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MÉTODOS AVANZADOS DE ANÁLISIS DE IMAGEN DE RESONANCIA MAGNÉTICA CEREBRAL APLICADOS AL ESTUDIO DE LA OBESIDAD

Doctorando

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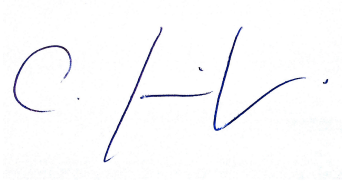

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Resumen

El aumento de la prevalencia de obesidad en las sociedades contemporáneas es uno de los principales problemas de salud pública a nivel mundial. Según la Organización Mundial de la Salud la obesidad se ha convertido en una epidemia global. Estudios recientes postulan que hábitos poco saludables, como un mayor sedentarismo, así como los problemas existentes para controlar la ingesta de alimentos, en nuestros ambientes llenos de estímulos de comida altamente calórica y barata, puede ser una de las principales causas de este problema. Estudios de neuroimagen han demostrado que el procesamiento de comida en personas con exceso de peso se relaciona con patrones diferenciales de activación y conectividad, especialmente de regiones que forman parte de los sistemas de recompensa y toma de decisiones. Por tanto es relevante estudiar el funcionamiento del sistema de recompensa cerebral no sólo ante la comida, sino ante otros tipos de reforzadores como el dinero o reforzadores sociales que pueden tener un mayor impacto en la calidad de vida de las personas con exceso de peso.

Basándose en estos corolarios, el objetivo principal de la presente Tesis Doctoral es caracterizar el procesamiento cerebral de distintos tipos de recompensas (p.e., comida, dinero, recompensa social) en personas con sobrepeso y obesidad frente a individuos con normopeso.

Para ello, se realizaron los tres estudios que componen esta tesis doctoral. En el primero de ellos se compararon los patrones de activación cerebral al procesar distintos estímulos, alimenticios y económicos, en adultos con obesidad y con sobrepeso versus adultos con normopeso. El segundo estudio tenía como objetivo caracterizar y comparar la conectividad funcional durante el procesamiento de los mismos reforzadores, comida y dinero, en adultos con exceso de peso (sobrepeso y obesidad) versus normopeso. Para ello utilizamos una metodología basada en la teoría de grafos. Finalmente el tercer

estudio evaluó el procesamiento cerebral durante una tarea de recompensas y toma de decisiones en un contexto social; para ello, se seleccionó una población especialmente vulnerable a las presiones sociales como son los adolescentes con exceso de peso.

Los resultados obtenidos mostraron alteraciones diferenciales en los patrones de actividad y de conectividad funcional ante los distintos tipos de reforzadores. Específicamente se encontró una activación cerebral diferencial en función del tipo de reforzador, siendo estas alteraciones lineales con el IMC en el procesamiento de comida, y siguiendo una relación de U invertida con el IMC cuando se procesan recompensas monetarias. La conectividad funcional a nivel de redes también mostró características específicas en función del reforzador, encontrándose una reducción de la conectividad durante el procesamiento de comida y un aumento al procesar estímulos monetarios. Finalmente los adolescentes con exceso de peso mostraron una reducción en la activación cerebral de los circuitos de toma de decisiones sociales ligada a rasgos negativos de personalidad y decisiones interpersonales desventajosas.

En conclusión, los individuos con exceso de peso presentaron alteraciones en la activación y conectividad funcional del sistema de recompensa cerebral dependientes del estímulo que se procesa (p.e., comida, dinero, recompensa social), y del grado de obesidad. Estos resultados indican la importancia de diseñar tratamientos específicos para personas con distintos grados de obesidad.

I. INTRODUCCIÓN

Capítulo 1. Obesidad

Este primer capítulo de la tesis se estructura en seis apartados. En el primero de ellos se presentan datos epidemiológicos sobre la obesidad, que reflejan la relevancia clínica de este problema, y se introducen las últimas teorías neurocientíficas que han intentado aportar información para explicar el incremento sustancial de la prevalencia del *exceso de peso*. En el segundo apartado se exponen las consecuencias sociales que se relacionan con la obesidad tanto en adultos como en adolescentes. A continuación, se presentan los sistemas homeostáticos que se encargan de regular el consumo de alimentos, y cómo estos mecanismos tienen relevancia en otros circuitos cerebrales que se han visto relacionados con el exceso de peso, los sistemas de recompensa y toma de decisiones. En el cuarto apartado se revisa la literatura sobre estos sistemas cerebrales de recompensa y toma de decisiones, indicando las regiones cerebrales implicadas en cada uno ellos. Además, se describen los resultados obtenidos al estudiar los constructos de sensibilidad a la recompensa e impulsividad, íntimamente relacionados con el aumento de peso. En primer lugar se exponen las características en personas con *normopeso* y a continuación los resultados de los estudios en adultos y adolescentes con exceso de peso. En el quinto apartado de esta introducción se expone el modelo de adicción a la comida, un modelo que desde el campo de la neurociencia ha tratado de dar una explicación al problema de la obesidad. Este modelo que postula que la obesidad debe tratarse como un trastorno del cerebro, ha recibido recientemente diversas críticas evidenciando que es necesaria más investigación para confirmar su validez. Finalmente se introduce el concepto de la neuroeconomía, un campo que a partir de los procesos de decisión económica y social, trata de aportar información sobre cómo los sustratos cerebrales que sustentan estos procesos pueden estar también afectando a las decisiones de consumo alimenticio.

1. Epidemiología

La *obesidad* se ha convertido en las últimas décadas en uno de los principales problemas de salud pública a nivel mundial (World Health Organization, 2014). La Organización Mundial de la Salud (OMS) declaró en 1997 la obesidad como una epidemia global (World Health Organization, 1997), y en los últimos 30 años su prevalencia se ha duplicado, afectando en 2014 al 11% de los hombres y al 15% de las mujeres mayores de 18 años en todo el mundo (World Health Organization, 2014).

El *exceso de peso* se ha relacionado con un aumento de la mortalidad (Flegal et al., 2005) y es uno de los factores que incrementa el riesgo de padecer diabetes, hipertensión, enfermedades coronarias, infarto y ciertos tipos de cáncer (Flegal et al., 2013). Actualmente, el *sobrepeso* y la obesidad son la quinta causa más frecuente de mortalidad a nivel global y es responsable de al menos 3.4 millones de muertes al año (World Health Organization, 2009, World Health Organization, 2014). En cifras absolutas, 2100 millones de personas en todo el mundo tienen exceso de peso, y los problemas asociados a la obesidad constituyen un alto porcentaje del gasto sanitario (Ng et al, 2014). En España, según datos de la OMS, en 2014 uno de cada cuatro adultos es obeso (26.5 %) y casi dos de cada tres (65.6%) tienen sobrepeso (World Health Organization, 2014).

La obesidad se define genéricamente como un exceso de grasa corporal, pero la dificultad de hacer una cuantificación exacta provoca que diversas medidas antropométricas suelan ser utilizadas para determinar el grado de obesidad. Instituciones como la OMS o la International Obesity Task Force (IOTF), recomiendan utilizar el *Índice de Masa Corporal* (IMC), como medida para estimar la prevalencia de la obesidad. Este índice se calcula dividiendo el peso, en kilogramos, entre el cuadrado de la altura, en metros (Kg/m^2). La OMS definió los umbrales para personas adultas, donde

un IMC superior a 25 Kg/m^2 es considerado sobrepeso y medidas superiores a 30 Kg/m^2 obesidad (World Health Organization, 1997).

En el caso de los adolescentes, esta clasificación se realiza siguiendo las indicaciones del International Obesity Task Force (IOTF) (Cole & Lobstein, 2012) que sugiere utilizar niveles de IMC ajustados por edad y sexo para definir el sobrepeso y la obesidad. Según sus indicaciones, valores de percentil mayores de 85 se consideran sobrepeso mientras que el punto de corte para la obesidad se establece en el percentil 95. Según estos baremos, en 2013 casi uno de cada cuatro (23,1%) adolescentes españoles de entre 14 y 17 años tenía exceso de peso, mientras que la tasa de obesidad era del 6,7% (Sánchez-Cruz, 2013). Por tanto parece claro que el problema de la obesidad es necesario afrontarlo desde las primeras etapas del desarrollo y no sólo en la etapa adulta.

Otras medidas antropométricas utilizadas para determinar el grado de obesidad son el perímetro abdominal en centímetros y el índice cintura-cadera, calculado como el ratio entre el perímetro de la cintura y el de la cadera. Medidas superiores a 102 cm en hombres y a 88 cm en mujeres, para el perímetro abdominal, y mayores de 1 y de 0.85 en hombres y mujeres, respectivamente, para el ratio cintura-cadera se consideran indicadores de obesidad (World Health Organization, 1997). Ambas medidas, al igual que el IMC, se han relacionado con un incremento en el riesgo de padecer problemas cardiovasculares y otros trastornos metabólicos como la hipertensión o la hipercolesterolemia (Sardinha et al., 2016).

La obesidad es un trastorno complejo en el que influyen factores genéticos y metabólicos, así como hábitos de alimentación y de actividad física y problemas sociales. Debido a la heterogeneidad y alta concurrencia entre estos factores, resulta complicado establecer los motivos específicos del aumento de su prevalencia, pero diversos estudios

apuntan a que factores culturales y los cambios producidos en los estilos de vida, como la reducción del ejercicio físico y el mayor sedentarismo, así como la alta disponibilidad de alimentos altamente calóricos a precios relativamente asequibles pueden ser algunas de las principales causas de este crecimiento (Finkelstein et al., 2005, Stice et al.2013).

Desde el campo de la neurociencia se ha propuesto que la obesidad debe ser considerada como un trastorno del cerebro, en el que las alteraciones de los procesos neurobiológicos de procesamiento de recompensas y toma de decisiones explicarían la dificultad de las personas obesas para reducir peso (Koritzky et al., 2014). Los defensores de esta idea también arguyen los paralelismos existentes entre la obesidad y los trastornos adictivos (Volkow et al., 2013). La ventaja de esta aproximación neurocientífica es que permite profundizar en el estudio de circuitos cerebrales específicos y, por tanto, puede ayudar a desarrollar nuevos y mejores tratamientos para la obesidad, que optimicen la motivación y las decisiones de los pacientes obesos y además minimicen sus recaídas (Acosta et al., 2008). Por tanto, uno de los objetivos claves desde esta aproximación es conocer cuáles son los sistemas cerebrales encargados de regular las recompensas y las decisiones asociadas al consumo de comida.

2. Costes sociales asociados a la obesidad

Las decisiones de consumo no sólo están determinadas por el balance entre sensibilidad a la recompensa y toma de decisiones, sino que son también sensibles a las influencias y presiones sociales, que afectan de manera distinta a personas con normopeso y con exceso de peso. De hecho, existen evidencias de numerosos ámbitos que describen como el exceso peso tiene asociado una gran cantidad de costes sociales (Puhl & Heuer, 2009).

Las personas con exceso de peso presentan una mayor dificultad para encontrar pareja y establecer relaciones sociales (Puhl and Brownell, 2001), y se ha descrito que un incremento del 10% en la media de índice de masa corporal reduce los ingresos económicos de hombres y mujeres en un 3,27% y 1,86%, respectivamente (Brunello y D'Hombres, 2007). Asimismo, el exceso de peso también se asocia a menores niveles de satisfacción en el trabajo, en las relaciones de familia, y en las actividades sociales (Ball et al., 2004). Además, la obesidad se asocia, especialmente en mujeres, a síntomas de depresión (McElroy et al., 2004, Needham and Crosnoe, 2005) y ansiedad (Mestre et al., 2016) lo cual puede acompañarse de episodios de sobreingesta (Rosenbaum y White, 2015).

Estas consecuencias sociales de la obesidad se encuentran también en población adolescente los cuales presentan mayores niveles de estrés subjetivo (van Jaarsveldt et al., 2009), de insatisfacción corporal (Costa et al., 2016), y tienen un mayor riesgo de recibir presión social, burlas y discriminación (Griffiths et al., 2006; Hebebrand y Herpertz-Dahlman, 2009).

3. Sistemas de regulación alimentaria

Tradicionalmente, el hipotálamo ha sido considerado como el principal centro cerebral encargado del control de señales fisiológicas reguladoras de la ingesta (Horvath, 2005). En concreto, lesiones en la región ventromedial del hipotálamo se han relacionado con incrementos anormales del apetito y de la cantidad de alimento ingerido, considerándose esta zona el centro homeostático de la saciedad (Mayer & Marshall, 1956). Por el contrario, la zona del hipotálamo lateral se considera la responsable de la

reducción en la motivación hacia los alimentos y su actividad se relaciona con una disminución en la cantidad de alimento ingerido (Margules y Olds, 1962).

