, 2004) argumentan que la obesidad puede ser debida a un hipo-funcionamiento dopaminérgico. Esta hipótesis conocida como síndrome de deficiencia de recompensa propone que las personas en situación de riesgo para la obesidad, inicialmente experimentan menos recompensa cuando ingieren alimentos, lo cual les lleva a comer en exceso para compensar dicho déficit y como consecuencia, se produce una mayor actividad en las regiones que codifican el valor de la recompensa a través de un proceso de condicionamiento. Recientemente, Stice, Yokum, Burger, Epstein, & Small, 2011 han realizado un estudio con adolescentes de peso normal con alto riesgo vs. bajo riesgo para desarrollar obesidad en el futuro. Los datos indican que los adolescentes de peso normal con alto riesgo para la obesidad futura muestran una mayor activación del estriado en respuesta a la recepción de alimentos apetitosos. Por tanto, estos resultados están a favor de la hipótesis de que la vulnerabilidad inicial que da lugar a la obesidad podría ser un hiper-funcionamiento dopaminérgico y que el síndrome de deficiencia de recompensa podría ser una consecuencia más que una causa de la obesidad (Stice et al., 2011). En este sentido, se ha propuesto un modelo de vulnerabilidad dinámica, en el que la obesidad podría ir evolucionando y con el tiempo, producir cambios cerebrales como consecuencia del exceso consumo de comida. Dicho

modelo establece que es posible que una mayor sensibilidad a la recompensa podría ser un factor de riesgo inicial para comer en exceso, lo que llevaría a un aumento de peso. No obstante, la excesiva ingesta de alimentos podría sobrecargar el sistema dopaminérgico, dando como resultado una reducción de la actividad dopaminérgica. Esta disminución adaptativa en los receptores D2 podría contribuir a una insensibilidad del estriado ante la comida apetitosa, lo cual llevaría a una mayor ingesta de alimentos para poder compensar el déficit propiciando el mantenimiento de la obesidad. La evidencia a favor de este modelo comienza a aparecer tanto en adultos (Davis & Fox, 2008) como en niños (Verbeken, Braet, Lammertyn, Goossens, & Moens, 2012).

2.2. De la impulsividad a la compulsividad

Existe un amplio acuerdo en que la impulsividad no es un constructo unidimensional sino que probablemente consta de un número de dimensiones relacionadas (Dawe & Loxton, 2004). Dicho acuerdo está fundamentado principalmente por dos razones. Una de ellas es que generalmente las correlaciones entre las medidas de autoinformes y las medidas conductuales son muy bajas, lo cual sugiere que podrían estar midiendo aspectos diferentes de la conducta impulsiva. La otra es que incluso dentro de las tareas conductuales, las operativizaciones y los modelos explicativos utilizados son diferentes y a menudo, las correlaciones entre ellos es baja (Guerrieri, Nederkoorn, & Jansen, 2008b). Por tanto, la impulsividad es considerada un constructo multidimensional que engloba un conjunto de características. Dawe y Loxton (2004) proponen que las diferentes escalas que se derivan de los principales modelos teóricos propuestos para la impulsividad podrían ser clasificados en dos grandes dominios. El primero de ellos reflejaría la tendencia a actuar precipitadamente sin tener en cuenta las consecuencias que conllevaría dicha acción. El segundo dominio mostraría el impulso de obtener un estímulo de recompensa. Así, el primero de ellos, podría ser consecuencia de un pobre

control inhibitorio, en el que estarían implicados los mecanismos de control arriba-abajo. Para poder ejercer control inhibitorio son necesarias funciones ejecutivas como la autorregulación. Si la respuesta de inhibición está alterada, el acto de autorregulación que permite inhibir las respuestas preponderantes no es eficaz. El segundo de ellos podría ser debido a una mayor sensibilidad a la recompensa (Guerrieri et al., 2007), el cual ya ha sido tratado en el apartado anterior. Por tanto, este apartado estará centrado en el primero de los dominios mencionados, es decir, en los aspectos de la impulsividad que se relacionan con un pobre control inhibitorio.

Uno de los instrumentos que intenta medir la personalidad impulsiva es la escala UPPS-P (Whiteside & Lynam, 2001). Mobbs, Crépin, Thiéry, Golay, & Van der Linden (2010) proponen que las dimensiones de esta escala podrían estar relacionadas con la obesidad. Dicha escala podría ser dividida en dos componentes: uno motivacional, que comprendería la dimensión de búsqueda de sensaciones y otro de habilidades de autorregulación, que englobaría el resto de las dimensiones de dicha escala (urgencias, falta de premeditación y falta de perseverancia). Dichos autores hipotetizan que la hipersensibilidad a los estímulos alimenticios puede ser controlada con buenas habilidades de autorregulación y que por tanto, los problemas de exceso de peso aparecerían cuando las habilidades de autorregulación fallaran. La evidencia empírica parece apoyar la relación entre un pobre control inhibitorio y los problemas de exceso de peso. El grupo de Nederkoorn ha realizado varios estudios desde esta perspectiva y han encontrado que los adolescentes con menor control inhibitorio pierden menos peso durante el tratamiento (C. Nederkoorn, Braet, Van Eijs, Tanghe, & Jansen, 2006), que el control inhibitorio se relaciona negativamente con el IMC y que predice la reducción de exceso de peso en niños durante el periodo de un año (C. Nederkoorn, Jansen, Mulkens, & Jansen, 2007). Batterink, Yokum, & Stice (2010) encuentran que, tanto a nivel

conductual como neural, los adolescentes con mayor IMC muestran menor control inhibitorio. Resultados similares son encontrados por Maayan, Hoogendoorn, Sweat, & Convit (2011), concretamente, los adolescentes obesos, en comparación con los de peso normal, muestran un peor control inhibitorio a nivel conductual y una reducción de la materia gris de las áreas que se relacionan con el control inhibitorio, siendo dicha reducción más marcada en el cortex orbitofrontal. Otros estudios de neuroimagen también indican que un mayor IMC se relaciona con diferencias tanto estructurales como funcionales en las áreas relacionas con el control inhibitorio. Así, estudios de resonancia magnética estructural encuentran que en comparación con personas de peso normal, las personas con exceso de peso tenían una menor densidad de materia gris en el giro medio frontal del córtex prefrontal (CPF), una región implicada en la inhibición de respuestas inadecuadas y el control de las conductas dirigidas a objetivos (Pannacciulli et al., 2006) y que una menor materia gris en las regiones relacionadas con el control inhibitorio se relaciona con futuras ganancias de peso (Yokum, Ng, & Stice, 2012). De manera similar, un mayor IMC ha sido asociado con un menor metabolismo basal en el CPF y el giro cingulado, junto con alteraciones asociadas en los procesos de control inhibitorio (Volkow et al., 2009). En conjunto los resultados sugieren que un control inhibitorio ineficaz podría predisponer el desarrollo y mantenimiento de los problemas de exceso de peso.

Recientemente, el grupo de Pauli-Pott ha publicado unos estudios que parecen contradecir las conclusiones anteriores. En uno de ellos, (Pauli-Pott, Albayrak, Hebebrand, & Pott, 2010a) encuentran que los adolescentes con puntuaciones altas en impulsividad pierden más peso que los menos impulsivos. Una posible explicación podría ser que el estado de impulsividad tuviera efectos diferentes de la personalidad impulsiva, sin embargo, se necesitan más estudios que clarifiquen las diferencias entre

el estado de impulsividad y el rasgo, ya que la investigación sobre esta cuestión es muy escasa (Guerrieri et al., 2007). En otro estudio, Pauli-Pott, Albayrak, Hebebrand, & Pott (2010b) indican que la relación entre el exceso de peso y la impulsividad depende de la edad. Según sus resultados, una alta impulsividad está vinculada a un mayor peso corporal en los niños pequeños (8-10 años), mientras que en los adolescentes (12-14 años) esta asociación es menos pronunciada y tiende a ser invertida, una posible explicación a esta contradicción podríamos encontrarla en los sustratos cerebrales. Por lo general, se ha asumido que el control inhibitorio es ejercido por los mecanismo corticales de arriba-abajo, lo que implica que la impulsividad relacionada con los aspectos de la respuesta de inhibición podría resultar de una relajación de estos centros que ejercen el control. Sin embargo, en los últimos años, se ha producido una creciente apreciación de que tanto circuitos corticales como subcorticales podrían estar implicados en este aspecto de la impulsividad, particularmente la evidencia se inclina hacia los ganglios basales (Dalley, Everitt, & Robbins, 2011). Así, las contradicciones surgidas desde el estudio de Pauli-Pott et al. (2010b) podrían reflejar la maduración de los procesos inhibitorios relacionados con la edad (Bunge & Wright, 2007) o la transición entre impulsividad y compulsividad en el desarrollo de la obesidad, como ocurre en la adicción (Volkow et al., 2008).

Los trastornos impulsivos y compulsivos implican comportamientos repetitivos debidos a fallos en los mecanismos de control. La compulsividad ha sido definida como una acción inapropiada ante una situación, la cual persiste sin una relación obvia con el objetivo original y que a menudo conlleva consecuencias indeseables (Dalley et al., 2011). Los actos impulsivos parecen estar caracterizados por un aumento de la activación antes de cometer el acto impulsivo y por la obtención de placer, gratificación o alivio en el momento de consumar el acto. Así, las conductas impulsivas parecen estar

más relacionadas con los mecanismos de refuerzo positivo. En cambio, los actos compulsivos se caracterizan por el estrés y la ansiedad antes de realizar el acto compulsivo y por el alivio de la tensión o el malestar tras su realización, por lo que están más asociados con los mecanismos de refuerzo negativo (Koob & Volkow, 2010). Existen datos que sugieren que las personas con problemas de exceso de peso podrían tener serías dificultades para controlar su conducta de comer cuando ellas experimentan emociones intensas tanto positivas como negativas (Goossens, Braet, Van Vlierberghe, & Mels, 2009; Loxton, Dawe, & Cahill, 2011; Mobbs et al., 2010). En este sentido, Volkow et al. (2008) proponen que los cambios neuroadaptativos que se producen como consecuencia del consumo de drogas y que contribuyen a desarrollar la adicción podrían ser similares a los que se producirían por un excesivo consumo de comida apetitosa y que por tanto, contribuirían a desarrollar los problemas de exceso de peso. En el desarrollo de la adicción, la impulsividad parece dominar las primeras etapas y la compulsividad parece dominar las posteriores. Este cambio que se produce en las personas a nivel conductual podría ser debido a un cambio en la motivación que guía a la conducta, de tal manera que en las primeras etapas la conducta estaría motivada por el refuerzo positivo y en las etapas posteriores estaría motivada por el refuerzo negativo. Este cambio motivacional podría ser explicado recurriendo a los cambios neuroadaptativos que se producen como consecuencia del consumo excesivo (Koob & Volkow, 2010). Dichos cambios estarían en consonancia con el modelo de vulnerabilidad dinámica presentado en el apartado anterior, el cual propone que la obesidad podría ir evolucionando y con el tiempo, producir cambios cerebrales como consecuencia del exceso consumo de comida (Stice et al., 2011). Teniendo en cuenta los datos que provienen de los estudios de adicción y en relación con los datos aportados por los estudios acerca de la conducta de ingesta, Volkow et al. (2008) proponen que en

un primer momento, el consumo de comida apetitosa podría producir un incremento de dopamina en el núcleo accumbens. Estudios de neuroimgen en humanos han demostrado que los aumentos de dopamina en este núcleo están asociados con descripciones subjetivas de recompensa (por ejemplo, el placer, euforia, etc.) (Koob & Volkow, 2010). Por tanto, este núcleo desempeñaría un papel crítico en las fases iniciales. Sin embargo, como consecuencia del continuo y excesivo consumo se produciría una disminución de los receptores D2 del núcleo accumbens (Wang et al., 2001). Estos cambios en la reducción de la disponibilidad de receptores D2 de dopamina en el estriado ventral (donde se sitúa el núcleo accumbens) han sido asociados con cambios en las regiones prefrontales (por ejemplo, circunvolución cingulada y la corteza orbitofrontal) (Koob & Volkow, 2010). La circunvolución cingulada es una región implicada en el control inhibitorio y su alteración podría resultar en conductas impulsivas. Por otro lado, la activación de la corteza orbitofrontal relacionada con los aumentos de dopamina podrían contribuir a comportamientos compulsivos (Volkow et al., 2007). Así, mientras que en un primer momento la comida podría producir una liberación de dopamina en el estriado ventral (señalizando la recompensa), con las repetidas administraciones y el desarrollo de hábitos parece producirse un cambio en el aumento de dopamina que se dirigen hacia el estriado dorsal, el cual parece estar relacionado con las conductas motoras automáticas. Así, el estriado dorsal podría tener un papel menos activo en los efectos agudos del refuerzo pero ser clave en la transición entre la impulsividad y compulsividad (Volkow et al., 2008).

2.3. Funcionamiento ejecutivo: el modelo del marcador somático

Los procesos de control ejecutivo, o "funciones ejecutivas" son un conjunto integrado de habilidades de orden superior necesarias para poder llevar a cabo procesos

cognitivos implicados en la producción, supervisión y control de conductas dirigidas a objetivos, además de estar implicadas en la regulación de los estados emocionales que se consideran adaptativos para la consecución de esos objetivos (Bechara, Damasio, & Damasio, 2000). Ejemplos de funciones ejecutivas son la memoria de trabajo, el control inhibitorio, la flexibilidad cognitiva o la toma de decisiones. Las funciones ejecutivas podrían estar relacionadas con las dificultades de controlar la ingesta de alimentos a través de múltiples mecanismos. Así, la memoria de trabajo podría ser crucial para mantener presente los objetivos que guían la conducta alimenticia (Berthoud & Morrison, 2008; Kenny, 2011). El control inhibitorio ayudaría a regular las emociones intensas que parecen propiciar el excesivo consumo de alimentos (Goossens et al., 2009; Mobbs et al., 2010; Loxton et al., 2011). La flexibilidad cognitiva podría ser útil para cambiar los comportamientos que estuvieran propiciando los problemas de exceso de peso. La toma de decisiones podría ser crítica a la hora de decidir el tipo y la cantidad de alimentos que se quieren ingerir. Sin embargo, a día de hoy, existen pocos estudios que investiguen el rol que las funciones ejecutivas podrían desempeñar en el desarrollo o mantenimiento de los problemas de exceso de peso.

Varios instrumentos han sido usados o desarrollados para captar el rendimiento de las funciones ejecutivas, algunos ejemplos son: el subtest de Letras y Números (Wechsler, 2003) para la memoria de trabajo, el Color-word interference test Stroop (Delis, Kaplan, & Kramer, 2001) para el control inhibitorio y la flexibilidad, o la Iowa gambling task (Bechara et al., 2000) para la toma de decisiones. A día de hoy, los datos aún son escasos y existen algunas contradicciones, sin embargo, la evidencia empírica indica que un elevado IMC se relaciona negativamente con el rendimiento en tareas de función ejecutiva (Gunstad et al., 2007). Más concretamente, hay estudios que indican que los adolescentes con exceso de peso, en comparación con los de peso normal, tiene

un peor rendimiento en tareas que evalúan la atención y la flexibilidad (Cserjési, Molnár, Luminet, & Lénárd, 2007), la planificación, la inhibición, la flexibilidad y la toma de decisiones (Verdejo-García, et al., 2010) y que los adolescentes con obesidad extrema muestran una pobre ejecución en tareas de inhibición y flexibilidad (Lokken, Boeka, Austin, Gunstad, & Harmon, 2009). Además, Verdejo-García et al., (2010) encontraron una fuerte relación negativa entre el IMC y la flexibilidad. El sustrato neural de las funciones ejecutivas parece residir principalmente en el córtex prefrontal. El córtex prefrontal dorsolateral parece estar más relacionado con las funciones de memoria, inhibición y flexibilidad, mientras que el córtex orbitofrontal parece estar más implicado en la toma de decisiones y los procesos emocionales que las guían, de ahí las importantes conexiones que este área mantiene con el córtex cingulado y la ínsula (Verdejo-García & Bechara, 2009). El córtex orbitofrontal podría ser subdividido en dos: la parte ventromedial que estaría implicada en el valor de la recompensa y la parte ventrolateral que se requeriría cuando una respuesta que ha sido asociada previamente con la recompensa debe ser suprimida (Small, Zatorre, Dagher, Evans, & Jones-Gotman, 2001). Hasta el momento, los estudios de neuroimagen acerca de cómo el exceso de peso puede influir en el funcionamiento ejecutivo de los adolescentes son muy escasos. En conjunto, los resultados sugieren que un menor volumen y un hipofuncionamiento de las regiones relacionadas con el control inhibitorio, unido a una hiperactivación de las regiones relacionadas con la recompensa estarían relacionados con un elevado IMC (Batterink et al., 2010; Maayan et al., 2011).

La idea de que la obesidad podría estar relacionada con una mayor sensibilidad a la recompensa y un pobre control inhibitorio comienza a tener respaldo empírico (Appelhans et al., 2011; Berg et al., 2011; Loxton et al., 2011; Nederkoorn, Houben, Hofmann, Roefs, & Jansen, 2010). En este sentido, los problemas de exceso de peso

podrían ser entendidos como una alteración en los mecanismos de toma de decisiones que permiten dirigir la conducta hacia metas adaptativas. Así, las personas con exceso de peso tenderían a sobreestimar el valor de recompensa de los alimentos apetitosos y esta sobreestimación sesgaría la toma de decisiones hacia una ingesta excesiva, ignorando sus posibles consecuencias negativas a largo plazo. Esta visión se refleja en el modelo del marcador somático (Damasio, 1994). El modelo del marcador somático propone que la toma de decisiones es un proceso guiado por señales emocionales (marcadores somáticos) que anticipan los resultados prospectivos de distintas opciones de respuesta, marcándolas como positivas o negativas para el organismo de acuerdo con una lógica homeostática (Paulus, 2007; Verdejo-García & Bechara, 2009). Estas señales somáticas, que se proyectan a través de diversas vías de comunicación cuerpo-cerebro (p.e., ruta vagal u hormonal), influirían sobre los procesos motivacionales y de decisión. Desde este modelo, se postularía que la obesidad está asociada con la alteración de al menos dos mecanismos complementarios: (1) se produce una valoración exagerada del valor motivacional o hedónico de los alimentos apetitosos, produciendo señales somáticas muy intensas que podrían atenuar la influencia de señales homeostáticas; y (2) se produce un déficit en los mecanismos de control y autorregulación que en condiciones normales controlan conductas inapropiadas para las demandas actuales. Este modelo también ha sido propuesto para explicar las alteraciones ejecutivas que manifiestan las personas drogodependientes (Verdejo-García & Bechara, 2009) y comienzan a aparecer datos que apoyan este modelo para explicar los problemas de exceso de peso. Stice et al. (2011) encuentran que los adolescentes de peso normal con alto riesgo vs. bajo riesgo para desarrollar obesidad en el futuro muestran una mayor activación de las áreas somatosensoriales en respuesta a la comida. Los autores sugieren que los adolescentes en riesgo para desarrollar obesidad podrían exhibir una mayor

sensibilidad hacia la recompensa en general, pero que quizá ésta podría necesitar del acompañamiento de una mayor activación de las áreas somatosensoriales en respuesta a la comida para que hubiera un riesgo específico de desarrollar obesidad frente a otros problemas de adicción. Las áreas somatosensoriales y la ínsula están relacionadas con el procesamiento de la información visceroceptiva y su valoración hedónica (Berthoud & Morrison, 2008), por lo que podría hipotetizarse que una mayor activación de estas áreas ante la comida apetitosa podría producir una sobreestimación del valor reforzante del alimento y fuertes señales somáticas que atenuaran las señales homeostáticas que regulan la ingesta, propiciando la tendencia a decidir seguir comiendo a pesar de que las necesidades fisiológicas estuvieran cubierta y sin tener en cuenta las posibles consecuencias negativas que este exceso de ingesta podría tener sobre la salud.

El paradigma más frecuentemente usado para evaluar la toma de decisiones es la Iowa gambling task (Bechara et al., 2000). Inicialmente fue desarrollado para investigar alteraciones en los procesos de toma de decisiones de pacientes neurológicos con lesiones en el córtex prefrontral ventromedial y proporcionar apoyo empírico a la hipótesis del marcador somático (Verdejo-García & Bechara, 2009). Esta tarea se caracteriza principalmente por tener que tomar decisiones en situaciones de riesgo e incertidumbre, con el objetivo de conseguir la mayor cantidad de dinero virtual. Para ello, los participantes tienen que escoger cartas de 4 barajas diferentes, dos de ellas, producen una alta ganancia inmediata pero grandes pérdidas en el futuro (a largo plazo estas barajas son desfavorables, pues hacen perder dinero) y las otras dos, proporcionan un pequeña ganancia inmediata pero pocas pérdidas en el futuro (estas barajas son ventajosas, pues a largo plazo son las que proporcionan mayores ganancias). Esta tarea ha sido utilizada en personas con problemas de exceso de peso. En comparación con las personas de peso normal, los resultados indican que las personas con exceso de peso

tienen un peor rendimiento en esta tarea, encontrándose estos resultados tanto en adultos (Brogan, Hevey, O'Callaghan, Yoder, & O'Shea, 2011; Davis, Levitan, Muglia, Bewell, & Kennedy, 2004) como en adolescentes (Verdejo-García, et al., 2010). Los estudios que comparan la ejecución de las personas con exceso de peso vs. otras poblaciones (peso normal, anorexia, bulimia y trastorno por atracón) encuentran que las personas de peso normal tienen un mejor rendimiento que los grupos clínicos, pero no se encuentran diferencias entre los diferentes grupos clínicos (Brogan, Hevey, & Pignatti, 2010; Danner, Ouwehand, van Haastert, Hornsveld, & de Ridder, 2012; Fagundo et al., 2012). Por tanto, esta característica parece ser común en los problemas relacionados con la conducta de ingesta. La principal diferencia con respecto a las personas con peso normal parece ser que los grupos clínicos no aprenden a lo largo de la tarea. Los autores especulan, que aunque de forma diferente en cada grupo clínico, los que podría subyacer sería una alteración del circuito fronto-estriado, que reflejaría la dificultad de tomar decisiones adecuadas respecto a una correcta ingesta de alimentos (Brogan et al., 2011). Con respecto al modelo del marcador somático, esta alteración podría ser interpretada como una hipersensibilidad a la recompensa y/o insensibilidad al castigo, o ambas, que le impide ver las consecuencias tanto positivas como negativas a largo plazo. La aplicación del modelo del marcador somático al contexto de la obesidad tiene importantes implicaciones clínicas, ya que el grado de disfunción motivacional y de alteración de los procesos de control de impulsos y toma de decisiones puede predecir de manera significativa el grado de severidad y el éxito del tratamiento (Nederkoorn et al., 2006). Existen estudios que indican que el consumo de comida apetitosa se relaciona con un peor funcionamiento ejecutivo (Riggs, Spruijt-Metz, Sakuma, Chou, & Pentz, 2010) y que el rendimiento de las funciones ejecutivas mejora tras la pérdida de peso (Siervo et al., 2011). Por tanto, en el contexto del modelo sería importante

desarrollar estrategias de tratamiento que intervengan de manera sistemática sobre el doble mecanismo dañado: valoración motivacional y control de impulsos/ toma de decisiones. Este tipo de intervención sería especialmente recomendable en adolescentes, debido a las características neuropsicológicas que se asocian con esta etapa de desarrollo cerebral (Chambers, Taylor, & Potenza, 2003).

3. Singularidades psicobiológicas del neurodesarrollo en la adolescencia

La adolescencia es el período entre la niñez y la edad adulta que abarca cambios en el desarrollo físico, psicológico y social (Ernst, Pine, & Hardin, 2006). Durante esta etapa, las modificaciones anatómicas, funcionales y metabólicas producidas en el cerebro permiten que los adolescentes vayan adquiriendo progresivamente estilos emocionales y cognitivos adultos (Chambers et al., 2003). La adolescencia parece caracterizarse por un desequilibrio madurativo en el sistema fronto-estriado, donde el sistema estriado ha alcanzado su madurez mientras que el córtex prefrontal aún permanece en desarrollo. En este sentido, y en relación a los modelos teóricos anteriormente presentados, existen diferentes hipótesis o modelos que resaltan la contribución de unos sistemas frente a otros, cuando intentan explicar qué es lo que motiva el comportamiento adolescente (Ernst & Fudge, 2009). Estas singularidades de la etapa adolescente podrían contribuir a una mayor vulnerabilidad hacia el desarrollo de los problemas de exceso de peso.

Chambers et al. (2003) enfatizan el rol de la sensibilidad a la recompensa. Estos autores proponen que las funciones que dependen de la maduración del córtex prefrontal, como por ejemplo, el control inhibitorio y las habilidades de autorregulación no son del todo eficaces, ya que en esta etapa el córtex prefrontal no ha alcanzado aún su máximo nivel de desarrollo. Sin embargo, el sistema estriado, responsable de los

procesos de recompensa y motivación ya está relativamente maduro, por lo que su actividad prevalece sobre la del córtex prefrontal. Esta relativa inmadurez del sistema de control y autorregulación acompañada de una relativa madurez del sistema de recompensa hacen que durante la adolescencia exista una mayor motivación para buscar e involucrarse en nuevas experiencias, sobre todo, las que tienen que ver con situaciones de recompensa. La mayor motivación para participar en nuevas actividades proporciona experiencias que facilitan la maduración de la corteza prefrontal, pero al mismo tiempo, suponen un periodo de vulnerabilidad hacia cierto tipo de comportamientos donde las habilidades de autorregulación o el control inhibitorio podrían ser claves. En este sentido, podría hipotetizarse que los adolescentes podrían estar más motivados hacia el consumo de alimentos apetitosos y podrían tener más dificultades para controlar su ingesta, debido a la mayor prevalencia del sistema de recompensa.

Por otra parte, otros autores interpretan el comportamiento adolescente destacando más la inmadurez de las regiones prefrontales y el riesgo genético que el desequilibrio madurativo en el sistema fronto-estriado. Casey, Jones, y Hare (2008) señalan que el comportamiento adolescente a menudo se caracteriza por la impulsividad y el riesgo. Según estos autores, la impulsividad está asociada a la inmadurez del córtex prefrontal y disminuye progresivamente con la edad por el desarrollo madurativo de estas regiones. En cambio, la toma de riesgo está relacionada con un aumento de la actividad del núcleo accumbens, la cual incrementa durante la adolescencia, en comparación con la infancia y la etapa adulta. Sin embargo, si se perciben las consecuencias negativas de las conductas de riesgo, la actividad del núcleo accumbens respecto a la recompensa es menor. Por tanto, según estos autores, la impulsividad se relaciona con la inmadurez de las regiones que ejercen el control sobre los impulsos y las conductas arriesgadas se asocian a una mayor actividad del núcleo accumbens, siendo éstas más acentuadas

durante la etapa adolescente. En resumen, esta propuesta teórica defiende que el comportamiento adolescente no puede ser explicado recurriendo solo a la impulsividad o inmadurez de las regiones que ejercen el control sobre los impulsos, sino que hay que tener en cuenta la toma de riesgo. En conjunto, ambos factores hacen más comprensible el comportamiento adolescente y por otra parte, explican mejor las diferencias individuales en relación a asumir conductas de riesgo o la vulnerabilidad/predisposición ante cierto tipo de comportamientos. En relación a los problemas de exceso de peso, desde esta perspectiva podría hipotetizarse que la mayor vulnerabilidad hacia el consumo de alimentos apetitosos podría verse acentuada en esta etapa, lo que unido a la inmadurez de las regiones que regulan o controlan los impulsos podría llevar a un mayor consumo de alimentos apetitosos y como consecuencia, podría existir una mayor probabilidad de desarrollar problemas de exceso de peso.

Por último, en cuando al modelo del marcador somático, los datos apuntaban que lo que podría subyacer a la dificultad de tomar decisiones adecuadas respecto a una correcta ingesta de alimentos podría ser una alteración en el circuito fronto-estriado. Dicha alteración podría ser consecuencia de una hipersensibilidad a la recompensa, una insensibilidad al castigo, o ambas, lo cual impediría ver las consecuencias tanto positivas como negativas a largo plazo (Brogan et al., 2011). En este sentido, Ernst et al. (2006) han propuesto un modelo tríadico en el que asumen que una conducta motivada resulta del balance de tres sistemas neurales: estriado ventral (conducta de aproximación), amígdala (conducta de evitación) y córtex prefrontal ventral (autorregulación conductual). Teniendo en cuenta lo dicho en párrafos anteriores, el comportamiento adolescente se caracteriza principalmente por una mayor activación del estriado ventral (núcleo accumbens) que se refleja en una mayor sensibilidad hacia la recompensa o conducta de aproximación y por una inmadurez del córtex prefrontal

ventral que se relaciona con el dominio del sistema de recompensa o con una menor capacidad para controlar los impulsos (Casey et al., 2008; Chambers et al., 2003). Ernst et al. (2006) incluyen en su modelo el papel del sistema de evitación. Según estos autores, durante la adolescencia la amígdala y otras estructuras relacionadas con la codificación de las señales de peligro y las respuestas ante las señales de alerta están alteradas. Como consecuencia, los adolescentes, en comparación con los adultos, son menos sensibles al riesgo y a los estímulos potencialmente peligrosos. En resumen, los autores proponen que durante la adolescencia, en comparación con la etapa adulta, existe un mayor impacto de los resultados positivos sobre el estriado ventral y un menor impacto de los resultados negativos sobre la amígdala. Basándose en su modelo, los autores proponen que durante la adolescencia la actividad del sistema de recompensa prevalece sobre la del sistema de evitación, mientras que la inmadurez del sistema de autorregulación falla en equilibrar adaptativamente estos dos sistemas motivacionales. Con respecto a los problemas de exceso de peso, desde este modelo podría hipotetizarse que los adolescentes podrían sobreestimar las señales hedónicas producidas por el consumo de alimentos apetitosos, atenuando las señales homeostáticas que regulan el apetito y propiciando la tendencia a decidir seguir comiendo a pesar de que las necesidades fisiológicas estuvieran cubiertas y sin tener en cuenta las consecuencias negativas que este exceso de ingesta podría tener sobre la salud.

4. Algunas consideraciones sobre el tratamiento de la obesidad adolescente

El creciente y continuo aumento de la prevalencia de sobrepeso y obesidad adolescente (Lee et al., 2011; Ogden, 2012), del incremento de la severidad de ésta (Lobstein et al., 2004) y de la creciente evidencia que relaciona los problemas de exceso de peso con consecuencias negativas tanto para la salud, a corto y largo plazo, como para el ámbito social y económico (Gortmaker et al., 2011) hacen más que necesaria la

búsqueda de estrategias eficaces que puedan prevenir y disminuir esta epidemia. En el caso de la población adolescente, esta búsqueda se hace más necesaria si cabe, ya que parece que si la obesidad no se corrige en esta etapa, ésta tiende a cronificarse y las consecuencias con las que se asocia la obesidad podrían ser más severas (Whitaker et al., 1997). Además, la adolescencia parece constituir un periodo donde existe una mayor vulnerabilidad para desarrollar este problema y una menor motivación para buscar y cumplir con el tratamiento de ésta (Acosta et al., 2008).

Según estudios recientes, las intervenciones multi-componentes basadas en el comportamiento son consideradas como la primera línea de tratamiento. Dichas intervenciones incluyen: (i) asesoramiento dietético saludable, (ii) asesoramiento o participación en programas de actividad física y (iii) manejo de técnicas conductuales, como por ejemplo, control estimular, establecimiento de metas, solución de problemas, etc., con el fin de establecer y mantener los cambios en la dieta y la actividad física (Acosta et al., 2008; Whitlock, O'Connor, Williams, Beil, & Lutz, 2010). Estas intervenciones, en comparación con las de otro tipo (farmacológicas, grupo control, o donde no se incluyen los tres componentes), muestran mejores efectos tanto a corto como a largo plazo en la salud de los adolescentes (Kelly & Melnyk, 2008; Wilfley et al., 2007). Sin embargo, existen pocos estudios que evalúen sus efectos a largo plazo y algunos estudios indican la remisión de estos efectos (McGovern et al., 2008). Tampoco existen datos concluyentes acerca de la intensidad y duración que deberían tener las intervenciones pediátricas (Wilfley et al., 2007).

Debido a la falta de consistencia en los métodos y en el rigor de las medidas que evalúan los posibles efectos, no existe suficiente evidencia para determinar qué tipo de programa multi-componente es más eficaz para hacer frente a la obesidad en la adolescencia (Kelly & Melnyk, 2008). No obstante, empiezan a aparecer algunos

indicios. Así, parece que los adolescentes adscritos a programas que contemplan una mayor participación por parte de los padres pierden más peso que los adolescentes que acuden a programas donde la participación de los padres en las sesiones es menor (Kelly & Melnyk, 2008; Wilfley et al., 2007) y que las intervenciones con fuertes componentes cognitivos-conductuales parecen tener mejores resultados, ya que el entrenamiento de estas habilidades podría ser clave para impulsar la confianza y motivación de los adolescentes para participar en este tipo de programas y además, podría ayudarles a mejorar sus decisiones sobre los hábitos y estilos de vida saludables (Kelly & Melnyk, 2008). Por tanto, la investigación futura debería ir encaminada a identificar los componentes que logran resultados más eficaces y persistentes, así como las características de los participantes que se relacionan con una mayor eficacia de los tratamientos (Wilfley et al., 2007).

II. JUSTIFICACIÓN Y OBJETIVOS

CAPÍTULO 2

JUSTIFICACIÓN Y OBJETIVOS DE LA TESIS

1. Justificación y objetivo principal

Los cambios acontecidos en las últimas décadas en el sistema alimentario mundial (mayor palatabilidad de la comida, extensa variedad de alimentos, alimentos baratos de fácil y rápido acceso, continua presencia de estímulos alimentarios, mayor densidad de energía en los alimentos, mayor tamaño de las porciones, etc.) parecen estar contribuyendo al incremento de la incidencia de la obesidad (Swinburn et al., 2011). Estudios recientes apuntan que cuando personas vulnerables se exponen a estos ambientes, las señales de hambre pueden ser impulsadas por las señales hedónicas del ambiente, en ausencia de necesidades metabólicas (Zheng et al., 2009). Así, la conducta de ingesta puede verse influenciada por las condiciones ambientales y las predisposiciones individuales. Estas nuevas características de los alimentos hacen que distintos sistemas cerebrales –más allá de los sistemas de regulación de la ingesta- participen en la conducta de comida. Estos sistemas incluyen el sistema de recompensa, el sensorio-motor o el ejecutivo, responsable del control de impulsos o hábitos.