El circuito hipotalámico hace un seguimiento del equilibrio entre la energía consumida y las necesidades corporales mediante diversas señales endocrinas y metabólicas, que actúan sobre el hipotálamo medial, y ejercen una función reguladora de la homeostasis energética. Sin embargo, a nivel cerebral, no sólo el hipotálamo está implicado en el control de la ingesta (Rolls, 2008). Las hormonas que modulan la actividad del hipotálamo (p.e., leptina, grelina o insulina) regulan también la actividad neuronal en regiones subcorticales y límbicas del cerebro, implicadas en la motivación, el procesamiento de recompensas y el aprendizaje de hábitos, las cuales también tienen una repercusión directa sobre el consumo de comida (Farooqi, 2007, Thanos, 2008). En concreto, cuando el cuerpo se encuentra en situación de privación, el estómago aumenta el nivel de producción de grelina, estimulando la motivación hacia el consumo de alimentos. Por el contrario, la presencia de niveles altos de insulina y leptina, hormonas segregadas por el páncreas y el tejido adiposo respectivamente, pueden reducir la motivación hacia la comida y modular los sistemas de neurotransmisores y los circuitos neuronales encargados de procesar las recompensas vinculadas a la comida (Figlewicz y Sipols, 2010). Estos circuitos, que incluyen las vías dopaminérgicas con origen en el mesencéfalo ventral, son los encargados de promover una mayor predisposición a la sobreingesta cuando se visualizan alimentos altamente apetecibles o con gran aporte energético (Stice et al., 2013). Por tanto, la capacidad de los individuos para inhibir estas señales en nuestras sociedades actuales llenas de estímulos obesogénicos y la habilidad para controlar la cantidad de alimento que se ingiere serán dos predictores del riesgo de desarrollar exceso de peso (Berthoud, 2007).

En conclusión, debido a los grandes cambios experimentados en los últimos años en cuanto a la composición y disponibilidad de los alimentos, el medio ambiente y los estilos de vida, las decisiones sobre la ingesta diaria de alimentos han dejado de ser una cuestión meramente homeostática y han pasado a ser una cuestión de toma de decisiones, donde la elección de nuestra dieta está en gran parte guiada por el valor recompensante que le asignamos a estos productos, tanto como por influencias metabólicas. Por tanto, los sistemas cerebrales implicados en el procesamiento de recompensas alimenticias, toma de decisiones e impulsividad (p.e., la corteza prefrontal, el cuerpo estriado) pueden jugar un papel fundamental en el consumo de alimentos y los hábitos alimentarios, en ocasiones "puenteando" la influencia de los sistemas homeostáticos de regulación metabólica, ya que éstos últimos fueron originalmente establecidos para asegurar la supervivencia pero no para regular el consumo de alimentos en un contexto medioambiental y económico caracterizado por la abundancia y diversidad de productos (Zheng y Berthoud, 2007).

4. Sistemas cerebrales relacionados con obesidad

En los últimos años, numerosos estudios de neuroimagen han encontrado que las preferencias y los deseos de consumo alimenticio, la alta resistencia a las intervenciones dietéticas de las personas con obesidad o el consumo de grandes cantidades de comida podrían relacionarse con la descompensación entre los sistemas cerebrales que asignan el valor recompensante de los alimentos y los sistemas encargados de controlar la toma de decisiones en función del contexto y los objetivos a medio y largo plazo (Volkow et al., 2008a). Además, la descompensación entre estos dos sistemas será mayor cuanto mayor sea índice de masa corporal (Volkow et al., 2008b). De acuerdo con estos estudios, la

ingesta excesiva y la obesidad estarían asociadas con una disfunción del sistema de recompensa, que provocaría una inflación del valor subjetivo asignado a ciertos alimentos apetitosos (Rolls, 2011), a una devaluación de la capacidad de regulación de los sistemas prefrontales implicados en el control ejecutivo y la toma de decisiones (Verdejo-García et al., 2010; Volkow et al., 2009), y a un aumento en la impulsividad (Burger y Stice, 2011) lo cual provocaría una incapacidad para inhibir las conductas de ingesta de alimentos.

La descompensación entre el sistema de recompensa y toma de decisiones se encuentra aún más acentuada en la adolescencia, un periodo caracterizado por una hipersensibilidad a la búsqueda de sensaciones recompensantes y una falta de madurez del sistema inhibitorio y de toma de decisiones (Geier, 2013). Mayores niveles de sensibilidad a la recompensa e impulsividad se han relacionado con exceso de peso en adolescentes (van den Berg et al., 2011) y estudios de neuroimagen han concluido que los mecanismos de maduración de los sustratos cerebrales de sensibilidad a la recompensa y toma de decisiones tienen un efecto sobre la impulsividad en la etapa adulta (Christakou et al, 2011) lo cual sería un factor de riesgo de ser obeso.

4.1 Sistema de recompensa cerebral

El conocimiento del funcionamiento del sistema de recompensa cerebral es crucial para entender mejor el fenómeno de la obesidad. Como se exponía en el apartado anterior, los circuitos neuronales, así como los neurotransmisores y señales periféricas que informan al sistema nervioso central del estado metabólico y nutricional del individuo, tienen un impacto en las redes cerebrales de la motivación, especialmente en las vías dopaminérgicas que confluyen entre el área tegmental ventral y el núcleo accumbens

(Lutter y Nestler, 2009; Figlewicz y Sipols, 2010). Biológicamente, este sistema aumenta la motivación hacia la comida en circunstancias de carencia alimenticia, mientras que disminuye los aspectos recompensantes de la comida cuando la persona se encuentra en un estado de saciedad (Rangel, 2013). Elevados niveles de grasa corporal pueden también interrumpir la correcta comunicación entre las hormonas reguladoras de la ingesta y los sistemas de recompensa, provocando alteraciones en la sensibilidad a la recompensa y el control cognitivo (Volkow et al., 2011).

Desde un punto de vista neurocientífico, existe evidencia de que el procesamiento de la recompensa en el cerebro depende de una red cerebral compuesta por diversas regiones, incluyendo el estriado, la corteza prefrontal, el cíngulo anterior, la ínsula o las regiones dopaminérgicas del mesencéfalo (Haber y Knutson, 2010). Estudios de neuroimagen han mostrado cierta especialización dentro de este sistema, donde, por ejemplo, la activación del estriado ventral es indicador del grado de valoración subjetiva que el cerebro asigna a distintos reforzadores relevantes como la comida o el dinero (Hariri et al., 2006; Passamonti et al., 2009), mientras que la ínsula anterior parece estar más relacionada con la integración de la información interoceptiva con procesos de recompensa y toma de decisiones (Craig, 2009).

Pese a que el procesamiento genérico de distintos tipos de reforzadores suele involucrar la mayor parte de las regiones descritas en el párrafo anterior, se ha descrito cierta segregación en la red cerebral de recompensa en función del tipo de reforzador (Sescousse 2013). Así, reforzadores primarios como la comida o los estímulos eróticos parecen involucrar más a regiones límbicas como la ínsula anterior, mientras que el procesamiento monetario, relacionado con recompensas secundarias, muestra una mayor relación con regiones orbitofrontales (Sescousse, 2013). En este sentido, y con

respecto a la obesidad, existe la duda de si las posibles alteraciones de este sistema cerebral de la recompensa ocurren también de manera segregada en función del reforzador o si por el contrario existe una disfunción genérica independiente del estímulo a procesar. La existencia de un déficit genérico predeciría que las personas obesas tendrán problemas en evaluar cualquier tipo de reforzador (p.e., dinero, sexo) y por tanto tendría un mayor impacto en todas sus decisiones y en su calidad de vida (Rangel, 2013).

4.1.1 Sensibilidad a la recompensa

Desde un punto de vista neuropsicológico, el constructo que se relaciona con la actividad del sistema de recompensa cerebral es la sensibilidad a la recompensa. La sensibilidad a la recompensa suele ser evaluada con una de las escalas del cuestionario "Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al 2001). Este cuestionario evalúa tanto el grado de expectativa durante la anticipación a una recompensa como el placer obtenido por la actividad emocional. Los ítems del cuestionario comprenden diversos tipos de reforzadores (p.e., dinero, drogas, sexo o reconocimiento social) por lo que es un buen indicador de la sensibilidad general a la recompensa. De manera relevante, los estudios de neuroimagen han confirmado en individuos con normopeso la relación entre puntuaciones de sensibilidad a la recompensa y la activación de regiones dopaminérgicas del cerebro, como el núcleo accumbens y el mesencéfalo ventral, durante la visualización de alimentos apetitosos (Beaver et al., 2006) y durante una tarea con incentivo monetario (MID) (Costumero et al., 2013).

Por otro lado, los estudios sobre sensibilidad a la recompensa realizados en individuos con exceso de peso han mostrado que la relación entre el índice de masa corporal y las

puntuaciones de esta variable muestra una relación en forma de U invertida, siendo la correlación positiva en individuos con normopeso y sobrepeso, pero negativa en obesos, tanto en adultos como en adolescentes (Davis y Fox., 2008; Verbeken et al., 2012 Dietrich et al., 2014). Estudios de neuroimagen realizados con técnicas de tomografía por emisión de positrones (PET) aportan evidencias en este sentido, revelando que la disponibilidad de receptores de dopamina D2/D3 en el estriado siguen esta misma tendencia, con una mayor respuesta en la población con sobrepeso y una reducción en los obesos (Horstmann et al., 2015). Estos resultados sugieren que los mecanismos cerebrales de procesamiento genérico de la recompensa pueden ser distintos en función del grado de exceso de peso.

4.2 Sistemas cerebrales que regulan la toma de decisiones

Los cambios experimentados en las sociedades contemporáneas, llenas de estímulos alimenticios y comidas de alto contenido calórico a precios bajos, ha provocado que las conductas alimentarias estén cada vez más guiadas por los procesos superiores de toma de decisiones tanto como por las necesidades homeostáticas (Zheng & Berthoud, 2007).

Dentro de los circuitos cerebrales que se han relacionado con la toma de decisiones en el contexto de la alimentación, la corteza orbitofrontal medial parece estar implicada en el proceso de integración de la información visceral, motivacional y afectiva que guía nuestra toma de decisiones hacia objetivos relevantes, como puede ser la comida (Kringelbach, 2005). Esta región se encarga de regular el valor subjetivo de los reforzadores en función del contexto de decisión y de sus posibles repercusiones a largo plazo, influyendo en las pautas de consumo (Hare, et al., 2009; Verdejo-García y Bechara, 2009). Estudios de resonancia magnética han mostrado que esta región se activa

durante la elección de menús en individuos con normopeso (Arana et al., 2003), y que su respuesta ante comidas apetitosas correlaciona con la activación de regiones del sistema de recompensa como el estriado o la amígdala (Passamonti et al., 2009).

Otras regiones implicadas en el control cognitivo de la toma de decisiones son las cortezas prefrontal dorsolateral y orbitofrontal lateral que regulan las respuestas ante estímulos inmediatos en función del contexto y los objetivos a largo plazo (Fellows y Farah, 2005). La activación de estas regiones se ha relacionado con la capacidad de controlar la ingesta durante una dieta (Hare et al., 2009). Igualmente, se ha observado que mediante la aplicación de *estimulación transcraneal* con corriente continua en la corteza dorsolateral, es posible producir una reducción en el deseo subjetivo de consumir ciertos alimentos (Fregni et al, 2008).

4.2.1 Impulsividad

Otro factor que se asocia con problemas para controlar la ingesta es la impulsividad. Genéricamente se define la impulsividad como la tendencia a actuar sin la reflexión adecuada en el momento de tomar decisiones. Cuestionarios como el UPPS-P (Whiteside y Lynam, 2001) o el Barrat Impulsiveness Scale (BIS) (Patton et al., 1995) o tareas neuropsicológicas como el go/no-go o el stop-signal task (Logan et al., 1997), han sido utilizados para explorar la relación entre la impulsividad y la obesidad.

Los valores de impulsividad medidos con cuestionarios correlacionan positivamente con la cantidad de calorías ingeridas (Guerrieri et al., 2007), con la activación del circuito de recompensa en respuesta a imágenes de comida (Beaver et al., 2006), y con los valores de IMC en adultos (Rydén et al., 2003) y adolescentes (Braet et al., 2007; Thamotharan et al., 2013) y negativamente con la pérdida de peso durante un tratamiento dietético

(Nederkoorn et al., 2006). Las respuestas impulsivas durante una tarea de stop-signal también correlacionaron con la cantidad de alimento ingerido (Guerrieri et al., 2007) y con el IMC (Bonato and Boland, 1983, Nederkoorn et al., 2006). Además, se han encontrado correlaciones entre el índice de masa corporal y problemas de control inhibitorio y los sustratos cerebrales que los soportan (corteza prefrontal) durante una tarea de go-nogo (Batterink, et al., 2010).

Las tareas de descuento asociado a la demora, en las cuales los participantes tienen que elegir entre una recompensa pequeña, pero inmediata, o una mayor, transcurrido un cierto tiempo, se han utilizado también para evaluar los procesos de impulsividad en obesos (Volkow y Baler, 2015). Utilizando un paradigma de este tipo y reforzadores alimenticios, se encontró que los sujetos con mejor control inhibitorio tenían más éxito a la hora de perder peso y que esta pérdida de peso correlacionaba también con la actividad en las cortezas prefrontales ventromedial y dorsolateral. De hecho, la conectividad entre estas dos regiones predecía el éxito en el seguimiento dietético y el control de impulsos (Weygandt et al., 2013). Del mismo modo con un paradigma similar, pero usando reforzadores económicos, se encontró una relación significativa entre la impulsividad y disfunciones ejecutivas relacionadas con alteraciones de la corteza prefrontal. Esta asociación predecía la posterior ganancia de peso en sujetos obesos (Kishinevsky et al., 2012; Stoeckel, 2013).

5. Modelo de adicción a la comida

Basándose en las evidencias que muestran un solapamiento en las alteraciones cerebrales existentes entre los trastornos adictivos y la obesidad, se ha postulado un modelo de adicción a la comida, similar a los trastornos adictivos a sustancias del *DSM*

(Volkow y O'Brien, 2007; Volkow et al., 2008). Entre las características de las personas con obesidad que son comunes a las personas con adicción, y que apoyan este modelo se encuentran: el control inhibitorio deteriorado, un aumento de la reactividad cerebral y de la motivación hacia el reforzador problemático (comida o droga), alteraciones en la conducta y en hábitos y problemas de regulación emocional (Volkow et al., 2008). Por tanto, es interesante trasladar al contexto de la obesidad los estudios previos sobre los sistemas de recompensa y toma de decisiones realizados en población adicta.

A pesar de la gran influencia de este modelo de adicción a la comida, tanto el sobrepeso como la obesidad son estados muy heterogéneos, y aún es necesaria mucha más investigación para establecer claramente si este modelo es válido en todas las personas con exceso de peso, o si es específico de determinados perfiles de personas obesas (Carter et al., 2016). Estudios recientes han relacionado las similitudes entre obesidad y adicciones a patrones específicos de sobreingesta, como el trastorno por atracón (Ziauddeen y Fletcher, 2013), más que a fenotipos más típicos de obesidad (Stice et al., 2013) y, si bien el trastorno por atracón está relacionado con la obesidad, no todos los que padecen este problema son obesos, y tampoco todos los obesos presentan este trastorno.

6. Introducción a la neuroeconomía

Tal y como comentábamos en el capítulo 2 de esta tesis, la valoración de recompensas y la toma de decisiones están también influenciadas por presiones sociales. Los problemas existentes en población con exceso de peso al valorar y tomar decisiones alimentarias pueden estar también reflejados en otros procesos de decisión social. En este contexto,

se han comenzado a investigar las bases cerebrales de la toma de decisiones económicas en personas con exceso de peso en contextos sociales, es decir, en condiciones de negociación, confianza y reciprocidad. Los sistemas cerebrales que sustentan estos procesos han sido estudiados en sujetos sanos por el novedoso campo de la neuroeconomía (Crockett et al., 2008; van den Bos et al., 2009). El paradigma más utilizado para evaluar estos procesos de toma de decisiones en un contexto social es la tarea del Ultimatum Game (Sanfey, 2003). Durante esta tarea se produce una situación de conflicto entre dos personas que deben repartir una cantidad de dinero. Una de las dos personas (el ofertante) decide cómo repartir entre ambos una cantidad de dinero, considerando que si el receptor acepta, los dos obtendrán lo acordado, mientras que si rechaza, ninguno obtendrá nada. En la administración habitual de la tarea, las personas evaluadas toman el rol del receptor de la oferta y deben decidir si aceptan o rechazan un conjunto de ofertas realizadas por un ofertante real. Estas ofertas suelen variar desde situaciones justas donde los dos obtienen alrededor del 50% de la cantidad a repartir, hasta situaciones denominadas muy injustas donde sólo se les ofrece un 15% del total. En el proceso de toma de decisión, especialmente en ofertas injustas, se produce una situación de conflicto donde la aceptación de la oferta resulta en una situación ventajosa, puesto que siempre se obtiene una cantidad de dinero, pero se puede experimentar una situación emocional negativa, debido a que el reparto no sea equitativo, lo que empuja a la persona a rechazar la oferta, pese a no obtener nada. De manera consistente con estos datos, se ha encontrado que los principales sustratos cerebrales involucrados en esta tarea son la ínsula anterior, la corteza prefrontal dorsolateral y la corteza cingulada anterior, implicados en la percepción de la injusticia, la evaluación cognitiva de la oferta y la evaluación del conflicto entre cognición y emoción, respectivamente (Gabay et al., 2014). Sin embargo, hasta la fecha no existe evidencia de la influencia de estos patrones

neuroeconómicos de decisión social sobre la conducta nutricional y de consumo de alimentos.

Capítulo 2. Estudios de neuroimagen y obesidad

En los últimos años se han realizado un gran número de estudios de neuroimagen que han permitido estudiar la estructura y el funcionamiento cerebral en personas con exceso de peso, y que han intentado aportar evidencia a favor o en contra del modelo de adicción a la comida. Este capítulo describe los estudios que se han realizado hasta la fecha en población con exceso de peso, tanto en adultos como en adolescentes.

Este capítulo se divide en cuatro secciones que se corresponden con las cuatro aproximaciones distintas que se han utilizado para evaluar la estructura y el funcionamiento del cerebro: (i) estudios de medicina nuclear, (ii) estudios estructurales mediante resonancia magnética, (iii) análisis de activación cerebral mediante resonancia magnética funcional y (iv) análisis de conectividad funcional. Cada una de las secciones comienza con un resumen de la técnica utilizada en cada caso y algunos resultados obtenidos en población con normopeso. A continuación se presentan los resultados de los estudios realizados en población con exceso de peso adulta y se finaliza con los hallazgos específicos en adolescentes, si los hubiera.

1. Estudios de Medicina Nuclear

Los estudios de neuroimagen que han utilizado técnicas de medicina nuclear comprenden principalmente dos técnicas: la tomografía por emisión de positrones (PET) y la tomografía computarizada de emisión monofotónica (SPECT). En ambos casos, se utilizan distintos isótopos radiactivos unidos a determinadas moléculas, lo que forma un radioligando. Estos radioligandos son introducidos en el cuerpo por vía intravenosa, y en función de la molécula de la que estén compuestos, interactúan con determinadas moléculas del organismo, permitiendo cuantificar su actividad o

localización. En el caso del PET, más utilizado para objetivos de investigación, los isótopos más utilizados son el Flúor-18, generalmente ligado a moléculas de glucosa (fluorodesoxiglucosa), lo que permitirá cuantificar el consumo de glucosa cerebral y el Carbono-11, generalmente ligado a moléculas relacionadas con la neurotransmisión dopaminérgica (p.e., raclopride), lo que permitirá estudiar este sistema de neurotransmisión. Esta última técnica es de gran utilidad en el estudio del sistema de recompensa cerebral, puesto que la dopamina es un neurotransmisor clave en la modulación de la recompensa y la motivación (Comings & Blum, 2000).

Estudios previos en adultos sanos con normopeso utilizando tomografía por emisión de positrones (PET), mostraron que la ingesta de comida activa la actividad dopaminérgica en diversas regiones cerebrales (p.e., corteza prefrontal, estriado, ínsula, mesencéfalo), siendo proporcional la cantidad de dopamina disponible en el estriado dorsal con el grado de placer experimentado al comer (Small et al, 2003), mientras que estos niveles disminuyen con el nivel de saciedad (Small et al, 2001).

Los primeros estudios realizados en población obesa evidenciaron una disminución de la disponibilidad de receptores de dopamina D_2 en obesos mórbidos, siendo esta disminución proporcional a la actividad metabólica prefrontal y al IMC de los sujetos (Wang et al., 2001; Volkow et al., 2008). Estos resultados sugerían que del mismo modo que ocurre en adicciones a sustancias, en las personas obesas existe una alteración de los circuitos dopaminérgicos que implicaría una pérdida del control inhibitorio de la conducta (Volkow et al., 2012). Estudios posteriores han confirmado que si se considera un rango más amplio de IMC, la respuesta dopaminérgica del estriado sigue una relación en forma de U invertida (Horstmann et al., 2015), confirmándose la disminución en

personas con alto grado de obesidad, pero encontrándose un incremento a medida que aumenta el IMC en los rangos de normopeso y obesidad.

2. Estudios con resonancia magnética

Los estudios realizados con resonancia magnética cuentan con diversas ventajas con respecto a los de medicina nuclear. Por un lado son estudios no invasivos, ya que el propio metabolismo actúa como elemento de contraste y no es necesario introducir ninguna sustancia radioactiva en el organismo. Además, la resolución espacial y temporal de la que dispone es sustancialmente mejor que la del PET o SPECT permitiendo la localización de regiones más específicas del cerebro y el estudio de funciones cerebrales concretas mediante la estimulación del participante con determinados estímulos.

2.1 Estudios de neuroimagen estructural

Numerosos estudios han explorado las diferencias morfológicas cerebrales en población con exceso de peso, a partir de adquisiciones de *imágenes ponderadas en T1*, utilizando para ello técnicas de "Voxel-Based Morphometry" (VBM), así como metodologías de medición del grosor cortical. Estos análisis permiten cuantificar el tamaño cerebral, así como el volumen de cada uno de sus componentes, materia gris, materia blanca y líquido cefalorraquídeo. Además permite la segmentación cerebral por regiones de interés de modo que se puede cuantificar y comparar la cantidad de materia gris y materia blanca existente en determinadas regiones cerebrales. Estos estudios se complementan con análisis de integridad de la microestructura de la sustancia blanca realizados a partir de adquisiciones de *imágenes por tensor de difusión (DTI)*. Con este último tipo de análisis

es posible estudiar la forma e integridad estructural de los axones que conforman los tractos de sustancia blanca cerebral.

Consistentemente, se ha encontrado una relación negativa entre el índice de masa corporal y el volumen total de materia gris (Taki et al., 2008; Raji et al., 2010; Brooks et al., 2013; Karlsson et al., 2013; Bobb et al., 2014), así como una reducción del volumen regional de diversas áreas cerebrales, relacionadas con el control de impulsos y el procesamiento de la recompensa (p.e., giro frontal inferior, corteza orbitofrontal, estriado, corteza cíngulada anterior y regiones occipitales) (Pannacciulli et al., 2006; Taki et al., 2008; Walther et al., 2010; Raji et al., 2010; Brooks et al., 2013; Karlsson et al., 2013; Kurth et al., 2013; Opel et al., 2015). Con respecto a la materia blanca se han obtenido resultados contradictorios en adultos, encontrándose correlaciones positivas entre el IMC y el volumen global (Yokum et al, 2012) y el volumen regional en zonas frontales, temporales y parietales (Walther et al, 2010) y correlaciones negativas en regiones límbicas (Karlsson et al., 2013).

Los análisis de grosor cortical también han encontrado una relación entre elevados valores de IMC y reducciones de materia gris en adultos en el cíngulo anterior y la ínsula (Hassenstab et al, 2012), la corteza orbitofrontal (Marqués-Iturra et al, 2013) y la corteza prefrontal ventromedial y occipital (Veit et al., 2014). Estos hallazgos sugieren la existencia de alteraciones en regiones relacionadas con autocontrol, toma de decisiones y comportamiento dirigido a metas y serían consecuencia de una combinación de un incremento de la valoración de las recompensas y un reducido autocontrol, conduciendo una vez más a una mala toma de decisiones alimentarias.

Por último, los análisis realizados a partir de las adquisiciones de DTI han encontrado alteraciones en la integridad de la materia blanca cerebral de adultos con exceso de

peso, principalmente en tres estructuras: el cuerpo calloso, que une ambos hemisferios (Stanek et al., 2011; Xu et al., 2013; Mueller et al., 2011; Verstynen et al., 2013), el fornix que conecta el hipocampo con otras regiones cerebrales (Stanek et al., 2011; Xu et al., 2013) y el cíngulo, relacionado tanto con procesos emocionales como cognitivos (Marks et al., 2011).

Dentro del espectro del exceso de peso algunos estudios han comparado la estructura cerebral de adultos con sobrepeso frente a otros con obesidad, encontradose reducciones de materia gris (Gustand, et al., 2008; Yokum et al., 2012), de grosor cortical en zonas frontales (Medic et al., 2016) y alteraciones genéricas en materia blanca (Stanek et al., 2011) en aquellos con mayor IMC. Estos resultados indican una mayor afectación cerebral relacionada con un mayor grado de exceso de peso.

2.1.1 Estudios de neuroimagen estructural en adolescentes

Con respecto a la población adolescente, dos estudios realizados no encontraron relación entre IMC y volumen global de materia gris ni grosor cortical (Moreno-López et al., 2012; Sharkey et al, 2015), si bien si existía una relación positiva en el grupo control entre el volumen de materia gris en las cortezas somatosensoriales y los valores de la sensibilidad a la recompensa e impulsividad, que no existía en los sujetos con sobrepeso (Moreno-López et al., 2012). Por otro lado se encontraron reducciones de materia gris local en la corteza orbitofrontal, relacionada con disfunción ejecutiva (Maayan et al., 2011). Con respecto a la materia blanca, un estudio reciente halló una mejora en su integridad relacionada con una intervención basada en ejercicio físico (Schaeffer et al., 2014).

2.2 Estudios de activación cerebral

En los últimos años ha crecido enormemente la cantidad de estudios, que utilizando resonancia magnética funcional, han explorado el funcionamiento cerebral de personas con exceso de peso, utilizando para ello distintos tipos de tareas. Los estudios de actividad cerebral se basan en mediciones de la señal BOLD (blood-oxygen-level-dependent) obtenida durante adquisiciones de resonancia magnética funcional (Ogawa et al., 1993). Brevemente, la actividad neuronal provoca cambios en la ratio oxihemoglobina/desoxihemoglobina que son captados por un escáner de resonancia magnética y transformados en imágenes. Los estudios de resonancia magnética funcional permiten, mediante la realización de determinadas tareas, obtener mapas de activación cerebral que reflejan las regiones implicadas en determinados procesos cerebrales.

2.2.1 Tareas con reforzador alimenticio

La mayor parte de los estudios de neuroimagen funcional y obesidad han utilizado paradigmas de procesamiento de estímulos alimenticios, especialmente aquellos con un alto valor hedónico, mediante la visualización de imágenes o mediante la administración de alimentos líquidos en el escáner.