Recientemente se ha propuesto que la sobrealimentación podría reflejar un desequilibrio entre los circuitos motivacionales (por su implicación en los procesos de recompensa y condicionamiento) y los circuitos que controlan e inhiben las respuestas preponderantes (Volkow et al., 2008). Diversos estudios tanto de tipo conductual como de neuroimagen indican que los problemas de exceso de peso podrían relacionarse con alteraciones neurocognitivas y emocionales, especialmente con aquellas habilidades encargadas de organizar y programar conductas dirigidas a objetivos (funciones ejecutivas) y que el entrenamiento de dichas habilidades podría mejorar la eficacia de los tratamientos dirigidos a reducir el exceso de peso (Appelhans et al., 2011; Mobbs et al., 2010). En el caso de la población adolescente, la búsqueda de nuevas estrategias que mejoren los resultados de los tratamientos se hace más que necesaria, ya que parece que

si la obesidad no se corrige en esta etapa, ésta tiende a cronificarse y las consecuencias con las que se asocia la obesidad podrían ser más severas (Whitaker et al., 1997). Además, las alteraciones neurocognitivas y emocionales que parecen estar relacionadas con la obesidad podrían estar acentuadas en esta etapa debido a los procesos de neurodesarrollo que acontecen durante la adolescencia (Ernst & Fudge, 2009). Dentro de este contexto es donde encuentra justificación la realización de esta tesis doctoral. El estudio de las características neuropsicológicas y de los mecanismos cerebrales asociados al exceso de peso en adolescentes podría contribuir a esclarecer los factores neuropsicológicos que se asocian con la obesidad. Los resultados derivados de esta tesis podrían resultar de enorme utilidad tanto a nivel teórico, permitiendo el avance de la identificación de los factores neuropsicológicos que podrían promover y/o mantener los problemas de exceso de peso, como a nivel clínico, contribuyendo a mejorar las intervenciones pediátricas dirigidas a reducir los problemas de exceso de peso.

El **objetivo principal** de esta tesis consiste en explorar los factores de personalidad y neuropsicológicos así como sus correlatos neuroanatómicos asociados con el exceso de peso en adolescentes. Asimismo, se examinará la anatomía y la función de las regiones cerebrales que subyacen a los procesos de toma de decisiones en adolescentes con exceso de peso.

2. Objetivos específicos e hipótesis

Para la consecución de nuestro objetivo principal se llevaron a cabo cuatro estudios que desarrollan objetivos más específicos que desglosamos a continuación. Cada estudio se corresponde con uno de los cuatro artículos que componen esta tesis.

En nuestro primer estudio el objetivo fue examinar la relación entre los factores de personalidad (sensibilidad al refuerzo y al castigo), el Índice de Masa Corporal y las variables neuropsicológicas de impulsividad y flexibilidad en adolescentes con exceso

de peso frente a adolescentes con peso normal. Para ello, realizamos una evaluación multidimensional de rasgos impulsivos (usando la escala UPPS-P) y una evaluación neurocognitiva que incluía índices sensibles a los déficits de inhibición y flexibilidad (usando el test Stroop).

Basándonos en la evidencia previa, la hipótesis planteada para este estudio fue que la sensibilidad a la recompensa y el IMC predecirían puntuaciones más altas en impulsividad en los adolescentes con exceso de peso.

Este estudio está publicado en la revista *Obesity* (Delgado-Rico, Schmidt Río-Valle, González-Jiménez, Campoy, & Verdejo-García, 2012) y se encuentra íntegramente en el Anexo I.

Los resultados de nuestro primer estudio indicaban que el aumento de peso estaba caracterizado por un pobre control inhibitorio ante emociones intensas y problemas de flexibilidad. Por ello, el objetivo de nuestro segundo estudio se dirigió a explorar si el entrenamiento en regulación emocional y control inhibitorio (integrados dentro de una intervención multi-componente) produce cambios significativos en estos procesos y si estos cambios se acompañan de reducciones en el IMC.

La hipótesis planteada fue que el entrenamiento en regulación emocional y control inhibitorio dentro de una intervención multi-componente mejoraría dichas habilidades y que estas mejoras irían acompañadas de reducciones contingentes en el IMC.

Este estudio está publicado en la revista *Behavioural pharmacology* (Delgado-Rico, Schmidt Río-Valle, Albein-Urios, et al., 2012) y se encuentra íntegramente en el Anexo II.

Los objetivos de nuestro tercer estudio estuvieron dirigidos a: (i) examinar las posibles diferencias en sensibilidad a la recompensa y al castigo, medidas de personalidad impulsiva y control inhibitorio en relación con el volumen de materia gris

entre adolescentes con exceso de peso frente a adolescentes con peso normal y (ii) detectar diferencias en el volumen de materia gris entre ambos grupos.

Las hipótesis planteadas para este estudio fueron: (i) que el volumen regional de los sistemas de recompensa –el núcleo estriado y las regiones somatosensoriales estarían relacionadas con la sensibilidad a la recompensa, mientras que el volumen regional del cortex prefrontal correlacionaría con la impulsividad y el control cognitivo, y (ii) que los adolescentes con exceso de peso presentarían un menor volumen de materia gris en el cortex prefrontal.

Este estudio está publicado en la revista *PLoS One* (Moreno-López, Soriano-Mas, Delgado-Rico, Schmidt Río-Valle, & Verdejo-García, 2012) y se encuentra íntegramente en el Anexo III.

Por último, el objetivo de nuestro cuarto estudio fue explorar los sustratos cerebrales del proceso de toma de decisiones bajo condiciones de riesgo y recompensa en adolescentes con exceso de peso vs. peso normal.

La hipótesis planteada para este estudio fue que los sistemas cerebrales implicados en la toma de decisiones relacionadas con el riesgo y la recepción de recompensa (cortex orbitofrontal, ínsula y estriado) mostrarían una activación anormal en los adolescentes con exceso de peso en comparación con los de peso normal.

Este estudio está enviado a la revista *Obesity* (Delgado-Rico, Soriano-Más, Verdejo-Román, Schmidt Río-Valle & Verdejo-García, en revisión) y se encuentra íntegramente en el Anexo VI.

III. MEMORIA DE TRABAJOS

CAPÍTULO 3

BMI PREDICTS EMOTION-DRIVEN IMPULSIVITY AND COGNITIVE INFLEXIBILITY IN ADOLESCENTS WITH EXCESS WEIGHT

Delgado-Rico, E., Schmidt Río-Valle, J. S., González-Jiménez, E., Campoy, C., & Verdejo-García, A. (2012). BMI predicts emotion-driven impulsivity and cognitive inflexibility in adolescents with excess weight. *Obesity*, *20*(8), 1604–1610.

Introduction

The prevalence of childhood overweight and obesity has been increasing worldwide over the past 30 years, whereas the search for effective interventions is still currently unfulfilling (Gortmaker et al., 2011). The drastic psychosocial changes shared by all Western societies (e.g., the unrestricted access to food products and the explosion of the food market) have modified the way we perceive food and regulate food intake, being these processes increasingly modulated by external reward cues at the expense of appropriate nutrient sensing (Berthoud & Morrison, 2008). In the last years, excessive eating and obesity are increasingly viewed as a brain-related dysfunction, whereby reward-driven urges for pleasurable foods "hijack" context-driven frontal-executive control (Volkow et al., 2011; Zheng et al., 2009). The risk for this imbalance is higher among adolescents, since they stand amidst neurodevelopmental processes essential to fine-tune the links between the reward system and the executive control system (Ernst & Fudge, 2009; Sturman & Moghaddam, 2011). Neurobiological studies mainly support this notion—adolescents at high-risk for obesity have heightened activation of the reward system in response to receipt of palatable food (Stice et al., 2011), and obese adolescents have significantly reduced orbitofrontal volumes (Maayan et al., 2011). However, the neuropsychological correlates of excessive weight and its associated neuroadaptations are not yet well specified—despite the fact that cognitive strategies directed to restore these systems are lined up as promising interventions for pediatric obesity (Acosta et al., 2008).

A strand of evidence suggests that excessive weight adolescents have prominent deficits in impulsivity and inhibitory control (Batterink et al., 2010; Nederkoorn et al., 2006). However, the link between excess weight and impulsivity depends on age—high

impulsivity is linked to higher body weight in young kids (8–10 years old), whereas in adolescents (12–14 years old) this association is less pronounced and tends to be inversed—low impulsivity associated with higher weight (Pauli-Pott et al., 2010b). This interaction may reflect age-related maturation of inhibitory processes (Bunge & Wright, 2007), or a transition between impulsivity and compulsivity in the development of obesity—similar to what is found in addiction (Volkow et al., 2008). Germane to the latter notion, a second strand of evidence indicates that excessive eating is mainly associated with decline of flexibility skills—a cognitive proxy of compulsivity (Dalley et al., 2011). Germane to this notion, neurocognitive studies in children and adolescents have shown that BMI specifically negatively correlates with performance on cognitive switching probes (Cserjési et al., 2007; Verdejo-García et al., 2010).

A related unresolved issue is that of the impact of the personality factors of sensitivity to reward (SR) and sensitivity to punishment (SP) on neuropsychological deficits in adolescent overweight and obesity. This is relevant because psychometric studies indicate that SR positively correlates with trait impulsivity, whereas SP positively correlates with compulsivity— with the exception of positive correlations between SP and the impulsivity dimension of urgency (emotion-driven impulsivity (Meda et al., 2009; Verdejo-García, Lozano, Moya, Alcázar, & Pérez-García, 2010)). Davis, Strachan, et al. (2004) demonstrated that SR significantly predicted higher scores on a measure of emotional eating— overeating when under strong negative states, and they proposed a mediational path between SR, negative emotion-driven eating, and BMI. This result is fitting with evidence showing that both SR and SP correlate with negative urgency (the tendency to experience strong impulses under conditions of negative affect) in obese adults (Mobbs et al., 2010). Therefore, the association between these personality factors and excessive eating seems well-established. However, further

dissociation of the differential role of SR vs. SP, and of their relative impact on inhibitory control vs. inflexibility is needed to achieve a better understanding of how personality impacts neuropsychological profiles in obese adolescents.

In this study, we aimed to examine the link between personality factors (SR and SP), BMI, and outcome measures of impulsivity vs. flexibility in—otherwise healthy—excessive weight adolescents. We conducted a multidimensional assessment of trait impulsivity (using the UPPS-P scale) and neurocognitive assessments with discriminant validity to dissociate inhibition vs. flexibility deficits (using the process-approach version of the Stroop test). According to previous evidence, we predicted that BMI and SR would significantly predict higher scores on emotion-driven impulsivity among adolescents with excess weight.

Methods and Procedures

Participants

Sixty-three adolescents (age range 12–17) participated in this study. Participants were classified as obese (n = 26), overweight (n = 16), or normal weight (n = 21) according to the International Obesity Task Force (IOTF) criteria defined by Cole et al. (2000). The demographical data and endocrine characteristics of participants—classified as excess weight vs. normal weight—are summarized in Table 1.

Table 1. Demographical and clinical descriptive data of the normal weight and excess weight groups: sex, SES, age, BMI and endocrine parameters.

	Normal weight (*n*=21)	Excess weight (*n*=42)	
	n (%)	*n* (%)	x^2
Sex			0.14
Male	11 (52.4)	14 (33.3)	
Female	10 (47.6)	28 (66.7)	
SES (Annual Income €) [a]			0.10
0 – 11.533 €	5 (26.3)	2 (5)	
11.533 – 18.200 €	3 (15.8)	13 (32.5)	
18.200 – 26.548 €	5 (26.3)	18 (45.0)	
26.548 – 41.292 €	3 (15.8)	4 (10.0)	
41.292 – 3.144.000 €	3 (15.8)	3 (7.5)	
	Mean (SD) / Range	*Mean (SD)* / Range	*t*
Age	14.14 (1.459) / 12 – 17	14.19 (1.38) / 12 - 17	-0.13
BMI	19.84 (2.642) / 14.78 – 24.57	29.15 (4.51) / 22.06 – 38.21	-10.31[b]
Biochemical parameters			
Insulin	9.60 (2.68) / 6 – 14.3	16.23 (12.38) / 1.5 – 52	-2.70[b]
Basal glucose	86.68 (13.85) / 69 – 130	86.39 (9.42) / 68 – 106	0.10
Triglycerides	69.53 (24.32) / 37 – 119	96.15 (43.24) / 45 – 235	-2.50[b]
HDL	60.89 (16.75) / 39 – 113	50.58 (12.77) / 33 – 78	2.63[b]
Total cholesterol	157.79 (32.34) / 99 – 215	158.85 (26.41) / 113 – 222	-0.13

Note. HDL: High-density lipoprotein cholesterol; SES: Socioeconomic status; [a] Quintiles for SES are defined according to data from the Financial Survey for Spanish Families, http://www.bde.es/webbde/es/estadis/eff/eff.html; [b] $p \leq 0.05$.

We recruited them through educational centers and national health services in order to participate in a larger study aimed to test a novel multidisciplinary intervention for adolescent excess weight. To be included, they had to meet the following criteria: (i) age range between 12 and 17 years old, (ii) BMI values falling within the intervals categorized as overweight or obesity according to the IOTF—for excess weight adolescents, or normal weight values, (iii) normal endocrine characteristics—assessed by Complete Blood Count determinations showing within-normal range levels of insulin, basal glucose, triglycerides, high-density lipoprotein cholesterol, and total cholesterol, and (iv) absence of past/current evidence of medical or psychological disorders. The adolescents with normal weight were recruited in the same demographic areas and had to meet the same inclusion criteria—with the exception of (ii). In order to avoid the inclusion of underweight adolescents within this group, we also checked if potential participants fell within normal BMI values according to age- and gender-adjusted Spanish-specific norms (Sobradillo et al., 2004) —none of the selected participants met criteria for low weight. All participants completed the Millon Adolescent Clinical Inventory (MACI (Aguirre, 2004)) and the Eating Disorder Inventory 2 (EDI-2 (Garner, 1998)) in order to assess the presence of clinically significant psychopathological traits. Results are presented as Supplementary Table. In brief, they showed that both groups did not significantly differ on MACI-indexed personality patterns, expressed concerns (EC) or clinical syndromes (CS), with the exceptions of submissive patterns—increased in excess weight adolescents, and peer insecurity—increased in normal weight adolescents. EDI-2 results gave a similar picture – none of the excess weight participants had clinically significant disorders; nonetheless, as a group, they scored significantly higher than their peers on the drive for thinness and body dissatisfaction scales.

Supplementary Table. Descriptive scores and group-comparisons for subscales of the MACI and EDI-2.

	Normal weight (n=21) *Mean (SD)*	Excess weight (n=42) *Mean (SD)*	*t*
MACI - PP Introversive	45.95 (20.25)	37.93 (18.23)	1.587
MACI - PP Inhibited	44.48 (21.35)	42.57 (15.41)	0.405
MACI - PP Doleful	38.48 (15.56)	37.33 (17.22)	0.256
MACI - PP Submissive	52.95 (22.02)	67.74 (23.70)	-2.388[a]
MACI - PP Dramatizing	59.14 (26.20)	68.26 (24.04)	-1.378
MACI - PP Egotistic	63.33 (25.37)	64.52 (26.99)	-0.168
MACI - PP Unruly	50.10 (26.57)	47.19 (18.91)	0.500
MACI - PP Forceful	53.86 (22.15)	46.62 (14.59)	1.357
MACI - PP Conforming	64.14 (28.94)	77.19 (24.24)	-1.887
MACI - PP Oppositional	42.52 (15.97)	41.62 (15.09)	0.220
MACI - PP Self-demeaning	40.62 (15.62)	40.95 (14.68)	-0.083
MACI - PP Borderline tendency	41.86 (19.98)	35.48 (17.23)	1.313
MACI - PP Identity diffusion	46.05 (21.15)	36.48 (18.34)	1.855
MACI - EC Self-devaluation	48.71 (22.10)	48.71 (21.43)	0.000
MACI - EC Body disaproval	56.00 (23.43)	63.79 (25.39)	-1.176
MACI - EC Sexual Discomfort	55.95 (23.18)	63.64 (20.29)	-1.352
MACI - EC Peer insecurity	51.90 (22.30)	40.79 (17.88)	2.140[a]
MACI - EC Social Insensitivity	59.90 (25.56)	52.00 (25.01)	1.174
MACI - EC Family discord	48.86 (21.12)	51.02 (17.42)	-0.433
MACI - EC Childhood abuse	45.20 (16.10)	35.57 (19.15)	1.943
MACI - CS Eating dysfunctions	53.48 (15.79)	62.02 (21.78)	-1.598
MACI - CS Substance-abuse proneness	44.71 (24.83)	37.17 (20.69)	1.276
MACI - CS Delinquent predisposition	55.05 (23.14)	47.71 (18.98)	1.343
MACI - CS Impulsive propensity	48.57 (27.81)	42.17 (21.97)	0.997
MACI - CS Anxious feelings	54.33 (26.71)	56.67 (21.37)	-0.375
MACI - CS Depressive affect	45.43 (20.45)	46.71 (19.67)	-20.241
MACI - CS Suicidal tendency	46.52 (13.93)	43.38 (17.58)	0.714
EDI-2 - Drive for thinness	50.62 (25.50)	69.69 (23.28)	-2.970[a]
EDI-2 - Bulimia	56.55 (18.84)	57.83 (17.21)	-0.271
EDI-2 - Body Dissatisfaction	53.43 (28.88)	73.50 (24.55)	-2.883[a]
EDI-2 - Inefectiveness	63.19 (25.23)	50.26 (26.65)	1.847
EDI-2 - Perfectionism	61.48 (27.25)	55.29 (27.98)	0.835
EDI-2 - Interpersonal Distrust	59.14 (26.02)	41.93 (26.45)	2.448[a]
EDI-2 - Interoceptive Awareness	54.95 (28.55)	47.15 (29.91)	0.990
EDI-2 - Maturity Fears	45.90 (24.30)	55.68 (26.41)	-1.421
EDI-2 - Ascetism	54.86 (21.60)	51.07 (26.34)	0.569
EDI-2 - Impulse Regulation	39.86 (24.58)	40.62 (29.31)	-0.102
EDI-2 - Social Insecurity	60.05 (24.36)	45.62 (25.93)	2.123[a]

Measures

SR and SP. Sensitivity to Punishment and Reward Questionnaire (SPSRQ (Torrubia et al., 2001)): The SPSRQ is a 48 yes–no response item questionnaire aimed to measure two neuropsychological systems driving motivated behavior: the behavioral activation system (SR) and the behavioral inhibition system (SP). The total scores from each scale (SP and SR) were obtained for analyses.

BMI. BMI was calculated for each participant as the ratio of weight in kilograms divided by the square of height in meters.

Impulsivity. UPPS-P Scale (Verdejo-García, Lozano, et al., 2010; Whiteside & Lynam, 2001): 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 four dimensions were included in the original version of the UPPS scale (Whiteside & Lynam, 2001); the fifth dimension has been included based on recent work by Cyders et al. (2007) and Smith et al. (2007). Sensation seeking (12 items) incorporates two aspects: (i) a tendency to enjoy and pursue activities that are exciting, and (ii) an openness to trying new experiences that may or may not be dangerous; (lack of) perseverance (10 items) refers to the 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 (12 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.

Response inhibition and switching. Delis–Kaplan Executive Function System (D-KEFS) Color-Word Interference Test Stroop (CWIT Stroop (Delis et al., 2001)): This paper and pencil test is based on the Boston process approach (Milberg, Hebben, & Kaplan, 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 (C) that are administered to determine whether poor performance is because of 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 normative scores of response inhibition (C3 − C1), or response switching (C4 − C3).

Statistical analyses.

We used independent-sample *t*-tests to examine differences between groups on demographic, personality, clinical (endocrine characteristics), and outcome variables—in these analyses, overweight and obese adolescents were collapsed to form the excess

weight group. We examined intercorrelations between these variables by group using Pearson correlation coefficients. To test the main study hypotheses, we conducted three-step level hierarchical multiple regression models to examine the influence of (i) age, (ii) SR and SP personality traits, and (iii) BMI on the outcome measures of impulsivity (UPPS), disinhibition (Stroop inhibition), and inflexibility (Stroop switching). We computed the changes in R^2 associated with the inclusion of each of these steps on the prediction model in order to estimate their separate (and aggregated) contribution to prediction of outcome variables.

Results

Group comparisons

Results are presented in Table 2. Excess weight and normal weight adolescents did not significantly differ on sensitivity to punishment, UPPS dimensions of positive and negative urgency, and lack of premeditation and perseverance. Normal weight adolescents showed increased sensitivity to reward (SPSRQ) and elevated sensation seeking (UPPS-P), but effect sizes were medium (Cohen's d = 0.5), and these differences would not survive correction for multiple comparisons (P < 0.006). No differences were found on performance on the Stroop test.

Table 2. Descriptive scores and group comparisons for measures of sensitivity to punishment/reward (SPSRQ), impulsivity (UPPS-P) and response inhibition and switching (CWIT Stroop).

	Normal weight *Mean (SD)*	Excess weight *Mean (SD)*	*t*	Cohen's *d*
SPSRQ Sensitivity to Reward	12.05 (5.22)	9.55 (4.20)	2.052[a]	0.55
SPSRQ Sensitivity to Punishment	10.62 (5.50)	9.93 (4.97)	0.502	0.13
UPPS-P Negative Urgency	26.29 (7.14)	27.55 (7.31)	-0.651	0.17
UPPS-P Lack of Premeditation	26,38 (5.77)	25.19 (5.65)	0.783	0.21
UPPS-P Lack of Perseverance	23,38 (4.84)	21.79 (4.26)	1.339	0.36
UPPS-P Sensation Seeking	33,81 (6.38)	29.98 (7.25)	2.056[a]	0.55
UPPS-P Positive Urgency	24,67 (6.99)	25.48 (8.25)	-0.385	0.10
CWIT Stroop Response Inhibition	12.24 (2.62)	11.55 (1.94)	1.180	0.31
CWIT Stroop Response Switching	8.24 (2.53)	8.83 (2.45)	-0.900	0.24

[a]Significant differences between the groups.

Correlations

Results are displayed in Table 3. Due to the high number of analyses, and to avoid inflated type I error, here we only refer to significant correlations at $P < 0.01$. In the excessive weight group, SR was positively correlated with negative urgency and positive urgency. SP was only positively correlated with negative urgency. In addition, negative urgency was positively correlated with BMI. In the normal weight group, SR was significantly positively correlated with negative urgency, positive urgency, and lack of perseverance. Endocrine markers did not show significant correlations with personality or neuropsychological indices.

Table 3. Correlations between age, BMI, endocrine parameters, UPPS-P, SPSRQ and STROOP variables for each group.

Normal weight (*n* = 21)															
	BMI	**I**	**BG**	**Tri**	**C**	**HDL**	**NU**	**Pre**	**Per**	**SS**	**PU**	**SP**	**SR**	**RI**	**RS**
Age	0.243	−0.330	0.145	0.073	−0.205	−0.054	0.025	−0.185	−0.072	−0.024	0.279	0.082	0.288	0.200	0.085
BMI		−0.552	0.258	0.166	−0.376	−0.551a	−0.025	0.000	0.039	−0.224	0.019	−0.052	−0.121	0.203	0.123
I			−0.522	0.079	0.262	0.778b	−0.374	−0.625	−0.111	−0.364	−0.388	0.186	−0.125	0.391	−0.631
BG				0.070	0.196	−0.276	−0.176	−0.122	−0.072	0.091	−0.113	−0.252	−0.323	−0.216	0.282
Tri					0.224	−0.239	−0.036	0.080	0.016	0.040	−0.088	−0.217	0.227	0.290	−0.205
C						0.388	0.164	0.036	0.005	−0.030	0.249	−0.022	−0.017	−0.354	−0.186
HDL							−0.291	−0.356	−0.154	−0.207	−0.189	0.261	−0.239	−0.062	−0.183
NU								0.545a	0.585b	0.460a	0.816b	0.156	0.596b	−0.310	0.146
Pre									0.474a	0.557b	0.300	−0.286	0.290	−0.567b	0.233
Per										0.454a	0.423	0.535a	0.581b	−0.444a	0.433a
SS											0.452a	−0.062	0.531a	−0.296	0.174
PU												0.214	0.714b	−0.300	0.104
SP													0.297	0.027	0.241
SR														−0.161	0.177
RI															−0.521a
Excess weight (*n* = 42)															
	BMI	**I**	**BG**	**Tri**	**C**	**HDL**	**NU**	**Pre**	**Per**	**SS**	**PU**	**SP**	**SR**	**RI**	**RS**
Age	0.198	0.003	0.040	−0.063	0.159	0.083	0.156	0.139	0.454b	0.173	0.205	0.034	0.200	0.187	0.089
BMI		0.458a	0.102	−0.159	−0.168	0.014	0.477b	0.161	0.315a	0.245	0.360a	0.355a	0.261	0.210	0.215
I			0.275	0.332	−0.372a	−0.410a	0.457a	−0.208	0.051	−0.006	0.420a	0.313	0.093	−0.130	0.345
BG				0.090	−0.169	−0.354a	0.217	0.333a	−0.111	−0.046	0.037	0.050	0.197	−0.015	−0.047
Tri					0.138	−0.400b	−0.148	−0.125	−0.148	−0.191	−0.169	−0.173	−0.053	−0.044	−0.081
C						0.552b	−0.180	−0.035	0.105	−0.143	−0.237	−0.062	−0.009	0.031	0.029
HDL							−0.067	0.079	0.148	0.032	−0.126	0.166	−0.024	0.154	0.155
NU								0.378a	0.078	0.437b	0.791b	0.462b	0.522b	0.011	0.240
Pre									0.027	0.197	0.312a	−0.258	0.325a	−0.045	0.091
Per										−0.010	0.014	0.125	−0.096	0.127	−0.149
SS											0.348a	0.003	0.434b	−0.120	0.324a
PU												0.261	0.508b	0.064	0.174
SP													0.237	0.158	0.021
SR														−0.047	0.310a
RI															−0.334a

BG, basal glucose; C, total cholesterol; HDL, high-density lipoprotein cholesterol; I, insulin; NU, negative urgency; Per, perseverance; Pre, premeditation; PU, positive urgency; RI, response inhibition; RS, response switching; SP, sensitivity punishment; SPSRQ, sensitivity to punishment/reward; SR, sensitivity reward; SS, sensation seeking; STROOP, CWIT Stroop inhibition and switching; Tri, triglycerides; UPPS-P, impulsivity. [a]$P \leq 0.05$; [b]$P \leq 0.01$

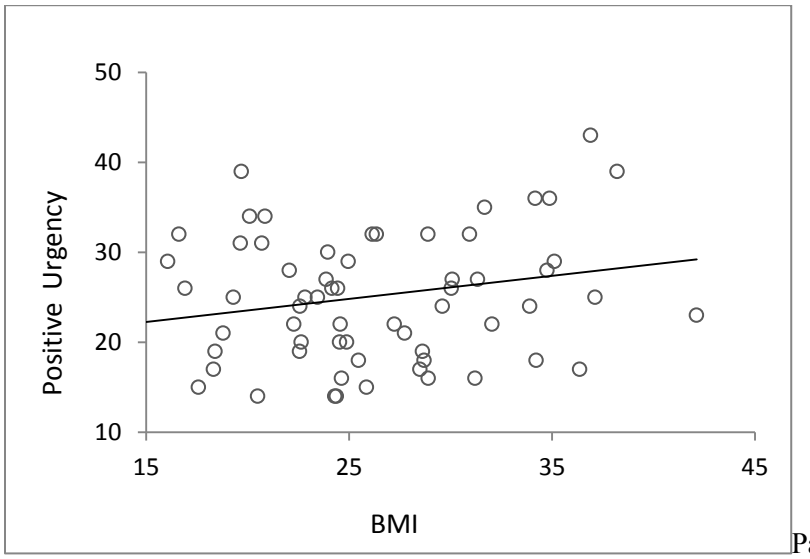
Regression models

Results are presented in Table 4. Age only predicted scores on lack of perseverance. The block including personality traits (SR and SP) significantly predicted scores on the impulsivity dimensions of sensation seeking, lack of premeditation, positive and negative urgency (SR was the main predictor of all models with the exception of the one on lack of premeditation predicted by both SR and SP), but failed to predict performance on the Stroop test. Inclusion of BMI significantly increased the predictive capacity of age and personality traits on the impulsivity dimensions of positive and negative urgency, and on performance in the Stroop-switching condition. Figure 1 graphically displays the associations between BMI and each of these variables.

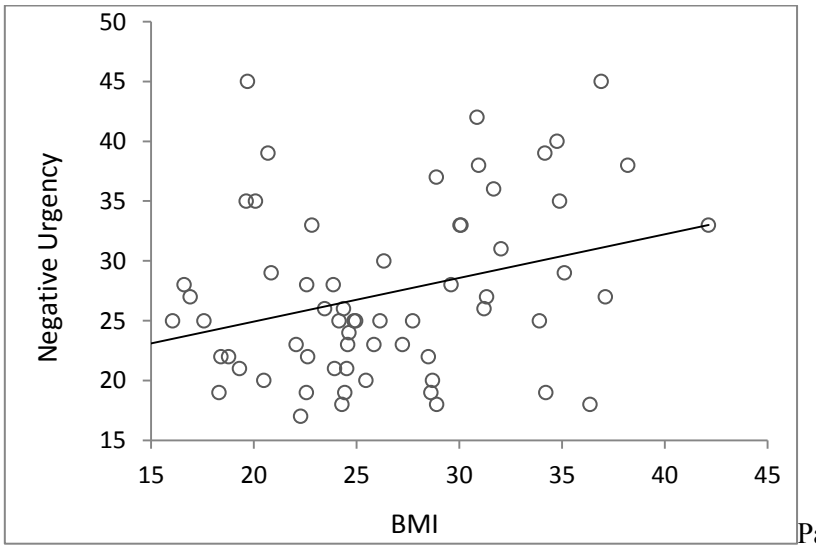
Table 4. Multiple regression models testing the association between age, SPSRQ and BMI on UPPS-P and STROOP.

	Age *R² change* (*p*-value)	SP/SR *R² change* (*p*-value)	BMI *R² change* (*p*-value)	Full model *R² adjusted* (*p*-value)	Significant contributors
Impulsivity – UPPS-P					
Negative Urgency	0.014	0.293	0.106	0.374	SR (0.000)
	(0.347)	(0.000)	(0.002)	(0.000)	BMI (0.002)
Premeditation	0.001	0.234	0.11	0.197	SP (0.002)
	(0.848)	(0.000)	(0.350)	(0.001)	SR (0.001)
Perseverance	0.064	0.081	0.002	0.048	Age (0.044)
	(0.044)	(0.066)	(0.737)	(0.044)	
Sensation Seeking	0.010	0.256	0.001	0.229	SR (0.000)
	(0.431)	(0.000)	(0.760)	(0.000)	
Positive Urgency	0.050	0.257	0.049	0.312	SR (0.000)
	(0.075)	(0.000)	(0.039)	(0.000)	BMI (0.039)
CWIT Stroop					
Response Inhibition	0.031	0.023	0.007	-0.003	--
	(0.161)	(0.488)	(0.517)	(0.437)	
Response Switching	0.010	0.044	0.067	0.061	BMI (0.039)
	(0.432)	(0.258)	(0.039)	(0.103)	

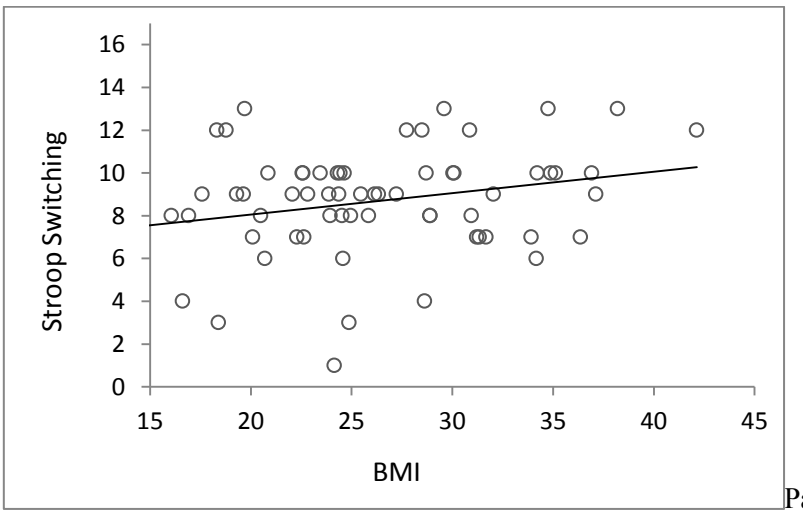
Figure 1. Regression slopes showing significant associations between BMI and Positive Urgency (Panel A), Negative Urgency (Panel B), and Stroop Switching (Panel C).



Panel A



Panel B



Panel C

Discussion

Our findings show that BMI positively predicts levels of positive and negative urgency, and negatively predicts Stroop-switching performance in adolescents with overweight and obesity. SR significantly predicts positive and negative urgency, sensation seeking, and lack of premeditation, but fails to predict cognitive performance in the Stroop test. These findings demonstrate that increases in BMI are specifically associated with elevations in emotion-driven impulsivity and cognitive inflexibility, supporting a dimensional path in which adolescents with excess weight increase their proneness to overindulge when under strong affective states, and their difficulties to switch or reverse habitual behavioral patterns.

Excess weight adolescents, compared with their normal weight peers, had very similar psychological concerns, personality characteristics, and executive control performance. The main significant differences—of medium size—emerged for the traits of SR and sensation seeking, but in both cases excess weight individuals had diminished levels of these traits. Therefore, our findings are not supportive of the "hard" conception of adolescent obesity as a dysfunction characterized by hypersensitivity to reward and disrupted inhibitory control (Volkow et al., 2008, 2011); in fact, the only trait correlated with BMI within the excess weight group was sensitivity to punishment. Conversely, our dimensional approach showed that BMI is significantly associated with increased impulsivity—but only under strong affective states, and poorer cognitive switching. Since sensitivity to punishment and urgency are psychometrically correlated in healthy youths (Cyders et al., 2007), and both have shown significant associations with dysfunctional thought control and compulsivity (Meda et al., 2009; Schmidt, Gay, Ghisletta, & Van der Linden, 2010), our findings

suggest that adolescent obesity is better characterized by negative reinforcing mechanisms triggering habitual behaviors—then difficult to reverse, than by rash-spontaneous impulsivity mechanisms (Dawe & Loxton, 2004). It is interesting to note that this point is straightforward in the case of the link between SP, negative urgency, and compulsivity, but less intuitive to explain the effects of BMI on positive urgency. Taking into account the personality profile of the excess weight group, we believe that this path may be explained in similar terms, because adolescents with excess weight would tend to be constrained (i.e., they are submissive and dependent) until they find themselves in very positive mood, whereby they would feel entitled to overindulge. The overall pattern of increased sensitivity to punishment is consistent to that found in the whole spectrum of eating disorders (Harrison, Treasure, & Smillie, 2011).

The fact that BMI scores predict Stroop- switching but not Stroop inhibition scores is neatly indicative of the notion that flexibility is the main neuropsychological correlate of adolescent excess weight. This finding is in agreement with those of previous studies showing that neurocognitive deficits associated with poor set-shifting and increased perseveration are typical of children and adolescent with excess weight (Cserjési et al., 2007; Maayan et al., 2011; Verdejo-García, Pérez-Expósito, et al., 2010). Nonetheless, there is also evidence of robust deficits in working memory and inhibitory control—taxed with the classic Stroop Color-Word test—in excess weight adolescents having considerably higher BMI levels (mean of 39.86 vs. 29.15 in this study (Maayan et al., 2011)). Altogether, these findings suggest that impaired flexibility is an early cognitive correlate of the disorder (Cserjési et al., 2007), which linearly declines as a function of increased adiposity (Cserjési et al., 2007; Verdejo-García, Pérez-Expósito, et al., 2010); however, the deleterious effects of excess weight on neurocognition may progressively extend to other aspects of executive control as the disorder becomes more severe

(Maayan et al., 2011). Interestingly, flexibility deficits are also found in other eating disorders, including anorexia and bulimia (Tchanturia et al., 2004, 2011), and evidence on the stability of these deficits suggests that it may be a trait or an endophenotype related to eating disorders (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Tenconi et al., 2010; Tchanturia et al., 2011). Complementarily, the available evidence in childhood and adolescent obesity suggest that increased inflexibility may also reflect a transition from impulsive to compulsive states—impulsivity correlates with BMI in 8- to 10- year-old kids but not in adolescents (Pauli-Pott et al., 2010b). This notion would actually give support to proposed parallels between obesity and addiction (Acosta et al., 2008; Volkow et al., 2008). Irrespective of their etiology, flexibility deficits may compromise recovery potential in obesity in a number of ways, including inability to reverse habitual feeding patterns or to change unhealthy lifestyles.