Estudios de neuroimagen en participantes sanos han mostrado que la comida es un potente reforzador cerebral y tanto la simple observación de imágenes de comida, como el consumo de alimentos activa regiones del sistema de refuerzo cerebral (O'Doherty et al., 2002; Kringelbach et al,. 2003).

Los adultos con obesidad, en comparación con grupos control con normopeso, han demostrado consistentemente una mayor activación de regiones del sistema de

recompensa cerebral al procesar estímulos de comida altamente calórica, en comparación con comida baja en calorías o con estímulos neutros (Rothemund et al., 2007; Stoeckel et al., 2008; Grosshans et al., 2012; Nummenmaa et al., 2012). Esta respuesta incrementada en individuos obesos ante estímulos de comida se ha observado tanto en estados de privación como de saciedad (Martin et al, 2010; Dimitropoulos et al., 2012) y se ha relacionado con los niveles de leptina e insulina (Grosshans et al., 2012; Jastreboff et al., 2013; Simon et al., 2014), con altos niveles de estrés crónico (Tryon et al., 2013), con un peor seguimiento de un tratamiento de pérdida de peso (Murdaugh et al., 2012), con incrementos de peso en adultos con bajo autocontrol (Lawrence et al, 2012), con niveles de deseo por la comida (Jastreboff et al., 2013) y con puntuaciones de adicción a la comida medido con el Yale Food Addiction Scale (Gearhardt et al., 2011).

Durante la ingesta de alimentos recompensantes, principalmente batidos o chocolate líquido, se ha encontrado una relación negativa entre IMC y la actividad del caudado dorsal (Stice et al., 2008; Babbs et al., 2013) así como una menor activación cuanto mayor sea el aumento de peso en 6 meses (Stice et al., 2010). Esta hipoactivación en la corteza orbitofrontal, es más acusada cuanto mayor son las puntuaciones en la escala de adicción a la comida (Gearhardt et al., 2011) y las del caudado se relacionan con mayor impulsividad (Babbs et al., 2013). Por el contrario, otros estudios encontraron una mayor activación en el grupo con obesidad durante el consumo de batido de chocolate en regiones frontales, operculares, y estriatales (Ng et al., 2011; Babbs et al., 2013).

2.2.1.1 Tareas con reforzador alimenticio en adolescentes

El visionado de alimentos por adolescentes obesos se ha relacionado principalmente con una mayor activación de regiones frontales y estriatales implicadas en recompensa, motivación y control cognitivo (Bruce et al., 2010; Stice et al., 2010; Yokum et al., 2011;

Jensen et al., 2015) que correlacionan con menores puntuaciones de autoestima (Davids et al., 2009). En este último estudio, sin embargo, se encontró una menor activación del caudado, el cíngulo anterior y el hipocampo (Davids et al., 2009). Finalmente, en un estudio realizado con adolescentes con exceso de peso, estos mostraron incrementos de activación tanto durante la espera como durante el consumo de batido de chocolate en regiones de la corteza gustativa (ínsula, opérculo frontal) y en regiones somatosensoriales (opérculo parietal), si bien la activación del caudado dorsal mostró una relación negativa con el IMC (Stice et al., 2008).

En general, estos resultados apuntan a una respuesta incrementada tanto en adultos como en adolescentes con exceso de peso al procesar imágenes de comida apetitosa. Por el contrario, los resultados durante el consumo de alimentos es más controvertido, encontrándose indistintamente relaciones positivas y negativas con el IMC. Esta discrepancia puede deberse a la diversidad de paradigmas utilizados en cada estudio, así como al de sustancias utilizadas como reforzadores.

2.2.2 Tareas con otro tipo de reforzadores

Como hemos expuesto, existe una gran cantidad de literatura sobre el procesamiento cerebral de estímulos alimenticios en personas con exceso de peso, pero aún existe poca evidencia sobre si existe la misma disfunción durante el procesamiento de otros estímulos, lo cual aportaría información sobre si los obesos presentan una alteración específica con la comida o un déficit general en el procesamiento de la recompensa.

Los estudios que han explorado la reactividad cerebral en personas con exceso de peso ante otro tipo de reforzadores no han aportado evidencia consistente. Dos estudios han utilizado la tarea de incentivo monetario (MID) para evaluar el procesamiento de

reforzadores económicos en adultos obesos. Balodis et al., (2013) encontró un incremento en la activación cerebral en el estriado ventral y la corteza prefrontal ventromedial durante la anticipación de la recompensa en los adultos con exceso de peso en comparación con los controles pero no encontró resultados significativos durante la fase de recepción de la recompensa. Por el contrario, Simon et al, (2015) no encontró relación entre el índice de masa corporal y el procesamiento de recompensas monetarias. Por otro lado, utilizando un paradigma de predicción de recompensas se encontró un incremento en la señal BOLD en diversas regiones relacionadas con el sistema de recompensa: ínsula, estriado, y corteza orbitofrontal (Opel et al., 2015).

2.2.2.1 Tareas con otro tipo de reforzadores en adolescentes

Finalmente, la literatura en el procesamiento de recompensas económicas en adolescentes tampoco muestra resultados consistentes. Mientras que en un estudio el grupo con exceso de peso mostró una menor activación de regiones cerebrales sensibles al riesgo, ínsula anterior, y una mayor activación de regiones del sistema de recompensa, mesencéfalo, durante la anticipación de una recompensa (Delgado-Rico, et al., 2013), en otro no se encontraron diferencias entre adolescentes con alto y bajo riesgo de padecer obesidad durante la anticipación, pero si durante la recepción (Stice et al., 2011).

2.2.3. Estudios sobre función ejecutiva en adultos y adolescentes

La obesidad también se ha asociado con la existencia de déficits en distintos procesos de control ejecutivo como inhibición, flexibilidad, memoria de trabajo y toma de decisiones, tanto en adultos como en adolescentes (Fagundo et al., 2012; Verdejo-García, 2010, Reinert et al., 2013). Basándose en esta evidencia, diversos estudios de neuroimagen han estudiado los sustratos neuronales de estos procesos. Sujetos obesos evidenciaron

una mayor activación de regiones prefrontales y límbicas (ínsula anterior) durante la condición de interferencia en una tarea de Stroop (Balodis et al., 2013). También se ha encontrado que mujeres adolescentes obesas muestran procesos inhibitorios alterados así como una reducción de la actividad frontal en una tarea go/no-go (Batterink et al., 2010). Por último, durante una tarea 2-back, adultos obesos mostraron una menor activación de regiones parietales respecto a personas con normopeso y sobrepeso (Gonzales et al., 2010). Este ultimo estudios refuerza la idea de que pueden existir diferencias específicas entre personas con sobrepeso y obesas.

2.3 Estudios de conectividad funcional

Por último, la conectividad funcional se define como la dependencia temporal entre eventos neurofisiológicos espacialmente distantes (Aertsen et al., 1989; Friston et al., 1993). Los análisis de conectividad funcional permiten, a partir de patrones de activación, realizar mapas estadísticos que reflejan el nivel de comunicación funcional entre distintas regiones del cerebro. Tres aproximaciones son las que usualmente se han utilizado para los análisis de conectividad funcional cerebral. El primer método que se utilizó, fue la aproximación basada en semilla (Biswal et al., 1995) donde se correlaciona la actividad durante el tiempo de adquisición en una determinada región cerebral, la semilla, con el resto del cerebro. Esta metodología cuenta con el hándicap de que es necesaria una hipótesis previa para seleccionar la semilla y por tanto los resultados están restringidos al funcionamiento relacionado con esa región (van del Heuvel & Hulshoff Pol, 2010). Entre las ventajas de este método está la relativa simpleza de los análisis y la directa interpretación de sus resultados (Buckner & Vincent, 2007). Este método es útil en situaciones en las que se desea comprobar un modelo teórico sobre

una región cerebral o se desea explorar la conectividad cerebral de un área del que se conoce alguna disfunción.

Partiendo de la necesidad de realizar análisis de conectividad a cerebro completo, se comenzaron a desarrollar metodologías sin hipótesis previa, los cuales permitían explorar los patrones de conectividad sin la necesidad de seleccionar una región a priori. Numerosos métodos han sido sugeridos para realizar esta aproximación, como por ejemplo análisis de componentes principales (PCA) (Friston, 1993), análisis de componentes independientes (ICA) (Calhoun et al., 2001) o de "normalized cut clustering" (Van den Heuvel et al., 2009). Los métodos basados en componentes independientes, ICA, han sido los más utilizados ya que han mostrado un alto nivel de consistencia entre estudios (Damoiseaux et al., 2006). Brevemente, los métodos ICA están diseñados para buscar una serie de redes independientes, que en su conjunto, expliquen los patrones de actividad cerebral registrados. La principal desventaja de los métodos ICA es la dificultad existente en algunas ocasiones para interpretar los mapas de conectividad obtenidos, lo cual complica la posible aplicación clínica de estos (Fox & Raichle, 2007).

Por último, a partir de la evidencia de que el cerebro se conecta formando redes (Cajal, 1995, Bressler, 1995), estudios neurocientíficos se han valido de la *teoría de grafos*, la rama de las matemáticas que estudia redes de elementos interconectados, para estudiar la conectividad funcional del cerebro (Fornito et al., 2015). Según la teoría de grafos, una red es un sistema formado por nodos que se conectan entre sí a través de una serie de conexiones y por tanto el cerebro se puede modelar del mismo modo (Rubinov & Sporns, 2010). Para realizar este tipo de análisis es necesario un procesado laborioso que consistente en los siguientes pasos: (i) Definición de los nodos de la red: tres

opciones se pueden utilizar para definir las regiones de interés cerebrales que actuarán como nodos de la red a estudiar. En adquisiciones de EEG o MEG suelen utilizarse como nodos las ubicaciones de los electrodos sobre el cráneo. Por el contrario, en estudios de resonancia se utilizan indistintamente aproximaciones teóricas, seleccionando regiones funcionales de atlas existentes, o empíricas, a partir de datos previos de activación. (ii) Definición de conexiones: Dependiendo del tipo de datos con los que se trabaje es necesario definir la métrica que cuantificará las conexiones entre nodos. Algunos ejemplos pueden ser la coherencia espectral en el caso de Magnetoencefalografía, la probabilidad de conexión entre regiones para datos de tractografía o la correlación entre señales temporales en adquisiciones de resonancia magnética funcional. (iii) Generación de las matrices de asociación y adyacencias: Una vez definidos los nodos y los valores de las conexiones entre ellos, se ordenan los datos formando una matriz, matriz de asociación, donde cada fila/columna refleja uno de los nodos y en la intersección se incluye el valor de conectividad entre ellos. Más tarde se define un valor umbral que determinará si esa conexión es suficientemente intensa para ser considerada significativa, generándose una matriz binaria, la matriz de adyacencias. (iv) Cálculo de los parámetros de la red. El último paso consiste en el cálculo de los valores que caracterizan cada red de modo que permitan la comparación estadística entre distintas redes (Bullmore & Sporns, 2009).

Al igual que ocurría con los estudios de activación cerebral en obesos, la gran mayoría de las investigaciones realizadas sobre conectividad funcional en individuos con exceso de peso se han llevado a cabo durante la realización de tareas con reforzadores alimenticios. En los últimos años sin embargo han sido publicados diversos artículos que

exploran también la conectividad funcional en personas con exceso de peso durante adquisiciones en reposo.

2.3.1 Tareas con reforzador alimenticio

Mientras que algunos estudios en adultos obesos han encontrado un incremento de conectividad funcional en áreas estriatales y de la *red cerebral por defecto* durante el procesamiento de comida altamente apetitosa (Stoeckel et al., 2009; Tregellas et al., 2011; Nummenmaa et al., 2012; Kullmann et al., 2013; Carnell et al., 2014) otros estudios encontraron reducciones de conectividad funcional involucrando principalmente áreas frontales (Stoeckel et al., 2009; Kullmann et al., 2013; García-García et al., 2013). Estos resultados sugieren que en los adultos obesos existe una hiperactivación de redes vinculadas al procesamiento de la recompensa alimenticia, pero una disfunción en áreas implicadas en control de conducta.

2.3.2 Tareas con otro tipo de reforzadores

Hasta donde conocemos, en el estudio realizado con reforzadores monetarios, los estudios disponibles no han encontrado diferencias en conectividad funcional entre grupos (Opel et al., 2015).

2.3.3 Resting-state

Una de las opciones más utilizadas para el estudio de la conectividad cerebral es la realización de adquisiciones en reposo, denominadas "Resting-State", que permiten medir la actividad del cerebro cuando no se está realizando ninguna tarea concreta. Durante este tipo de adquisiciones se pide a la persona que se encuentra en la resonancia que se mantenga lo más relajada posible, sin pensar en nada concreto

durante los minutos que dure la prueba. Las imágenes obtenidas durante esta tarea, permiten medir la correlación temporal de pequeñas fluctuaciones de baja frecuencia (<0.1 Hz) y larga distancia que emergen en el cerebro durante la adquisición y que se pueden interpretar como la actividad basal del cerebro sin que medie ningún estímulo (van del Heuvel & Hulshoff Pol, 2010).

Los estudios realizados durante adquisiciones en resting-state mostraron incrementos de conectividad funcional en obesos en la red cerebral por defecto (Frank et al., 2012; Kulmann et al., 2012), en la *red de saliencia* (García-García et al., 2013), en conexiones fronto-estriatales (Black et al., 2014), y en conexiones entre áreas límbicas (Lips et al., 2014) y reducciones de conectividad en el cíngulo anterior y la ínsula (Kullmann et al., 2012).

Debido a su importancia en la función homeostática, en los últimos años se han realizado investigaciones específicas sobre la conectividad cerebral del hipotálamo. En general se han se han encontrado incrementos de conectividad funcional en personas obesas entre el hipotálamo y áreas visuales (Hinkle et al., 2013), áreas de procesamiento de recompensas (Kilpatrick et al., 2014), áreas de control cognitivo (Lips et al., 2014) y áreas interoceptivas (Wijngaarden et al., 2015).

II. JUSTIFICACIÓN, OBJETIVOS E HIPÓTESIS

Capítulo 3. Justificación y objetivos de la tesis

1. Justificación y objetivo principal

Los estudios de neuroimagen existentes han demostrado que el procesamiento de comida en personas con exceso de peso se relaciona con patrones diferenciales de activación y conectividad, especialmente de regiones que forman parte de los sistemas de recompensa y toma de decisiones (Carnell et al. 2014). Estas diferencias se relacionan con alteraciones en la evaluación del valor recompensante de los alimentos y en la toma de decisiones dietéticas. Por tanto, el sistema de recompensa cerebral parece tener un rol fundamental en la modulación de la toma de decisiones.

Hasta ahora, la mayor parte de los estudios sobre la población con problemas de obesidad se han centrado en la caracterización de estos sistemas ante estímulos alimenticios, pero resulta relevante investigar si las alteraciones del sistema de recompensa cerebral ocurren de modo análogo ante otro tipo de reforzadores, ya sean económicos o sociales, o si por el contrario existe una disfunción genérica independiente del estímulo a procesar. La existencia de un déficit genérico implica que las personas obesas tendrían problemas en evaluar cualquier tipo de reforzador (p.e., dinero, sexo), conllevando un impacto más amplio sobre sus decisiones y su calidad de vida (Rangel, 2013). La existencia de distintas alteraciones ante distintos estímulos también puede ser relevante para establecer estrategias de intervención especificas en personas con exceso de peso, puesto que indicará si se debe trabajar su conducta sólo ante reforzadores de comida, o por el contrario, hacerlo desde un punto de vista más global.

En base a esto, una caracterización funcional del sistema de recompensa cerebral, tanto a nivel de activación como en conectividad, ante distintos tipos de reforzadores puede

aportar información novedosa sobre estos sistemas en personas con exceso de peso. Para ello resulta interesante estudiar el procesamiento cerebral ante estímulos directamente relevantes para la obesidad, como la comida, pero también ante reforzadores universales, como son el dinero o las recompensas sociales. Asimismo, la existencia de un marcado componente de problemas sociales asociados a la obesidad hace que resulte interesante evaluar el procesamiento cerebral en un contexto social con una población especialmente vulnerable a las presiones sociales como es la adolescencia.

Por otro lado, la existencia de diferencias estructurales entre adultos con sobrepeso y obesidad (Gustand, et al., 2008; Yokum et al., 2012; Medic et al., 2016; Stanek et al., 2011), así como la evidencia de que la disponibilidad de receptores de dopamina en el estriado, un marcador del procesamiento genérico de la recompensa, muestra una relación en forma de U invertida con el IMC (Horstmann et al. 2015), sugiere que sería interesante comparar los correlatos cerebrales del procesamiento de recompensas entre estos dos grupos de población. La existencia de diferencias entre personas con sobrepeso y personas con obesidad nos podría mostrar la evolución en la severidad de los problemas asociados al exceso de peso e informaría el diseño de intervenciones específicas para personas con distintos grados de obesidad.

Finalmente, en los últimos años se ha producido un gran avance en el desarrollo de metodologías de análisis aplicadas a la neuroimagen. La teoría de grafos, una rama de las matemáticas que estudia redes de elementos interconectados, viene siendo utilizada para caracterizar la conectividad funcional de las redes cerebrales en distintas patologías como depresión (Peng et al., 2014), esquizofrenia (Fornito et al., 2011) o epilepsia (Besson et al., 2014) (ver revisión Fornito et al., 2015). Pero hasta donde

sabemos nunca ha sido utilizada para caracterizar la conectividad funcional durante la realización de una tarea en personas con exceso de peso. Como se ha expuesto a lo largo del capítulo 2 de esta tesis, los distintos estudios que han evaluado la conectividad funcional en personas con exceso de peso han aportado resultados contradictorios. Esta metodología permite realizar una caracterización de la conectividad de todo el cerebro por lo que su utilización puede aportar información complementaria a la existente y que aclare la disyunción existente. Del mismo modo, los análisis de ecuaciones estructurales son una herramienta muy útil para intentar encontrar relaciones de causalidad en las correlaciones existentes entre la respuesta cerebral y distintas variables conductuales y neuropsicológicas por lo que pueden aportar información sobre cómo el procesamiento cerebral está relacionado con distintos aspectos de los problemas sociales asociados a la obesidad.

En este contexto donde la evidencia muestra que los circuitos de recompensa cerebral tiene un papel fundamental en el aumento de la prevalencia de la obesidad, el **objetivo principal** de la presente Tesis Doctoral es caracterizar el procesamiento cerebral de distintos tipos de recompensas en personas con sobrepeso y obesidad frente a individuos con normopeso.

2. Objetivos específicos

Del objetivo principal se derivan tres objetivos específicos que se corresponden con los tres estudios que componen esta tesis.

1. Comparar los patrones de activación del sistema de recompensa cerebral evocados por distintos tipos de reforzadores, alimenticios y monetarios, en adultos con

sobrepeso y obesidad frente a adultos con normopeso, específicamente la relación existente entre estas activaciones y el índice de masa corporal.

2. Caracterizar y comparar la conectividad funcional cerebral durante el procesamiento de reforzadores alimenticios y monetarios en adultos con exceso de peso en comparación con adultos con normopeso, utilizando para ello una aproximación desde la teoría de grafos.

3. Caracterizar los sistemas cerebrales de recompensa y toma de decisiones en un contexto social en adolescentes con exceso de peso frente a controles, y su relación con medidas neuropsicológicas y conductuales.

3. Hipótesis

Las principales hipótesis que se derivan de estos objetivos son:

Hipótesis 1: Durante el procesamiento de estímulos alimenticios con alto contenido calórico, los adultos con exceso de peso, en comparación con los adultos con normopeso, evidenciarán una mayor activación del sistema de recompensa cerebral. Por el contrario, durante el procesamiento de estímulos monetarios, se espera encontrar una relación cuadrática en forma de U invertida entre la activación cerebral y el IMC.

Hipótesis 2: Los adultos con exceso de peso mostrarán una disrupción de las redes cerebrales implicadas en el control de la conducta y el procesamiento de la recompensa (principalmente conexiones fronto-estriatales) durante el procesamiento de recompensas económicas y alimenticias.

Hipótesis 3: Los adolescentes con exceso de peso presentarán una disminución de la actividad cerebral en regiones implicadas en el procesamiento de recompensas sociales (estriado, amígdala), así como de toma de decisiones (corteza cingulada anterior, ínsula). Estas disfunciones mostrarán relaciones significativas con medidas de sensibilidad a la recompensa, rasgos de personalidad relacionados con obesidad y el comportamiento durante la tarea (tasa de aceptación de ofertas).

III. MEMORIA DE TRABAJOS

Capítulo 4.

BRAIN REWARD SYSTEM'S ALTERATIONS IN RESPONSE TO FOOD AND MONETARY STIMULI IN OVERWEIGHT AND OBESE INDIVIDUALS

Juan Verdejo-Román, Raquel Vilar-López, Juan F. Navas, Carles Soriano-Mas, Antonio Verdejo-García. (Under review) Brain reward system's alterations in response to food and monetary stimuli in overweight and obese individuals. *International Journal of Obesity.*

1. Introduction

Between 1980 and 2013 the prevalence of overweight and obesity has increased from 857 million to 2.1 billion people worldwide, becoming a major global health challenge (Ng et al., 2014). Specifically, overweight and obesity are associated with increased risk of cardiovascular disease, stroke, type II diabetes and different types of cancer, being a consistent risk factor for these conditions when Body Mass Index (BMI) is above 23 kg/m^2 (Ng et al., 2014). In Western societies, cheap availability of high palatable foods is a primary driver of the growing obesity epidemic (Finkelstein et al. 2005). Foods rich in sugar and fat stimulate the brain reward network, bypassing the homeostatic mechanisms that control food intake, and hence fostering eating, even in the absence of energetic needs (Volkow et al. 2011; Stice et al. 2013).

Current neurobiological theories are advocating for a "food addiction model" of obesity, given overlapping neurobiological alterations between individuals with obesity and substance addictions (Volkow et al., 2007; Burger & Stice; 2011; Kenny, 2011; Volkow et al., 2013). Specifically, this model posits that individuals with overweight and obesity display increased responsivity of the brain's reward system to food stimuli, leading to a loss of control over food intake (Volkow et al., 2013). In spite of the growing influence of this food addiction model, overweight and obesity are heterogeneous conditions, and more neurobiological research is needed to establish if this notion is relevant across the different manifestations of excessive weight, or to particular phenotypes (Carter et al., 2016). Currently available functional magnetic resonance imaging (fMRI) studies have shown that sensory cues of high-palatable food evoke increased neural activation in the striatum and related regions of the brain reward network in both overweight and obese individuals versus normal weight controls (Rothemund et al., 2007; Stoeckel et al, 2008;

Fletcher et al., 2010; Martin et al., 2010; Jastreboff et al., 2013; Carnell et al., 2014). Positron Emission Tomography (PET) studies have also shown reduced striatal dopamine D2 binding potential in severely obese individuals (BMI≥40) (Wang et al., 2001). However, striatal dopamine D2 binding potential is increased in individuals with more moderate degree of excess weight for height (Guo et al., 2014).

Altogether, PET studies suggest that overweight and obesity may have unique neural underpinnings, and it has been proposed that the association between BMI and dopaminergic/reward network activity follows an inverted U-shape curve; that is, the association is positive in overweight individuals, but negative in obese individuals (Horstamn et al., 2015). This proposed model is clinically significant and needs to be formally tested. If individuals with overweight versus obesity value food and other rewards via different brain mechanisms, delineation of these mechanisms would lead to better understanding of the underlying neurobiology of these disorders and, potentially, to more specific interventions for overweight and/or obesity.

General reward sensitivity has been customarily indexed in neuroimaging studies with the Monetary Incentive Delay (MID) task (Costumero et al., 2013). In normal weight individuals, MID-evoked brain activations in the midbrain, striatum and orbitofrontal cortex have been associated with trait reward sensitivity (Costumero et al., 2013), and the food addiction model would predict a stronger involvement of these regions in people with excess weight. However, currently available studies have yielded contradictory findings. Balodis et al. (2013) showed increased reward system activation during the MID task in obese individuals versus controls, although no differences were found during reward feedback. Conversely, Simon et al. (2015) did not found a significant association between BMI and MID-evoked neural activation. Therefore,

existing studies have not yet clearly ascertained the association between excess weight and brain responses to monetary stimuli, or overlapping and/or unique patterns of brain activation related to monetary versus food stimuli. The latter is relevant because the low prices of highly palatable foods have contributed to increase their subjective value, and thus to food choices leading to the obesity epidemic (Rangel, 2013).

In this study, we aimed to compare brain activations evoked by food and monetary rewards in individuals with obesity, overweight and normal weight; and to determine the association between reward-evoked brain activations and BMI. We hypothesized that, in response to high palatable foods, excess weight participants, would display increased activation of key regions of the brain reward system, and particularly the striatum (Simon et al., 2015). We also hypothesized that in response to monetary rewards, which is a biological index of generalized sensitivity to reward, there would be an inverted U-shape association between brain's reward system activation and BMI (Horstman et al., 2015).

2. Methods and Materials

Participants

Eighty-one healthy adults, aged between 25 and 45 years old were recruited for this study. They were classified in three groups on the basis of BMI: 39 Normal weights (NW); 21 Overweight (OW) and 21 Obese (OB). Participants' sociodemographic characteristics, and BMI and fat percentage data are displayed in Table 1.

The inclusion criteria were defined as follows: (i) BMI falling within the intervals categorized as overweight (BMI between 25 and 30 kg/m^2), obesity (BMI over 30 kg/m^2) or normal weight (BMI between 19 and 25 kg/m^2); (ii) right-handedness. The

exclusion criteria were: (i) history or current evidence of medical or psychiatric disorders that co-occur with obesity (e.g., diabetes, hypertension, binge eating, bulimia nervosa, depression) indicated with clinical assessments conducted by professional nurses and psychologists; (ii) abnormalities on Magnetic Resonance Imaging (MRI) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects).

Table 1: Sociodemographic characteristic and body composition by group.