Strengths of this study include the careful selection of the excess weight adolescents, who were matched to their normal weight peers in biochemical and psychological indices; this selection allowed us to elegantly test the neuropsychological assumptions without any medical or psychological confounder. In addition, we used specific well-validated indices of inhibition vs. switching skills, which are regarded as neurocognitive probes of impulsive vs. compulsive behavioral patterns (Dalley et al., 2011), providing a novel approach to the notion that the development of obesity holds several parallels with the neuroadaptations that characterize addiction (Volkow et al., 2008). Relevant shortcomings include the relatively small sample size, which is nonetheless sufficient to implement the regression models we run (Hair, Anderson, Tatham, & Black, 1995), and the lack of naturalistic or psychometric measures of compulsive or binge-like food intake—which may have strengthen the theoretical links we raised. In conclusion, our findings are supportive of a dimensional approach to

adolescent obesity, by which increases in weight and adiposity are associated with less ability to control impulses under strong affects and impaired cognitive flexibility.

Referencias

Las referencias pueden consultarse en el apartado de REFERENCIAS.

CAPÍTULO 4

EFFECTS OF A MULTICOMPONENT BEHAVIORAL INTERVENTION ON IMPULSIVITY AND COGNITIVE DEFICITS IN ADOLESCENTS WITH EXCESS WEIGHT

Delgado-Rico, E., Schmidt Río-Valle, J. S., Albein-Urios, N., Caracuel, A., González-Jiménez, E., Piqueras, M. J., … Verdejo-García, A. (2012). Effects of a multicomponent behavioral intervention on impulsivity and cognitive deficits in adolescents with excess weight. *Behavioural pharmacology*, *23*(5-6), 609–615

Introduction

The prevalence of adolescent overweight and obesity has increased markedly over the last two decades, rapidly reaching epidemic levels (Lee et al., 2011). Conversely, the quest for effective treatment approaches remains unfulfilling, and only multicomponent interventions have shown efficacy for adolescents' weight reduction (McGovern et al., 2008; Wilfley et al., 2007). This is a particularly challenging issue because adolescents represent a particularly vulnerable group in whom the likelihood of developing chronic obesity problems is high (Whitaker et al., 1997) and the motivation to seek and comply with treatment is low (Acosta et al., 2008; Poobalan, Aucott, Precious, Crombie, & Smith, 2010). Hence, there is a need to identify and potentiate active components of these interventions that may increase their power to produce enduring weight changes in adolescents (Kelly & Melnyk, 2008). We reason that these active components should relate to cognitive skills and personality-related individual differences that typically emerge during adolescence, such as inhibitory control and emotion regulation (Nigg, 2000).

In recent years, burgeoning evidence from neuroscience studies has indicated that BMI in adolescents is associated positively with increased activation of brain emotional systems (frontal operculum, insula) (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008) and correlated negatively with the activation of the neural network supporting inhibitory control (several regions of the prefrontal cortex) in response to highly appetizing food stimuli (Batterink et al., 2010). Higher BMI levels are also correlated significantly with emotional aspects of impulsive personality, such as positive and negative urgency – the tendency to commit impulsive acts when feeling good or bad (Delgado-Rico, Schmidt Río-Valle, González-Jiménez, et al., 2012). Furthermore, adolescents with excess weight show enhanced emotional reactivity (Gallant et al., 2010) and a range of

cognitive executive performance decreases in tasks of inhibitory control, flexibility, and decision-making (Verdejo-García, Pérez-Expósito, et al., 2010). These decreases in performance are associated with volumetric reductions in the orbitofrontal cortex (Maayan et al., 2011), a key hub for emotion regulation and impulse control (Bechara, 2005).

Overall, evidence suggests that adolescents with excess weight have a poor balance between (increased) emotional processing and (lower) inhibitory control. This poor balance may relate to increased food procurement and intake during discrete eating episodes (Appelhans et al., 2011; Nederkoorn, Guerrieri, Havermans, Roefs, & Jansen, 2009) but also to more enduring dysfunctional diet patterns leading to weight gain (Anzman & Birch, 2009; Nederkoorn et al., 2010) or to worse treatment prognosis (Nederkoorn et al., 2006). Critically, the impact of these domains may be amplified during adolescence, as this developmental period is inherently characterized by sudden elevations in emotional reactivity and progressive fine tuning of inhibitory control (Brenhouse & Andersen, 2011). Therefore, interventions for emotion regulation and inhibitory control should become important aspects of multicomponent interventions in adolescents, and in the improvement of these domains, should correlate with treatment success.

In this study, we aimed to explore whether training of emotion regulation and inhibitory control (engrained in the broader framework of a multidisciplinary treatment intervention) would produce significant changes in these processes and whether these changes are accompanied by contingent reductions in BMI.

Methods

Design

We used a longitudinal design with two assessments: before and after treatment. We collected baseline measures of the different dimensions of impulsive personality (UPPS-P scale), cognitive performance (letter number sequencing, Stroop and Iowa gambling task), BMI, and the usual biochemical parameters (insulin, basal glucose, triglycerides, and cholesterol). In the week after baseline assessments, we initiated the multicomponent treatment intervention, which lasted for 12 weeks. The same tests (using parallel versions of cognitive performance tests when available) were repeated in the week after completion of the intervention. The study was approved by the Ethical Committee for Research in Humans of the University of Granada; all procedures were conducted in accordance with the Declaration of Helsinki.

Sampling context

Forty-two adolescents with excess weight (14 males and 28 females) participated in our study. The age range was 12–17 years; the mean (±SD) was 14.19 (1.38) years. Their BMI [weight/height^2 (kg/m^2)], as measured at the onset of the study, was 22.06–38.21 and the mean (±SD) BMI was 29.15 (4.50) kg/m^2. All study participants provided a blood sample for a blood test including insulin, basal glucose, triglycerides, and cholesterol. A more detailed description of the sociodemographic and clinical data is shown in Table 1.

Table 1. Descriptive scores for sex, socioeconomic status, age, BMI, and biochemical parameters.

	n	**(%)**
Sex		
Men	14	33.3
Women	28	66.7
SES (Annual Income €)[1]		
0 – 11.533 €	2	5
11.533 – 18.200 €	13	32.5
18.200 – 26.548 €	18	45.0
26.548 – 41.292 €	4	10.0
41.292 – 3.144.000 €	3	7.5
	Mean (SD)	**range**
Age	14.19 (1.38)	12 - 17
BMI	29.152 (4.51)	22.06 – 38.21
Biochemical parameters		
Insulin	16.23 (12.38)	1.5 – 52.5
Basal glucose	86.39 (9.41)	68.0 – 106.0
Triglycerides	96.15 (43.24)	45.0 – 235.0
Total cholesterol	158.85 (26.41)	113.0 – 222.0

Note. SES: Socioeconomic status; BMI: Body Mass Index. [1] Quintiles for SES are defined according to data from the Financial Survey for Spanish Families,http://www.bde.es/webbde/es/estadis/eff/eff.html.

We recruited participants from educational centers and from the Endocrinology Unit of the Hospital 'Virgen de las Nieves' in Granada (Spain). For inclusion in the study, participants had to fulfill the following criteria: (i) age range between 12 and 17, (ii) BMI levels within the range of overweight or obesity according to the International Obesity Task Force criteria defined by Cole et al. (2000), (iii) absence of past/current evidence of medical or psychological disorders, and (iv) at least one of the parents had to be actively involved throughout the treatment process. Parents had to sign an informed consent for the adolescents to participate in the study. They were enrolled in a larger study aimed at testing a novel multi-component behavioral intervention for adolescent excess weight, the aim of which was to alter eating-related lifestyles and improve cognitive-behavioral skills and physical activity (BRAINOBE Study).

Measures

Biometric parameters:

Body mass index. BMI was obtained from direct measures of weight and height (both at study onset and after the intervention) and calculated for each participant as the ratio [weight(kg)/height (m^2)].

Biochemical parameters. Blood tests yielded data for insulin (mU/ml), basal glucose (mg/dl), triglycerides (mg/dl), and total cholesterol levels (mg/dl).

Questionnaire measures of impulsivity. UPPS-P impulsive behavior scale (Whiteside & Lynam, 2001; Spanish version, Verdejo-García, Lozano, et al., 2010). This scale is a 59-item inventory designed to measure five distinct personality pathways to impulsive behavior: negative urgency, lack of perseverance, lack of premeditation, sensation seeking, and positive urgency. Urgency (26 items) refers to the tendency to experience strong impulses under conditions of negative effect (negative urgency – 12 items) or positive effect (positive urgency – 14 items); lack of perseverance (10 items) refers to the 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, sensation seeking (12 items) incorporates two aspects: (a) a tendency to enjoy and pursue activities that are exciting and (b) an openness to trying new experiences that may or may not be dangerous. Each item on the UPPS-P is rated on a four-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.

Neuropsychological assessment:

Letter number sequencing. Wechsler intelligence scale for children (Wechsler, 2003; Spanish version, Corral, Arribas, Santamaría, Sueiro, & Pereña, 2010). Participants are read a sequence in which letters and numbers are combined, and are asked to reproduce the sequence heard, first placing the numbers in ascending order and then the letters in alphabetical order. The dependent variable from this test is the number of correct answers.

Color-word interference test Stroop. Delis–Kaplan executive functions system (Delis et al., 2001). This test consists of four different conditions, each containing 50 items. The first condition presents patches of colors and participants have to name them as quickly and accurately as they can. The second condition presents the words 'red', 'blue', and 'green' printed in black ink and participants are asked to read the words written aloud. The third condition introduces the condition of interference: the words 'red', 'blue', and 'green' are printed in incongruent color inks and participants have to name the color and ignore the word. In the fourth condition, the items are similar to condition three but participants have to switch their response between naming the color of the ink (in most trials) and reading the word (when the item is inside a small box). The main dependent variables from this test are the composite time measures: inhibition versus color naming (time part 3 – time part 1), inhibition/ switching versus combined naming + reading (time part 4) – (time part 1 + 2), and inhibition/switching versus inhibition (time part 4 – time part 3) (Delis et al., 2001).

Iowa gambling task (Bechara et al., 2000). This is a measure of decision-making involving both uncertainty and risk. Participants have to make a series of choices between four decks of cards that yield different reward/punishment contingencies.

Unbeknownst to the participants, two of the decks (A and B) are considered risky (yield high rewards but even higher penalties) and two of the decks (C and D) are considered safe (yield low rewards but even lower penalties). Moreover, two of the decks (A and C) provide constant reward/punishment contingencies, whereas two of the decks (B and D) provide irregular reward/punishment contingencies. The main dependent variable is obtained by applying the formula [(C + D) – (A + B)] to the participants' choices. Positive scores represent the relative preference for the safe advantageous decks, whereas negative scores represent the relative preference for the risky disadvantageous decks.

Multicomponent treatment intervention

The multicomponent intervention was conducted in small groups of 10–12 participants each, and was implemented for 12 consecutive weeks (one session/week) across four different waves (n = 42). The intervention included three intertwined modules: (a) a psychosocial module, (b) a nutritional module, and (c) a physical activity module. The psychosocial module was implemented in weekly workshops dedicated to the training of specific skills including cognitive skills (inhibitory control, planning, and conflict resolution) and affective skills (emotional expression and regulation). The nutritional module consisted of prescription and monitoring of personalized diets designed as a function of sex, age, and BMI z-scores (Moreno et al., 2006). We applied guidelines for caloric restriction of – 10% for BMI SD > 1, – 20% for BMI 1 < SD < 2, – 30% for BMI SD > 3, and – 30% for BMI SD > 4. For all diets, we set a minimum caloric limit of 1500 kcal. Dietary prescriptions were implemented during sessions 2, 5, and 8, corresponding to the prescription of closed diets (3 weeks), supervision and prescription of closed diets with selected meals (3 weeks), and supervision and

prescription of extensive diets (3 weeks), respectively. Monitoring of dietary compliance was con-ducted every week during personal appointments of the participants and their parents with the psychologist and the nutritionist. During these sessions, compliance was monitored through interview and review of meal registries, and supported by counseling on strategies to facilitate adequate observance (Martínez-Gómez et al., 2009). The physical activity module consisted of prescription and monitoring of a personalized physical activity program aimed at achieving the standard minimum physical exercise for this age group – around 1 h/day (Martinez-Gomez et al., 2009; Muñoz et al., 2010). The exercise prescribed consisted of at least 1 h of moderate-to-vigorous intensity aerobic exercise for 3–5 days/week, depending on the individual physical activity level. Energy expenditure was estimated in metabolic equivalent values (Ainsworth et al., 2000) for each activity and the frequency and intensity of the activities of the exercise program (walking, biking, running, swimming, etc.). The energy expenditure range obtained was from 15 to 23 kcal/kg of body weight/week. A more detailed description of the program is shown in Table 2.

Table 2. Detailed description of the multicomponent behavioral intervention: distribution of sessions, and duration, objectives, structure, and attendants for each session.

Session	Duration (min)	Objectives	Structure (min)	Attendants
1	60	Induction		Adolescents and parents
2	150	Prescription of personalized diets and physical activity programs		Adolescents and parents
3	70	Monitoring and planning of physical activity Psychology I: attention. Healthy lifestyles	20 50	Adolescents
4	70	Monitoring of physical activity Psychology II: attentional slips. Self-esteem	20 50	Adolescents
5	130	Monitoring of physical activity Diet adjustments Psychology III: stimulus control and reinforcement management	20 60 50	Adolescents and parents
6	70	Monitoring of physical activity Psychology IV: inhibitory control of behavior and emotions	20 50	Adolescents
7	120	Physical activity: ongoing assessment and adjustment	60	Adolescents and parents
		Psychology V: working memory. Expression and processing of positive and negative emotions	60	Adolescents
8	120	Diet adjustments	60	Adolescents and parents
		Psychology VI: goal planning. Coping with critiques	60	Adolescents
9	70	Monitoring of physical activity Psychology VII: goal achievement: planning, decision-making and monitoring. Social skills: 'Learning to say no'	20 50	Adolescents
10	60	Psychology VIII: relapse prevention: identification/management of 'at risk' situations. Asking for help	60	Adolescents
11	70	Monitoring of physical activity Psychology IX: relapse prevention: problem solution	20 50	Adolescents
12	60	Rehearsal of key points	50	Adolescents and parents

Data analyses

Statistical analyses were implemented on the Predictive Analytics Software SPSS version 18 (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, USA). We first used related-sample t-tests to examine the differences between baseline and post-treatment measures of impulsivity (UPPS-P), cognitive performance (letter number sequencing, Stroop and Iowa gambling task), and BMI. For those measures showing significant differences between baseline and after treatment (treatment-related changes), we calculated standardized 'change scores' by regressing baseline scores over post-treatment scores and saving the standardized residuals. Next, we used linear regression models using 'change scores' of impulsivity and cognitive performance as predictor variables and 'change scores' of BMI as the treatment outcome variable.

Results

Changes in biometrical variables

The results are presented in Table 3. The main treatment outcome variable – BMI – showed a statistically significant reduction after treatment. We also observed a significant decrease in cholesterol levels.

Table 3. Descriptive scores and statistics of BMI and biochemical parameters (insulin, basal glucose, triglycerides, and total cholesterol) pretreatment and post-treatment measures.

	Pre-treatment		**Post-treatment**			
	Mean (SD)	**Range**	***Mean (SD)***	***Range***	***t***	***Cohen's d***
BMI	29.36 (4.50)	22.06–38.21	27.31 (4.41)	20.28–37.44	8.438*	0.5
Biochemical parameters						
Insulin	16.23 (12.38)	1.5–52.5	13.99 (6.95)	3.4–42.6	1.155	0.2
Basal glucose	86.39 (9.41)	68.0–106.0	87.56 (8.67)	69.0–108.0	– 0.529	0.1
Triglycerides	96.15 (43.24)	45.0–235.0	96.10 (40.83)	46.0–232.0	0.006	0
Cholesterol	158.85 (26.41)	113.0–222.0	149.39 (24.89)	108.0–199.0	2.568*	0.4

*$p < 0.01$.

Changes in impulsivity and cognitive measures

The results are presented in Table 4. In relation to impulsivity levels, we found a significant reduction in negative urgency scores (UPPS-P). In relation to cognitive performance, there were significant improvements in performance on Stroop response inhibition and switching indices.

Table 4. Descriptive scores and statistics of impulsivity measures (UPPS-P) and outcome neuropsychological variables (letter number sequencing, Stroop and Iowa gambling task) pretreatment and post-treatment measures.

	Pre-treatment		**Pos-treatment**			
	Mean (SD)	**range**	***Mean (SD)***	**range**	***t***	***Cohen's d***
UPPS-P						
NU	27.68 (7.47)	18-45	25.03 (7.45)	13-41	2.642*	0.35
Pre	25.20 (5.79)	14-44	24.98 (5.22)	16-42	0.294	0.04
Per	21.53 (4.19)	13-30	21.18 (5.17)	12-36	0.396	0.07
SS	30.30 (7.27)	13-42	32.33 (7.70)	17-48	-1.822	0.27
PU	25.53 (8.40)	14-51	23.90 (9.34)	14-56	1.057	0.18
LNS	10.33 (2.99)	4-16	10.18 (2.92)	3-16	0.386	0.05
Stroop						
RI	11.57 (1.99)	7-16	11.72 (1.47)	9-15	-0.506	0.09
RIS	9.67 (2.14)	4-16	10.40 (2.02)	6-14	-2.308*	0.35
RS	9.00 (2.32)	1-13	9.15 (1.70)	3-13	-0.431	0.07
IGT	-0.48 (19.21)	-52-60	8.15 (34.79)	-96-80	-1.791	0.32

Total scores are reported for UPPS-P and Iowa gambling task. Scaled scores are reported for letter number sequencing and Stroop. IGT, Iowa gambling task, ABCD version; LNS, letter number sequencing; NU, negative urgency; Per, lack of perseverance; Pre, lack of premeditation; PU, positive urgency; RI, response inhibition; RIS, response inhibition and switching; RS, response switching; SS, sensation seeking; Stroop, color-word interference test Stroop; UPPS-P, UPPS-P impulsive behavior scale. *$p < 0.05$.

Association between changes in impulsivity and cognition and body mass index reductions

The results are presented in Table 5 and Figs 1 and 2. The models were set using the change scores of impulsivity and cognition as predictors, and the BMI change as the dependent variable; this modeling fits with the assumption that impulsivity and cognition reflect processes targeted during the intervention, whereas BMI reductions represent the main treatment outcome. We observed that change scores of negative urgency (UPPS-P) predicted change scores of BMI; greater reductions of negative urgency predicted greater reductions of BMI (Fig. 1). In relation to cognitive performance, we observed that change scores of Stroop response inhibition and switching predicted change scores of BMI; in this case, greater improvements on Stroop performance predicted greater reductions in BMI (Fig. 2).

Table 5. Standardized residuals scores impulsivity measures (UPPS-P) and outcome neuropsychological variables (letter number sequencing, Stroop, and Iowa gambling task) on change score BMI using standard regression models.

	F	*p*	R^2 adjusted
UPPS-P (total score)			
Negative urgency	6.086	0.02*	0.11
Lack of premeditation	0.158	0.69	– 0.02
Lack of perseverance	1.147	0.29	0.00
Sensation seeking	0.760	0.39	– 0.01
Positive urgency	2.950	0.09	0.05
Letter number sequencing (scaled score)	1.069	0.31	0.00
Stroop (scaled score)			
Response inhibition	5.049	0.03*	0.09
Response inhibition and switching	8.836	0.00*	0.17
Response switching	3.202	0.08	0.05
Iowa gambling task (total score)	0.149	0.70	– 0.02

Stroop, color-word interference test stroop; UPPS-P, UPPS-P impulsive behavior scale. *$p < 0.05$.

Fig. 1. Association between pre-treatment and post-treatment changes in negative urgency and changes in BMI.

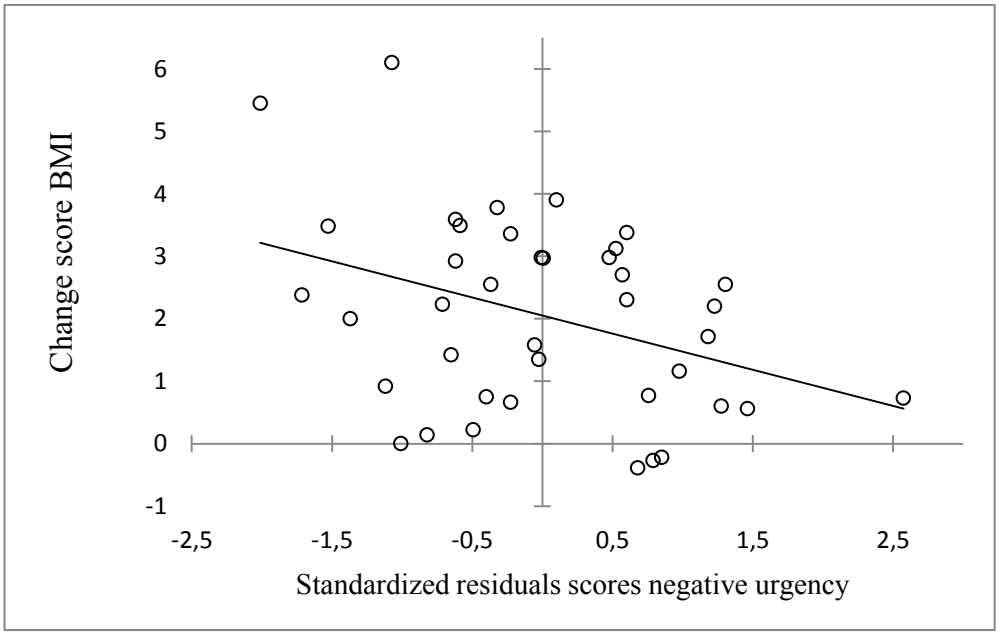
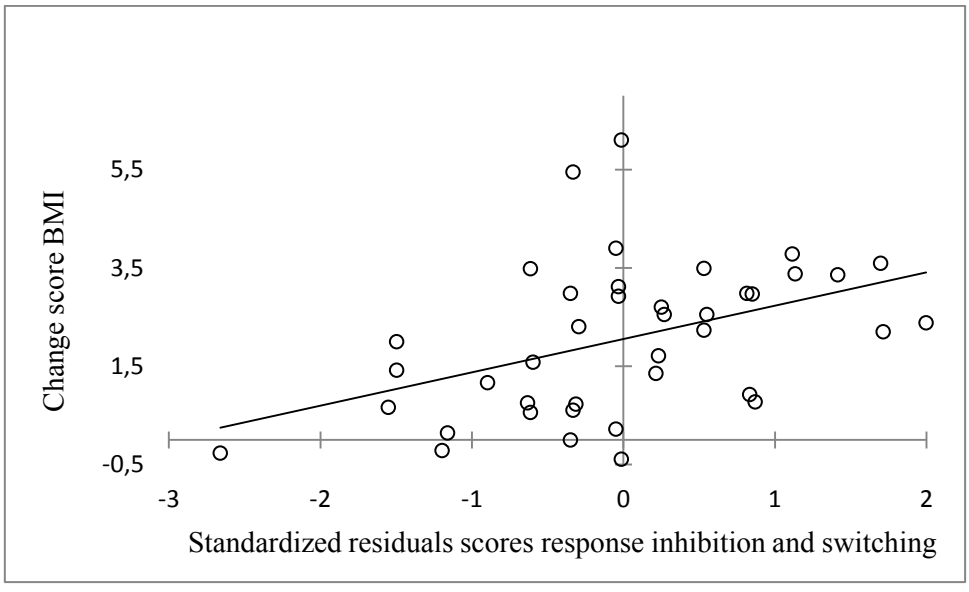


Fig. 2. Association between pre-treatment and post-treatment changes in Stroop-indexed inhibitory control and changes in BMI.



Discussion

Our data showed that the multicomponent behavioral intervention produced significant medium-sized effects on BMI loss, accompanied by a significant decrease in cholesterol levels. This finding is in agreement with the results from previous meta-analyses yielding a modest beneficial effect of combined lifestyle interventions on adolescent weight loss (McGovern et al., 2008; Wilfley et al., 2007). In the quest for active components of the intervention that may predict individual differences in treatment success, we found that those adolescents showing greater reductions in negative-emotion-driven impulsivity (negative urgency) and greater improvement of cognitive inhibitory control skills also showed greater loss of adiposity. However, other cognitive skills, such as working memory or decision-making, did not change during treatment. Overall, these findings support our main assumption that changes in inhibitory control and emotional regulation are associated with better outcomes of adolescent obesity treatment. We speculate that the basis for this association is that a better balance between emotional reactivity and impulse control may favor better achievement of weight control strategies and ultimately BMI loss. However, we acknowledge that the correlational nature of our study precludes us from inferring causality and that alternative accounts (e.g. BMI loss facilitates inhibitory control and emotion regulation) are also plausible.

The results on the dimension of negative urgency are consistent with basic findings linking increased trait impulsivity with excess weight among children and adolescents (Fields, Sabet, Peal, & Reynolds, 2011; van den Berg et al., 2011). They are also in agreement with clinical findings showing that lower levels of trait self-control and higher levels of emotional eating powerfully predict a lower ability to lose weight

during behavioral interventions in adults (Blair, Lewis, & Booth, 1990; Crescioni et al., 2011). More specifically, those aspects of impulsivity that are strongly linked to motivational drives (sensitivity to reward and punishment) and emotional regulation (negative urgency) seem to be particularly predictive of excessive food intake and excess weight problems (Jansen et al., 2009; Mobbs et al., 2010). Critically, these traits are sensitized during adolescence, which is characterized by sudden elevations in emotional reactivity but still immature inhibitory control (Brenhouse & Andersen, 2011). Therefore, we reason that negative urgency (the dimension of impulsivity more clearly associated with emotion regulation) might be a relevant correlate of clinical outcome in adolescent obesity and a potentially useful target to address during behavioral and pharmacological interventions. In agreement with this notion, evidence suggests that adolescents who seek treatment for overweight problems experience greater loss of control in association with sensitized emotional states, such as stress or anxiety (Goossens et al., 2009). Furthermore, emotional control problems during adolescence predict long-term stability of weight problems and the emergence of other psychiatric disorders (Patton, Coffey, & Sawyer, 2003). Conversely, the training of this component may significantly improve the outcomes of interventions for adolescent obesity; this notion is supported by recent evidence showing that mindfulness-based training, tapping affective regulation skills, is associated with weight loss in obese adults (Alberts, Mulkens, Smeets, & Thewissen, 2010).

The results also showed that improvement in inhibitory control and shifting skills (Stroop) predicted BMI loss in this sample of excess-weight adolescents. Interestingly, there is evidence that the development of these executive skills (inhibition and shifting) moderates temperamental elevations of emotional reactivity (White, McDermott, Degnan, Henderson, & Fox, 2011), providing a theoretical link between negative

urgency and Stroop findings, and suggesting that the amelioration of inhibitory control skills (through behavioral or pharmacological interventions) may be accompanied by improvements in emotional regulation. Adequate inhibitory control seems to be critical for the successful achievement and maintenance of weight loss; for example, the Stroop interference effect to appetizing food words is reduced among long-term weight-loss maintainers, as compared with obese controls (Phelan et al., 2011). Recent studies have provided evidence of the efficacy of behavioral interventions for reducing inhibitory control deficits in other clinical populations (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011); therefore, future studies should examine the impact of these interventions on weight loss during adolescence. Nonetheless, a recent study showed the paradoxical effects of motor disinhibition overweight loss ability in adolescents: high-impulsive adolescents lost more weight than those who were less impulsive (Pauli-Pott et al., 2010a). This apparent discrepancy may be related to the distinct role of different facets of impulsivity in relation to the clinical problems and their treatment; for example, a certain degree of motor excitability should be a positive factor for adequate treatment engagement. This link can be reflected in our finding that sensation-seeking scores – especially in relation to the search for novel activities – increased in excess-weight adolescents during treatment. However, inadequate control of negative emotions or prepotent action tendencies is more plausibly linked to poorer treatment outcome, as shown here.

Conclusion

We can conclude that changes in negative urgency and inhibitory control accompany changes in BMI loss during a multicomponent intervention for weight loss among

adolescents. Because the design is correlational and we did not use a control group, future studies should clarify whether these associations reflect a causal effect between these variables or just overlapping improvements associated with a third variable (e.g. increases in attention procurement or motivation).

Referencias

Las referencias pueden consultarse en el apartado de REFERENCIAS.

CAPÍTULO 5

BRAIN STRUCTURAL CORRELATES OF REWARD SENSITIVITY AND IMPULSIVITY IN ADOLESCENTS WITH NORMAL AND EXCESS WEIGHT

Moreno-López, L., Soriano-Mas, C., Delgado-Rico, E., Schmidt Río-Valle, J., & Verdejo-García, A. (2012). Brain structural correlates of reward sensitivity and impulsivity in adolescents with normal and excess weight. *PLoS One, 7(11)* e49185.

Introduction

Overweight and obesity are the ultimate consequence of an energy imbalance between consumed and expended calories. Nevertheless, the fact that -in the context of an unlimited access to food- not everyone becomes obese indicates that there are important individual differences in the susceptibility to develop such disorders. Although a number of psychological factors have been proposed to explain the development and maintenance of obesity (Stice, Presnell, Shaw, & Rohde, 2005), in the past few years, the motivational traits associated with reward and punishment sensitivity, and the personality and neuropsychological dimensions associated with impulse control, have been highlighted as relevant modulators of such susceptibility (Dawe & Loxton, 2004; Ziauddeen et al., 2012) . The impact of these factors on eating behaviour seems to be particularly influential during adolescence (Delgado-Rico, Schmidt Río-Valle, González-Jiménez, et al., 2012; van den Berg et al., 2011), a developmental period in which both motivational tendencies and impulse control skills strongly modulate goal-directed behaviour (Ernst & Fudge, 2009).

The study of the brain structures associated with these motivational, personality and neuropsychological variables in obese adolescents could provide more sensitive information about excess weight during adolescence, since regional brain anatomy indices may be considered a more stable measurement ultimately linked to both personality and cognitive modulators associated to the development of particular disorders (Whittle, Allen, Lubman, & Yücel, 2006). Previous evidence from structural imaging studies have revealed that obese adolescents have lower total gray matter (GM) volumes and reduced regional GM volumes in the orbitofrontal cortex compared to lean controls (Maayan et al., 2011; Yokum et al., 2012). Moreover, in the Yokun et al.

(2012) study, higher body mass indices (BMIs) were correlated to volume changes in brain regions involved in reward processing (striatum), memory (middle temporal/parahippocampal gyri), and somatosensory processing (rolandic operculum), whereas reduced regional GM volumes in the prefrontal cortex correlated with steeper rates of BMI increase at 1-year follow-up. Furthermore, Maayan et al. (2011) found that obese adolescents were characterized by increased trait disinhibition scores and poorer cognitive control, and that both features correlated with the reduced GM volumes in the orbitofrontal cortex. These findings indicate that volumetric brain measures are useful to characterize the neurobiological underpinnings of adolescent obesity, and that brain structural volumes are associated with both disease-specific features (e.g., BMI) and impulsive personality and cognitive control functions.

Such findings are broadly in agreement with the results from functional imaging studies in obese adolescents and adults, in which these regions seem to play different roles. For example, during the processing of food rewards striatal activation is decreased whereas activations of prefrontal and somatosensory regions are increased in obese adolescents (Stice et al., 2008, 2011). There is also evidence of increased resting activity in the somatosensory cortices of obese adults (Wang et al., 2002). Moreover, the hippocampus is selectively engaged during gastric stimulation and this activation correlates with emotional eating and lack of control in obese adults (Wang et al., 2006). Such results have led to hypothesize that decreased striatal functioning and increased somatosensory functioning may be associated with increased reward sensitivity in obese individuals, whereas increased hippocampal and prefrontal reactivity may relate to the balance between the emotional appeal of food and the cognitive control of eating behavior (Stice et al., 2008; Wang et al., 2002, 2006)

In this study we used magnetic resonance imaging (MRI) and voxel based morphometry (VBM) procedures to assess regional brain anatomy in adolescents with excess weight. The aim of the study was twofold: firstly, to detect regional GM volume differences between adolescents with excess weight and adolescents with normal weight, and secondly, to examine possible differences in the way reward and punishment sensitivity, impulsive personality and cognitive control relate to regional GM volumes in both groups. We performed both a region of interest (ROI) and a whole-brain analyses approach. The ROIs were selected based on previous evidence of their involvement in adolescent obesity, and included the prefrontal cortex, the somatosensory cortices, the medial temporal lobe (including hippocampus), and the striatum. In agreement with previous evidence, we hypothesized that adolescents with excess weight will have decreased regional GM in the prefrontal cortex, whereas regional volumes of the striatum and the somatosensory regions will be related to reward sensitivity, and regional volumes of the prefrontal cortex will correlate with impulsivity and cognitive control.

Methods

Participants

Fifty-two adolescents (12-17 years old) participated in the study. The participants were initially classified as adolescents with normal weight (n=16, mean BMI=20.26, SD=2.8), overweight (n=16, mean BMI=24.85, SD=1.42) or obesity (n=20, mean BMI=31.46, SD=2.91) according to their BMI following the International Obesity Task Force (IOTF) criteria defined by Cole et al. (2000). However, since we did not find significant differences between the excess weight groups (overweight vs. obesity) in

any of the psychological or imaging variables assessed, we decided to merge these two groups in a single "excess weight group". Participants were recruited through educational centers and the endocrinology service of the hospital "Virgen de las Nieves" in Granada (Spain). Selection criteria were: (i) age between 12-17 years old, (ii) absence of a positive eating disorder history (Eating Disorder Inventory, EDI-2) (Garner, 1998), (iii) absence of personality disorders assessed by the Millon Adolescent Clinical Inventory (MACI) (Aguirre, 2004), and (iv) absence of past history or current existence of relevant medical problems (based on clinical history and a blood test). For both groups, evidence of significant abnormalities on MR images, contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects) and history of loss of consciousness (LOC) for longer than 30 minutes or LOC with any neurological consequence were also exclusionary.

This study was approved by the Ethics Committee of the University of Granada. All subjects and their parents provided written informed consent before participating in the study.

Instruments and assessment procedures

Assessments were conducted across two independent sessions. During the first session we administered the personality and cognitive measures (see descriptions below), together with a battery of cognitive tests whose results will be reported separately. The second session involved the MRI scanning, which lasted approximately 15 minutes.

Measure of reward and punishment sensitivity. Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ): This questionnaire is a self-report measure made up of 48 items, half of which assess the participant's appetitive

motivational system, or reward sensitivity, and the other half the avoidance motivational system, or punishment sensitivity (Torrubia et al., 2001). The reward and punishment sensitivity scales are reported to show adequate internal consistency, as well as convergent, construct and discriminate validity (Caseras, Àvila, & Torrubia, 2003).

Measure of impulsivity. UPPS-P Scale (Whiteside & Lynam, 2001; Verdejo-García, Lozano, 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-P scale (Whiteside & Lynam, 2001); the fifth dimension has been included on the basis of recent work by Cyders et al. (2007), and Smith et al. (2007). Sensation seeking (12 items) incorporates two aspects: 1) a 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 it; and finally urgency 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-P 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.

Measure of inhibitory control. Color-Word Interference Test–Stroop (Delis–Kaplan Executive Functions System) (Delis, et al., 2001): The test consists of three different parts, each containing 50 items. Part 1 (Colour Naming) presents patches of colors and

participants have to name them as quickly and accurately as possible. Part 2 (Reading) presents the words "red", "blue" and "green" printed in black ink, and participants have to read the words aloud. Part 3 (Inhibition) introduces the interference effect: the words "red", "blue" and "green" are printed in incongruent colors, and participants have to name the color and ignore the word. The main dependent variable derived from this test was Inhibition (time to complete Part 3 – time to complete Part 1).

MRI acquisition and pre-processing

Participants were scanned on a 3T whole body MRI scanner (Phillips Achieva X-series) operating with an eight-cannel 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 mm^2, 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 GM; normalize GM segments (using DARTEL normalization) to a GM template in MNI space; modulate normalized GM images with the Jacobian determinants (derived from the flow-fields of 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).

Data analysis

Measures of reward/punishment, impulsivity and inhibitory control

We first analyzed the assumption of normal distribution of dependent variables using Kolgomorov-Smirnov tests. Likewise, we also assessed the homogeneity of variances between the study groups by means of Levene's tests. Both assumptions were met and therefore we conducted independent-sample t-tests to examine between-group differences in reward/punishment sensitivity, impulsivity and inhibitory control using SPSS 15.0 for Windows (SPSS Inc., Chicago IL). Significance threshold was set at $p<0.05$.

Image analysis

GM differences between normal weight and excess weight groups

The general linear model was used to conduct between-group voxel-wise comparisons within SPM8. Group differences in regional GM volumes were tested using both a ROI and a whole-brain approach. Regarding ROI analyses, the ROIs selected were the orbitofrontal cortex, the dorsolateral prefrontal cortex, the somatosensory cortices (including SI and SII), the medial temporal lobe, and the striatum (all regions were assessed bilaterally). We used the WFU Pickatlas (Homack, Lee, & Riccio, 2005) to delineate these regions and create image masks that were used to restrict voxel-wise analyses to the region of interest (thus applying Small Volume Correction (SVC) procedures). In these analyses, the total volume of GM (TVGM) was modeled as a linear confound to account for global volume variability, and although study groups did not significantly differ in gender, to fully discard a potential impact of the apparent gender imbalance between our study groups, we also included this variable as a confounding covariate. Regarding whole brain analyses, we used the same

statistical model, although the analyses were not restricted to any particular region. Significance threshold was set at $p<0.05$ after family-wise error (FWE) correction for multiple comparisons across the region of interest ($pFWE\text{-}SVC<0.05$) or across the whole brain ($pFWE<0.05$).

Correlation analyses with personality and neuropsychological scores

Correlations between regional GM volumes and the scores of the different scales were also assessed within SPM8 by means of independent sample t-tests, in where the score of interest was modeled in interaction with the variable group (excess weight vs. normal weight participants). Confound variables and the significance thresholds were the same as above. Likewise, we also applied a ROI approach followed by a whole-brain analysis. Correlations were voxel-wise assessed within each group, and regions where significant findings were detected were further investigated to ascertain the existence of a between-group interaction in the pattern of correlations; that is, to verify that correlations were uniquely present in one of the study groups.

Results

Sample characteristics

The participants' demographic characteristics – classified as normal weight vs. excess weight – are summarized in Table 1. The excess weight and normal weight groups were statistically matched on gender, age, years of education and socioeconomic status. As expected, relative to normal weight participants, excess weight participants had significantly greater weight ($t_{50}= -5.385$, $p<0.005$) and BMI ($t_{50} = -7.371$, $p<0.005$).

Table 1. Sociodemographic and biometric characteristics of study subjects.

	Normal weight (n=16)	**Excess weight (n=36)[a]**	**Test**
Age (years)	14.13 (1.36)	14.22 (1.4)	(t_{50} = -0.162, 0.872)
Years of education	10.13 (1.36)	10.19 (1.45)	(t_{50} = -0.162, 0.872)
Gender (male/female)	7/9	10/26	(x^2 = 1.284, 0.257)
SES (annual income €)[b]			(x^2 = 6.400, 0.171)
0 – 11.533 €	3	2	
11.533 – 18.200 €	2	11	
18.200 – 26.548 €	5	17	
26.548 – 41.294 €	3	2	
41.294 – 5.585.000 €	2	3	
Height	161.82 (9.87)	161.82 (7.55)	(t_{50} = 0.001, 0.999)
Weight	53.33 (11.02)	75.19 (14.45)	(t_{50} = -5.385, 0.000)
BMI[c]	20.26 (2.8)	28.53 (4.07)	(t_{50} = -7.371, 0.000)

[a] The excess weight group is composed of participants originally classified as having overweight (n=16) or obesity (n=20) according to the International Obesity Task Force criteria; [b] SES: Socioeconomic status. Quintiles for SES are defined according to data from the Financial Survey for Spanish Families, http://www.bde.es/webbde/es/estadis/eff/eff.html; [c] BMI: Body mass index.

Reward/punishment sensitivity, impulsivity and inhibitory control measures

There were no significant between-group differences in any of the measurements assessed (Table 2).

Table 2. Between-group comparison of impulsivity and SPSRQ scores.

	Normal weight (n=16)	Excess weight (n=36)	Test
SPSRQ[a]			
Reward sensitivity	11.25 (5.42)	9.28 (4.27)	(t_{50} = 1.414, 1.972)
Punishment sensitivity	11.06 (4.77)	9.47 (5.02)	(t_{50} = 1.071, 1.59)
UPPS-P			
Sensation seeking	32.94 (6.5)	28.94 (7.19)	(t_{50} = 1.414, 1.972)
Lack of perseverance	23.69 (5.3)	21.75 (4.34)	(t_{50} = 1.071, 1.59)
Lack of premeditation	26.63 (5.35)	25.58 (5.91)	(t_{50} = 1.414, 1.972)
Negative urgency	26.38 (7.59)	26.53 (7.1)	(t_{50} = 1.071, 1.59)
Positive urgency	24.25 (7.02)	24.36 (8.11)	(t_{50} = 1.414, 1.972)
Stroop			
Inhibition	12.25 (2.35)	11.75 (2)	(t_{50} = .790, 0.433)

[a] SPSRQ: Sensitivity to Punishment and Sensitivity to Reward Questionnaire.

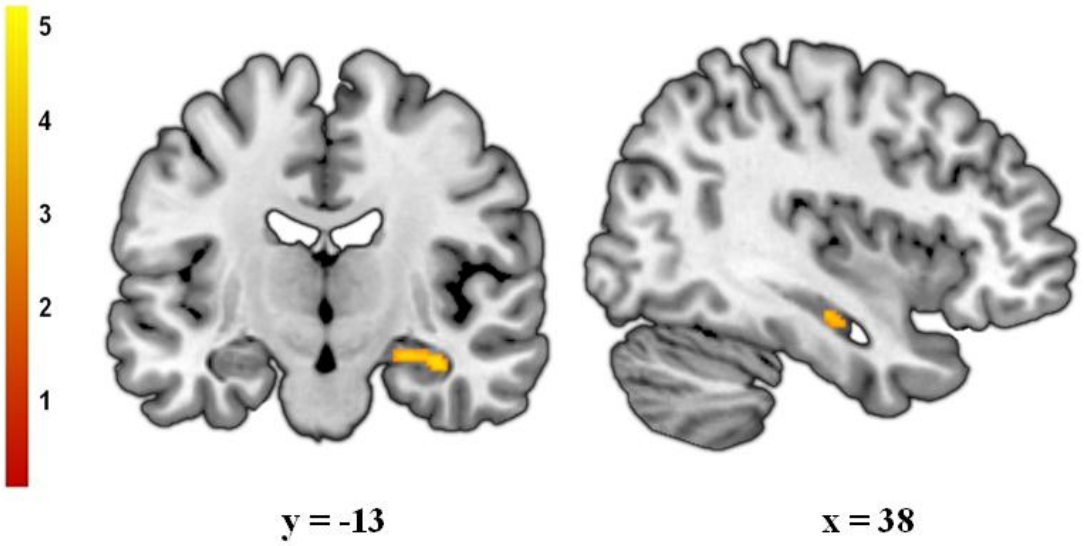
Image analyses

Regional GM differences between normal weight and excess weight groups

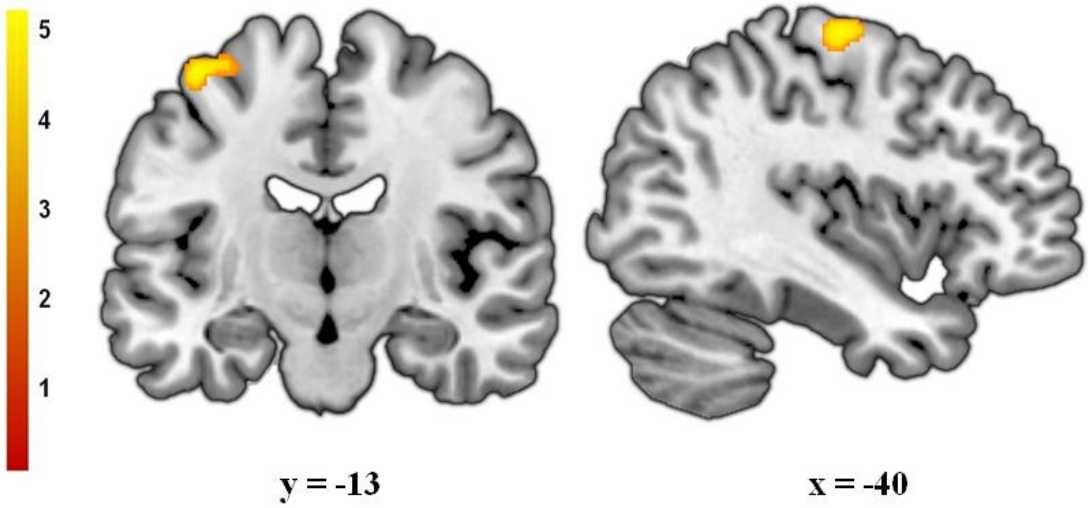
ROI analyses reported a significant volume increase in the right hippocampus of excess weight participants in comparison to normal weight subjects (Figure 1). Regarding the whole-brain analyses, there were no significant between-group differences at pFWE<0.05. Nevertheless, at a more lenient significance threshold of p<0.001 (uncorrected, k>250 voxels), we found a significant volume increase in the left precentral region of normal weight subjects (see Supplementary Figure 1). In addition, in order to further investigate the relationship between BMI and regional GM volumes,

we also correlated BMI values against voxel-wise GM volumes, finding no results at a corrected statistical threshold beyond those observed in the qualitative comparisons.

Figure 1. Clusters of significant gray matter volume increase in excess weight compared with normal weight subjects.



Supplementary Figure 1.



Correlation analyses with personality and neuropsychological scores

Regarding ROI analyses, we found significant correlations between regional GM volumes and the scores of the behavioral tests only in normal weight participants. On the one hand, reward sensitivity and UPPS-P positive urgency scores were negatively associated with the GM volume of the left secondary somatosensory cortex (SII) in control subjects (Table 3 - Figures 2 and 3), whereas these correlations were not observed in the excess weight group. No further correlations were observed with the other personality dimensions. On the other hand, we observed a significant positive correlation between the inhibition score derived from the Stroop test and the volume of the left dorsolateral prefrontal cortex (Table 3 and Figure 4). Again, this correlation was not observed in excess weight participants. No further results were observed in whole-brain analyses.

Table 3. Correlations of SPSRQ, impulsivity and inhibitory control scores with brain anatomy in normal weight subjects.

Anatomical region	K	T	pFWE-SVC<0.05	x	y	z
SPSRQ – Reward sensitivity						
Negative Correlation						
SII L[a]	267	4.51	0.028	-60	-7	11
UPPS-P – Positive urgency						
Negative correlation						
SII L	260	4.89	0.010	-63	-7	15
Stroop – Inhibition						
Positive correlation						
DLPFC L[b]	498	5.01	0.006	-61	6	24

[a]SII L, left secondary somatosensory cortex; [b]DLPFC L, left dorsolateral prefrontal cortex. Significant peaks are given in MNI coordinates. The corresponding anatomical names were obtained using the aal toolbox for SPM8.

Figure 2. Between-group interaction between regional gray matter volume and reward sensitivity.

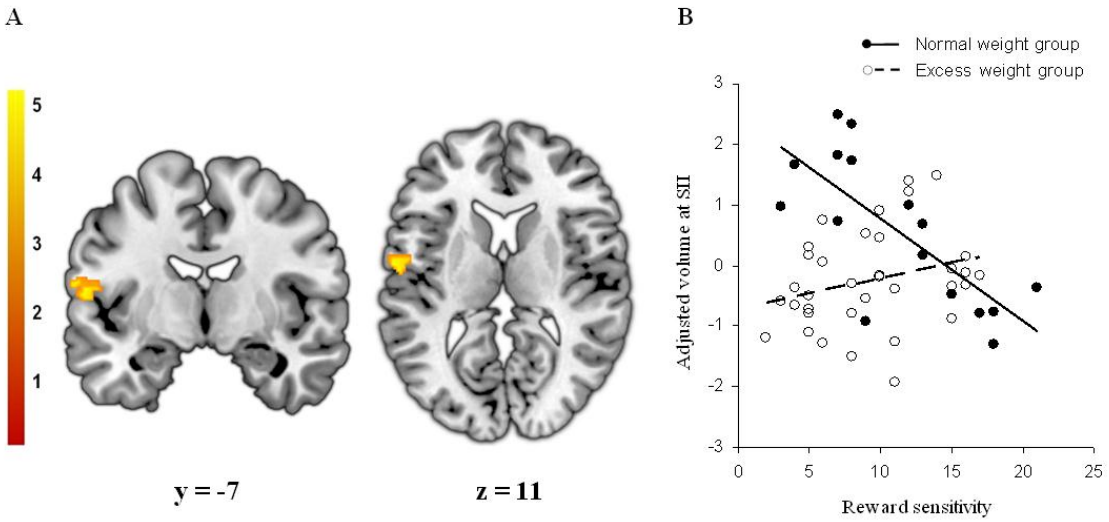


Figure 3. Between-group interaction between regional gray matter volume and positive urgency.

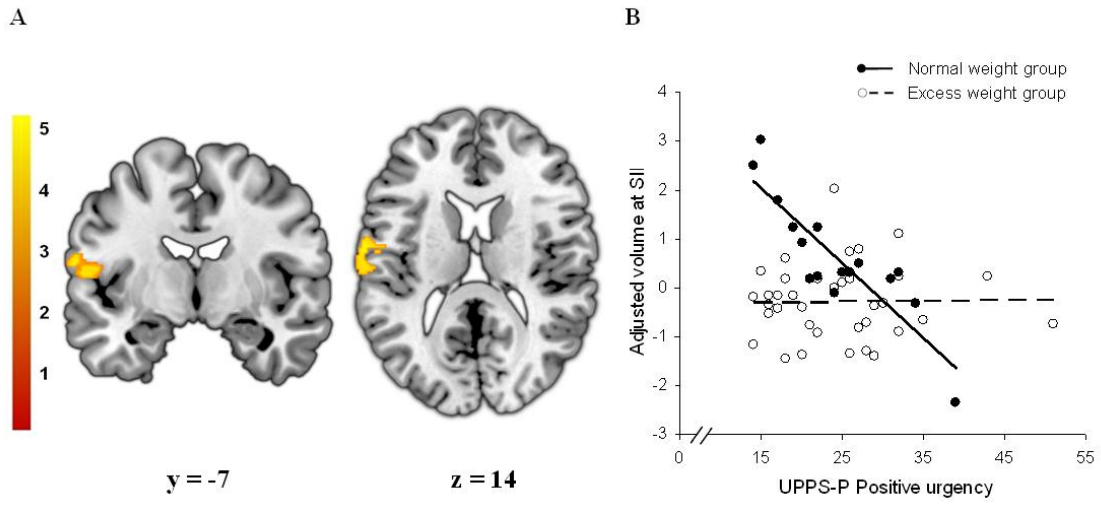
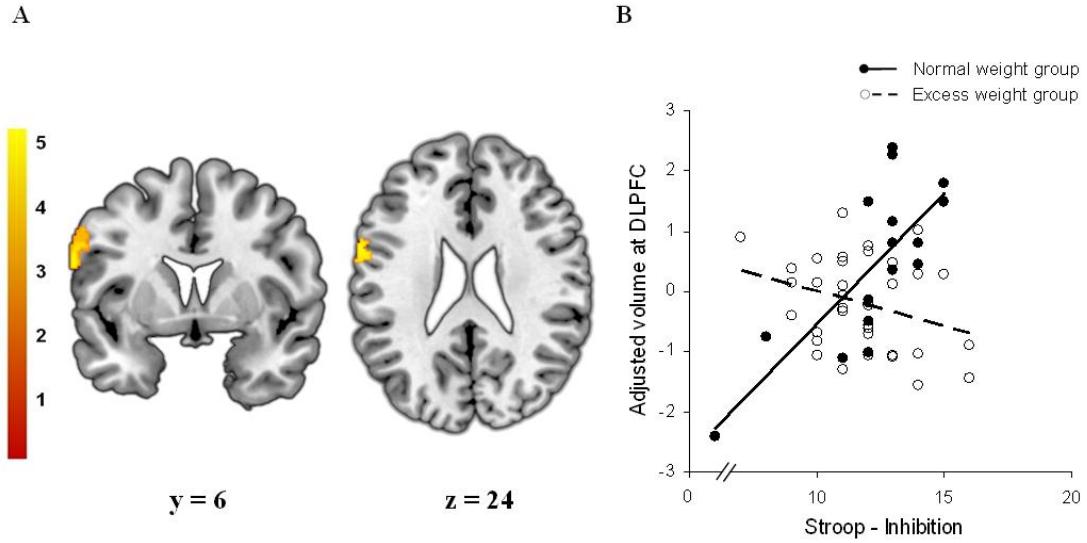


Figure 4. Between-group interaction between regional gray matter volume and response inhibition.



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Discussion

In this study we aimed to examine voxel-wise differences in regional GM volume between excess weight and normal weight adolescents, and to explore differences in the way reward and punishment sensitivity, impulsivity and inhibitory control related to regional GM volumes in both groups. In partial agreement with initial hypotheses, we found that adolescents with excess weight (the combined group of overweight and obese participants) have structural abnormalities in one predefined ROI, the right hippocampus. Specifically, the excess weight adolescents had increased right hippocampal GM regional volumes compared to lean controls. Furthermore, reward sensitivity and positive urgency scores negatively correlated with left SII regional volumes in lean controls but not in excess weight adolescents. Similarly, Stroop performance scores positively correlated with left dorsolateral prefrontal cortex regional

volumes in controls but not excess weight adolescents. In contrast with initial assumptions, we did not find significant alterations in the striatum or the orbitofrontal cortex, or different associations between these regions and personality and cognitive measures.

The finding of an increased right hippocampal volume in excess weight adolescents is in fitting with the role of this region in the processing of motivational signals associated with appetite (Maldjian, Laurienti, Kraft, & Burdette, 2003). For example, functional imaging studies have shown that right hippocampal activation is significantly associated with food cues-induced insulin release in obese adolescents (Tracy, Jarrard, & Davidson, 2001) and with direct gastric stimulation in obese adults (Wang et al., 2006). Furthermore, the gastric stimulation-induced increases of hippocampal activity were associated with scores of emotional eating and lack of control (Wang et al., 2006), supporting the role of this region in the incentive motivation and cognitive control of eating behavior in obesity.

Correlation analyses showed that the regional volume of SII was associated with reward sensitivity and positive urgency in lean controls but not in excess weight adolescents. Within SII, the specific region of correlation with reward sensitivity and positive urgency was the subcentral gyrus, or Brodmann area 43, also known as area OP4 (Wallner-Liebmann et al., 2010). This area occupies the most lateral aspect of SII, adjacent to the representation of the oral cavity within the primary somatosensory cortex, and thus it is mainly involved in the processing of somatosensory information, including the sensory input relevant for gustatory awareness (Eickhoff, Amunts, Mohlberg, & Zilles, 2006, 2010). Interestingly, somatosensory processing regions have been associated with reward sensitivity in healthy individuals with high scores in this

personality trait (Veldhuizen et al., 2011). Moreover, somatosensory regions consistently show increased activations towards food cues in both adolescents at risk of developing obesity (Stice et al., 2008) and in obese adolescents (Stice et al., 2008). The fact that the negative associations of personality measures with SII volume were only observed within healthy controls would suggest that in excess weight subjects the normal function of somatosensory regions in relation to reward sensitivity and impulsivity is missed or hijacked by disease-specific mechanisms. The latter notion would be similar to what is found in addiction, in which drug craving rewires the function of stimulus-valuation and response control brain regions (Shishida, Hashizume, Onoda, Okamoto, & Yamawaki, 2006), putatively modifying the link between trait impulsivity and brain structure (Garavan et al., 2000). In this case, the function of SII may be rewired by the persistent activation of somatosensory regions during anticipation or encoding of sensory and hedonic aspects of palatable food, as shown by fMRI studies (Stice et al., 2008, 2011; Moreno-López, Catena, et al., 2012).

Unlike previous studies (Maayan et al., 2011; Yokum et al., 2012) we did not find significant structural abnormalities in the prefrontal cortex of excess weight adolescents. However, we found a positive association between cognitive inhibitory control (Stroop performance) and a cluster located in the left dorsolateral prefrontal cortex of normal weight subjects. This region has been shown to mediate the link between aerobic fitness and response inhibition in ageing adults, suggesting a link between physical fitness, production of neurotrophic agents (including insulin-like growth factor-1) and protection of higher-order executive skills (Stoeckel et al., 2008). Such region may play a similar role in the developing adolescent brain, and thus in terms of individual differences in response inhibition in normal weight adolescents, which is once again absent in the excess weight group. In agreement with such a notion, over-activity of this

region during response inhibition has previously been observed in adolescents compared to healthy adult groups (Weinstein et al., 2012). More research is needed to understand why this link is altered in excess weight adolescents, but the impact of adiposity on vascular health and insulin production may particularly impact frontal brain regions and executive functions (Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010).

The potential limitations of our study include the decision to merge the overweight and obese subgroups, the lack of significant behavioral performance differences, and the lack of significant volumetric differences in a priori regions of interest such as the orbitofrontal cortex and the striatum. The first decision was based on the observation that comparisons between obese and overweight subgroups failed to yield any significant findings. In addition, the study of dimensional measures of adiposity (BMI) did not either add significant results beyond the categorical diagnosis comparison (normal vs. non normal BMIs). Therefore, we consider that these findings actually reflect that the association between BMI and brain anatomy is better captured by a qualitative analysis comparing participants with vs. without clinical problems related to excess weight. With regard to the lack of behavioral differences and of GM differences in the prefrontal cortex and the striatum, we acknowledge that these negative results are somehow opposed to previous findings, and may reflect the fact that our sample was composed of less severe individuals than those of previous studies including higher BMIs and individuals with other comorbidities (Maayan et al., 2011; Willeumier, Taylor, & Amen, 2011). In addition, it might be also argued that the unequal number of voxels included in the different ROIs assessed might have favored the detection of significant differences in smaller regions, such as the medial temporal lobe (in opposition to orbitofrontal or dorsolateral prefrontal cortices, for instance). In any case,

we also performed a whole-brain analysis, and, even at an uncorrected significances threshold, we only observed a volume decrease in the left precentral region of excess weight participants, but no findings were observed in the prefrontal cortex or the striatum.

In summary, here we report that, in comparison to lean controls, adolescents with excess weight (including participants meeting criteria for overweight and obesity) have increased right hippocampal volume, a brain region related to emotional and motivational aspects of food intake. Somewhat unexpectedly, personality and cognitive measures were mainly correlated with the volume of the second somatosensory region, although significant findings were also observed in the dorsolateral prefrontal cortex in relation to measures of inhibitory control. In any case, the lack of significant differences in the behavioral measures and the fact that correlation analyses grasped some of the potential correlates of adolescent obesity in the prefrontal cortex supports our initial assumption that the assessment of the correlations between neuroimaging and behavioural data is more sensitive than any of these two approaches on its own.

Referencias

Las referencias pueden consultarse en el apartado de REFERENCIAS.

CAPÍTULO 6

DECREASED INSULAR AND INCREASED MIDBRAIN ACTIVATION DURING DECISION-MAKING UNDER RISK IN ADOLESCENTS WITH EXCESS WEIGHT

Delgado-Rico, E., Soriano-Más, C., Verdejo-Román, J., Schmidt Río-Valle, J., & Verdejo-García, A. (2012). Decreased insular and increased midbrain activation during decision-making under risk in adolescents with excess weight. *Obesity* (en revisión).

Introduction

The prevalence of adolescent overweight and obesity has sharply increased over the last two decades, rapidly reaching epidemic levels (Lee et al., 2011; Ogden, 2012). To account for this rise, recent theoretical models underscore the role of decision-making skills as a key asset to regulate caloric intake in modern environments, since these are characterized by unrestricted access to food and strong media-driven appeals to eat caloric products (Morrison & Berthoud, 2007). Decision-making skills are particularly relevant in the case of adolescents, in whom brain developmental transitions seem to be hardwired to maximize reward at the expense of risk (Ernst & Fudge, 2009). Neuroimaging studies have demonstrated that adolescents have hypersensitive striatal response to reward prediction (Cohen et al., 2010; Galvan et al., 2006) and heightened activation of brain regions involved in fostering risk-taking (orbitofrontal cortex, (OFC)) during decision-making (Van Leijenhorst et al., 2010). Obesity-induced neural adaptations may further rewire these brain systems; in adults, excessive body mass index (BMI) levels are associated with reduced striatal dopamine function and lower metabolism of the OFC (Volkow et al., 2008, 2009).

In agreement with these notions, burgeoning evidence from neuroscience studies indicates that adolescents with excess weight have increased activation of brain systems involved on sensory-emotional processing (frontal operculum, insula) (Stice et al., 2008) and deficient activation of the neural network supporting cognitive control of choice (several regions of the prefrontal cortex) in response to highly appetizing food stimuli (Batterink et al., 2010). Behaviorally, excess weight adolescents have demonstrated decision-making deficits in cognitive tests measuring the ability to choose between safe and risky (superficially rewarding) choices (Verdejo-García, Pérez-

Expósito, et al., 2010). Furthermore, obese adolescents have increased cognitive disinhibition correlated with lower gray matter volumes in the OFC (Maayan et al., 2011). However, no studies to date have explored the neural substrates of decision-making under conditions of risk and reward in excess weight adolescents.

In this study, we used functional Magnetic Resonance Imaging (fMRI) to explore the brain substrates of decisions under risk in excess weight adolescents. Decision-making was challenged using the Risky Gains task, which opposes a safe less rewarding choice with more rewarding risky choices. This task has shown to robustly activate the brain systems involved in choice-related risk taking and reward receipt (including the OFC, insula and striatum). We expected abnormal activation of this brain system in excess weight adolescents compared to normal weight controls.

Methods and procedures

Participants

Fifty two adolescents (age range 12-17) participated in this study. They were classified in three groups (obese (n=21), overweight (n=15), or normal weight (n=16)) according to their BMI, following the criteria of the International Obesity Task Force (IOTF) defined by Cole et al. (2000), or, in normal weight adolescents, according to age- and sex-adjusted Spanish-specific norms (Sobradillo et al., 2004). The demographical data and BMI of participants are summarized in Table 1. Participants were recruited from the Endocrinology Service of the Hospital "Virgen de las Nieves" in Granada, Spain, and from schools located in the same geographical area. To be included, they had to meet the following criteria: (i) age range between 12 and 17 years-

old, (ii) BMI values falling within the intervals categorized as overweight or obesity according to the IOTF (excess weight adolescents), or normal weight values (normal weight adolescents), (iii) absence of past/current evidence of neurological or psychological disorders, (iv) absence of significant abnormalities on MRI (Magnetic Resonance Imaging) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects) and (v) absence of history of brain injury involving loss of consciousness (LOC) for longer than 5 minutes. All of them had normal or corrected-to-normal vision.

The study was approved by the Ethical Committee for Research in Humans of the University of Granada; all procedures were conducted in accordance with the Declaration of Helsinki. All participants and their parents were debriefed about study aims and detailed procedures, and both signed an informed consent form agreeing participation.

Table 1. Socio-demographic characteristics and Body Mass Index for each study group.

	Obese (n=21)	**Overweight (n=15)**	**Normal weight (n=16)**
	n	n	n
Sex			
Male	6	4	7
Female	15	11	9
	Mean (SD)	*Mean (SD)*	*Mean (SD)*
Age	14.29 (1.31)	14.07 (1.67)	13.88 (1.36)
BMI	31.33 (2.92)	24.65 (1.26)	20.19 (2.80)

Experimental task

We used Risky-Gains task described by Paulus, Rogalsky, Simmons, Feinstein, & Stein (2003). The task consisted of 96 trials (5 s/ trial). In each trial, participants are presented with the numbers 20, 40 and 80 in a fixed order. The task requires the participant to acquire as many points as possible by choosing between safe (20 points) and risky (40, 80 points) options. Each number (20, 40 or 80) is presented on the screen for 1 s and participants are instructed to press a button while the selected number in on the screen in order to win the corresponding amount of points. The first number in the sequence (20) is always a safe choice (the participant always receives 20 points). However, the two subsequent choices (40 and 80) can be rewarded (+40/+80) or punished (−40/−80); in the latter cases meaning that that the trial ends and the participant loses 40 or 80 points, respectively. Thus, although the subject may gain more points per trial by waiting until the 40 or 80 choices appear on the screen, there is also a risk of losing 40 or 80 points. Points accumulate from trial to trial and the stake is shown at the top of the screen, being continuously updated. Participants received feedback immediately after making a response, so they could adapt their behavior to the feedback received.

Fifty-four trials belonged to the non-punished trial type category, in which participants could get as much as 80 points, while 24 were -40 punished and 18 were -80 punished trial types. Relevantly, the final score did not depend on subject's choices, so, there was no advantage in selecting safe or risky options.

Imaging data acquisition

A 3.0 T clinical MRI scanner, equipped with an eight-channel phased-array head coil, was used (Intera Achieva, Philips Medical Systems, Eindhoven, The Netherlands),

which was during task performance, a T2*-weighted echo-planar imaging (EPI) was collected, (repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, field of view (FOV) = 230 x 230 mm, 96 x 96 matrix, flip angle = 90º, 21 4 mm axial slices, 1 mm gap, 243 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. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology Inc., Northridge, California, USA), and responses were recorded through Evoke Response Pad System (Resonance Technology Inc., Northridge, California, USA).

Imaging data processing and analysis

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

Data analyses

We defined 3 conditions of interest: (i) safe response (20 points trials) (ii) risky response (40 and 80 points trials) and (iii) punishment feedback (-40 and -80 points trials). The first two conditions were modeled as the time elapsed from the beginning of the trial to the participants' response. The last condition was modeled as the time

elapsed between feedback presentation and the end of the trial. Accordingly, two contrasts were defined to study brain activations: a risky versus (vs.) safe choices contrast, and a reward vs. punishment feedback contrast.

A one-sample t-test was conducted to assess intra-group activations (normal weight, overweight and obese) in each of the two contrasts of interest. The statistical threshold was set at $p<0.05$ False Discovery Rate (FDR) whole-brain corrected. Between-group comparisons were conducted using a mixed model ANOVA and linear contrasts to determine whether brain activations were related to BMI indices: normal weight vs. overweight vs. obese. Moreover, two-sample t-test comparisons were also conducted to assess significant differences in brain activation between each group-pair (i.e., normal weight vs. overweight; normal weight vs. obese; overweight vs. obese). In these analyses, significance threshold was set at $p<0.001$ (uncorrected).

Results

Behavioral results

Nine participants were excluded from the study because they made less than 4 risky choices, thus invalidating contrast interpretation. Also, four scans were excluded because of excessive motion artifacts. As a result, imaging data from 14 obese (mean age (+/- standard deviation (SD)) was of 14.07 (± 1.33), 9 female and 5 male, and BMI (weight/height² (kg/m²)) was 31.14 (± 2.66)), 13 overweight (mean age = 14.15 (± 1.77), 9 female and 4 male, BMI= 24.73 (± 1.34)) and 13 normal weight (mean age = 13.69 (± 1.18), 8 female and 5 male, BMI = 20.36 (± 2.49)) adolescent were used in the analysis.

Percentage of safe and risky responses per each group

The percentage of safe and risky responses is presented in Table 2. Participants with overweight showed a higher percentage of safe responses in comparison to the other two groups, although the interaction between group and response type was non-significant [F (2.37) = 2.089, p= 0.14].

Table 2. Percentage of safe and risky responses in the three study groups.

	Rate (%)	
	Safe	Risky
	Mean (SD)	*Mean (SD)*
Normal weight	45.94 (16.99)	54.06 (16.99)
Overweight	58.89 (12.26)	41.11 (12.26)
Obese	49.32 (19.90)	50.68 (19.90)

Neuroimaging results

Risky-Safe Contrast

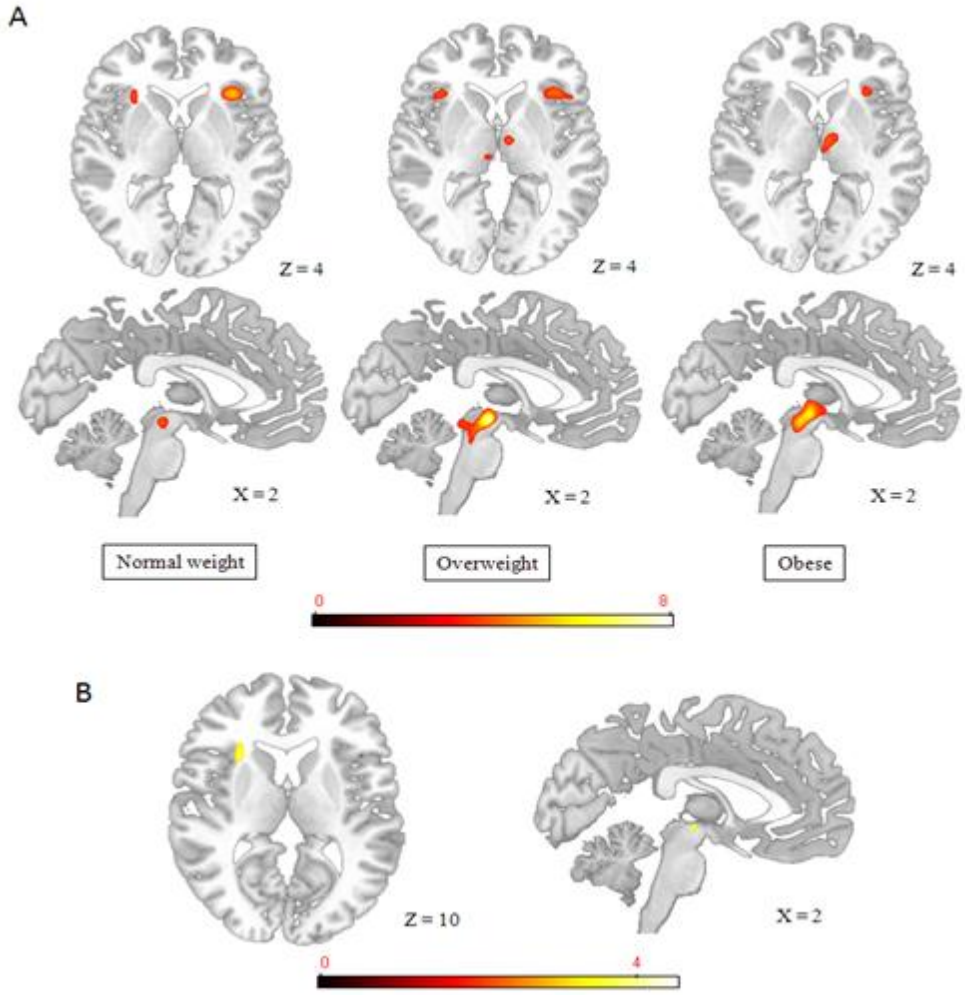
Results for Risky-Safe contrast are presented in Table 3. Within-subjects contrasts (whole-brain analyses) showed that each of the three groups activated the right inferior frontal gyrus/anterior insula region during risky (vs. safe) choices. In addition, a significant midbrain activation was also observed in overweight and obese groups (see Figure 1A). Linear contrasts showed that activation of the left inferior frontal/anterior insula region during risky choices was progressively smaller with increasing BMI (normal weight > overweight > obese). Likewise, midbrain activation during risky choices significantly increased with BMI (obese > overweight > normal weight) (see

Figure 1B). Pair-wise comparisons between all groups are presented in Supplementary Table 1.