	Normal weight (n = 39) Mean (SD)	Overweight (n = 21) Mean (SD)	Obese (n = 21) Mean (SD)	P-value
Age	33.08 (6.73)	35.00 (6.31)	32.19 (5.81)	0.345
Sex (male/female)	18 / 21	10 / 11	10 / 11	0.992
Years of education	18.18 (3.75)	17.86 (3.58)	17.14 (3.75)	0.599
Monthly income				
<600€	20.5%	9.5%	10.0%	
601-1000€	10.3%	9.5%	15.0%	
1001-1500€	20.5%	28.6%	25.0%	0.650
1501-2000€	17.9%	14.3%	15.0%	
2001-2499€	10.3%	9.5%	30.0%	
>2500€	20.5%	28.6%	5%	
BMI (kg/m^2)	22.20 (1.76)	27.35* (1.59)	33.43* (2.56)	<0.001
Fat (%)	19.66 (5.96)	28.23* (7.56)	33.99* (8.97)	<0.001

*P <0.05 compared to Normal Weight group.

All participants had normal or corrected-to-normal vision. They were recruited through media advertisements and received a financial compensation. The study was approved

by the Ethics Committee for Research in Humans of the University of Granada (Spain) and was conducted in accordance with the Declaration of Helsinki. All participants signed written informed consent.

Experimental Procedure

Participants underwent two reward related tasks during an fMRI session. Each of these tasks involved the processing of different rewards: food and money.

To ensure that every subject knew all the food stimuli to be used in the food reward fMRI task, two weeks before scanning participants attended to a catered tasting session. During that session subjects were gathered in a room and allowed to eat 18 different foods. These products had been previously classified based in their palatability: high palatable food, including sweet and fatty food (e.g., chocolate, cheese cake, burger) and plain food (e.g., yoghurt, omelet, orange). These sessions were conducted at 6:00 pm, and each participant should taste each food. All the fMRI sessions were conducted between one and three hours after lunch. At the beginning of this session BMI and fat percentage were obtained using a body composition analyzer TANITA BC-420 (GP Supplies Ltd., London, UK). To control the satiety level, participants rated their subjective degree of appetite on a 10-cm visual analog scale (VAS) three times along the fMRI session: prior to scan, immediately before the food-stimuli task and immediately after leaving the MRI room.

fMRI Tasks

Food reward: We used a modified version of the Willingness to pay task (Plassmann et al., 2007). Participants watched each of the 18 previously tasted foods once. Each stimulus was presented in the screen for 2 seconds and after that, they had 4 seconds to

answer: “How much would you pay for it?” They could choose between four prices, ranging from 20 cents to 10 euros. Each selection was followed by a variable time between 3 and 5 seconds of baseline during which a cross fixation was presented on the screen. Our main interest was to contrast group differences between high palatable and plain food trials.

Monetary reward: We used an adaptation of the Monetary Incentive Delay task (Nestor et al., 2010), based on the original task employed by Knutson et al. (2001). At the beginning of each trial, participants were shown one of two cues (green or blue square) indicating potential winnings or no financial outcome at the end of the trial. The incentive value of each trial was signaled by means of the number of horizontal lines crossing the square (one line for 0.2€, two for 1€ and three for 5€). Each cue was presented for a fixed duration of 750msec. Subsequently, a cross-fixation was shown during a variable period of 3 to 5 sec, and after this interval participants had to perform a reaction-time task: respond to a white target star appearing for a variable length of time (150–450 ms) with a button press. Then participants received feedback (hit/miss) about the accuracy of their response for 750ms, together with the information about the amount of money won in that trial (when adequate, i.e., correct responses in reward cued trials) and their cumulative total at that point of the experiment. Finally, another fixation period (750 ms) was included before the next trial. Therefore, total trial duration ranged between 5700 and 7000 ms. Participants performed 24 trials of each type of cue yielding a total of 96 trials.

Imaging analyses explored brain activity changes during two periods, the reward-anticipatory period, which included the cue presentation, the variable waiting delay and the actual response period, and the reward-feedback period, involving the presentation

of visual feedback (hit/miss). Specifically, a linear contrast (High reward > Medium reward > Low reward > No outcome trials) was defined at the first level (within-subject) to explore brain activation during reward-anticipation, while a Win > Miss contrast was used for the reward-feedback period. Therefore, this task yields two main conditions of interest: reward anticipation (High vs. Medium vs. Low vs. No reward) and reward feedback (Win vs. Miss).

Imaging data acquisition and preprocessing

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). During task performance, three T2*-weighted echo-planar imaging (EPI) sequences were acquired according to the following parameters: Repetition time (TR) = 2000 ms, Echo time (TE) = 35 ms, Field of view (FOV) = 230 x 230 mm, 96 x 96 matrix, flip angle = 90°, and a total of 21 axial slices of 4 mm with a 1 mm gap). Specifically, we collected 149 scans for the food reward task and 432 scans for the monetary reward task. 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 also 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). The functional images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks, Natick, MA, USA). Preprocessing included re-slicing to the mean image of the time series, slice timing

correction, normalization, using affine and smoothly non- linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum (FWHM) = 8 mm). Data were high-pass filtered to remove low-frequency noise (1/128 Hz) and corrected for temporal autocorrelation using an autoregressive AR model.

Outside scanner behavioral measures

Sensitivity to Reward was measured with The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al., 2001). This questionnaire has demonstrated internal consistency; construct validity, and significant associations with reward and punishment relevant brain systems (Costumero et al., 2013).

Statistical analyses

Behavioral analyses: Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We tested between-group differences in demographic, body composition and sensitivity to reward variables with one-way ANOVAs, followed by post-hoc two sample t-tests. We conducted a series of mixed-design ANOVAs to analyze putative interactions between study groups and variables of interest (i.e., fMRI tasks conditions), followed by post-hoc within- and between-group analyses.

Neuroimaging analyses:

Task regressors were convolved with the SPM8 canonical hemodynamic response function. To prevent motion artifacts, six head motion parameters were entered as regressors of no interest in all first-level analyses. One-sample t-tests were conducted

on the resulting first-level contrast images to assess across-group activations in each of the contrasts. Next, we conducted a series of three-group ANOVAs to assess between-group differences using the same first-level contrast images.

Due to the existence of an a priori hypothesis about changes in brain activity within the reward system, all statistical analyses were spatially restricted to such region of interest. Such mask was defined empirically according to the results obtained from a large series of previous studies assessing reward system function by means of fMRI examination. Specifically, similar to other studies (Contreras-Rodríguez et al. 2016), we used the reward system mask provided by Neurosynth (www.neurosynth.org). This mask includes brain regions that have shown to be associated with reward processing via meta-analytic research (i.e., striatum, anterior and posterior cingulate cortices, supplementary motor area, prefrontal cortices, insula, dopaminergic midbrain, hippocampus, amygdala and intraparietal cortices). Statistical significance threshold was corrected for multiple comparisons using a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1,000 Monte Carlo simulations, using the AlphaSim algorithm as implemented in the SPM REST toolbox (Song et al., 2011). Input parameters included a brain mask of 51517 voxels (the reward system mask), an individual voxel threshold probability of 0.005 and a cluster connection radius of 5 mm. At 11.0 and 9.2 mm FWHM smoothness for the food and monetary task contrasts, respectively, corresponded to a minimum cluster extent (KE) of 220 and 154 voxels to satisfy a Family-wise error (FWE) corrected P value of P_{FWE} <0.05.

To exclude potential confounds linked to sex differences, we replicated all contrasts of interest controlling for sex. Results were equivalent, and hence we only report results

for the non-covaried analyses. We also performed specific men vs. female analysis and did not find significant between-group differences.

To examine the association between brain activations and BMI, we conducted curve fit analyses in SPSS. The peak beta eigenvalues from each cluster of significant between-group differences was extracted and related with BMI values.

3. Results

Behavioral measures

Appetite and Sensitivity to Reward measurements:

We found no significant between-group differences or interactions between Group and Time for subjective measures of appetite ($F(4,146) = 0.638$, $P = 0.599$). Likewise, we did not found any significant between-group differences in sensitivity to reward scores. The relationship between BMI and sensitivity to reward scores followed a non-significant inverted U-shape curve ($R^2 = 0.040$, $P = 0.204$).

fMRI behavioral measures

Food reward task

We found a significant "Group x Food Type" interaction ($F(2,77) = 4.162$, $P = 0.019$). Paired within-group contrasts showed that OB and OW groups paid more money for high-palatable food than for plain food ($P = 0.002$ and $P < 0.001$), unlike the NW group ($P = 0.220$). Paired between-group contrasts showed that OB paid significantly less money for plain food compared to NW ($t(58) = 2.24$, $P = 0.020$). We found no group differences for high palatable food.

Monetary reward

We found a significant "Group x Reward" interaction (F(6,231) = 2.67, P = 0.030). Within-group analyses showed a significant effect of cue type (F(2,7) = 4,608, P = 0.013), indicating that all participants made faster responses in high incentive trials. Between groups comparisons showed that OB had significant slower reaction time in neutral (t(57) = 2.315, P = 0.028) and low incentive trials (t(57) = 2.160, P = 0.035) compared to NW. Behavioral results are summarized in Table 2.

Table 2: Behavioral data on trait sensitivity to reward and performance on fMRI tasks.

	Normal weight (n = 39) Mean (SD)	Overweight (n = 21) Mean (SD)	Obese (n = 21) Mean (SD)	ANOVA P-value
Sensitivity to reward	10.31 (3.89)	10.14 (3.81)	9.76 (4.00)	0.875
Willingness to Pay: Money paid (€)				
High-palatable food	2.63 (1.75)	3.03 (2.26)	2.49 (1.25)	0.605
Plain food	2.36 (1.63)	1.81 (1.27)	1.42* (1.01)	0.045
Monetary Incentive Delay: Response Time (s)				
Neutral	0.246 (0.038)	0.252 (0.052)	0.279* (0.059)	0.042
Low	0.227 (0.033)	0.233 (0.048)	0.249* (0.046)	0.137
Medium	0.231 (0.037)	0.234 (0.043)	0.242 (0.047)	0.612
High	0.219 (0.032)	0.222 (0.036)	0.230 (0.040)	0.507

*P <0.05 in relation to Normal Weight group.

Neuroimaging

Food reward task

During high-palatable versus plain food participants significantly activated bilaterally the dorsal caudate, the nucleus accumbens, the ventral putamen, the ventral tegmental area, the intraparietal, ventromedial and dorsolateral prefrontal and anterior cingulate cortices, and the anterior insula extending to the lateral orbitofrontal gyrus (Table S1 and Figure 1).

Group comparisons showed that OB subjects displayed significantly increased activations bilaterally in the dorsal caudate and nucleus accumbens compared to both NW and OW participants. In addition, OB group had significantly increased activation in the anterior cingulate cortex compared to the NW group (Table S1 and Figure 1).

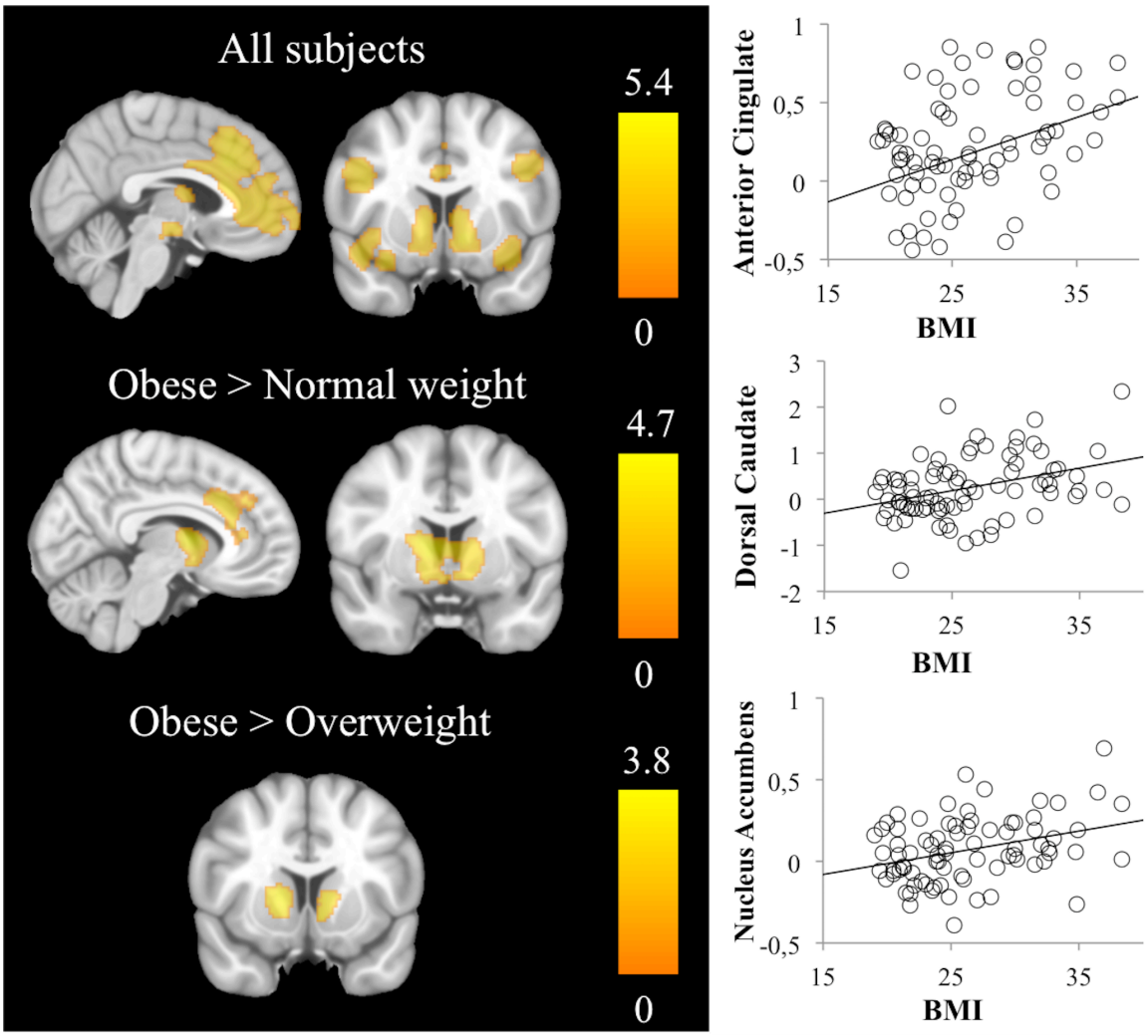
Post hoc analyses showed a linear and positive correlation between BMI and bilaterally activation in the dorsal caudate (Right: $r = 0.408$, $R^2 = 0.166$, $P < 0.001$; Left: $r = 0.299$, $R^2 = 0.089$, $P = 0.007$), the nucleus accumbens (Right: $r = 0.333$, $R^2 = 0.111$, $P = 0.003$; Left: $r = 0.312$, $R^2 = 0.097$, $P = 0.005$) and the dorsal anterior cingulate gyrus ($r = 0.351$, $R^2 = 0.123$, $P = 0.002$).