Table 3. Brain activations observed in Risky vs. Safe choices in within -group (one-sample) and between-group (linear contrasts) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	**Y**	**Z**		
Normal weight							
Inferior frontal gyrus / Insula	47/13	R	36	24	0	2288	5.52
Overweight							
Midbrain	---	L/R	4	-20	-10	2056	7.88
Inferior frontal gyrus / Insula	47	R	38	24	-2	280	4.78
Obese							
Midbrain		L/R	6	-16	-6	992	6.40
Inferior frontal gyrus	47	R	34	22	-14	48	4.64
Normal weight>Overweight>Obese							
Insula	13	L	-26	22	10	920	4.26
Obese>Overweight>Normal weight							
Midbrain		R	4	-18	-8	264	3.72

Figure 1.



Supplementary Table 1. Brain activations observed in Risky vs. Safe choices between-group (t-test) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
Normal weight > Overweight							
Insula	13	L	-26	20	12	160	4.03
Normal weight > Obese							
Insula	13	L	-26	22	10	64	3.65
Overweight > Normal weight							
Midbrain		R	4	-18	-10	112	3.89

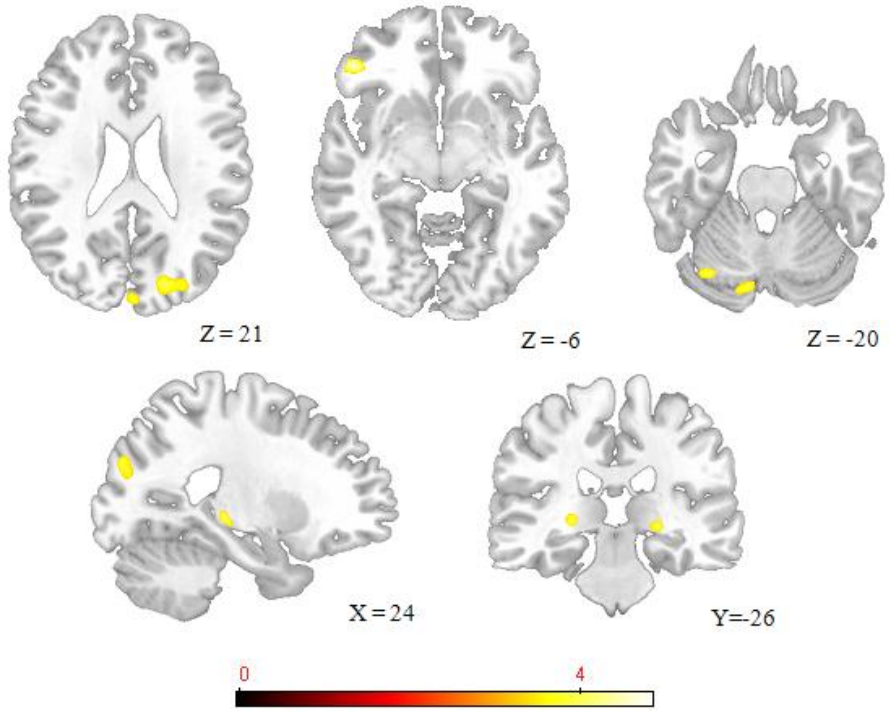
Reward-Punishment Contrast

Results for Reward-Punishment contrast are presented in Table 4. Whole-brain analysis for each groups showed a significant activation in the reward system (inferior frontal gyrus and nucleus accumbens), and the occipital lobe in all groups during reward (vs. punish) feedback. The linear contrast showed that activations observed during rewarded trials in the inferior frontal gyrus, the thalamus, the cerebellum, and the hippocampal and parahippocampal region were significantly related to BMI (obese > overweight > normal weight) (see Figure 2). No regions of greater activation in normal weight subjects were observed. Pair-wise comparisons are presented in Supplementary Table 2.

Table 4. Brain activations observed in Rewarded vs. Punished trials in within-group (one-sample) and between-group (linear contrasts) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
Normal weight							
Superior Frontal Gyrus	8/9	R	20	30	52	2760	7.28
Caudate		R	22	-8	30	2528	5.54
Caudate		L	-18	12	20	3480	5.48
Middle Occipital Gyrus	18/19	L	-18	-98	10	1128	5.05
Middle Occipital Gyrus		R	24	-96	10	112	3.97
Angular	40	R	46	-66	42	248	4.12
Overweight							
Cerebellum Posterior Lobe		L/R	-14	-84	-24	27224	7.09
Occipital Lobe	18/19	L/R	0	-84	-4	8804	6.72
Inferior Frontal Gyrus	47/11	L	-34	40	-18	648	6.50
Inferior Frontal Gyrus	11	R	34	44	-18	208	3.21
Caudate		L	-18	10	16	3672	6.39
Caudate		R	18	24	-12	2248	5.89
Parahippocampal Gyrus		R	22	-26	-30	1032	4.18
Middle Frontal Gyrus	10	R	12	48	6	1968	3.98
Middle Frontal Gyrus	10	L	-36	56	6	792	3.44
Hippocampal/Parahippocampal Gyrus		R	26	-26	-6	2128	3.43
Temporal Inferior	37	R	50	-56	-24	424	3.35
Fusiform	20	L	-38	-14	-22	376	3.07
Obese							
Occipital Superior / Cuneus	18	L	-12	-102	14	2440	6.07
Caudate		L	-20	0	22	1296	4.88
Caudate		R	20	12	-16	152	4.36
Inferior Frontal Gyrus	47	L	-18	22	-14	184	4.22
Hippocampus		R	26	-28	-2	160	4.00
Obese > Overweight > Normal weight							
Inferior Frontal Gyrus	47/11	L	-46	36	-6	1520	4.81
Thalamus		L	-24	-26	0	200	4.29
Superior Occipital Gyrus	18/19	R	18	-86	28	2160	4.27
Cerebellum Posterior Lobe		L	-30	-70	-28	576	4.12
Hippocampal/Parahippocampal Gyrus		R	26	-28	-4	392	4.12

Figure 2.



Supplementary Table 2. Brain activations observed in Rewarded vs. Punished between-group (t-test) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume (mm^3)	*t*
			X	Y	Z		
Obese > Normal weight							
Inferior Frontal Gyrus	47/11	L	-46	36	-6	1520	4.66
Thalamus		L	-24	-26	0	88	3.97
Hippocampus		R	26	-28	-4	392	3.70
Superior Occipital Gyrus	18/19	R	18	-82	26	128	3.55
Overweight > Normal weight							
Cerebellum		L/R	-14	-84	-24	1752	5.35
Inferior Frontal Gyrus	11	L	-34	40	-18	112	5.27
Occipital Lobe	19	R	26	-86	26	2608	4.65
Precuneus	7 / 19	L	-14	-76	40	4480	4.64
Cerebellum Posterior Lobe		L	-30	-68	-32	2608	4.37
Thalamus / Caudate		R	16	-6	18	456	4.03
Inferior Frontal Gyrus	47	L	-50	38	-8	64	3.53
Hippocampus		R	26	-26	-8	36	3.46
Inferior Frontal Gyrus	47	L	-48	38	-6	64	3.37
Overweight > Obese							
Precentral Gyrus	6	R	30	-16	64	672	4.10

Discussion

The main findings from this study were that excess weight adolescents, compared to normal weight peers, have decreased left insular activation and increased midbrain activation during risk-based decision-making. In addition, excess weight adolescents have increased inferior frontal gyrus, thalamus, parahippocampal and posterior activation in response to reward receipt. These brain activation differences emerged in absence of significant between-groups differences on behavioral choice, such that they genuinely reflect different approaches to decision-making as a function of weight status. Therefore, we reason that excess weight adolescents may have dysfunctional patterns of brain activation related to risk evaluation and reward processing during decision-making. In real-life scenarios, these differential patterns may contribute to explain choices leading to excessive food intake in this group of adolescents.

The first relevant finding refers to significantly decreased left anterior insular activation during the period preceding actual choice in the excess weight groups. Conversely, excess weight adolescents showed increased activation in the midbrain, a hub of ascending monoaminergic bundles. The anterior insula is importantly involved in signaling the probability of aversive outcomes, thus guiding risk prediction and choices oriented to minimize losses (Bossaerts, 2010; Venkatraman, Payne, Bettman, Luce, & Huettel, 2009). Accordingly, patients with insula damage fail to adjust their bets by the odds of winning in a risk-taking gamble task; they bet similarly high amounts of money irrespective of outcome probability (Clark et al., 2008). This is consistent with the finding that excess weight adolescents have increased preference for risky decks in the Iowa Gambling Task (Verdejo-García, Pérez-Expósito, et al., 2010). The insula is also strongly associated with interoceptive sensitivity (the ability to perceive bodily

feedback to regulate internal state), which is decreased as a function of increased body weight in adolescents (Striegel-Moore et al., 2000). Individual differences in interoceptive sensitivity significantly shape cognitive-affective processes including decision-making; for example, individuals with good interoceptive sensitivity tend to select less risky choices in the Iowa task (Werner, Jung, Duschek, & Schandry, 2009). Overall, the evidence suggests that excess weight adolescents may have abnormal insular-mediated processing of interoceptive information relevant for decision-making. On the other hand, they seem to rely on midbrain dopamine regions to ponder risky vs. safe options, probably biasing preference towards immediate reinforcement (Cohen et al., 2010; Galvan et al., 2006). In real-life decision-making, these deficits may promote excessive meal intake at the expense of negative consequences, either immediate (e.g., belly ache) or postponed (e.g., restriction of social activities).

In line with results from the pre-decisional stage, the second finding referred to increased inferior frontal gyrus activation in response to reward vs. punishment feedback in the excess weight group. This region has been associated with evaluation of reward outcome following risk-based decisions among healthy adolescents (Yaxley et al., 2011). In addition, this region, along with others identified in the same contrast (e.g., parahippocampus, cerebellum), has been linked to incentive motivation towards food stimuli in adolescents (Holsen et al., 2005). Therefore, our findings are suggestive of the notion that, in excess weight adolescents, the persistent stimulation of incentive motivational systems by seeking of high caloric food may hypersensitize the brain substrates of reward processing in this group. Since the evaluation of outcomes is thought to slot in formation of preferences for subsequent decisions (Ernst & Paulus, 2005), decision-making in excess weight adolescents may be overridden by sensory-emotional aspects of reward to the expense of risk (E Stice et al., 2011). This notion is

in line with proposed parallels between obesity and addiction (Acosta et al., 2008; Volkow et al., 2008), based on the array of reward-related neurobiological alterations associated with increased BMI, including reduced striatal dopamine function and lower metabolism of the OFC (Volkow et al., 2008, 2009). In sum, excess weight adolescents show hyper-processing of reward outcomes in the inferior frontal gyrus and other brain regions importantly involved in reward and arousal processing, which may sensitize their decisional balance towards the rewarding properties of food products.

The main conclusion of this study is that adolescents with excess weight have reduced activation in brain regions signaling risk, and increased activation in regions signaling reward during anticipation of decisions involving risk and reward. In addition, post-decision reward processing produced increased activation of several regions involved in emotional salience as a function of increased weight. These results demonstrate for first time abnormal patterns of brain activation during decisions involving risk and reward in adolescents with excess weight. Future studies are warranted to explore whether these basic deficits are associated with persistent behavioral patterns fostering choice of highly rewarding food products at the expense of long-term health risks.

Referencias

Las referencias pueden consultarse en el apartado de REFERENCIAS.

IV. DISCUSIÓN GENERAL, CONCLUSIONES Y PERSPECTIVAS FUTURAS

CAPÍTULO 7

DISCUSIÓN GENERAL, CONCLUSIONES Y PERSPECTIVAS FUTURAS

1. Discusión general

Los objetivos de esta tesis pueden resumirse en dos focos de interés principales. El primero, analizar el efecto relativo de las variables de personalidad (sensibilidad al refuerzo y al castigo) en comparación con el IMC (severidad de la obesidad) sobre el estado neuropsicológico de adolescentes con problemas de exceso de peso, así como evaluar la asociación entre los cambios en dicho estado neuropsicológico y las reducciones de peso alcanzadas por estos adolescentes durante un tratamiento multi-componente. El segundo foco estaba dirigido a examinar la anatomía de las regiones cerebrales y explorar el sustrato cerebral de la toma de decisiones bajo condiciones de riesgo y recompensa en adolescentes con exceso de peso.

En relación con nuestro primer foco de interés, los resultados obtenidos mostraron que la sensibilidad a la recompensa predecía significativamente los niveles de impulsividad (urgencia positiva y negativa, búsqueda de sensaciones y falta de premeditación) pero no el rendimiento en pruebas de flexibilidad. En cambio, los valores de IMC predecían de manera positiva y específica los niveles de urgencia (positiva y negativa) y de manera negativa el rendimiento en flexibilidad. Respecto a si el entrenamiento en habilidades neuropsicológicas mejoraba la eficacia de los tratamientos, encontramos que los adolescentes que más reducían sus niveles de impulsividad bajo estados emocionales negativos intensos (urgencia negativa) y más mejoraban sus habilidades de control inhibitorio (respuesta de inhibición y cambio) eran los que más reducían su IMC. Otras habilidades como la memoria de trabajo o la toma de decisiones no predecían mejoras tras la intervención. Por último, los resultados mostraron correlaciones significativas entre la estructura cerebral y las medidas de personalidad y cognitivas solo en los adolescentes con peso normal. Concretamente, la sensibilidad a la recompensa y la urgencia positiva se asociaron negativamente con el

volumen de materia gris en el cortex somatosensorial secundario izquierdo mientras que el rendimiento en inhibición correlacionó positivamente con el volumen del cortex prefrontal dorsolateral izquierdo.

En relación con nuestro segundo foco de interés, los resultados mostraron que los adolescentes con exceso de peso presentaban un mayor volumen de materia gris en el hipocampo derecho en comparación con los de peso normal. Por otro lado, los resultados indicaron que los adolescentes con exceso de peso mostraban una menor activación en la ínsula izquierda y una mayor activación en el mesencéfalo durante la toma de decisiones bajo condiciones de riesgo y recompensa. Además, exhibían una mayor activación en el giro frontal inferior ante la respuesta de recepción de recompensa. Estas diferencias en activación cerebral se observaron en ausencia de diferencias significativas a nivel conductual entre ambos grupos.

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

1.1. Implicaciones teóricas

Los resultados de nuestros estudios contribuyen a esclarecer el perfil de personalidad y neuropsicológico asociado a los problemas de exceso de peso en adolescentes. Así, nuestros resultados apoyan los datos de estudios previos que señalan que las personas con problemas de exceso de peso podrían tener dificultades para controlar su conducta de comer cuando experimentan emociones intensas tanto positivas como negativas (Goossens et al., 2009; Mobbs et al., 2010; Loxton et al., 2011) y corroboran la relación negativa entre el IMC y la flexibilidad cognitiva (Cserjési et al., 2007; Lokken et al., 2009; Verdejo-García, Pérez-Expósito, et al., 2010). La ausencia de correlaciones significativas entre las regiones cerebrales y las medidas de personalidad y cognitivas en

adolescentes con exceso de peso podrían sugerir una pérdida de la asociación normal entre la estructura cerebral y los procesos psicológicos y neuropsicológicos que sustentan. Esta hipótesis sería congruente con los resultados aportados por Stice et al. (2011). Estos autores proponen que los adolescentes con mayor riesgo para desarrollar obesidad podrían exhibir una mayor sensibilidad hacia la recompensa en general, pero podrían necesitar del acompañamiento de una mayor activación de las áreas somatosensoriales en respuesta a la comida para que hubiera un riesgo específico de desarrollar obesidad. Las áreas somatosensoriales y la ínsula parecen estar relacionadas con el procesamiento de la información visceroceptiva y su valoración hedónica (Berthoud & Morrison, 2008) y mantienen importantes conexiones con el córtex orbitofrontal, el cual está implicado en la toma de decisiones y los procesos emocionales que las guían (Verdejo-García & Bechara, 2009). En consonancia con el modelo del Marcador Somático propuesto por Damasio (1994) se podría decir que una mayor activación de estas áreas ante la comida apetitosa podría producir una sobreestimación del valor reforzante del alimento y fuertes señales somáticas que atenuaran las señales homeostáticas que regulan la ingesta, propiciando la tendencia a decidir seguir comiendo a pesar de que las necesidades fisiológicas estuvieran cubierta y sin tener en cuenta las posibles consecuencias negativas que este exceso de ingesta pudiera tener sobre la salud.

Los hallazgos aportados por los patrones de activación durante la neuroimagen indican que los adolescentes con exceso de peso presentan un mayor volumen de materia gris en el hipocampo derecho. Esta región tradicionalmente ha sido relacionada con el aprendizaje y la memoria pero estudios recientes señalan que el hipocampo podría modular la conducta de ingesta mediante el procesamiento de las señales de saciedad y por su implicación en la motivación de incentivos (Tracy et al., 2001; Wang

et al., 2006). La mayor densidad de materia gris en esta área en los adolescentes con exceso de peso podría sugerir la existencia de cambios estructurales asociados con la excesiva motivación hacia los estímulos de comida apetitosa. Por otro lado, durante la toma de decisiones bajo condiciones de riesgo y recompensa, los adolescentes con exceso de peso muestran un aumento en la activación de las regiones que señalizan la recompensa y una reducción en la activación de las regiones cerebrales que señalizan el riesgo.

Tomando en conjunto estos resultados, podría derivarse que los adolescentes con exceso de peso podrían ser más sensibles a las propiedades reforzante de los alimentos, sobreestimar su valor reforzante e ignorar los riesgos que conlleva el excesivo consumo de alimentos y, por tanto, podrían estar más predispuestos a elegir basándose en la recompensa inmediata. Este patrón de toma de decisiones se ha encontrado en personas que tienen problemas con la comida. Así, las personas con exceso de peso tienen un peor rendimiento en la Iowa Gambling Task, encontrándose estos resultados tanto en adultos (Brogan et al., 2011; Davis, Levitan, et al., 2004) como en adolescentes (Verdejo-García, Pérez-Expósito, et al., 2010). Otros estudios que comparan la ejecución de las personas con exceso de peso vs. otras poblaciones (peso normal, anorexia, bulimia y trastorno por atracón) encuentran que las personas de peso normal tienen un mejor rendimiento que los grupos clínicos, pero no se encuentran diferencias entre los diferentes grupos clínicos (Brogan et al., 2010; Danner et al., 2012; Fagundo et al., 2012).

En resumen, nuestros datos podrían servir de apoyo al modelo de vulnerabilidad dinámica (Davis & Fox, 2008; Stice et al., 2011; Verbeken et al., 2012) explicado en apartados anteriores. Según este modelo, la obesidad podría ir evolucionando y con el tiempo, producir cambios cerebrales como consecuencia del excesivo consumo de

alimentos. Este modelo establece que una mayor sensibilidad a la recompensa podría ser un factor de riesgo inicial para comer en exceso y que posteriormente, debido a los cambios cerebrales, podría producirse una insensibilidad ante la recompensa y promover un mayor consumo para compensar este déficit. En este sentido nuestros resultados sugieren que los adolescentes con exceso de peso podrían tener problemas para controlar sus impulsos ante estados emocionales intensos y que podrían tener una mayor motivación hacia los estímulos de comida apetitosa, sobreestimar su valor reforzante e ignorar los riesgos que conlleva el exceso de ingesta, lo cual podría propiciar un mayor consumo de alimentos apetitosos y como consecuencia la ganancia de peso. Por otro lado, los problemas en flexibilidad cognitiva podrían apuntar el inicio de los cambios cerebrales que supondrían la transición entre impulsividad y compulsividad en el desarrollo de la obesidad, como ocurre en los trastornos de adicción (Volkow et al., 2008).

No obstante, nuestros resultados también podrían ser explicados desde el modelo del Marcador Somático (Damasio, 1994). Desde esta perspectiva se podría especular que los adolescentes con exceso de peso podrían interpretar inadecuadamente los marcadores somáticos como consecuencia de una posible alteración en el procesamiento de las señales somáticas y motivacionales, lo cual les llevaría a tomar decisiones erróneas en cuanto al tipo y cantidad de alimentos que ingieren propiciando así el mantenimiento y desarrollo de la obesidad. Este patrón de toma de decisiones podría acentuarse aún más durante la adolescencia debido a las singularidades neuropsicológicas de esta etapa (Ernst et al., 2006; 2009). Por tanto, la adolescencia podría constituir un periodo de mayor vulnerabilidad (Acosta et al., 2008), en la cual la obesidad podría tender a cronificarse si no se interviene (Whitaker et al., 1997).

1.2. Implicaciones clínicas

Nuestros datos muestran que la intervención multi-componente produjo una reducción significativa del IMC, mostrando un tamaño del efecto medio. Estos resultados apoyan los datos de meta-análisis previos que informan que las intervenciones combinadas tienen efectos moderados sobre la pérdida de peso en adolescentes (McGovern et al., 2008; Wilfley et al, 2007). Por otro lado, nuestros resultados indican que la regulación emocional y el control inhibitorio están asociados con mejores resultados tras el tratamiento y que otras habilidades como la memoria de trabajo o la toma de decisiones no predicen mejoras tras la intervención. Estos resultados son congruentes con estudios anteriores y podrían contribuir a incrementar el éxito de los tratamientos.

Existen varios estudios que indican que estados emocionales negativos intensos podrían jugar un rol en la tendencia a sobrealimentarse (Mobbs et al., 2010; Loxton et al., 2011). Mobbs et al. (2010) proponen que la hipersensibilidad a los estímulos alimenticios puede ser controlada con buenas habilidades de autorregulación y que por tanto, los problemas de exceso de peso aparecerían cuando las habilidades de autorregulación fallaran. En este sentido y en consonancia con nuestros datos podría especularse que el entrenamiento en habilidades de regulación emocional podría mejorar los resultados de los tratamientos. Por otro lado, la evidencia empírica también parece apoyar la relación entre un pobre control inhibitorio y los problemas de exceso de peso. El grupo de Nederkoorn ha realizado varios estudios desde esta perspectiva y han encontrado que los adolescentes con menor control inhibitorio pierden menos peso durante el tratamiento (Nederkoorn et al., 2006), que el control inhibitorio se relaciona negativamente con el IMC y que predice la reducción de exceso de peso en niños durante el periodo de un año (Nederkoorn et al., 2007). Houben y Jansen (2011)

sugieren que el entrenamiento en control inhibitorio podría ayudar a mejorar el control sobre el consumo de alimentos apetitosos.

En resumen nuestros datos apoyan los resultados de estudios previos (Appelhans et al., 2011; Berg et al., 2011; Guerrieri et al., 2008a; Nederkoorn et al., 2010) que apuntan que la obesidad podría estar relacionada con una mayor reactividad emocional y un pobre control inhibitorio. Estos rasgos podrían estar incrementados durante la etapa adolescente, ya que dicho periodo parece caracterizarse por la relativa inmadurez del sistema de control y autorregulación y una relativa madurez del sistema de recompensa. Por tanto, cabría suponer que, como muestran nuestros datos, el entrenamiento de las habilidades de regulación emocional y control inhibitorio durante la adolescencia mejoraría el resultado de los tratamientos. Esta suposición estaría de acuerdo con la evidencia que sugiere que la pérdida de control podría resultar de unas inadecuadas estrategias de afrontamiento ante estados emocionales negativos y que, por tanto, los tratamientos de obesidad deberían centrarse en la enseñanza de estrategias de afrontamiento más eficaces (Goossens et al., 2009).

Por último, estos resultados podrían estar limitados por algunos condicionantes. Por un lado, la naturaleza correlacional de nuestros estudios no permiten inferir causalidad y, por tanto, otras explicaciones alternativas podrían ser posibles. Con el desarrollo de estudios longitudinales se podrá determinar si un elevado IMC produce alteraciones en las habilidades neuropsicológicas y estructuras y funcionamiento cerebral, si estas características son las que promueven un incremento del IMC o si la relación entre ambas es bidireccional. Por otro lado, la ausencia de un grupo control y medidas de seguimiento también nos impiden conocer con mayor claridad los beneficios a corto y largo plazo de nuestra intervención multi-componente.

2. Conclusiones

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

1. La adiposidad se asocia específicamente con una mayor impulsividad ante emociones intensas (tanto positivas como negativas) y con problemas de flexibilidad cognitiva.

2. La intervención multi-componente produce una reducción significativa del IMC, encontrándose un tamaño del efecto medio.

3. El entrenamiento de las habilidades de regulación emocional y control inhibitorio en programas multi-componente mejora la eficacia de estos tratamientos dirigidos a reducir la obesidad adolescente.

4. En contraste con el grupo control, los adolescentes con exceso de peso no muestran asociaciones significativas entre la anatomía de las regiones del córtex somatosensorial secundario y el córtex prefrontal dorsolateral y los procesos motivacionales y neurocognitivos que sustentan dichas regiones.

5. Los adolescentes con exceso de peso muestran una reducción en la activación de las regiones cerebrales que señalizan el riesgo y un aumento en la activación de las regiones que señalizan la recompensa durante la anticipación de las decisiones que involucran riesgo y recompensa.

6. Los adolescentes con exceso de peso presentan un aumento en la activación de las regiones cerebrales implicadas en la relevancia emocional en respuestas recompensadas en un paradigma de toma de decisiones.

3. Perspectivas futuras

A continuación se enumeran algunas de las perspectivas futuras de investigación teórica que se derivan de esta tesis:

1. Profundizar en la determinación de si la transición entre impulsividad y compulsividad está asociada al desarrollo de la obesidad. Para abordar esta cuestión podrían llevarse a cabo estudios longitudinales que correlacionaran la transición entre estos rasgos con la evolución de la obesidad o analizar si estos rasgos se relacionan con diferentes niveles de severidad de obesidad.

2. Determinar que alteraciones neurofuncionales son las que se relacionan con un riesgo futuro de desarrollar obesidad. Esto podría investigarse en hijos de obesos o en adolescentes con riesgo de desarrollar obesidad.

3. Analizar el procesamiento de las señales somáticas y motivacionales ante estímulos de comida apetitosa frente a otros estímulos de valencia positiva o comida neutral, así como la modulación ejercida por estos estados emocionales sobre los procesos de toma de decisiones en adolescentes con exceso de peso. Aproximaciones recomendables serían el empleo de medidas psicofisiológicas o paradigmas de resonancia magnética funcional que permitieran examinar los mecanismos emocionales (marcadores somáticos) implicados en los procesos de toma de decisiones.

Algunas de las perspectivas futuras de investigación clínica que se derivan de esta tesis son las siguientes:

1. Profundizar en la identificación de componentes neuropsicológicos que mejoran la eficacia de las intervenciones pediátricas.

2. Desarrollar estudios longitudinales que permitan determinar la intensidad y duración de los tratamientos que logran resultados más eficaces y persistentes en el tiempo.

DOCTORADO INTERNACIONAL

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVE

1. Summary

This dissertation consists of a total of seven chapters grouped into four sections: (i) introduction, (ii) rationale and objectives, (iii) developed research studies summary, (iv) general discussion, conclusions and future perspectives.

The introductory section consists of Chapter 1 where we will discuss the clinical relevance of the problems of excess weight, neuropsychological perspectives to address obesity and some considerations on the singularities neuropsychological of adolescence and aspects of obesity treatment at this stage.

The second section contains Chapter 2 for which we provide the rationale for conducting this work, the main and specific objectives and hypotheses that are intended for the same.

The third section consists of four chapters that compose a set of four empirical research studies. Chapter 3 is a study on the relationship between personality factors (sensitivity to reward and punishment), the Body Mass Index (BMI) and neuropsychological measures of impulsivity and flexibility. Results of this research showed that adiposity increases is related to higher levels of impulsivity under intense emotions and cognitive flexibility problems.

Chapter 4 contains a study on the effectiveness of a multi-component treatment for adolescents with excess weight. Results showed that the multi-component intervention produced a significant reduction in BMI, showing a medium size effect. Furthermore, it was found that the recovery of neuropsychological skills improved treatment´s capacity to reduce the BMI. Specifically, we found that adolescents throughout the treatment who reduced their levels of impulsivity under intense negative emotional states (negative urgency) and presented greater improvements in inhibition response

and change were those who lost more weight after treatment. Nevertheless other skills such as working memory or decision making do not predict improvement after the intervention.

Chapter 5 presents a study of the association between brain structure and personality measures (assessed through the Sensitivity to Punishment and Reward Questionnaire (SPSRQ) and the UPPS-P scale) and cognitive measures (assessed by the Stroop task) in adolescents with excess weight compared to normal weight adolescents. In addition, we examined the anatomy of the brain regions in adolescents of both groups. On one hand, results indicated significant correlations only in normal weight adolescents. Specifically, the sensitivity to reward and positive urgency were negatively associated with gray matter volume in the secondary somatosensory cortex and response inhibition correlated positively with the volume in the dorsolateral prefrontal cortex. Furthermore, results showed that adolescents with excess weight had increased gray matter volume in the right hippocampus compared with normal-weight adolescents.

Chapter 6 was a study on the brain substrate of decision making under conditions of risk and reward. Results showed that during the decision making process of adolescents with excess weight compared with normal-weight, showed a lower activation in the left insula and greater activation in the midbrain. As far as the response towards the reception of reward, adolescents with excess weight showed greater activation in the inferior frontal gyrus. These differences in brain activation were observed in the absence of significant differences between groups behavioral level.

In the fourth and final section, Chapter 7, we held a joint discussion of the findings across different studies with special emphasis on theoretical and clinical implications. We also present a section of conclusions and future research perspectives.

2. Conclusions

From the results of this thesis, we derive the following conclusions:

1. Adiposity is associated specifically to higher levels of impulsivity under intense emotions (both positive and negative) and cognitive flexibility problems.

2. The multi-component intervention produced a significant reduction in BMI, finding a medium size effect.

3. The training of emotional regulation skills and inhibitory control improve the efficacy of treatments aimed at reducing adolescent obesity.

4. In contrast to the control group, teens who have excess weight do not show significant associations between the anatomy regions of the secondary somatosensory cortex and the prefrontal dorsolateral cortex and the motivational and neurocognitive processing related to these brain regions.

5. Adolescents with excess weight show a reduction in the activation of brain regions that indicate the risk and increased activation of regions that indicate the reward during anticipation of decisions that involve risk and reward.

6. After decision making and confronted with reward results, adolescents with excess weight have an increased activation of brain regions involved in emotional salience.

3. Future perspective

Below we list some of the future perspectives of theoretical research that arise from this thesis:

1. Deepening the determination of whether the transition between impulsivity and compulsivity is associated with the development of obesity. To address this issue longitudinal studies that correlate the transition between these traits with the development of obesity could be carried out or analyze whether these traits are associated with different levels of severity of obesity.

2. To determine which neurofunctional changes are related with future risk of developing obesity. This could be investigated in obese children or adolescents at risk for obesity.

3. Analyze the somatic and motivational signal processing when exposed to appetizing food stimuli over other stimuli of positive valence or neutral food and modulation exerted by these emotional states on decision-making processes in adolescents with excess weight vs. normal weight. Recommended approach would be the use of psychophysiological measures or fMRI paradigms that allow to examine the emotional mechanisms (somatic markers) involved in the decision-making processes.

Some of the future perspectives in the clinical research resulting from this thesis are:

1. Intensify the identification of the neuropsychological components that improve the effectiveness of pediatric interventions.

2. Develop longitudinal studies to determine the intensity and duration of treatments that achieve more effective results and persistent over time.

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ANEXOS

ANEXO I

BMI Predicts Emotion-Driven Impulsivity and Cognitive Inflexibility in Adolescents With Excess Weight

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Adolescent obesity is increasingly viewed as a brain-related dysfunction, whereby reward-driven urges for pleasurable foods "hijack" response selection systems, such that behavioral control progressively shifts from impulsivity to compulsivity. In this study, we aimed to examine the link between personality factors (sensitivity to reward (SR) and punishment (SP), BMI, and outcome measures of impulsivity vs. flexibility in—otherwise healthy—excessive weight adolescents. Sixty-three adolescents (aged 12–17) classified as obese (*n* = 26), overweight (*n* = 16), or normal weight (*n* = 21) participated in the study. We used psychometric assessments of the SR and SP motivational systems, impulsivity (using the UPPS-P scale), and neurocognitive measures with discriminant validity to dissociate inhibition vs. flexibility deficits (using the process-approach version of the Stroop test). We tested the relative contribution of age, SR/SP, and BMI on estimates of impulsivity and inhibition vs. switching performance using multistep hierarchical regression models. BMI significantly predicted elevations in emotion-driven impulsivity (positive and negative urgency) and inferior flexibility performance in adolescents with excess weight—exceeding the predictive capacity of SR and SP. SR was the main predictor of elevations in sensation seeking and lack of premeditation. These findings demonstrate that increases in BMI are specifically associated with elevations in emotion-driven impulsivity and cognitive inflexibility, supporting a dimensional path in which adolescents with excess weight increase their proneness to overindulge when under strong affective states, and their difficulties to switch or reverse habitual behavioral patterns.

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INTRODUCTION

The prevalence of childhood overweight and obesity has been increasing worldwide over the past 30 years, whereas the search for effective interventions is still currently unfulfilling (1). The drastic psychosocial changes shared by all Western societies (e.g., the unrestricted access to food products and the explosion of the food market) have modified the way we perceive food and regulate food intake, being these processes increasingly modulated by external reward cues at the expense of appropriate nutrient sensing (2). In the last years, excessive eating and obesity are increasingly viewed as a brain-related dysfunction, whereby reward-driven urges for pleasurable foods "hijack" context-driven frontal-executive control (3,4). The risk for this imbalance is higher among adolescents, since they stand amidst neurodevelopmental processes essential to fine-tune the links between the reward system and the executive control system (5,6). Neurobiological studies mainly support this notion—adolescents at high-risk for obesity have heightened activation of the reward system in response to receipt of palatable food (7), and obese adolescents have significantly reduced orbitofrontal volumes (8). However, the neuropsychological correlates of excessive weight and its associated neuroadaptations are not yet well specified—despite the fact that cognitive strategies directed to restore these systems are lined up as promising interventions for pediatric obesity (9).

A strand of evidence suggests that excessive weight adolescents have prominent deficits in impulsivity and inhibitory control (10,11). However, the link between excess weight and impulsivity depends on age—high impulsivity is linked to higher body weight in young kids (8–10 years old), whereas in adolescents (12–14 years old) this association is less pronounced and tends to be inversed—low impulsivity associated with higher weight (12). This interaction may reflect age-related maturation of inhibitory processes (13), or a transition

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between impulsivity and compulsivity in the development of obesity—similar to what is found in addiction (14). Germane to the latter notion, a second strand of evidence indicates that excessive eating is mainly associated with decline of flexibility skills—a cognitive proxy of compulsivity (15). Germane to this notion, neurocognitive studies in children and adolescents have shown that BMI specifically negatively correlates with performance on cognitive switching probes (16,17).

A related unresolved issue is that of the impact of the personality factors of sensitivity to reward (SR) and sensitivity to punishment (SP) on neuropsychological deficits in adolescent overweight and obesity. This is relevant because psychometric studies indicate that SR positively correlates with trait impulsivity, whereas SP positively correlates with compulsivity—with the exception of positive correlations between SP and the impulsivity dimension of urgency (emotion-driven impulsivity (18,19)). Davis (20) demonstrated that SR significantly predicted higher scores on a measure of emotional eating—overeating when under strong negative states, and they proposed a mediational path between SR, negative emotion-driven eating, and BMI. This result is fitting with evidence showing that both SR and SP correlate with negative urgency (the tendency to experience strong impulses under conditions of negative affect) in obese adults (21). Therefore, the association between these personality factors and excessive eating seems well-established. However, further dissociation of the differential role of SR vs. SP, and of their relative impact on inhibitory control vs. inflexibility is needed to achieve a better understanding of how personality impacts neuropsychological profiles in obese adolescents.

In this study, we aimed to examine the link between personality factors (SR and SP), BMI, and outcome measures of impulsivity vs. flexibility in—otherwise healthy—excessive weight adolescents. We conducted a multidimensional assessment of trait impulsivity (using the UPPS-P scale) and neurocognitive assessments with discriminant validity to dissociate inhibition vs. flexibility deficits (using the process-approach version of the Stroop test). According to previous evidence, we predicted that BMI and SR would significantly predict higher scores on emotion-driven impulsivity among adolescents with excess weight.

METHODS AND PROCEDURES

Participants

Sixty-three adolescents (age range 12–17) participated in this study. Participants were classified as obese (n = 26), overweight (n = 16), or normal weight (n = 21) according to the International Obesity Task Force (IOTF) criteria defined by Cole (22). The demographical data and endocrine characteristics of participants—classified as excess weight vs. normal weight—are summarized in **Table 1**. We recruited them through educational centers and national health services in order to participate in a larger study aimed to test a novel multidisciplinary intervention for adolescent excess weight. To be included, they had to meet the following criteria: (i) age range between 12 and 17 years old, (ii) BMI values falling within the intervals categorized as overweight or obesity according to the IOTF—for excess weight adolescents, or normal weight values, (iii) normal endocrine characteristics—assessed by

Table 1 Demographical and clinical descriptive data of the normal weight and excess weight groups: sex, SES, age, BMI, and endocrine parameters

	Normal weight (n = 21)	Excess weight (n = 42)	
	n (%)	n (%)	x^2
Sex			0.14
Male	11 (52.4)	14 (33.3)	
Female	10 (47.6)	28 (66.7)	
SES (annual income €)[a]			0.10
0–11.533 €	5 (26.3)	2 (5)	
11.533–18.200 €	3 (15.8)	13 (32.5)	
18.200–26.548 €	5 (26.3)	18 (45.0)	
26.548–41.292 €	3 (15.8)	4 (10.0)	
41.292–3.144.000 €	3 (15.8)	3 (7.5)	
	Mean (s.d.)/range	Mean (s.d.)/range	t
Age	14.14 (1.459)/12–17	14.19 (1.38)/12–17	–0.13
BMI	19.84 (2.642)/14.78–24.57	29.15 (4.51)/22.06–38.21	–10.31[b]
Biochemical parameters			
Insulin	9.60 (2.68)/6–14.3	16.23 (12.38)/1.5–52	–2.70[b]
Basal glucose	86.68 (13.85)/69–130	86.39 (9.42)/68–106	0.10
Triglycerides	69.53 (24.32)/37–119	96.15 (43.24)/45–235	–2.50[b]
HDL	60.89 (16.75)/39–113	50.58 (12.77)/33–78	2.63[b]
Total cholesterol	157.79 (32.34)/99–215	158.85 (26.41)/113–222	–0.13

HDL, high-density lipoprotein cholesterol; SES, socioeconomic status.
[a]Quintiles for SES are defined according to data from the Financial Survey for Spanish Families, http://www.bde.es/webbde/es/estadis/eff/eff.html;[b] $P \leq 0.05$.

Complete Blood Count determinations showing within-normal range levels of insulin, basal glucose, triglycerides, high-density lipoprotein cholesterol, and total cholesterol, and (iv) absence of past/current evidence of medical or psychological disorders. The adolescents with normal weight were recruited in the same demographic areas and had to meet the same inclusion criteria—with the exception of (ii). In order to avoid the inclusion of underweight adolescents within this group, we also checked if potential participants fell within normal BMI values according to age- and gender-adjusted Spanish-specific norms (23)—none of the selected participants met criteria for low weight. All participants completed the Millon Adolescent Clinical Inventory (MACI (24)) and the Eating Disorder Inventory 2 (EDI-2 (25)) in order to assess the presence of clinically significant psychopathological traits. Results are presented as **Supplementary Table S1** online). In brief, they showed that both groups did not significantly differ on MACI-indexed personality patterns, expressed concerns (EC) or clinical syndromes (CS), with the exceptions of submissive patterns—increased in excess weight adolescents, and peer insecurity—increased in normal weight adolescents. EDI-2 results gave a similar picture—none of the excess weight participants had clinically significant disorders; nonetheless, as a group, they scored significantly higher than their peers on the drive for thinness and body dissatisfaction scales.

Measures

SR and SP. Sensitivity to Punishment and Reward Questionnaire (SPSRQ (26)): The SPSRQ is a 48 yes–no response item questionnaire aimed to measure two neuropsychological systems driving motivated behavior: the behavioral activation system (SR) and the behavioral inhibition system (SP). The total scores from each scale (SP and SR) were obtained for analyses.

BMI. BMI was calculated for each participant as the ratio of weight in kilograms divided by the square of height in meters.

Impulsivity. UPPS-P Scale (19,27): 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 four dimensions were included in the original version of the UPPS scale (27); the fifth dimension has been included based on recent work by Cyders *et al*. (28) and Smith *et al*. (29). Sensation seeking (12 items) incorporates two aspects: (i) a tendency to enjoy and pursue activities that are exciting, and (ii) an openness to trying new experiences that may or may not be dangerous; (lack of) perseverance (10 items) refers to the 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 (12 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.

Response inhibition and switching. Delis–Kaplan Executive Function System (D-KEFS) Color-Word Interference Test Stroop (CWIT Stroop (30)): This paper and pencil test is based on the Boston process approach (31), 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 (C) that are administered to determine whether poor performance is because of 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 normative scores of response inhibition (C3 – C1), or response switching (C4 – C3).

Statistical analyses. We used independent-sample *t*-tests to examine differences between groups on demographic, personality, clinical (endocrine characteristics), and outcome variables—in these analyses, overweight and obese adolescents were collapsed to form the excess weight group. We examined intercorrelations between these variables by group using Pearson correlation coefficients. To test the main study hypotheses, we conducted three-step level hierarchical multiple regression models to examine the influence of (i) age, (ii) SR and SP personality traits, and (iii) BMI on the outcome measures of impulsivity (UPPS), disinhibition (Stroop Inhibition), and inflexibility (Stroop switching). We computed the changes in R^2 associated with the inclusion of each of these steps on the prediction model in order to estimate their separate (and aggregated) contribution to prediction of outcome variables.

RESULTS

Group comparisons

Results are presented in **Table 2**. Excess weight and normal weight adolescents did not significantly differ on sensitivity

Table 2 Descriptive scores and group comparisons for measures of sensitivity to punishment/reward (SPSRQ), impulsivity (UPPS-P), and response inhibition and switching (CWIT Stroop)

	Mean (s.d.)			
	Normal weight	Excess weight	*t*	Cohen's *d*
SPSRQ sensitivity to reward	12.05 (5.22)	9.55 (4.20)	2.052[a]	0.55
SPSRQ sensitivity to punishment	10.62 (5.50)	9.93 (4.97)	0.502	0.13
UPPS-P negative urgency	26.29 (7.14)	27.55 (7.31)	–0.651	0.17
UPPS-P lack of premeditation	26,38 (5.77)	25.19 (5.65)	0.783	0.21
UPPS-P lack of perseverance	23,38 (4.84)	21.79 (4.26)	1.339	0.36
UPPS-P sensation seeking	33,81 (6.38)	29.98 (7.25)	2.056[a]	0.55
UPPS-P positive urgency	24,67 (6.99)	25.48 (8.25)	–0.385	0.10
CWIT Stroop response inhibition	12.24 (2.62)	11.55 (1.94)	1.180	0.31
CWIT Stroop response switching	8.24 (2.53)	8.83 (2.45)	–0.900	0.24

[a]Significant differences between the groups.

[Q4] **Table 3 Correlations between age, BMI, endocrine parameters, UPPS-P, SPSRQ, and STROOP variables for each group**

Normal weight (*n* = 21)

	BMI	I	BG	Tri	C	HDL	NU	Pre	Per	SS	PU	SP	SR	RI	RS
Age	0.243	−0.330	0.145	0.073	−0.205	−0.054	0.025	−0.185	−0.072	−0.024	0.279	0.082	0.288	0.200	0.085
BMI		−0.552	0.258	0.166	−0.376	−0.551[a]	−0.025	0.000	0.039	−0.224	0.019	−0.052	−0.121	0.203	0.123
I			−0.522	0.079	0.262	0.778[b]	−0.374	−0.625	−0.111	−0.364	−0.388	0.186	−0.125	0.391	−0.631
BG				0.070	0.196	−0.276	−0.176	−0.122	−0.072	0.091	−0.113	−0.252	−0.323	−0.216	0.282
Tri					0.224	−0.239	−0.036	0.080	0.016	0.040	−0.088	−0.217	0.227	0.290	−0.205
C						0.388	0.164	0.036	0.005	−0.030	0.249	−0.022	−0.017	−0.354	−0.186
HDL							−0.291	−0.356	−0.154	−0.207	−0.189	0.261	−0.239	−0.062	−0.183
NU								0.545[a]	0.585[b]	0.460[a]	0.816[b]	0.156	0.596[b]	−0.310	0.146
Pre									0.474[a]	0.557[b]	0.300	−0.286	0.290	−0.567[b]	0.233
Per										0.454[a]	0.423	0.535[a]	0.581[b]	−0.444[a]	0.433[a]
SS											0.452[a]	−0.062	0.531[a]	−0.296	0.174
PU												0.214	0.714[b]	−0.300	0.104
SP													0.297	0.027	0.241
SR														−0.161	0.177
RI															−0.521[a]

Excess weight (*n* = 42)

	BMI	I	BG	Tri	C	HDL	NU	Pre	Per	SS	PU	SP	SR	RI	RS
Age	0.198	0.003	0.040	−0.063	0.159	0.083	0.156	0.139	0.454[b]	0.173	0.205	0.034	0.200	0.187	0.089
BMI		0.458[a]	0.102	−0.159	−0.168	0.014	0.477[b]	0.161	0.315[a]	0.245	0.360[a]	0.355[a]	0.261	0.210	0.215
I			0.275	0.332	−0.372[a]	−0.410[a]	0.457[a]	−0.208	0.051	−0.006	0.420[a]	0.313	0.093	−0.130	0.345
BG				0.090	−0.169	−0.354[a]	0.217	0.333[a]	−0.111	−0.046	0.037	0.050	0.197	−0.015	−0.047
Tri					0.138	−0.400[b]	−0.148	−0.125	−0.148	−0.191	−0.169	−0.173	−0.053	−0.044	−0.081
C						0.552[b]	−0.180	−0.035	0.105	−0.143	−0.237	−0.062	−0.009	0.031	0.029
HDL							−0.067	0.079	0.148	0.032	−0.126	0.166	−0.024	0.154	0.155
NU								0.378[a]	0.078	0.437[b]	0.791[b]	0.462[b]	0.522[b]	0.011	0.240
Pre									0.027	0.197	0.312[a]	−0.258	0.325[a]	−0.045	0.091
Per										−0.010	0.014	0.125	−0.096	0.127	−0.149
SS											0.348[a]	0.003	0.434[b]	−0.120	0.324[a]
PU												0.261	0.508[b]	0.064	0.174
SP													0.237	0.158	0.021
SR														−0.047	0.310[a]
RI															−0.334[a]

BG, basal glucose; C, total cholesterol; HDL, high-density lipoprotein cholesterol; I, insulin; NU, negative urgency; Per, perseverance; Pre, premeditation; PU, positive urgency; RI, response inhibition; RS, response switching; SP, sensitivity punishment; SPSRQ, sensitivity to punishment/reward; SR, sensitivity reward; SS, sensation seeking; Tri, triglycerides; UPPS-P, impulsivity.
[a]$P \leq 0.05$; [b]$P \leq 0.01$.

[Q5] **Table 4 Multiple regression models testing the association between age, SPSRQ, and BMI on UPPS-P and STROOP**

	Age	SP/SR	BMI	Full model	
	R^2 change (*P* value)	*R^2 change* (*P* value)	*R^2 change* (*P* value)	*R^2 adjusted* (*P* value)	Significant contributors
Impulsivity—UPPS-P					
Negative urgency	0.014 (0.347)	0.293 (0.000)	0.106 (0.002)	0.374 (0.000)	SR (0.000) BMI (0.002)
Premeditation	0.001 (0.848)	0.234 (0.000)	0.11 (0.350)	0.197 (0.001)	SP (0.002) SR (0.001)
Perseverance	0.064 (0.044)	0.081 (0.066)	0.002 (0.737)	0.048 (0.044)	Age (0.044)
Sensation seeking	0.010 (0.431)	0.256 (0.000)	0.001 (0.760)	0.229 (0.000)	SR (0.000)
Positive urgency	0.050 (0.075)	0.257 (0.000)	0.049 (0.039)	0.312 (0.000)	SR (0.000) BMI (0.039)
CWIT Stroop					
Response inhibition	0.031 (0.161)	0.023 (0.488)	0.007 (0.517)	–0.003 (0.437)	—
Response switching	0.010 (0.432)	0.044 (0.258)	0.067 (0.039)	0.061 (0.103)	BMI (0.039)

CWIT Stroop, response inhibition and switching; SP, sensitivity to punishment; SR, sensitivity to reward; SPSRQ, sensitivity to punishment/reward; UPPS-P, impulsivity.

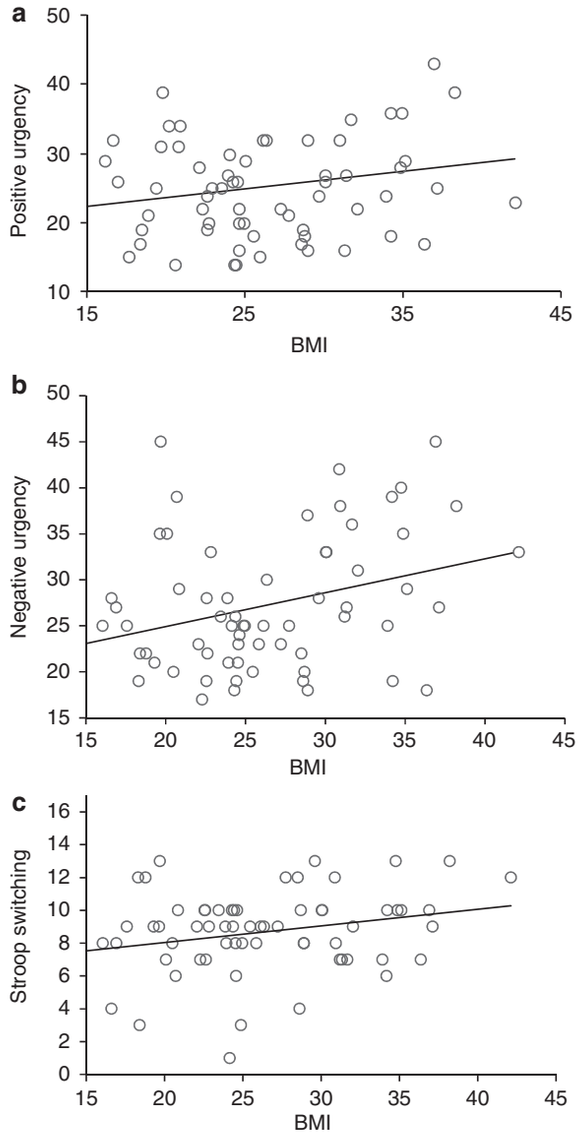
to punishment, UPPS dimensions of positive and negative urgency, and lack of premeditation and perseverance. Normal weight adolescents showed increased sensitivity to reward (SPSRQ) and elevated sensation seeking (UPPS-P), but effect sizes were medium (Cohen's $d = 0.5$), and these differences would not survive correction for multiple comparisons ($P < 0.006$). No differences were found on performance on the Stroop test.

Correlations

Results are displayed in **Table 3**. Due to the high number of analyses, and to avoid inflated type I error, here we only refer to significant correlations at $P < 0.01$. In the excessive weight group, SR was positively correlated with negative urgency and positive urgency. SP was only positively correlated with negative urgency. In addition, negative urgency was positively correlated with BMI. In the normal weight group, SR was significantly positively correlated with negative urgency, positive urgency, and lack of perseverance. Endocrine markers did not show significant correlations with personality or neuropsychological indices.

Regression models

Results are presented in **Table 4**. Age only predicted scores on lack of perseverance. The block including personality traits (SR and SP) significantly predicted scores on the impulsivity dimensions of sensation seeking, lack of premeditation, positive and negative urgency (SR was the main predictor of all models with the exception of the one on lack of premeditation—predicted by both SR and SP), but failed to predict performance on the Stroop test. Inclusion of BMI significantly increased the predictive capacity of age and personality traits on the impulsivity dimensions of positive and negative urgency, and on performance in the Stroop-Switching condition. **Figure 1** graphically displays the associations between BMI and each of these variables.



[Q6]

Figure 1 Regression slopes showing significant associations between BMI and (**a**) positive urgency, (**b**) negative urgency, and (**c**) Stroop Switching

DISCUSSION

Our findings show that BMI positively predicts levels of positive and negative urgency, and negatively predicts Stroop-Switching

performance in adolescents with overweight and obesity. SR significantly predicts positive and negative urgency, sensation seeking, and lack of premeditation, but fails to predict cognitive performance in the Stroop test. These findings demonstrate that increases in BMI are specifically associated with elevations in emotion-driven impulsivity and cognitive inflexibility, supporting a dimensional path in which adolescents with excess weight increase their proneness to overindulge when under strong affective states, and their difficulties to switch or reverse habitual behavioral patterns.

Excess weight adolescents, compared with their normal weight peers, had very similar psychological concerns, personality characteristics, and executive control performance. The main significant differences—of medium size—emerged for the traits of SR and sensation seeking, but in both cases excess weight individuals had diminished levels of these traits. Therefore, our findings are not supportive of the "hard" conception of adolescent obesity as a dysfunction characterized by hypersensitivity to reward and disrupted inhibitory control (3,14); in fact, the only trait correlated with BMI within the excess weight group was sensitivity to punishment. Conversely, our dimensional approach showed that BMI is significantly associated with increased impulsivity—but only under strong affective states, and poorer cognitive switching. Since sensitivity to punishment and urgency are psychometrically correlated in healthy youths (28), and both have shown significant associations with dysfunctional thought control and compulsivity (18,32), our findings suggest that adolescent obesity is better characterized by negative reinforcing mechanisms triggering habitual behaviors—then difficult to reverse, than by rash-spontaneous impulsivity mechanisms (33). It is interesting to note that this point is straightforward in the case of the link between SP, negative urgency, and compulsivity, but less intuitive to explain the effects of BMI on positive urgency. Taking into account the personality profile of the excess weight group, we believe that this path may be explained in similar terms, because adolescents with excess weight would tend to be constrained (i.e., they are submissive and dependent) until they find themselves in very positive mood, whereby they would feel entitled to overindulge. The overall pattern of increased sensitivity to punishment is consistent to that found in the whole spectrum of eating disorders (34).

The fact that BMI scores predict Stroop-Switching but not Stroop inhibition scores is neatly indicative of the notion that flexibility is the main neuropsychological correlate of adolescent excess weight. This finding is in agreement with those of previous studies showing that neurocognitive deficits associated with poor set-shifting and increased perseveration are typical of children and adolescent with excess weight (8,16,17). Nonetheless, there is also evidence of robust deficits in working memory and inhibitory control—taxed with the classic Stroop Color-Word test—in excess weight adolescents having considerably higher BMI levels (mean of 39.86 vs. 29.15 in this study (8)). Altogether, these findings suggest that impaired flexibility is an early cognitive correlate of the disorder (16), which linearly declines as a function of increased adiposity (16,17); however, the deleterious effects of excess weight on neurocognition may progressively extend to other aspects of executive control as the disorder becomes more severe (8). Interestingly, flexibility deficits are also found in other eating disorders, including anorexia and bulimia (35,36), and evidence on the stability of these deficits suggests that it may be a trait or an endophenotype related to eating disorders (36–38). Complementarily, the available evidence in childhood and adolescent obesity suggest that increased inflexibility may also reflect a transition from impulsive to compulsive states—impulsivity correlates with BMI in 8- to 10-year-old kids but not in adolescents (12). This notion would actually give support to proposed parallels between obesity and addiction (9,14). Irrespective of their etiology, flexibility deficits may compromise recovery potential in obesity in a number of ways, including inability to reverse habitual feeding patterns or to change unhealthy lifestyles.

Strengths of this study include the careful selection of the excess weight adolescents, who were matched to their normal weight peers in biochemical and psychological indices; this selection allowed us to elegantly test the neuropsychological assumptions without any medical or psychological confounder. In addition, we used specific well-validated indices of inhibition vs. switching skills, which are regarded as neurocognitive probes of impulsive vs. compulsive behavioral patterns (15), providing a novel approach to the notion that the development of obesity holds several parallels with the neuroadaptations that characterize addiction (14). Relevant shortcomings include the relatively small sample size, which is nonetheless sufficient to implement the regression models we run (39), and the lack of naturalistic or psychometric measures of compulsive or binge-like food intake—which may have strengthen the theoretical links we raised. In conclusion, our findings are supportive of a dimensional approach to adolescent obesity, by which increases in weight and adiposity are associated with less ability to control impulses under strong affects and impaired cognitive flexibility.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

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DISCLOSURE

The authors declared no conflict of interest.

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ANEXO II

Effects of a multicomponent behavioral intervention on impulsivity and cognitive deficits in adolescents with excess weight

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The aim of this study was to explore the effects of a multidisciplinary behavioral intervention including cognitive behavioral therapy, structured physical activity, and dietary counseling on impulsive personality and cognitive skills and subsequent BMI loss in excess weight adolescents. Forty-two adolescents with excess weight (14 males and 28 females, range 12–17 years), as defined by the International Obesity Task Force Criteria, participated in our study. We used a longitudinal observational design with two assessments: before and after treatment. We collected baseline measures of impulsive personality (UPPS-P scale), cognitive performance (letter number sequencing, Stroop and Iowa gambling task), and biometric parameters. After 12 weeks of intervention, parallel measures were used to determine whether treatment-induced changes in impulsivity and cognition predicted changes in BMI. BMI showed a statistically significant reduction after treatment [from mean (SD) 29.36 (4.51) to 27.31 (4.41), Cohen's $d=0.5$]. Greater reductions in negative urgency (negative-emotion-driven impulsivity) and greater improvement in cognitive inhibitory control skills were associated with greater reductions in BMI. Because the design was correlational and lacked a control group, future studies should clarify whether these associations reflect a causal effect or just overlapping improvements associated with a third variable (e.g. increases in attention procurement or motivation). ***Behavioural Pharmacology*** **23:609–615 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The prevalence of adolescent overweight and obesity has increased markedly over the last two decades, rapidly reaching epidemic levels (Lee *et al.*, 2011). Conversely, the quest for effective treatment approaches remains unfulfilling, and only multicomponent interventions have shown efficacy for adolescents' weight reduction (Wilfley *et al.*, 2007; McGovern *et al.*, 2008). This is a particularly challenging issue because adolescents represent a particularly vulnerable group in whom the likelihood of developing chronic obesity problems is high (Whitaker *et al.*, 1997) and the motivation to seek and comply with treatment is low (Acosta *et al.*, 2008; Poobalan *et al.*, 2010). Hence, there is a need to identify and potentiate active components of these interventions that may increase their power to produce enduring weight changes in adolescents (Kelly and Melnyk, 2008). We reason that these active components should relate to cognitive skills and personality-related individual differences that typically emerge during adolescence, such as inhibitory control and emotion regulation (Nigg, 2000).

In recent years, burgeoning evidence from neuroscience studies has indicated that BMI in adolescents is associated positively with increased activation of brain emotional systems (frontal operculum, insula) (Stice *et al.*, 2008) and correlated negatively with the activation of the neural network supporting inhibitory control (several regions of the prefrontal cortex) in response to highly appetizing food stimuli (Batterink *et al.*, 2010). Higher BMI levels are also correlated significantly with emotional aspects of impulsive personality, such as positive and negative urgency – the tendency to commit impulsive acts when feeling good or bad (Delgado-Rico *et al.*, 2012). Furthermore, adolescents with excess weight show enhanced emotional reactivity (Gallant *et al.*, 2010) and a range of cognitive executive performance decreases in tasks of inhibitory control, flexibility, and decision-making

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(Verdejo-García *et al.*, 2010b). These decreases in performance are associated with volumetric reductions in the orbitofrontal cortex (Maayan *et al.*, 2011), a key hub for emotion regulation and impulse control (Bechara, 2005).

Overall, evidence suggests that adolescents with excess weight have a poor balance between (increased) emotional processing and (lower) inhibitory control. This poor balance may relate to increased food procurement and intake during discrete eating episodes (Nederkoorn *et al.*, 2009; Appelhans *et al.*, 2011) but also to more enduring dysfunctional diet patterns leading to weight gain (Anzman and Birch, 2009; Nederkoorn *et al.*, 2010) or to worse treatment prognosis (Nederkoorn *et al.*, 2006). Critically, the impact of these domains may be amplified during adolescence, as this developmental period is inherently characterized by sudden elevations in emotional reactivity and progressive fine tuning of inhibitory control (Brenhouse and Andersen, 2011). Therefore, interventions for emotion regulation and inhibitory control should become important aspects of multicomponent interventions in adolescents, and in the improvement of these domains, should correlate with treatment success.

In this study, we aimed to explore whether training of emotion regulation and inhibitory control (engrained in the broader framework of a multidisciplinary treatment intervention) would produce significant changes in these processes and whether these changes are accompanied by contingent reductions in BMI.

Methods

Design

We used a longitudinal design with two assessments: before and after treatment. We collected baseline measures of the different dimensions of impulsive personality (UPPS-P scale), cognitive performance (letter number sequencing, Stroop and Iowa gambling task), BMI, and the usual biochemical parameters (insulin, basal glucose, triglycerides, and cholesterol). In the week after baseline assessments, we initiated the multicomponent treatment intervention, which lasted for 12 weeks. The same tests (using parallel versions of cognitive performance tests when available) were repeated in the week after completion of the intervention. The study was approved by the Ethical Committee for Research in Humans of the University of Granada; all procedures were conducted in accordance with the Declaration of Helsinki.

Sampling context

Forty-two adolescents with excess weight (14 males and 28 females) participated in our study. The age range was 12–17 years; the mean (±SD) was 14.19 (1.38) years. Their BMI [weight/height^2 (kg/m^2)], as measured at the onset of the study, was 22.06–38.21 and the mean (±SD) BMI was 29.15 (4.50) kg/m^2. All study participants provided a blood sample for a blood test including insulin, basal glucose, triglycerides, and cholesterol. A more detailed description of the sociodemographic and clinical data is shown in Table 1.

We recruited participants from educational centers and from the Endocrinology Unit of the Hospital 'Virgen de las Nieves' in Granada (Spain). For inclusion in the study, participants had to fulfill the following criteria: (i) age range between 12 and 17, (ii) BMI levels within the range of overweight or obesity according to the International Obesity Task Force criteria defined by Cole *et al.* (2000), (iii) absence of past/current evidence of medical or psychological disorders, and (iv) at least one of the parents had to be actively involved throughout the treatment process. Parents had to sign an informed consent for the adolescents to participate in the study. They were enrolled in a larger study aimed at testing a novel multicomponent behavioral intervention for adolescent excess weight, the aim of which was to alter eating-related lifestyles and improve cognitive-behavioral skills and physical activity (BRAINOBE Study).

Biometric parameters

Body mass index

BMI was obtained from direct measures of weight and height (both at study onset and after the intervention) and calculated for each participant as the ratio weight (kg)/[height (m)]^2.

Biochemical parameters

Blood tests yielded data for insulin (μU/ml), basal glucose (mg/dl), triglycerides (mg/dl), and total cholesterol levels (mg/dl).

Table 1 Descriptive scores for sex, socioeconomic status, age, BMI, and biochemical parameters

	n (%)	
Sex		
Men	14 (33.3)	
Women	28 (66.7)	
SES (annual income)[a]		
€0–11.533	2 (5)	
€11.533–18.200	13 (32.5)	
€18.200–26.548	18 (45.0)	
€26.548–41.292	4 (10.0)	
€41.292–3.144.000	3 (7.5)	
	Mean (SD)	Range
Age	14.19 (1.38)	12–17
BMI	29.15 (4.50)	22.06–38.21
Biochemical parameters		
Insulin	16.23 (12.38)	1.5–52.5
Basal glucose	86.39 (9.41)	68.0–106.0
Triglycerides	96.15 (43.24)	45.0–235.0
Cholesterol	158.85 (26.41)	113.0–222.0

SES, socioeconomic status.
[a]Quintiles for SES are defined according to data from the Financial Survey for Spanish Families, *http://www.bde.es/webbde/es/estadis/eff/eff.html*.

Questionnaire measures of impulsivity

UPPS-P impulsive behavior scale (Whiteside and Lynam, 2001; Spanish version, Verdejo-García *et al.*, 2010a)

This scale is a 59-item inventory designed to measure five distinct personality pathways to impulsive behavior: negative urgency, lack of perseverance, lack of premeditation, sensation seeking, and positive urgency. Urgency (26 items) refers to the tendency to experience strong impulses under conditions of negative effect (negative urgency – 12 items) or positive effect (positive urgency – 14 items); lack of perseverance (10 items) refers to the 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, sensation seeking (12 items) incorporates two aspects: (a) a tendency to enjoy and pursue activities that are exciting and (b) an openness to trying new experiences that may or may not be dangerous. Each item on the UPPS-P is rated on a four-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.

Neuropsychological assessment

Letter number sequencing, Wechsler intelligence scale for children (Wechsler, 2003; Spanish version, Corral *et al.*, 2010)

Participants are read a sequence in which letters and numbers are combined, and are asked to reproduce the sequence heard, first placing the numbers in ascending order and then the letters in alphabetical order. The dependent variable from this test is the number of correct answers.

Color-word interference test Stroop, Delis–Kaplan executive functions system (Delis *et al.*, 2001)

This test consists of four different conditions, each containing 50 items. The first condition presents patches of colors and participants have to name them as quickly and accurately as they can. The second condition presents the words 'red', 'blue', and 'green' printed in black ink and participants are asked to read the words written aloud. The third condition introduces the condition of interference: the words 'red', 'blue', and 'green' are printed in incongruent color inks and participants have to name the color and ignore the word. In the fourth condition, the items are similar to condition three but participants have to switch their response between naming the color of the ink (in most trials) and reading the word (when the item is inside a small box). The main dependent variables from this test are the composite time measures: inhibition versus color naming (time part 3 – time part 1), inhibition/switching versus combined naming + reading (time part 4) – (time part 1 + 2), and inhibition/switching versus inhibition (time part 4 – time part 3) (Delis *et al.*, 2001).

Iowa gambling task (Bechara *et al.*, 2000)

This is a measure of decision-making involving both uncertainty and risk. Participants have to make a series of choices between four decks of cards that yield different reward/punishment contingencies. Unbeknownst to the participants, two of the decks (A and B) are considered risky (yield high rewards but even higher penalties) and two of the decks (C and D) are considered safe (yield low rewards but even lower penalties). Moreover, two of the decks (A and C) provide constant reward/punishment contingencies, whereas two of the decks (B and D) provide irregular reward/punishment contingencies. The main dependent variable is obtained by applying the formula $[(C + D) - (A + B)]$ to the participants' choices. Positive scores represent the relative preference for the safe advantageous decks, whereas negative scores represent the relative preference for the risky disadvantageous decks.

Multicomponent treatment intervention

The multicomponent intervention was conducted in small groups of 10–12 participants each, and was implemented for 12 consecutive weeks (one session/week) across four different waves ($n = 42$). The intervention included three intertwined modules: (a) a psychosocial module, (b) a nutritional module, and (c) a physical activity module. The psychosocial module was implemented in weekly workshops dedicated to the training of specific skills including cognitive skills (inhibitory control, planning, and conflict resolution) and affective skills (emotional expression and regulation). The nutritional module consisted of prescription and monitoring of personalized diets designed as a function of sex, age, and BMI z-scores (Moreno *et al.*, 2006). We applied guidelines for caloric restriction of -10% for BMI SD > 1, -20% for BMI $1 <$ SD < 2, -30% for BMI SD > 3, and -30% for BMI SD > 4. For all diets, we set a minimum caloric limit of 1500 kcal. Dietary prescriptions were implemented during sessions 2, 5, and 8, corresponding to the prescription of closed diets (3 weeks), supervision and prescription of closed diets with selected meals (3 weeks), and supervision and prescription of extensive diets (3 weeks), respectively. Monitoring of dietary compliance was conducted every week during personal appointments of the participants and their parents with the psychologist and the nutritionist. During these sessions, compliance was monitored through interview and review of meal registries, and supported by counseling on strategies to facilitate adequate observance (Martínez-Gómez *et al.*, 2009). The physical activity module consisted of prescription and monitoring of a personalized physical activity program aimed at achieving the standard minimum physical exercise for this age group – around 1 h/day (Martínez-Gómez *et al.*, 2009; Muñoz *et al.*, 2010). The exercise prescribed consisted of at least 1 h of moderate-to-vigorous intensity aerobic exercise for 3–5 days/week, depending on the individual physical activity level. Energy expenditure was estimated in metabolic equivalent values (Ainsworth

et al., 2000) for each activity and the frequency and intensity of the activities of the exercise program (walking, biking, running, swimming, etc.). The energy expenditure range obtained was from 15 to 23 kcal/kg of body weight/week. A more detailed description of the program is shown in Table 2.