Table S1: Activations and group differences during high palatable versus plain food in the willingness to pay task.

			MNI coordinates			CS	
	BA	Side	X	Y	Z	(voxels)	t-value
Activations							
Anterior Cingulate Gyrus	24, 32	R/L	-2	26	46	7942 (*)	5.32
Ventromedial PFC	10	R/L	-10	48	-6	7942 (*)	4.28
Dorsal Caudate		R/L	-2	-2	10	7942 (*)	4.15
Nucleus Accumbens		R	12	14	-2	7942 (*)	4.09
Nucleus Accumbens		L	-12	18	-4	7942 (*)	5.14
Ventral Tegmental Area		R/L	4	-10	-10	7942 (*)	3.36
Anterior Insula/OFC	13, 47	L	-28	22	-8	7942 (*)	4.80
Anterior Insula/OFC	13, 47	R	30	12	-18	1611	4.50
Intraparietal Cortex	7, 40	L	-38	-54	50	574	4,22
Intraparietal Cortex	7, 40	R	50	-46	42	354	3,44
Middle Frontal Gyrus	9, 46	R	42	4	32	432	4,43
Middle Frontal Gyrus	9	L	-42	14	30	252	3,81
Obese > Normal weight							
Dorsal Caudate		R	12	6	8	1237 (*)	4,62
Dorsal Caudate		L	-12	8	4	1237 (*)	3,78
Nucleus Accumbens		R	12	6	-4	1237 (*)	3,57
Nucleus Accumbens		L	-12	6	-4	1237 (*)	3,56
Anterior Cingulate Gyrus	24, 32	R/L	8	22	32	946	3,80
Obese > Overweight							
Dorsal Caudate		R	16	8	6	556 (*)	3,76
Dorsal Caudate		L	-10	10	4	556 (*)	3,24
Nucleus Accumbens		R	16	8	0	556 (*)	3,42
Nucleus Accumbens		L	-8	10	-4	556 (*)	3,19

BA: Brodmann area; CS: Cluster Size; * part of the large cluster; PFC: Prefrontal Cortex; OFC: Orbitofrontal Cortex

Figure 1: Left panel: Brain evoked activation and between-group differences during the food reward task. Right hemisphere is displayed on the right. The color bar indicates t-value. Right panel: Scatter plots showing a linear relationship between BMI and the peak activations from regions showing significant between-group differences.



Monetary reward

Reward anticipation contrast

Parametric increases in reward magnitude cues were associated with higher activations in bilateral dorsal and ventral striatum, midbrain (including ventral tegmental area), thalamus, amygdala-hippocampal complex, orbitofrontal cortex, middle frontal gyrus, anterior insula, and anterior and posterior cingulate and intraparietal and cortices (Table S2, Figure 2).

Group comparisons showed that OW individuals displayed significantly increased activation in the anterior cingulate cortex/supplementary motor area in comparison with both OB and NW groups. Likewise, OW individuals (but not OB individuals) showed a significantly increased activation in the ventral tegmental area, the ventral putamen, the lateral orbitofrontal cortex and the hippocampus-amygdala complex in comparison with NW participants (Table S2, Figure 2).

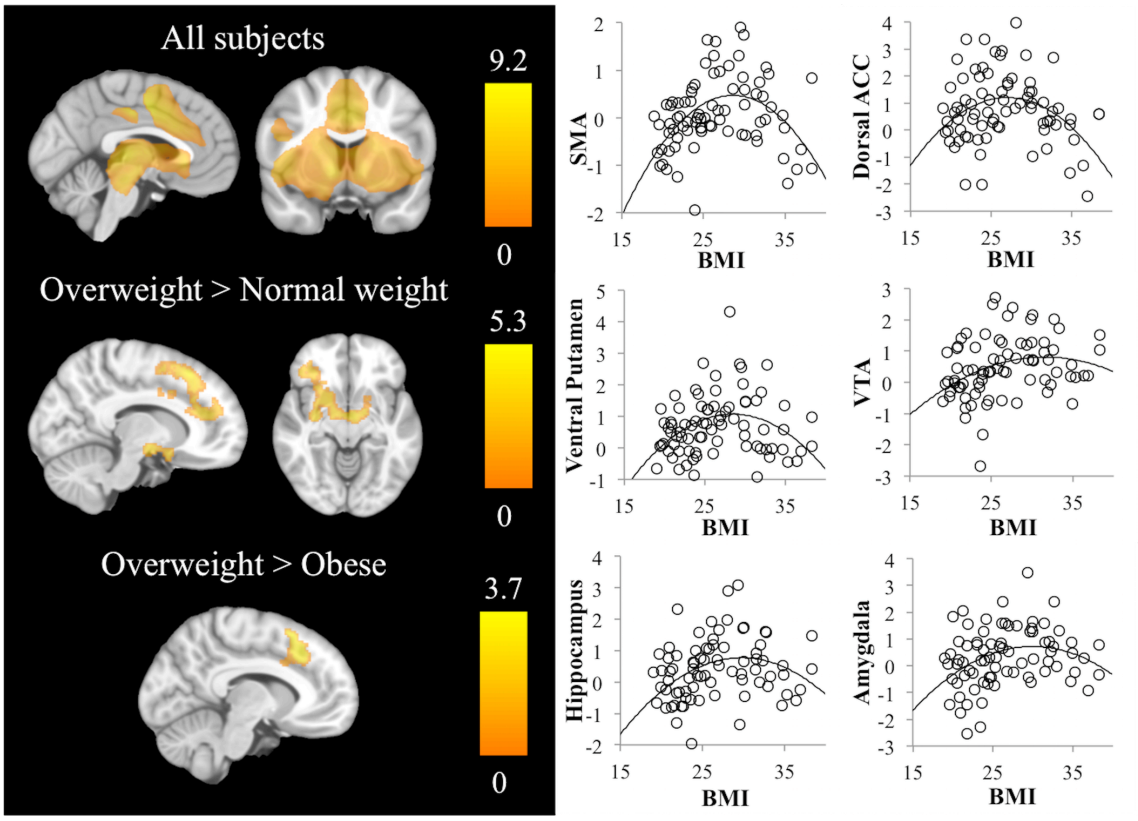
Curve fit analyses of the association between BMI and peak activations from the above analyses showed inverted-U associations for the supplementary motor area (R^2 = 0.240, P <0.001), dorsal anterior cingulate (R^2 = 0.144, P = 0.003), ventral tegmental area (R^2 = 0.103, P = 0.016), ventral putamen (right: R^2 = 0.137, P = 0.004; left: R^2 = 0.079, P = 0.043), hippocampus (R^2 = 0.135, P = 0.004) and amygdala (R^2 = 0.115, P = 0.009). Post-hoc analyses showed that the peaks of the inverted U ranged between 27 and 32 Kg/m^2.

Table S2: Activations and group differences during reward anticipation contrast in the monetary incentive delay task

			MNI coordinates				
	BA	Side	X	Y	Z	CS (voxels)	t-value
Activations							
Ventral Striatum		R	18	-10	-6	32253 (*)	9.12
Ventral Striatum		L	-14	-6	-8	32253 (*)	8.96
ACC	24, 32	R/L	-2	-4	46	32253 (*)	8.68
Thalamus		R/L	4	-22	6	32253 (*)	8.64
Midbrain		R/L	8	-20	-14	32253 (*)	7.95
Nucleus Accumbens		R	10	12	-4	32253 (*)	7.24
Nucleus Accumbens		L	-10	6	-4	32253 (*)	5.99
Insula	13	L	-26	26	12	32253 (*)	7.20
Insula	13	R	36	22	-8	32253 (*)	7.10
Dorsal Caudate		R	20	0	16	32253 (*)	6.88
Dorsal Caudate		L	-16	-4	18	32253 (*)	6.9
Hippocampus		R	36	-18	-16	32253 (*)	5.15
Hippocampus		L	-34	-18	-12	32253 (*)	5.60
Amygdala		R	22	4	-18	32253 (*)	4.97
Amygdala		L	-20	2	-16	32253 (*)	5.23
OFC	11, 47	R	32	46	-18	32253 (*)	3.89
OFC	11, 47	L	-26	48	-14	223	3.96
Intraparietal Cortex	7, 40	R	36	-44	48	441	6.07
Intraparietal Cortex	7, 40	L	-26	-52	44	599	6.24
Middle Frontal Gyrus	9, 46	R	48	8	20	323	5.70
PCC	23, 31	R/L	-2	-20	44	738	8.35
Overweight > Normal weight							
SFG/SMA	6, 8	R/L	12	26	50	1557 (*)	5.21
ACC	24, 32	R/L	14	46	18	1557 (*)	4.01
Ventral Tegmental Area		R/L	-4	-10	-8	1339 (*)	4.42
Orbitofrontal Cortex	47	R	32	32	-12	1339 (*)	3.61
Ventral Putamen		R	12	-6	-10	1339 (*)	3.73
Ventral Putamen		L	-16	-4	-8	1339 (*)	3.30
Hippocampus	34	R	32	-10	-10	1339 (*)	3.93
Amygdala		R	24	-4	-18	1339 (*)	3.45
Overweight > Obese							
SMA / ACC	8, 32	R/L	-10	24	40	306	3.62
Dorsal ACC	24, 32	R	8	12	30	215	3.29

BA: Brodmann area; CS: Cluster Size; * part of the large cluster; SMA: Supplementary Motor Area; ACC: Anterior Cingulate Cortex; SFG: Superior Frontal Gyrus; PCC: Posterior Cingulate Cortex; OFC: Orbitofrontal Cortex

Figure 2: Left panel: Brain evoked activation and between groups differences during monetary anticipation contrast. Right hemisphere is displayed on the right. The color bar indicates t-value. Right panel: Scatter plots showing a quadratic relationship (inverted U-shape) between BMI and the peak activations from regions showing significant between-group differences.



Reward feedback contrast

In win versus miss trials participants significantly activated the bilateral ventral and dorsal striatum, the amygdala-hippocampal complex, the orbitofrontal cortex, the middle frontal gyrus, the posterior cingulate, and the intraparietal cortices. Miss compared to win trials evoked activations including the anterior insula, the dorsal anterior cingulate cortex and the supplementary motor area. (Table S3, Figure 3).

Group comparisons in Win versus Miss trials showed that OB individuals compared to NW had increased activation in the rostral-ventral pons. Likewise, OB individuals compared to OW had increased activation in the nucleus accumbens. (Table S3, Figure 3).

Figure 3: Left panel: Brain evoked activation and between groups differences during monetary feedback contrast. Right hemisphere is displayed on the right. The color bar indicates t-value (hot colors for the win vs. miss contrast and cold colors for the miss vs. win contrast). Right panel: Scatter plots showing a linear relationship between BMI and the peak activations from regions showing significant between-group differences.