Data analyses

Statistical analyses were implemented on the Predictive Analytics Software SPSS version 18 (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, USA). We first used related-sample *t*-tests to examine the differences between baseline and post-treatment measures of impulsivity (UPPS-P), cognitive performance (letter number sequencing, Stroop and Iowa gambling task), and BMI. For those measures showing significant differences between baseline and after treatment (treatment-related changes), we calculated standardized 'change scores' by regressing baseline scores over post-treatment scores and saving the standardized residuals. Next, we used linear regression models using 'change scores' of impulsivity and cognitive performance as predictor variables and 'change scores' of BMI as the treatment outcome variable.

Results

Changes in biometrical variables

The results are presented in Table 3. The main treatment outcome variable – BMI – showed a statistically significant reduction after treatment. We also observed a significant decrease in cholesterol levels.

Changes in impulsivity and cognitive measures

The results are presented in Table 4. In relation to impulsivity levels, we found a significant reduction in negative urgency scores (UPPS-P). In relation to cognitive performance, there were significant improvements in performance on Stroop response inhibition and switching indices.

Association between changes in impulsivity and cognition and body mass index reductions

The results are presented in Table 5 and Figs 1 and 2. The models were set using the change scores of impulsivity and cognition as predictors, and the BMI change as the dependent variable; this modeling fits with the assumption that impulsivity and cognition reflect processes targeted during the intervention, whereas BMI reductions represent the main treatment outcome. We observed that change scores of negative urgency (UPPS-P) predicted change scores of BMI; greater reductions of negative urgency predicted greater reductions of BMI (Fig. 1). In relation to cognitive performance, we observed that change scores of Stroop response inhibition and switching predicted change scores of BMI; in this case, greater improvements on Stroop performance predicted greater reductions in BMI (Fig. 2).

Table 2 Detailed description of the multicomponent behavioral intervention: distribution of sessions, and duration, objectives, structure, and attendants for each session

Session	Duration (min)	Objectives	Structure (min)	Attendants
1	60	Induction		Adolescents and parents
2	150	Prescription of personalized diets and physical activity programs		Adolescents and parents
3	70	Monitoring and planning of physical activity	20	Adolescents
		Psychology I: attention. Healthy lifestyles	50	
4	70	Monitoring of physical activity	20	Adolescents
		Psychology II: attentional slips. Self-esteem	50	
5	130	Monitoring of physical activity	20	Adolescents and parents
		Diet adjustments	60	
		Psychology III: stimulus control and reinforcement management	50	
6	70	Monitoring of physical activity	20	Adolescents
		Psychology IV: inhibitory control of behavior and emotions	50	
7	120	Physical activity: ongoing assessment and adjustment	60	Adolescents and parents
		Psychology V: working memory. Expression and processing of positive and negative emotions	60	Adolescents
8	120	Diet adjustments	60	Adolescents and parents
		Psychology VI: goal planning. Coping with critiques	60	Adolescents
9	70	Monitoring of physical activity	20	Adolescents
		Psychology VII: goal achievement: planning, decision-making and monitoring. Social skills: 'Learning to say no'	50	
10	60	Psychology VIII: relapse prevention: identification/management of 'at risk' situations. Asking for help	60	Adolescents
11	70	Monitoring of physical activity	20	Adolescents
		Psychology IX: relapse prevention: problem solution	50	
12	60	Rehearsal of key points	50	Adolescents and parents

Table 3 Descriptive scores and statistics of BMI and biochemical parameters (insulin, basal glucose, triglycerides, and total cholesterol) pretreatment and post-treatment measures

	Pretreatment		Post-treatment			
	Mean (SD)	Range	Mean (SD)	Range	*t*	Cohen's *d*
BMI	29.36 (4.50)	22.06–38.21	27.31 (4.41)	20.28–37.44	8.438*	0.5
Biochemical parameters						
Insulin	16.23 (12.38)	1.5–52.5	13.99 (6.95)	3.4–42.6	1.155	0.2
Basal glucose	86.39 (9.41)	68.0–106.0	87.56 (8.67)	69.0–108.0	−0.529	0.1
Triglycerides	96.15 (43.24)	45.0–235.0	96.10 (40.83)	46.0–232.0	0.006	0
Cholesterol	158.85 (26.41)	113.0–222.0	149.39 (24.89)	108.0–199.0	2.568*	0.4

*$P<0.01$.

Table 4 Descriptive scores and statistics of impulsivity measures (UPPS-P) and outcome neuropsychological variables (letter number sequencing, Stroop and Iowa gambling task) pretreatment and post-treatment measures

	Pretreatment		Post-treatment			
	Mean (SD)	Range	Mean (SD)	Range	*t*	Cohen's *d*
UPPS-P						
NU	27.68 (7.47)	18–45	25.03 (7.45)	13–41	2.642*	0.4
Pre	25.20 (5.79)	14–44	24.98 (5.22)	16–42	0.294	0.04
Per	21.53 (4.19)	13–30	21.18 (5.17)	12–36	0.396	0.1
SS	30.30 (7.27)	13–42	32.33 (7.70)	17–48	−1.822	0.3
PU	25.53 (8.40)	14–51	23.90 (9.34)	14–56	1.057	0.2
LNS	10.33 (2.99)	4–16	10.18 (2.92)	3–16	0.386	0.1
Stroop						
RI	11.57 (1.99)	7–16	11.72 (1.47)	9–15	−0.506	0.1
RIS	9.67 (2.14)	4–16	10.40 (2.02)	6–14	−2.308*	0.4
RS	9.00 (2.32)	1–13	9.15 (1.70)	3–13	−0.431	0.1
IGT	−0.48 (19.21)	−52 to 60	8.15 (34.79)	−96 to 80	−1.791	0.3

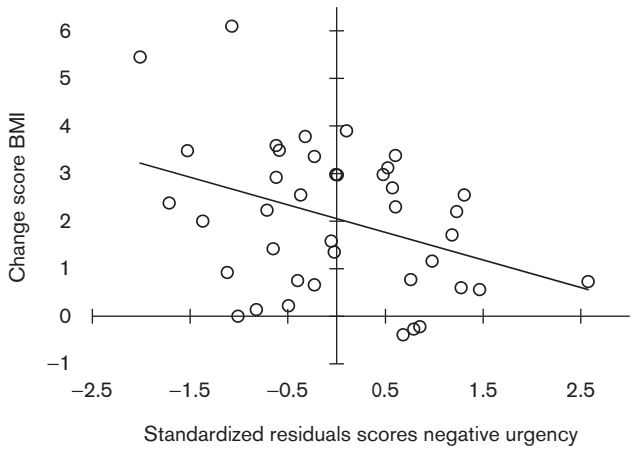
Total scores are reported for UPPS-P and Iowa gambling task. Scaled scores are reported for letter number sequencing and Stroop.
IGT, Iowa gambling task, ABCD version; LNS, letter number sequencing; NU, negative urgency; Per, lack of perseverance; Pre, lack of premeditation; PU, positive urgency; RI, response inhibition; RIS, response inhibition and switching; RS, response switching; SS, sensation seeking; Stroop, color-word interference test Stroop; UPPS-P, UPPS-P impulsive behavior scale.
*$P<0.05$.

Table 5 Standardized residuals scores impulsivity measures (UPPS-P) and outcome neuropsychological variables (letter number sequencing, Stroop, and Iowa gambling task) on change score BMI using standard regression models

	F	*P*	R^2 adjusted
UPPS-P (total score)			
Negative urgency	6.086	0.02*	0.11
Lack of premeditation	0.158	0.69	−0.02
Lack of perseverance	1.147	0.29	0.00
Sensation seeking	0.760	0.39	−0.01
Positive urgency	2.950	0.09	0.05
Letter number sequencing (scaled score)	1.069	0.31	0.00
Stroop (scaled score)			
Response inhibition	5.049	0.03*	0.09
Response inhibition and switching	8.836	0.00*	0.17
Response switching	3.202	0.08	0.05
Iowa gambling task (total score)	0.149	0.70	−0.02

Stroop, color-word interference test stroop; UPPS-P, UPPS-P impulsive behavior scale
*$P<0.05$.

Fig. 1

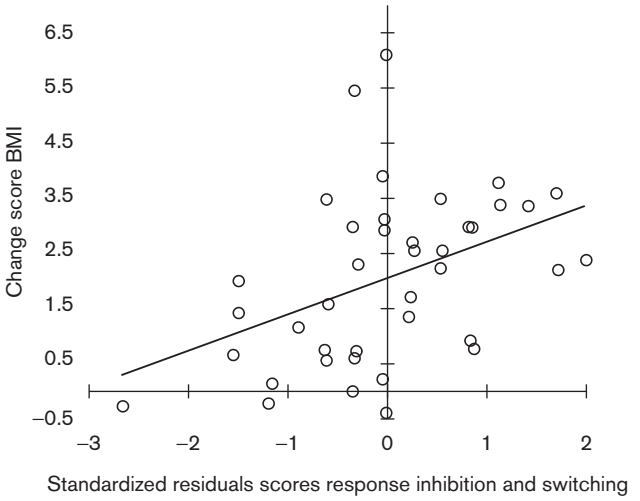


Association between pretreatment and post-treatment changes in negative urgency and changes in BMI.

Discussion

Our data showed that the multicomponent behavioral intervention produced significant medium-sized effects on BMI loss, accompanied by a significant decrease in cholesterol levels. This finding is in agreement with the results from previous meta-analyses yielding a modest beneficial effect of combined lifestyle interventions on adolescent weight loss (Wilfley *et al.*, 2007; McGovern *et al.*, 2008). In the quest for active components of the intervention that may predict individual differences in treatment success, we found that those adolescents showing greater reductions in negative-emotion-driven impulsivity (negative urgency) and greater improvement of cognitive inhibitory control skills also showed greater loss of adiposity. However, other cognitive skills, such as working memory or decision-making, did not change during treatment. Overall, these findings support our main assumption that changes in inhibitory control and emotional regulation are associated with better outcomes of adolescent obesity treatment. We speculate that the basis for this association is that a better balance between emotional reactivity and impulse control may favor better achievement of weight control strategies and ultimately BMI loss. However, we acknowledge that the correlational nature of our study precludes us from inferring causality and that alternative accounts (e.g. BMI loss facilitates inhibitory control and emotion regulation) are also plausible.

Fig. 2



Association between pretreatment and post-treatment changes in Stroop-indexed inhibitory control and changes in BMI.

The results on the dimension of negative urgency are consistent with basic findings linking increased trait impulsivity with excess weight among children and adolescents (Fields *et al.*, 2011; Van den Berg *et al.*, 2011). They are also in agreement with clinical findings showing that lower levels of trait self-control and higher levels of emotional eating powerfully predict a lower ability to lose weight during behavioral interventions in adults (Blair *et al.*, 1990; Crescioni *et al.*, 2011). More specifically, those aspects of impulsivity that are strongly linked to motivational drives (sensitivity to reward and punishment) and emotional regulation (negative urgency) seem to be particularly predictive of excessive food intake and excess weight problems (Jansen *et al.*, 2009; Mobbs *et al.*, 2010). Critically, these traits are sensitized during adolescence, which is characterized by sudden elevations in emotional reactivity but still immature inhibitory control (Brenhouse and Andersen, 2011). Therefore, we reason that negative urgency (the dimension of impulsivity more clearly associated with emotion regulation) might be a relevant correlate of clinical outcome in adolescent obesity and a potentially useful target to address during behavioral and pharmacological interventions. In agreement with this notion, evidence suggests that adolescents who seek treatment for overweight problems experience greater loss of control in association with sensitized emotional states, such as stress or anxiety (Goossens *et al.*, 2009). Furthermore, emotional control problems during adolescence predict long-term stability of weight problems and the emergence of other psychiatric disorders (Patton *et al.*, 2003). Conversely, the training of this component may significantly improve the outcomes of interventions for adolescent obesity; this notion is supported by recent evidence showing that mindfulness-based training, tapping affective regulation skills, is associated with weight loss in obese adults (Alberts *et al.*, 2010).

The results also showed that improvement in inhibitory control and shifting skills (Stroop) predicted BMI loss in this sample of excess-weight adolescents. Interestingly, there is evidence that the development of these executive skills (inhibition and shifting) moderates temperamental elevations of emotional reactivity (White *et al.*, 2011), providing a theoretical link between negative urgency and Stroop findings, and suggesting that the amelioration of inhibitory control skills (through behavioral or pharmacological interventions) may be accompanied by improvements in emotional regulation. Adequate inhibitory control seems to be critical for the successful achievement and maintenance of weight loss; for example, the Stroop interference effect to appetizing food words is reduced among long-term weight-loss maintainers, as compared with obese controls (Phelan *et al.*, 2011). Recent studies have provided evidence of the efficacy of behavioral interventions for reducing inhibitory control deficits in other clinical populations (Alfonso *et al.*, 2011); therefore, future studies should examine the impact of these interventions on weight loss during adolescence. Nonetheless, a recent study showed the paradoxical effects of motor disinhibition overweight loss ability in adolescents: high-impulsive adolescents lost more weight than those who were less impulsive (Pauli-Pott *et al.*, 2010). This apparent discrepancy may be related to the distinct role of different facets of impulsivity in relation to the clinical problems and their treatment; for example, a certain degree of motor excitability should be a positive factor for adequate treatment engagement. This link can be reflected in our finding that sensation-seeking scores – especially in relation to the search for novel activities – increased in excess-weight adolescents during treatment. However, inadequate control of negative emotions or prepotent action tendencies is more plausibly linked to poorer treatment outcome, as shown here.

Conclusion

We can conclude that changes in negative urgency and inhibitory control accompany changes in BMI loss during a multicomponent intervention for weight loss among adolescents. Because the design is correlational and we did not use a control group, future studies should clarify whether these associations reflect a causal effect between these variables or just overlapping improvements associated with a third variable (e.g. increases in attention procurement or motivation).

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Conflicts of interest

There are no conflicts of interest.

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ANEXO III

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PLOS ONE

Brain Structural Correlates of Reward Sensitivity and Impulsivity in Adolescents with Normal and Excess Weight

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Abstract

Introduction: Neuroscience evidence suggests that adolescent obesity is linked to brain dysfunctions associated with enhanced reward and somatosensory processing and reduced impulse control during food processing. Comparatively less is known about the role of more stable brain structural measures and their link to personality traits and neuropsychological factors on the presentation of adolescent obesity. Here we aimed to investigate regional brain anatomy in adolescents with excess weight vs. lean controls. We also aimed to contrast the associations between brain structure and personality and cognitive measures in both groups.

Methods: Fifty-two adolescents (16 with normal weight and 36 with excess weight) were scanned using magnetic resonance imaging and completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ), the UPPS-P scale, and the Stroop task. Voxel-based morphometry (VBM) was used to assess possible between-group differences in regional gray matter (GM) and to measure the putative differences in the way reward and punishment sensitivity, impulsivity and inhibitory control relate to regional GM volumes, which were analyzed using both region of interest (ROI) and whole brain analyses. The ROIs included areas involved in reward/somatosensory processing (striatum, somatosensory cortices) and motivation/impulse control (hippocampus, prefrontal cortex).

Results: Excess weight adolescents showed increased GM volume in the right hippocampus. Voxel-wise volumes of the second somatosensory cortex (SII) were correlated with reward sensitivity and positive urgency in lean controls, but this association was missed in excess weight adolescents. Moreover, Stroop performance correlated with dorsolateral prefrontal cortex volumes in controls but not in excess weight adolescents.

Conclusion: Adolescents with excess weight have structural abnormalities in brain regions associated with somatosensory processing and motivation.

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Introduction

Overweight and obesity are the ultimate consequence of an energy imbalance between consumed and expended calories. Nevertheless, the fact that -in the context of an unlimited access to food- not everyone becomes obese indicates that there are important individual differences in the susceptibility to develop such disorders. Although a number of psychological factors have been proposed to explain the development and maintenance of obesity [1], in the past few years, the motivational traits associated with reward and punishment sensitivity, and the personality and neuropsychological dimensions associated with impulse control, have been highlighted as relevant modulators of such susceptibility [2,3]. The impact of these factors on eating behaviour seems to be particularly influential during adolescence [4,5], a developmental period in which both motivational tendencies and impulse control skills strongly modulate goal-directed behaviour [6].

The study of the brain structures associated with these motivational, personality and neuropsychological variables in obese adolescents could provide more sensitive information about excess weight during adolescence, since regional brain anatomy indices may be considered a more stable measurement ultimately

linked to both personality and cognitive modulators associated to the development of particular disorders [7]. Previous evidence from structural imaging studies have revealed that obese adolescents have lower total gray matter (GM) volumes and reduced regional GM volumes in the orbitofrontal cortex compared to lean controls [8,9]. Moreover, in the Yokun et al. [8] study, higher body mass indices (BMIs) were correlated to volume changes in brain regions involved in reward processing (striatum), memory (middle temporal/parahippocampal gyri), and somatosensory processing (rolandic operculum), whereas reduced regional GM volumes in the prefrontal cortex correlated with steeper rates of BMI increase at 1-year follow-up. Furthermore, Maayan et al. [9] found that obese adolescents were characterized by increased trait disinhibition scores and poorer cognitive control, and that both features correlated with the reduced GM volumes in the orbitofrontal cortex. These findings indicate that volumetric brain measures are useful to characterize the neurobiological underpinnings of adolescent obesity, and that brain structural volumes are associated with both disease-specific features (e.g., BMI) and impulsive personality and cognitive control functions.

Such findings are broadly in agreement with the results from functional imaging studies in obese adolescents and adults, in which these regions seem to play different roles. For example, during the processing of food rewards striatal activation is decreased whereas activations of prefrontal and somatosensory regions are increased in obese adolescents [10,11]. There is also evidence of increased resting activity in the somatosensory cortices of obese adults [12]. Moreover, the hippocampus is selectively engaged during gastric stimulation and this activation correlates with emotional eating and lack of control in obese adults [13]. Such results have led to hypothesize that decreased striatal functioning and increased somatosensory functioning may be associated with increased reward sensitivity in obese individuals, whereas increased hippocampal and prefrontal reactivity may relate to the balance between the emotional appeal of food and the cognitive control of eating behaviour [10,12,13].

In this study we used magnetic resonance imaging (MRI) and voxel based morphometry (VBM) procedures to assess regional brain anatomy in adolescents with excess weight. The aim of the study was twofold: firstly, to detect regional GM volume differences between adolescents with excess weight and adolescents with normal weight, and secondly, to examine possible differences in the way reward and punishment sensitivity, impulsive personality and cognitive control relate to regional GM volumes in both groups. We performed both a region of interest (ROI) and a whole-brain analyses approach. The ROIs were selected based on previous evidence of their involvement in adolescent obesity, and included the prefrontal cortex, the somatosensory cortices, the medial temporal lobe (including hippocampus), and the striatum. In agreement with previous evidence, we hypothesized that adolescents with excess weight will have decreased regional GM in the prefrontal cortex, whereas regional volumes of the striatum and the somatosensory regions will be related to reward sensitivity, and regional volumes of the prefrontal cortex will correlate with impulsivity and cognitive control.

Methods

1. Participants

Fifty-two adolescents (12–17 years old) participated in the study. The participants were initially classified as adolescents with normal weight (n = 16, mean BMI = 20.26, SD = 2.8), overweight (n = 16, mean BMI = 24.85, SD = 1.42) or obesity (n = 20, mean BMI = 31.46, SD = 2.91) according to their BMI following the International Obesity Task Force (IOTF) criteria defined by Cole et al. [14]. However, since we did not find significant differences between the excess weight groups (overweight vs. obesity) in any of the psychological or imaging variables assessed, we decided to merge these two groups in a single "excess weight group". Participants were recruited through educational centers and the endocrinology service of the hospital "Virgen de las Nieves" in Granada (Spain). Selection criteria were: (i) age between 12–17 years old, (ii) absence of a positive eating disorder history (Eating Disorder Inventory, EDI-2) [15], (iii) absence of personality disorders assessed by the Millon Adolescent Clinical Inventory (MACI) [16], and (iv) absence of past history or current existence of relevant medical problems (based on clinical history and a blood test). For both groups, evidence of significant abnormalities on MR images, contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects) and history of loss of consciousness (LOC) for longer than 30 minutes or LOC with any neurological consequence were also exclusionary.

This study was approved by the Ethics Committee of the University of Granada. All subjects and their parents provided written informed consent before participating in the study.

2. Instruments and assessment procedures

Assessments were conducted across two independent sessions. During the first session we administered the personality and cognitive measures (see descriptions below), together with a battery of cognitive tests whose results will be reported separately. The second session involved the MRI scanning, which lasted approximately 15 minutes.

2.1 Measure of reward and punishment sensitivity. *Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ):* This questionnaire is a self-report measure made up of 48 items, half of which assess the participant's appetitive motivational system, or reward sensitivity, and the other half the avoidance motivational system, or punishment sensitivity [17]. The reward and punishment sensitivity scales are reported to show adequate internal consistency, as well as convergent, construct and discriminate validity [18].

2.2 Measure of impulsivity. *UPPS-P Scale* [19,20]: 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-P scale [19]; the fifth dimension has been included on the basis of recent work by Cyders et al. [21], and Smith et al. [22]. Each item on the UPPS-P is rated on a 4-point scale ranging from 1 (*strongly agree*) to 4 (*strongly disagree*). Sensation seeking (12 items) incorporates two aspects: 1) a 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 it; and finally urgency refers to the tendency to experience strong impulses under conditions of negative affect (negative urgency –12 items) or positive affect (positive urgency – 14 items). We obtained the total scores of each of these five UPPS–P dimensions for analyses. The Spanish version of the UPPS–P Impulsive Behavior scale have showed adequate levels of reliability and validity and is considered an useful instrument for assessment of impulsivity in Spanish-speaking population [20].

2.3 Measure of inhibitory control. *Color-Word Interference Test–Stroop* (Delis–Kaplan Executive Functions System) [23]: The

test consists of three different parts, each containing 50 items. Part 1 (Colour Naming) presents patches of colors and participants have to name them as quickly and accurately as possible. Part 2 (Reading) presents the words "red", "blue" and "green" printed in black ink, and participants have to read the words aloud. Part 3 (Inhibition) introduces the interference effect: the words "red", "blue" and "green" are printed in incongruent colors, and participants have to name the color and ignore the word. The main dependent variable derived from this test was Inhibition (time to complete Part 3 – time to complete Part 1). This test has showed adequate levels of reliability and validity and have been widely used in neuropsychology practice as a measure of inhibition and switching skills [23,24].

3. MRI acquisition and pre-processing

Participants were scanned on a 3T whole body MRI scanner (Phillips Achieva X-series) operating with an eight-cannel 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 $0.94\times0.94\times1.0$ mm resolution (160 slices, FOV = 240×240 mm^2, matrix 256×256), 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 GM; normalize GM segments (using DARTEL normalization) to a GM template in MNI space; modulate normalized GM images with the Jacobian determinants (derived from the flow-fields of the normalization step) to restore volumetric information; and finally smooth images with a 3-D Gaussian filter of 8 mm full width at half maximum (FWHM).

Data Analysis

1. Measures of reward/punishment, impulsivity and inhibitory control

We first analyzed the assumption of normal distribution of dependent variables using Kolgomorov-Smirnov tests. Likewise, we also assessed the homogeneity of variances between the study groups by means of Levene's tests. Both assumptions were met and therefore we conducted independent-sample t-tests to examine between-group differences in reward/punishment sensitivity, impulsivity and inhibitory control using SPSS 15.0 for Windows (SPSS Inc., Chicago IL). Significance threshold was set at $p<0.05$.

2. Image analysis

2.1 GM differences between normal weight and excess weight groups. The general linear model was used to conduct between-group voxel-wise comparisons within SPM8. Group differences in regional GM volumes were tested using both a ROI and a whole-brain approach. Regarding ROI analyses, the ROIs selected were the orbitofrontal cortex, the dorsolateral prefrontal cortex, the somatosensory cortices (including SI and SII), the medial temporal lobe, and the striatum (all regions were assessed bilaterally). We used the WFU Pickatlas [25] to delineate these regions and create image masks that were used to restrict voxel-wise analyses to the region of interest (thus applying Small Volume Correction (SVC) procedures). In these analyses, the total volume of GM (TVGM) was modeled as a linear confound to account for global volume variability, and although study groups did not significantly differ in gender, to fully discard a potential impact of the apparent gender imbalance between our study groups, we also included this variable as a confounding covariate. Regarding whole brain analyses, we used the same statistical model, although the analyses were not restricted to any particular region. Significance threshold was set at $p<0.05$ after family-wise error (FWE) correction for multiple comparisons across the region of interest (pFWE-SVC<0.05) or across the whole brain (pFWE<0.05).

2.2 Correlation analyses with personality and neuropsychological scores. Correlations between regional GM volumes and the scores of the different scales were also assessed within SPM8 by means of independent sample t-tests, in where the score of interest was modeled in interaction with the variable group (excess weight vs. normal weight participants). Confound variables and the significance thresholds were the same as above. Likewise, we also applied a ROI approach followed by a whole-brain analysis. Correlations were voxel-wise assessed within each group, and regions where significant findings were detected were further investigated to ascertain the existence of a between-group interaction in the pattern of correlations; that is, to verify that correlations were uniquely present in one of the study groups.

Results

1. Sample characteristics

The participants' demographic characteristics – classified as normal weight vs. excess weight – are summarized in Table 1. The excess weight and normal weight groups were statistically matched on gender, age, years of education and socioeconomic status. As expected, relative to normal weight participants, excess weight participants had significantly greater weight ($t_{50}=-5.385$, $p<0.005$) and BMI ($t_{50}=-7.371$, $p<0.005$).

2. Reward/punishment sensitivity, impulsivity and inhibitory control measures

There were no significant between-group differences in any of the measurements assessed (Table 2).

3. Image analyses

3.1 Regional GM differences between normal weight and excess weight groups. ROI analyses reported a significant volume increase in the right hippocampus of excess weight participants in comparison to normal weight subjects (Figure 1). Regarding the whole-brain analyses, there were no significant between-group differences at pFWE<0.05. Nevertheless, at a more lenient significance threshold of $p<0.001$ (uncorrected, $k>250$ voxels), we found a significant volume increase in the left precentral region of normal weight subjects (see Figure S1). In addition, in order to further investigate the relationship between BMI and regional GM volumes, we also correlated BMI values against voxel-wise GM volumes, finding no results at a corrected statistical threshold beyond those observed in the qualitative comparisons.

3.2 Correlation analyses with personality and neuropsychological scores. Regarding ROI analyses, we found significant correlations between regional GM volumes and the scores of the behavioral tests only in normal weight participants. On the one hand, reward sensitivity and UPPS-P positive urgency scores were negatively associated with the GM volume of the left secondary somatosensory cortex (SII) in control subjects (Table 3 - Figures 2 and 3), whereas these correlations were not observed in the excess weight group. No further correlations were observed with the other personality dimensions.

Table 1. Sociodemographic and biometric characteristics of study subjects.

	Normal weight (n = 16)	Excess weight (n = 36)[a]	Test
Age (years)	14.13 (1.36)	14.22 (1.4)	(t_{50} = −0.162, 0.872)
Years of education	10.13 (1.36)	10.19 (1.45)	(t_{50} = −0.162, 0.872)
Gender (male/female)	7/9	10/26	(x^2 = 1.284, 0.257)
SES (annual income €)[b]			(x^2 = 6.400, 0.171)
0–11.533 €	3	2	
11.533–18.200 €	2	11	
18.200–26.548 €	5	17	
26.548–41.294 €	3	2	
41.294–5.585.000 €	2	3	
Height	161.82 (9.87)	161.82 (7.55)	(t_{50} = 0.001, 0.999)
Weight	53.33 (11.02)	75.19 (14.45)	(t_{50} = −5.385, 0.000)
BMI[c]	20.26 (2.8)	28.53 (4.07)	(t_{50} = −7.371, 0.000)

[a]The excess weight group is composed of participants originally classified as having overweight (n = 16) or obesity (n = 20) according to the International Obesity Task Force criteria;
[b]SES: Socioeconomic status. Quintiles for SES are defined according to data from the Financial Survey for Spanish Families, http://www.bde.es/webbde/es/estadis/eff/eff.html;
[c]BMI: Body mass index.
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On the other hand, we observed a significant positive correlation between the inhibition score derived from the Stroop test and the volume of the left dorsolateral prefrontal cortex (Table 3 and Figure 4). Again, this correlation was not observed in excess weight participants. No further results were observed in whole-brain analyses.

Discussion

In this study we aimed to examine voxel-wise differences in regional GM volume between excess weight and normal weight adolescents, and to explore differences in the way reward and punishment sensitivity, impulsivity and inhibitory control related to regional GM volumes in both groups. In partial agreement with initial hypotheses, we found that adolescents with excess weight (the combined group of overweight and obese participants) have structural abnormalities in one predefined ROI, the right hippocampus. Specifically, the excess weight adolescents had increased right hippocampal GM regional volumes compared to lean controls. Furthermore, reward sensitivity and positive urgency scores negatively correlated with left SII regional volumes in lean controls but not in excess weight adolescents. Similarly, Stroop performance scores positively correlated with left dorsolateral prefrontal cortex regional volumes in controls but not excess weight adolescents. In contrast with initial assumptions, we did not find significant alterations in the striatum or the orbitofrontal cortex, or different associations between these regions and personality and cognitive measures.

The finding of an increased right hippocampal volume in excess weight adolescents is in fitting with the role of this region in the processing of motivational signals associated with appetite [26]. For example, functional imaging studies have shown that right hippocampal activation is significantly associated with food cues-induced insulin release in obese adolescents [27] and with direct

Table 2. Between-group comparison of impulsivity and SPSRQ scores.

	Normal weight (n = 16)	Excess weight (n = 36)	Test
SPSRQ[a]			
Reward sensitivity	11.25 (5.42)	9.28 (4.27)	(t_{50} = 1.414, 1.972)
Punishment sensitivity	11.06 (4.77)	9.47 (5.02)	(t_{50} = 1.071, 1.59)
UPPS-P			
Sensation seeking	32.94 (6.5)	28.94 (7.19)	(t_{50} = 1.414, 1.972)
Lack of perseverance	23.69 (5.3)	21.75 (4.34)	(t_{50} = 1.071, 1.59)
Lack of premeditation	26.63 (5.35)	25.58 (5.91)	(t_{50} = 1.414, 1.972)
Negative urgency	26.38 (7.59)	26.53 (7.1)	(t_{50} = 1.071, 1.59)
Positive urgency	24.25 (7.02)	24.36 (8.11)	(t_{50} = 1.414, 1.972)
Stroop			
Inhibition	12.25 (2.35)	11.75 (2)	(t_{50} = .790, 0.433)

[a]SPSRQ: Sensitivity to Punishment and Sensitivity to Reward Questionnaire.
doi:10.1371/journal.pone.0049185.t002

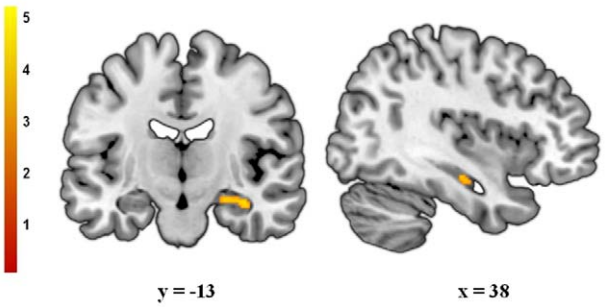

Figure 1. Clusters of significant gray matter volume increase in excess weight compared with normal weight subjects. Peak coordinates were located in the right hippocampus (x, y, *z*_ 38, −13, −18; t = 4.21; pFWE-SVC<0.05). Results are overlaid on coronal and sagittal sections of a normalized brain, and the numbers correspond to the 'y' and 'x' coordinates in MNI space. Color bar represents t value. For demonstration purposes the images are displayed at p<0.001 (uncorrected, k>50).
doi:10.1371/journal.pone.0049185.g001

gastric stimulation in obese adults [13]. Furthermore, the gastric stimulation-induced increases of hippocampal activity were associated with scores of emotional eating and lack of control [13], supporting the role of this region in the incentive motivation and cognitive control of eating behavior in obesity.

Correlation analyses showed that the regional volume of SII was associated with reward sensitivity and positive urgency in lean controls but not in excess weight adolescents. Within SII, the specific region of correlation with reward sensitivity and positive urgency was the subcentral gyrus, or Brodmann area 43, also known as area OP4 [28]. This area occupies the most lateral aspect of SII, adjacent to the representation of the oral cavity within the primary somatosensory cortex, and thus it is mainly involved in the processing of somatosensory information, including the sensory input relevant for gustatory awareness [29,30]. Interestingly, somatosensory processing regions have been associated with reward sensitivity in healthy individuals with high scores in this personality trait [31]. Moreover, somatosensory regions consistently show increased activations towards food cues in both adolescents at risk of developing obesity [10] and in obese adolescents [10]. The fact that the negative associations of personality measures with SII volume were only observed within healthy controls would suggest that in excess weight subjects the normal function of somatosensory regions in relation to reward sensitivity and impulsivity is missed or hijacked by disease-specific mechanisms. The latter notion would be similar to what is found in addiction, in which drug craving rewires the function of stimulus-valuation and response control brain regions [32], putatively modifying the link between trait impulsivity and brain structure [33]. In this case, the function of SII may be rewired by the persistent activation of somatosensory regions during anticipation or encoding of sensory and hedonic aspects of palatable food, as shown by fMRI studies [10,11,34].

Unlike previous studies [8,9] we did not find significant structural abnormalities in the prefrontal cortex of excess weight adolescents. However, we found a positive association between cognitive inhibitory control (Stroop performance) and a cluster located in the left dorsolateral prefrontal cortex of normal weight subjects. This region has been shown to mediate the link between aerobic fitness and response inhibition in ageing adults, suggesting a link between physical fitness, production of neurotrophic agents (including insulin-like growth factor-1) and protection of higher-order executive skills [35]. Such region may play a similar role in the developing adolescent brain, and thus in terms of individual differences in response inhibition in normal weight adolescents, which is once again absent in the excess weight group. In agreement with such a notion, over-activity of this region during response inhibition has previously been observed in adolescents compared to healthy adult groups [36]. More research is needed to understand why this link is altered in excess weight adolescents, but the impact of adiposity on vascular health and insulin production may particularly impact frontal brain regions and executive functions [37].

The potential limitations of our study include the decision to merge the overweight and obese subgroups, the lack of significant behavioral performance differences, and the lack of significant

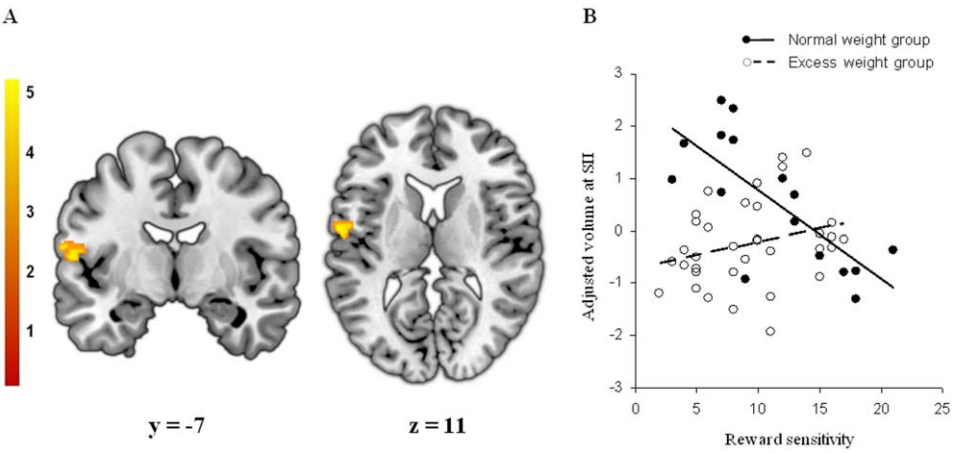

Figure 2. Between-group interaction between regional gray matter volume and reward sensitivity. A. Voxel-wise correlations between regional gray matter volume and reward sensitivity score specifically observed in normal weight subjects. Peak coordinate was located in the left secondary somatosensory cortex (SII, Brodmann area 43) (x, y, z = −60, −7, 11; t = 4.51; pFWE-SVC<0.05). Results are overlaid on coronal (left) and axial (right) sections of a normalized brain, and the numbers correspond to the 'y' and 'z' coordinates in MNI space, respectively. Color bar represents t value. For demonstration purposes the images are displayed at p<0.001 (uncorrected, k>100). B. Plot of the correlation between gray matter volume at the peak coordinate and the reward sensitivity score. Normal weight group (filled circles, solid line) showed a significant correlation between these two measures (r = −0.750; p<0.005), while in the excess weight group the correlation was not significant (r = 0.284; p>0.05).
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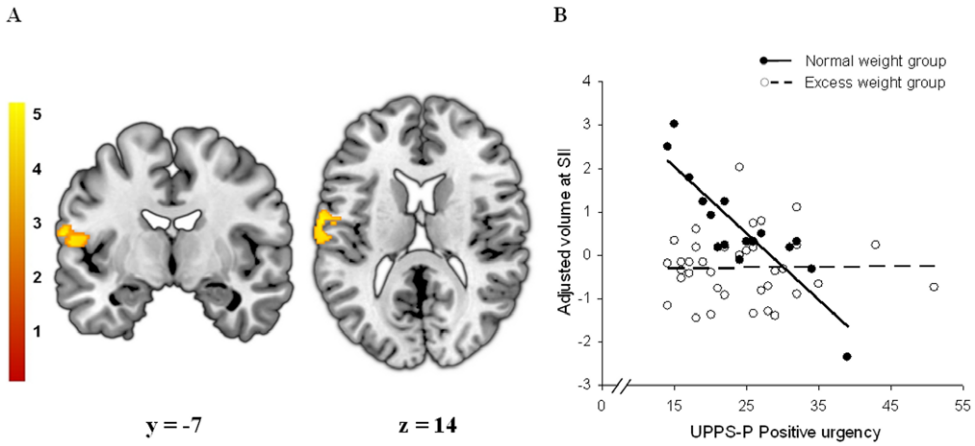

Figure 3. Between-group interaction between regional gray matter volume and positive urgency. A. Voxel-wise correlations between regional gray matter volume and positive urgency (UPPS-P) score specifically observed in normal weight subjects. Peak coordinate was located in the left secondary somatosensory cortex (SII, Brodmann area 43) (x, y, z = −63, −7, 15; t = 4.89; pFWE-SVC<0.05). Results are overlaid on coronal (left) and axial (right) sections of a normalized brain, and the numbers correspond to the 'y' and 'z' coordinates in MNI space, respectively. Color bar represents t value. For demonstration purposes the images are displayed at p<0.001 (uncorrected, k>100). B. Plot of the correlation between gray matter volume at the peak coordinate and the positive urgency score. Normal weight group (filled circles, solid line) showed a significant correlation between these two measures (r = −0.856; p<0.0005), while in the excess weight group the correlation was not significant (r = 0.058; p>0.05).
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volumetric differences in a priori regions of interest such as the orbitofrontal cortex and the striatum. The first decision was based on the observation that comparisons between obese and overweight subgroups failed to yield any significant findings. In addition, the study of dimensional measures of adiposity (BMI) did not either add significant results beyond the categorical diagnosis comparison (normal vs. non normal BMIs). Therefore, we consider that these findings actually reflect that the association between BMI and brain anatomy is better captured by a qualitative analysis comparing participants with vs. without clinical problems related to excess weight. With regard to the lack of behavioral differences and of GM differences in the prefrontal cortex and the striatum, we acknowledge that these negative results are somehow opposed to previous findings, and may reflect the fact that our sample was composed of less severe individuals than those of previous studies including higher BMIs and individuals with other comorbidities [9,38]. In addition, it might be also argued that the unequal number of voxels included in the different ROIs assessed might have favored the detection of significant differences in smaller regions, such as the medial temporal lobe (in opposition to orbitofrontal or dorsolateral prefrontal cortices, for instance). In any case, we also performed a

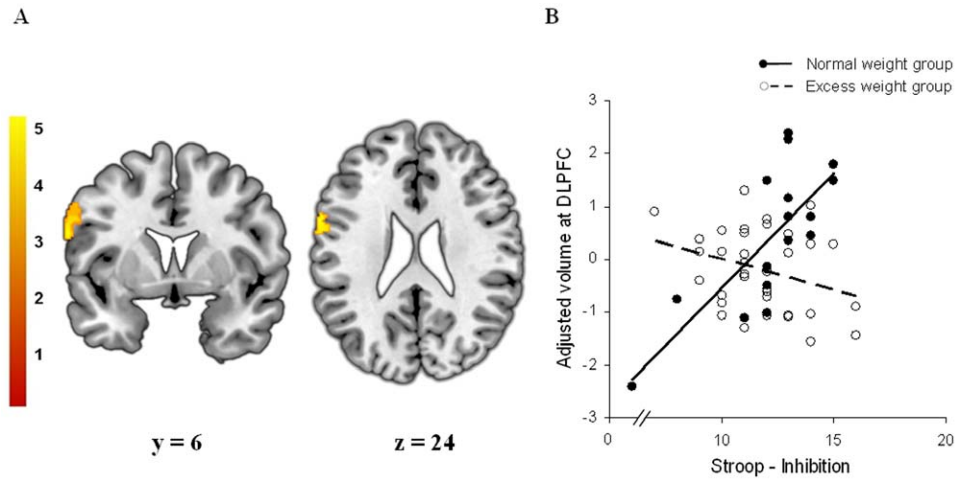

Figure 4. Between-group interaction between regional gray matter volume and response inhibition. A. Voxel-wise correlations between regional gray matter volume and the Stroop response inhibition score specifically observed in normal weight subjects. Peak coordinate was located in the left dorsolateral prefrontal cortex (Brodmann area 9) (x, y, z = −61, 6, 24; t = 5.01; pFWE-SVC<0.05). Results are overlaid on coronal (left) and axial (right) sections of a normalized brain, and the numbers correspond to the 'y' and 'z' coordinates in MNI space, respectively. Color bar represents t value. For demonstration purposes the images are displayed at p<0.001 (uncorrected, k>100). B. Plot of the correlation between gray matter volume at the peak coordinate and the Stroop response inhibition score. Normal weight group (filled circles, solid line) showed a significant correlation between these two measures (r = 0.769; p<0.005), while in the excess weight group the correlation was not significant (r = −0.327; p>0.05).
doi:10.1371/journal.pone.0049185.g004

Table 3. Correlations of SPSRQ, impulsivity and inhibitory control scores with brain anatomy in normal weight subjects.

Anatomical region	K	T	pFWE-SVC<0.05	x	y	z
SPSRQ – Reward sensitivity						
Negative Correlation						
SII L[a]	267	4.51	0.028	−60	−7	11
UPPS-P – Positive urgency						
Negative correlation						
SII L	260	4.89	0.010	−63	−7	15
Stroop – Inhibition						
Positive correlation						
DLPFC L[b]	498	5.01	0.006	−61	6	24

[a]SII L, left secondary somatosensory cortex;
[b]DLPFC L, left dorsolateral prefrontal cortex. Significant peaks are given in MNI coordinates. The corresponding anatomical names were obtained using the aal toolbox for SPM8.
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whole-brain analysis, and, even at an uncorrected significances threshold, we only observed a volume decrease in the left precentral region of excess weight participants, but no findings were observed in the prefrontal cortex or the striatum.

In summary, here we report that, in comparison to lean controls, adolescents with excess weight (including participants meeting criteria for overweight and obesity) have increased right hippocampal volume, a brain region related to emotional and motivational aspects of food intake. Somewhat unexpectedly, personality and cognitive measures were mainly correlated with the volume of the second somatosensory region, although significant findings were also observed in the dorsolateral prefrontal cortex in relation to measures of inhibitory control. In any case, the lack of significant differences in the behavioral measures and the fact that correlation analyses grasped some of the potential correlates of adolescent obesity in the prefrontal cortex supports our initial assumption that the assessment of the correlations between neuroimaging and behavioural data is more sensitive than any of these two approaches on its own.

Supporting Information

Figure S1 Clusters of significant gray matter volume increase in normal weight compared with excess weight subjects. Peak coordinates were located in the left precentral region (Brodmann area 6) (x, y, z_ −40, −13, 63; t = 4.65; p<0.001 (uncorrected, k>250). Results are overlaid on coronal and sagittal sections of a normalized brain, and the numbers correspond to the 'y' and 'x' coordinates in MNI space. Color bar represents t value. Voxels with p<0.001 (uncorrected, k>250) are displayed.
(TIF)

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Author Contributions

Conceived and designed the experiments: AVG CSM. Performed the experiments: EDR JSRV LML. Analyzed the data: CSM LML. Wrote the paper: LML CSM AVG.

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ANEXO IV

obesity

Decreased insular and increased midbrain activation during decision-making under risk in adolescents with excess weight

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Neural substrates of risk-based decisions in obese adolescents

Decreased insular and increased midbrain activation during decision-making under risk in adolescents with excess weight

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Neural substrates of risk-based decisions in obese adolescents

ABSTRACT

In this study, we used functional Magnetic Resonance Imaging (fMRI) to explore the brain substrates of decisions under risk in excess weight adolescents. Decision-making was challenged using the Risky Gains task, which opposes a safe less rewarding choice with more rewarding risky choices. This task has shown to engage brain systems involved in choice-related risk taking and reward processing (including the orbitofrontal cortex, insula and striatum). We expected abnormal activation of these regions in excess weight adolescents compared to normal weight controls. Neural activation was measured using fMRI in 52 adolescents (age range 12-17) classified in three groups as a function of body mass index: obese (n=21), overweight (n=15), or normal weight (n=16). During fMRI, subjects were challenged with the Risky-Gains task as described by Paulus et al. (1). Excess weight adolescents, compared to normal weight controls, showed decreased left insular and increased midbrain activations during anticipation of risky choices. In addition, excess weight adolescents showed increased activations of inferior frontal gyrus, parahippocampus, thalamus and posterior brain regions after reward receipt. In summary, adolescents with excess weight showed reduced activations in brain regions signaling risk and increased activations in regions signaling reward during anticipation of decisions involving risk and reward. In addition, post-decision reward outcomes produced an increased activation of regions involved in emotional salience in excess weight adolescents vs. controls.

Neural substrates of risk-based decisions in obese adolescents

INTRODUCTION

The prevalence of adolescent overweight and obesity has sharply increased over the last two decades, rapidly reaching epidemic levels (2,3). To account for this rise, recent theoretical models underscore the role of decision-making skills as a key asset to regulate caloric intake in modern environments, since these are characterized by unrestricted access to food and strong media-driven appeals to eat caloric products (4). Decision-making skills are particularly relevant in the case of adolescents, in whom brain developmental transitions seem to be hardwired to maximize reward at the expense of risk (5). Neuroimaging studies have demonstrated that adolescents have hypersensitive striatal response to reward prediction (6,7) and heightened activation of brain regions involved in fostering risk-taking (orbitofrontal cortex, (OFC)) during decision-making (8). Obesity-induced neural adaptations may further rewire these brain systems; in adults, excessive body mass index (BMI) levels are associated with reduced striatal dopamine function and lower metabolism of the OFC (9, 10).

In agreement with these notions, burgeoning evidence from neuroscience studies indicates that adolescents with excess weight have increased activation of brain systems involved on sensory-emotional processing (frontal operculum, insula) (11) and deficient activation of the neural network supporting cognitive control of choice (several regions of the prefrontal cortex) in response to highly appetizing food stimuli (12). Behaviorally, excess weight adolescents have demonstrated decision-making deficits in cognitive tests measuring the ability to choose between safe and risky (superficially rewarding) choices (13). Furthermore, obese adolescents have increased cognitive disinhibition correlated with lower gray matter volumes in the OFC (14). However, no studies to date have explored the neural substrates of decision-making under conditions of risk and reward in excess weight adolescents.

Neural substrates of risk-based decisions in obese adolescents

In this study, we used functional Magnetic Resonance Imaging (fMRI) to explore the brain substrates of decisions under risk in excess weight adolescents. Decision-making was challenged using the Risky Gains task, which opposes a safe less rewarding choice with more rewarding risky choices. This task has shown to robustly activate the brain systems involved in choice-related risk taking and reward receipt (including the OFC, insula and striatum). We expected abnormal activation of this brain system in excess weight adolescents compared to normal weight controls.

METHODS AND PROCEDURES

Participants

Fifty two adolescents (age range 12-17) participated in this study. They were classified in three groups (obese (n=21), overweight (n=15), or normal weight (n=16)) according to their BMI, following the criteria of the International Obesity Task Force (IOTF) defined by Cole et al. (15), or, in normal weight adolescents, according to age- and sex-adjusted Spanish-specific norms (16). The demographical data and BMI of participants are summarized in Table 1. Participants were recruited from the Endocrinology Service of the Hospital "Virgen de las Nieves" in Granada, Spain, and from schools located in the same geographical area. To be included, they had to meet the following criteria: (i) age range between 12 and 17 years-old, (ii) BMI values falling within the intervals categorized as overweight or obesity according to the IOTF (excess weight adolescents), or normal weight values (normal weight adolescents), (iii) absence of past/current evidence of neurological or psychological disorders, (iv) absence of significant abnormalities on MRI (Magnetic Resonance Imaging) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic

objects) and (v) absence of history of brain injury involving loss of consciousness (LOC) for longer than 5 minutes. All of them had normal or corrected-to-normal vision.

The study was approved by the Ethical Committee for Research in Humans of the University of Granada; all procedures were conducted in accordance with the Declaration of Helsinki. All participants and their parents were debriefed about study aims and detailed procedures, and both signed an informed consent form agreeing participation.

Insert table 1 here

Experimental task

We used Risky-Gains task described by Paulus et al., (1). The task consisted of 96 trials (5 s/ trial). In each trial, participants are presented with the numbers 20, 40 and 80 in a fixed order. The task requires the participant to acquire as many points as possible by choosing between safe (20 points) and risky (40, 80 points) options. Each number (20, 40 or 80) is presented on the screen for 1 s and participants are instructed to press a button while the selected number in on the screen in order to win the corresponding amount of points. The first number in the sequence (20) is always a safe choice (the participant always receives 20 points). However, the two subsequent choices (40 and 80) can be rewarded (+40/+80) or punished (−40/−80); in the latter cases meaning that that the trial ends and the participant loses 40 or 80 points, respectively. Thus, although the subject may gain more points per trial by waiting until the 40 or 80 choices appear on the screen, there is also a risk of losing 40 or 80 points. Points accumulate from trial to trial and the stake is shown at the top of the screen, being continuously updated. Participants received feedback immediately after making a response, so they could adapt their behavior to the feedback received.

Fifty-four trials belonged to the non-punished trial type category, in which participants could get as much as 80 points, while 24 were -40 punished and 18 were -80 punished trial types. Relevantly, the final score did not depend on subject's choices, so, there was no advantage in selecting safe or risky options.

Imaging data acquisition

A 3.0 T clinical MRI scanner, equipped with an eight-channel phased-array head coil, was used (Intera Achieva, Philips Medical Systems, Eindhoven, The Netherlands), which was during task performance, a T2*-weighted echo-planar imaging (EPI) was collected, (repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, field of view (FOV) = 230 x 230 mm, 96 x 96 matrix, flip angle = 90º, 21 4 mm axial slices, 1 mm gap, 243 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. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology Inc., Northridge, California, USA), and responses were recorded through Evoke Response Pad System (Resonance Technology Inc., Northridge, California, USA).

Imaging data processing and analysis

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

Data analyses

We defined 3 conditions of interest: (i) safe response (20 points trials) (ii) risky response (40 and 80 points trials) and (iii) punishment feedback (-40 and -80 points trials). The first two conditions were modeled as the time elapsed from the beginning of the trial to the participants' response. The last condition was modeled as the time elapsed between feedback presentation and the end of the trial. Accordingly, two contrasts were defined to study brain activations: a risky versus (vs.) safe choices contrast, and a reward vs. punishment feedback contrast.

A one-sample t-test was conducted to assess intra-group activations (normal weight, overweight and obese) in each of the two contrasts of interest. The statistical threshold was set at $p<0.05$ False Discovery Rate (FDR) whole-brain corrected. Between-group comparisons were conducted using a mixed model ANOVA and linear contrasts to determine whether brain activations were related to BMI indices: normal weight vs. overweight vs. obese. Moreover, two-sample t-test comparisons were also conducted to assess significant differences in brain activation between each group-pair (i.e., normal weight vs. overweight; normal weight vs. obese; overweight vs. obese). In these analyses, significance threshold was set at $p<0.001$ (uncorrected).

RESULTS

Behavioral results

Nine participants were excluded from the study because they made less than 4 risky choices, thus invalidating contrast interpretation. Also, four scans were excluded because of excessive motion artifacts. As a result, imaging data from 14 obese (mean age (+/- standard deviation (SD)) was of 14.07 (± 1.33), 9 female and 5 male, and BMI (weight/height² (kg/m²)) was 31.14 (± 2.66)), 13 overweight (mean age = 14.15 (± 1.77), 9 female and 4 male, BMI= 24.73 (± 1.34)) and 13 normal weight (mean age = 13.69 (± 1.18), 8 female and 5 male, BMI = 20.36 (± 2.49)) adolescent were used in the analysis.

Percentage of safe and risky responses per each group.

The percentage of safe and risky responses is presented in Table 2. Participants with overweight showed a higher percentage of safe responses in comparison to the other two groups, although the interaction between group and response type was non-significant [F (2.37) = 2.089, p= 0.14].

Inset Table 2 here

Neuroimaging results

Risky-Safe Contrast

Results for Risky-Safe contrast are presented in Table 3. Within-subjects contrasts (whole-brain analyses) showed that each of the three groups activated the right inferior frontal gyrus/anterior insula region during risky (vs. safe) choices. In addition, a significant midbrain activation was also observed in overweight and obese groups (see Figure 1A). Linear contrasts showed that activation of the left inferior frontal/anterior insula region during risky choices was progressively smaller with increasing BMI (normal weight > overweight > obese). Likewise, midbrain activation during risky choices significantly

increased with BMI (obese > overweight > normal weight) (see Figure 1B). Pair-wise comparisons between all groups are presented in Supplementary Table 1.

Inset Table 3, Figure 1 here

Reward-Punishment Contrast

Results for Reward-Punishment contrast are presented in Table 4. Whole-brain analysis for each groups showed a significant activation in the reward system (inferior frontal gyrus and nucleus accumbens), and the occipital lobe in all groups during reward (vs. punish) feedback. The linear contrast showed that activations observed during rewarded trials in the inferior frontal gyrus, the thalamus, the cerebellum, and the hippocampal and parahippocampal region were significantly related to BMI (obese > overweight > normal weight) (see Figure 2). No regions of greater activation in normal weight subjects were observed. Pair-wise comparisons are presented in Supplementary Table 2.

Inset Table 4, Figure 2 here

DISCUSSION

The main findings from this study were that excess weight adolescents, compared to normal weight peers, have decreased left insular activation and increased midbrain activation during risk-based decision-making. In addition, excess weight adolescents have increased inferior frontal gyrus, thalamus, parahippocampal and posterior activation in response to reward receipt. These brain activation differences emerged in absence of significant between-groups differences on behavioral choice, such that they genuinely reflect different approaches to decision-making as a function of weight status. Therefore, we reason that excess weight adolescents may have dysfunctional patterns of brain activation related to risk evaluation and

reward processing during decision-making. In real-life scenarios, these differential patterns may contribute to explain choices leading to excessive food intake in this group of adolescents.

The first relevant finding refers to significantly decreased left anterior insular activation during the period preceding actual choice in the excess weight groups. Conversely, excess weight adolescents showed increased activation in the midbrain, a hub of ascending monoaminergic bundles. The anterior insula is importantly involved in signaling the probability of aversive outcomes, thus guiding risk prediction and choices oriented to minimize losses (17,18). Accordingly, patients with insula damage fail to adjust their bets by the odds of winning in a risk-taking gamble task; they bet similarly high amounts of money irrespective of outcome probability (19). This is consistent with the finding that excess weight adolescents have increased preference for risky decks in the Iowa Gambling Task (13). The insula is also strongly associated with interoceptive sensitivity (the ability to perceive bodily feedback to regulate internal state), which is decreased as a function of increased body weight in adolescents (20). Individual differences in interoceptive sensitivity significantly shape cognitive-affective processes including decision-making; for example, individuals with good interoceptive sensitivity tend to select less risky choices in the Iowa task (21). Overall, the evidence suggests that excess weight adolescents may have abnormal insular-mediated processing of interoceptive information relevant for decision-making. On the other hand, they seem to rely on midbrain dopamine regions to ponder risky vs. safe options, probably biasing preference towards immediate reinforcement (6,7). In real-life decision-making, these deficits may promote excessive meal intake at the expense of negative consequences, either immediate (e.g., belly ache) or postponed (e.g., restriction of social activities).

In line with results from the pre-decisional stage, the second finding referred to increased inferior frontal gyrus activation in response to reward vs. punishment feedback in the excess weight group. This region has been associated with evaluation of reward outcome following risk-based decisions among healthy adolescents (22). In addition, this region, along with others identified in the same contrast (e.g., parahippocampus, cerebellum), has been linked to incentive motivation towards food stimuli in adolescents (23). Therefore, our findings are suggestive of the notion that, in excess weight adolescents, the persistent stimulation of incentive motivational systems by seeking of high caloric food may hypersensitize the brain substrates of reward processing in this group. Since the evaluation of outcomes is thought to slot in formation of preferences for subsequent decisions (24), decision-making in excess weight adolescents may be overridden by sensory-emotional aspects of reward to the expense of risk (25). This notion is in line with proposed parallels between obesity and addiction (26, 9), based on the array of reward-related neurobiological alterations associated with increased BMI, including reduced striatal dopamine function and lower metabolism of the OFC (9,10). In sum, excess weight adolescents show hyper-processing of reward outcomes in the inferior frontal gyrus and other brain regions importantly involved in reward and arousal processing, which may sensitize their decisional balance towards the rewarding properties of food products.

The main conclusion of this study is that adolescents with excess weight have reduced activation in brain regions signaling risk, and increased activation in regions signaling reward during anticipation of decisions involving risk and reward. In addition, post-decision reward processing produced increased activation of several regions involved in emotional salience as a function of increased weight. These results demonstrate for first time abnormal patterns of brain activation during decisions involving risk and reward in adolescents with excess

weight. Future studies are warranted to explore whether these basic deficits are associated with persistent behavioral patterns fostering choice of highly rewarding food products at the expense of long-term health risks.

Neural substrates of risk-based decisions in obese adolescents

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DISCLOSURE

The authors declared no conflicts of interest.

Neural substrates of risk-based decisions in obese adolescents

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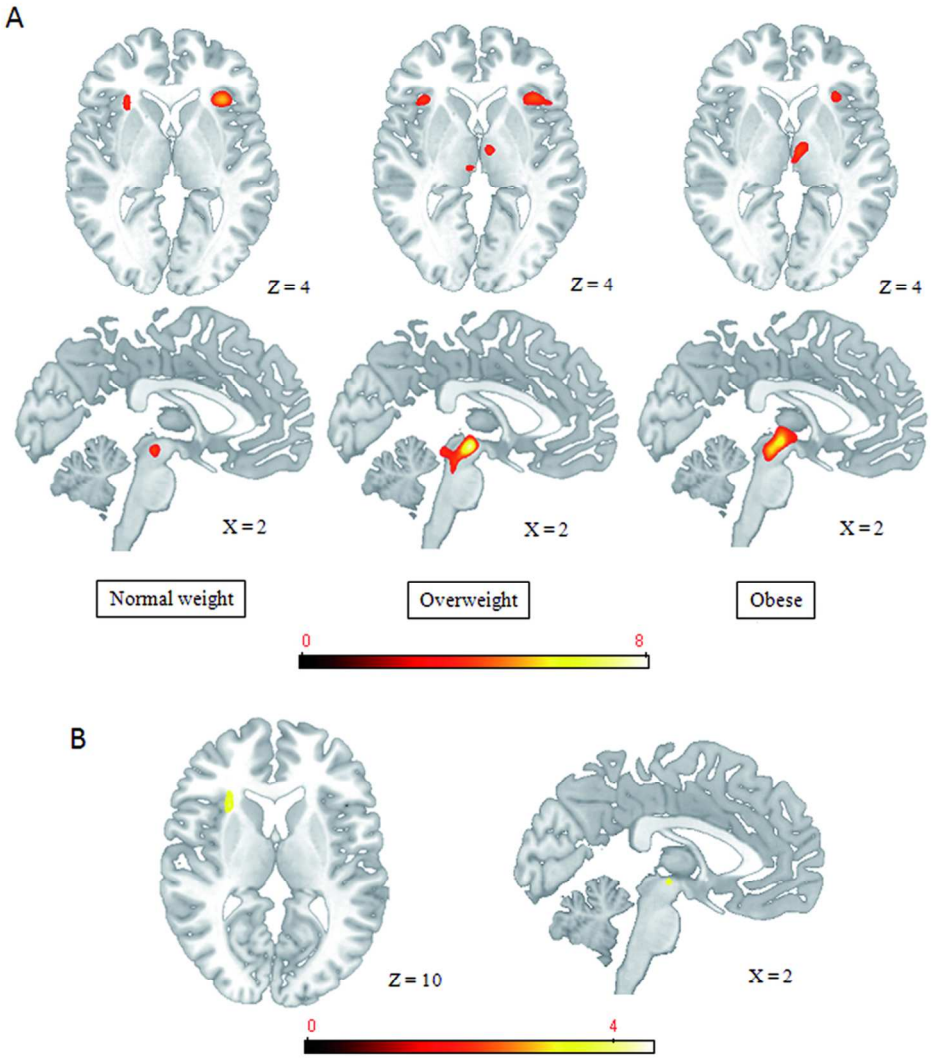
Neural substrates of risk-based decisions in obese adolescents

FIGURES LEGENDS

Figure 1. A. Within group activations observed for Risky vs. Safe choices overlaid on selected slices of a normalized brain. Inferior frontal/anterior insula activations (upper row) progressively decreased with increasing BMI, while midbrain activations (bottom row) showed the opposite pattern. **B. Left.** Cluster of increasing activation during Risky choices with decreasing BMI, located in the left inferior frontal/anterior insula region. **Right.** Cluster of increasing activation during risky choices with increasing BMI, located in the superior midbrain region. X and Z denote coordinates in standard MNI space. Voxels with $p<0.001$ (uncorrected) are displayed in all cases to provide a better description of the anatomical extension of findings. Color bar indicates T value. Right hemisphere is displayed on the right.

Figure 2. Clusters of increasing activation during Rewarded vs. Punished trials with increasing BMI, located in the left inferior frontal gyrus, thalamus, hippocampus gyrus, superior occipital gyrus (extending to medial cuneus) and cerebellum posterior lobe. X, Y and Z denote coordinates in standard MNI space. Voxels with $p<0.001$ (uncorrected) are displayed in all cases to provide a better description of the anatomical extension of findings. Color bar indicates T value. Right hemisphere is displayed on the right.



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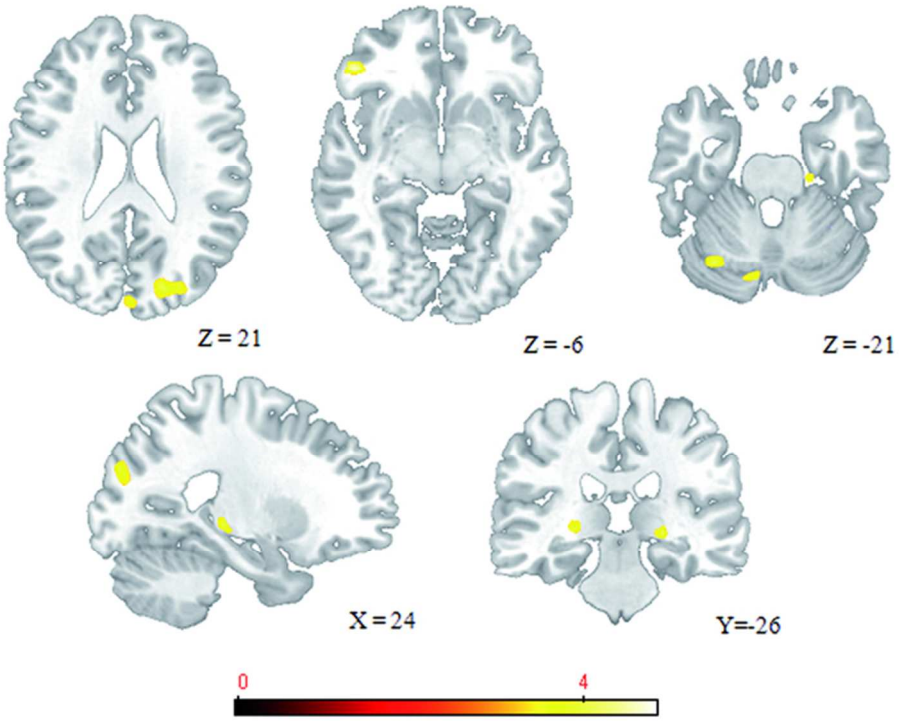

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Neural substrates of risk-based decisions in obese adolescents

Table 1. Socio-demographic characteristics and Body Mass Index for each study group.

	Obese (n=21)	Overweight (n=15)	Normal weight (n=16)
	n	n	n
Sex			
Male	6	4	7
Female	15	11	9
	Mean (SD)	*Mean (SD)*	*Mean (SD)*
Age	14.29 (1.31)	14.07 (1.67)	13.88 (1.36)
BMI	31.33 (2.92)	24.65 (1.26)	20.19 (2.80)

Neural substrates of risk-based decisions in obese adolescents

Table 2. Percentage of safe and risky responses in the three study groups.

	Rate (%)	
	Safe	Risky
	Mean (SD)	*Mean (SD)*
Normal weight	45.94 (16.99)	54.06 (16.99)
Overweight	58.89 (12.26)	41.11 (12.26)
Obese	49.32 (19.90)	50.68 (19.90)

Neural substrates of risk-based decisions in obese adolescents

Table 3. Brain activations observed in Risky vs. Safe choices in within -group (one-sample) and between-group (linear contrasts) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume	*t*
			X	Y	Z	(mm^3)	
Normal weight							
Inferior frontal gyrus / Insula	47/13	R	36	24	0	2288	5.52
Overweight							
Midbrain	---	L/R	4	-20	-10	2056	7.88
Inferior frontal gyrus / Insula	47	R	38	24	-2	280	4.78
Obese							
Midbrain		L/R	6	-16	-6	992	6.40
Inferior frontal gyrus	47	R	34	22	-14	48	4.64
Normal weight > Overweight>Obese							
Insula	13	L	-26	22	10	920	4.26
Obese > Overweight > Normal weight							
Midbrain		R	4	-18	-8	264	3.72

Neural substrates of risk-based decisions in obese adolescents

Table 4. Brain activations observed in Rewarded vs. Punished trials in within-group (one-sample) and between-group (linear contrasts) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume	*t*
			X	Y	Z	(mm^3)	
Normal weight							
Superior Frontal Gyrus	8/9	R	20	30	52	2760	7.28
Caudate		R	22	-8	30	2528	5.54
Caudate		L	-18	12	20	3480	5.48
Middle Occipital Gyrus	18/19	L	-18	-98	10	1128	5.05
Middle Occipital Gyrus		R	24	-96	10	112	3.97
Angular	40	R	46	-66	42	248	4.12
Overweight							
Cerebellum Posterior Lobe		L/R	-14	-84	-24	27224	7.09
Occipital Lobe	18/19	L/R	0	-84	-4	8804	6.72
Inferior Frontal Gyrus	47/11	L	-34	40	-18	648	6.50
Inferior Frontal Gyrus	11	R	34	44	-18	208	3.21
Caudate		L	-18	10	16	3672	6.39
Caudate		R	18	24	-12	2248	5.89
Parahippocampal Gyrus		R	22	-26	-30	1032	4.18
Middle Frontal Gyrus	10	R	12	48	6	1968	3.98
Middle Frontal Gyrus	10	L	-36	56	6	792	3.44
Hippocampal/Parahippocampal Gyrus		R	26	-26	-6	2128	3.43
Temporal Inferior	37	R	50	-56	-24	424	3.35
Fusiform	20	L	-38	-14	-22	376	3.07
Obese							
Occipital Superior / Cuneus	18	L	-12	-102	14	2440	6.07
Caudate		L	-20	0	22	1296	4.88
Caudate		R	20	12	-16	152	4.36
Inferior Frontal Gyrus	47	L	-18	22	-14	184	4.22

Neural substrates of risk-based decisions in obese adolescents

Hippocampus		R	26	-28	-2	160	4.00
Obese > Overweight > Normal weight							
Inferior Frontal Gyrus	47/11	L	-46	36	-6	1520	4.81
Thalamus		L	-24	-26	0	200	4.29
Superior Occipital Gyrus	18/19	R	18	-86	28	2160	4.27
Cerebellum Posterior Lobe		L	-30	-70	-28	576	4.12
Hippocampal/Parahippocampal Gyrus		R	26	-28	-4	392	4.12

Neural substrates of risk-based decisions in obese adolescents

Supplementary Table 1. Brain activations observed in Risky vs. Safe choices between-group (t-test) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume	*t*
			X	Y	Z	(mm^3)	
Normal weight > Overweight							
Insula	13	L	-26	20	12	160	4.03
Normal weight > Obese							
Insula	13	L	-26	22	10	64	3.65
Overweight > Normal weight							
Midbrain		R	4	-18	-10	112	3.89

Neural substrates of risk-based decisions in obese adolescents

Supplementary Table 2. Brain activations observed in Rewarded vs. Punished between-group (t-test) whole-brain analyses.

	BA	Side	MNI Coordinates			Volume	*t*
			X	Y	Z	(mm^3)	
Obese > Normal weight							
Inferior Frontal Gyrus	47/11	L	-46	36	-6	1520	4.66
Thalamus		L	-24	-26	0	88	3.97
Hippocampus		R	26	-28	-4	392	3.70
Superior Occipital Gyrus	18/19	R	18	-82	26	128	3.55
Overweight > Normal weight							
Cerebellum		L/R	-14	-84	-24	1752	5.35
Inferior Frontal Gyrus	11	L	-34	40	-18	112	5.27
Occipital Lobe	19	R	26	-86	26	2608	4.65
Precuneus	7 / 19	L	-14	-76	40	4480	4.64
Cerebellum Posterior Lobe		L	-30	-68	-32	2608	4.37
Thalamus / Caudate		R	16	-6	18	456	4.03
Inferior Frontal Gyrus	47	L	-50	38	-8	64	3.53
Hippocampus		R	26	-26	-8	36	3.46
Inferior Frontal Gyrus	47	L	-48	38	-6	64	3.37
Overweight > Obese							
Precentral Gyrus	6	R	30	-16	64	672	4.10