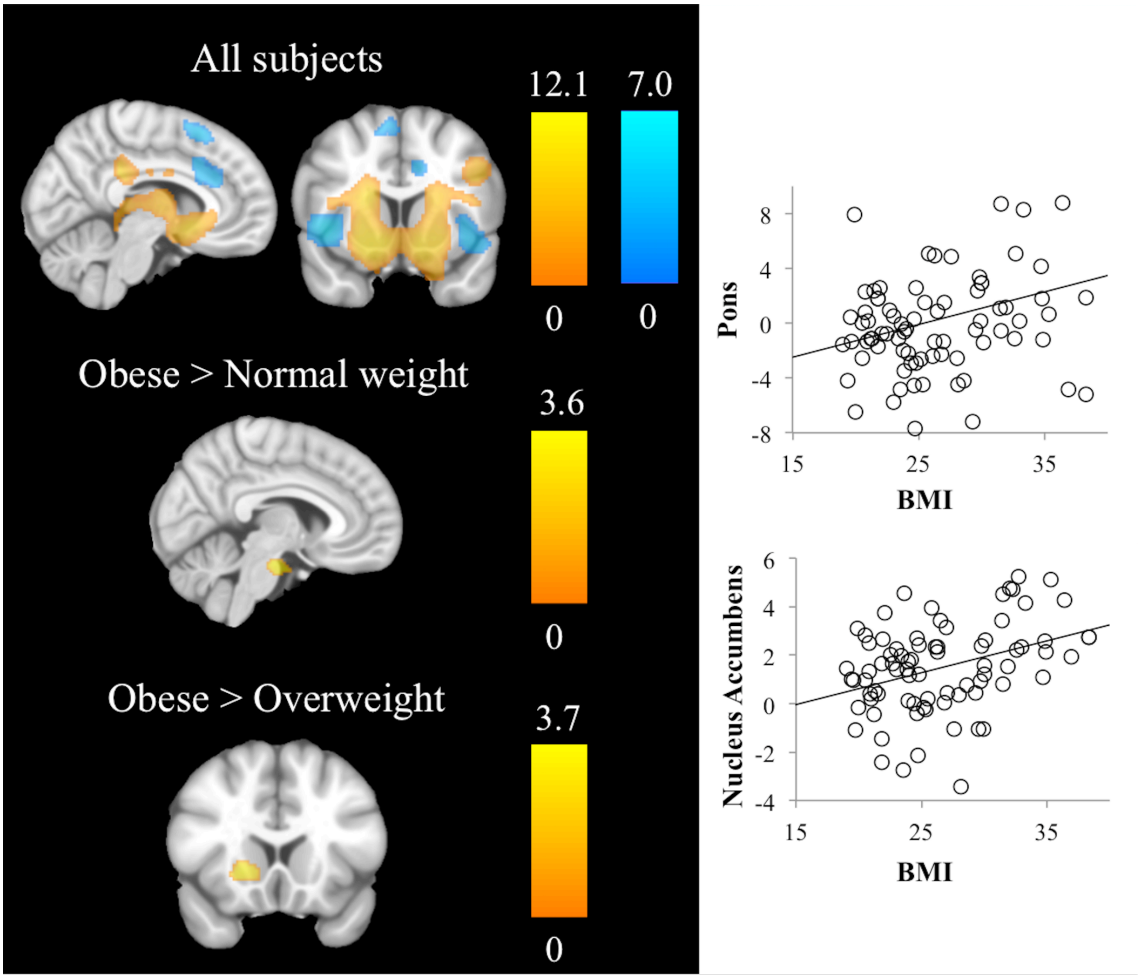


Table S3: Activations, deactivations and group differences during reward feedback contrast in the monetary incentive delay task

			MNI coordinates			CS	
	BA	Side	X	Y	Z	(voxels)	t-value
Activations							
Nucleus Accumbens		R	18	16	-6	15698 (*)	9.41
Nucleus Accumbens		L	-12	10	-14	15698 (*)	7.95
Ventral Putamen		R	20	14	-10	15698 (*)	9.11
Ventral Putamen		L	-18	14	-8	15698 (*)	7.74
Dorsal Caudate		R	10	6	18	15698 (*)	8.77
Dorsal Caudate		L	-18	2	20	15698 (*)	5.67
Orbitofrontal Cortex	11, 47	R	24	38	-12	15698 (*)	8.00
Orbitofrontal Cortex	11, 47	L	-32	38	-14	15698 (*)	7.07
Dorsal Putamen		R	24	-10	12	15698 (*)	6.97
Dorsal Putamen		L	-24	-10	8	15698 (*)	5.77
Hippocampus		R	32	-20	-18	15698 (*)	5.75
Hippocampus		L	-20	-18	-16	15698 (*)	6.21
PCC	31	R/L	-4	-40	30	15698 (*)	11.50
Intraparietal Cortex	7, 40	R	32	-60	46	446	8.60
Intraparietal Cortex	7, 40	L	-30	-64	42	742	12.04
PCC	23	R/L	-8	-56	14	190	9.01
Middle Frontal Gyrus	9	L	-44	6	28	301	6.61
Deactivations							
Anterior Insula	13	R	44	16	0	1002	6.97
Anterior Insula	13	L	-34	20	-12	813	4.63
SMA	8	R/L	6	20	56	225	4.09
Dorsal ACC	24, 32	R/L	-6	24	26	498	3.62
Obese > Normal weight							
Pons		R/L	6	-16	-24	227	3.60
Obese > Overweight							
Nucleus Accumbens		R	20	18	-2	177	3.70

BA: Brodmann area; CS: Cluster Size; * part of the large cluster; SMA: Supplementary Motor Area; ACC: Anterior Cingulate Cortex; PCC: Posterior Cingulate Cortex.

Curve fit analyses showed a linear and positive association between nucleus accumbens and pons activations and BMI scores ($r = 0.363$, $R^2 = 0.132$, $P = 0.001$, $r = 0.276$, $R^2 = 0.076$, $P = 0.014$). (Figure 3).

4. Discussion

We found that individuals with obesity and overweight have unique patterns of brain activation in response to food and monetary rewards. Specifically, individuals with obesity display enhanced food-evoked ventral and dorsal striatal activations compared to individuals with overweight and normal weight. Conversely, individuals with overweight display increased monetary-reward anticipation activations in widespread regions across the brain reward network. Monetary reward feedback, however, evoked greater responses in the rostral-ventral pons and nucleus accumbens in obese individuals versus normal weight and overweight subjects, respectively. Food and monetary-feedback evoked neural activations showed a linear positive relationship with BMI, whereas monetary-reward-anticipation evoked neural activations showed an inverted U-shape association with BMI.

The increased responsivity of the ventral and dorsal striatum to high-palatable food in obese individuals is consistent with previous fMRI studies showing increased striatal activation in response to food cues (Rothemund et al., 2007; Simon et al., 2014). Critically, we show that these alterations are specific to individuals with obesity (relative to overweight), and therefore they may reflect severity related neuroadaptations. This notion is consistent with food addiction models of obesity, which propose that this disorder is associated with ventral striatal neuroadaptations leading to incentive sensitization of food, and dorsal striatal neuroadaptations leading to food-related habits (Tomasi & Volkow, 2013). Our findings also extend available evidence by showing alterations in a food choice task, with greater ecological validity than passive observation of food cues (Fletcher et al., 2010). In fact, imaging findings were paralleled by behavioral results, which show that obese individuals assign less value to standard

food, which may bias their food choices towards highly palatable unhealthy food (Rangel, 2013).

The increased responsivity of the VTA/striatum, amygdala, orbitofrontal cortex, and medial prefrontal cortex in overweight individuals to anticipation of monetary rewards, and the inverted U-shaped relationship between activation of these regions and BMI is consistent with findings of dopamine-PET studies (Horstman et al., 2015). Indeed, brain activation in the MID task is regarded as a biological index of general sensitivity of the brain reward system (Costumero et al., 2013). Our findings clearly indicate that brain response to monetary-reward anticipation is increased in individuals with overweight, and comparatively decreased in individuals with obesity. This finding is relevant, as it indicates that strategies to prevent overweight might need to focus on downplaying general hyper-reactivity of the brain reward system, whereas strategies to prevent obesity might need to stimulate the brain reward system's responsivity to alternative reinforcers that can compete with food. It remains to be determined if overweight-specific reward system hyper-reactivity represents a different biological phenotype, or an "en-route" state leading to obesity. In any case, our results have theoretical implications for the understanding and prevention of overweight versus obesity.

The increased responsivity of the nucleus accumbens to monetary reward feedback in obese individuals is also consistent with the incentive sensitization model, although in this case with the "liking" or hedonic aspects of reward (and not the "wanting" or anticipation aspects) (Robinson & Berridge, 2003). The nucleus accumbens is the key "liking" hotspot of the brain, which is involved among other functions in amplifying the taste of food (Berridge et al., 2010). Likewise, our finding is similar to previous results in cocaine dependent users, which have greater activation of the nucleus accumbens during feedback processing in the MID task (Jia et al., 2011; Bustamante et al., 2014).

Therefore, our findings indicate that obese individuals have similar alterations in reward feedback processing to those observed among addiction populations.

This study has important strengths. The groups were well matched in key sociodemographic characteristics, such as age, years of education and socioeconomic status. We also applied strict eligibility criteria, which ruled out the presence of obesity related comorbid conditions, including medical comorbidities (i.e., diabetes, hypertension) and mental health problems (i.e., depression or eating disorders, such as binge eating or bulimia nervosa). We also maximized the ecological validity of assessments by pre-exposing participants to the food products of the neuroimaging task in a pre-scanner buffet session. Nevertheless, our findings also need to be understood in the context of some limitations. First, we used different tasks to assess food-related reward (Willingness to Pay) and monetary reward (Monetary Incentive Delay), and therefore we could not analyze interaction effects of food and monetary rewards on the brain reward system. Nonetheless, both tasks are well-validated measures of reward processing in relation to food and money stimuli. Moreover, the number of participants in each group was unequal: Obese and overweight groups were smaller than the normal weight group. We addressed this limitation by performing post-hoc tests of homogeneity of variance for all significant findings, which showed non-significant results (i.e., homogenous variances across groups) in all cases. Another potential limitation is the use of BMI as the main independent variable. Recent evidence has shown that measures of body fat, and particularly visceral fat, are more sensitive to brain health specifically among adolescents (Schwartz et al., 2014). We chose BMI over body fat because our measure of fat (bioelectrical impedance) does not allow reliable estimations of visceral versus subcutaneous fat, and BMI was more adequate than total body fat to classify adult participants of both sexes. Furthermore, BMI is regarded as a

reliable index of weight-to-height ratio and is the key indicator of overweight and obesity in population-based studies (Ng et al., 2014). An additional limitation is the non-significant curvilinear relationship between BMI and the behavioral measure of sensitivity to reward (SPSRQ). This negative finding can be explained by methodological differences between self-report and biological (neuroimaging) measures –the latter more objective and sensitive, and/or by the strict inclusion/exclusion criteria, which resulted in a narrow BMI range. This relationship has been previously demonstrated in a behavioral study with a broader BMI range (17 to 51 kg/m^2) relative to ours (19 to 38 kg/m^2) (Davis & Fox, 2008). Finally, we analyzed neuroimaging activations within discrete regions of the brain reward system, although these regions are known to be part of an integrated network. Therefore, future studies performing functional connectivity assessments of the reward system during food and monetary reward processing will probably be a relevant add-on to present findings.

In conclusion, our results support the food addiction model and previous evidence showing an increased food-cue reactivity in striatal areas and a greater subjective value of high palatable foods in excess weight adults. Conversely, a different pattern of activation was found during monetary reward anticipation, with an inverted U-shape relationship between brain reward system activation and BMI. These reinforcement-dependent differential processing should be confirmed using other natural reinforces, and further studies in overweight populations should also investigate whether overweight-specific reward system alterations represents a distinctive feature of this group or an “en route” state to obesity.

Capítulo 5.

INDEPENDENT FUNCTIONAL CONNECTIVITY NETWORKS UNDERPIN FOOD AND MONETARY REWARD SENSITIVITY IN OBESITY

Juan Verdejo-Román, Alex Fornito, Carles Soriano-Mas, Raquel Vilar-López, Antonio Verdejo-García. (Under review) independent functional connectivity networks underpin food and monetary reward sensitivity in obesity. *The Journal of Neuroscience.*

1. Introduction

Obesity is currently the most important health problem in developed countries, as it is linked to some of the leading causes of mortality (i.e., cardiovascular disease or diabetes) (Flegal et al., 2013). In recent decades, the prevalence of obesity has reached worldwide epidemic proportions (Ng et al., 2014) and this growth has been linked to the availability of highly processed food rich in sugar and fat (Stice et al, 2013). Obesity is increasingly conceptualized as a disorder of reward-based decision-making, according to cognitive neuroscience and neuroimaging evidence showing that obese people predominantly make food choices based on the rewarding aspects of food products, instead of their homeostatic or health properties (Volkow et al., 2011; Burger & Stice, 2011; Kenny, 2011).

Value-based choices rely on the function of a well-defined network of brain regions central to reward processing, including the anterior cingulate, orbitofrontal and dorsal prefrontal cortices, the ventral striatum, the dopaminergic midbrain and the amygdala and hippocampal complex (Haber & Knutson, 2010). Individuals with excess weight show significantly increased activation in these areas in response to high caloric food cues (Rothemund et al. 2007; Stoeckel et al., 2008; Martin et al., 2010; Dimitropoulos et al., 2012; Simon et al., 2014). However, despite evidence that these reward-related regions behave as an integrated network, it is as yet unclear how network-level disturbances relate to altered brain reward processing in obesity. Functional connectivity studies have examined discrete elements of the brain's reward-processing system (i.e., striatum, midbrain, amygdala, orbitofrontal cortex), but these studies have reported contradictory findings. While some studies in excess weight adults have found enhanced functional connectivity of striatal areas during processing of highly palatable

food (Stoeckel et al., 2009; Nummenmaa et al., 2012; Carnell et al., 2014) other studies found reduced functional connectivity mainly involving frontal areas (Stoeckel et al., 2009; Kullmann et al., 2013; García-García et al., 2013).

In addition, it remains unclear whether disruptions of the neural systems supporting reward-based decision-making in this population are specific to the processing of food-related stimuli or represent a general sensitization of reward processes. The existence of a general deficit of reward-processing, (i.e., independent of the specific stimulus), predicts that obese people will have generic problems in evaluating natural reinforcers, which will, in turn, have a broad impact on obese peoples' choices and quality of life (Rangel, 2013). Nevertheless, few studies have examined the brain's reward system activity in excess weight individuals during the processing of generic stimuli, such as monetary reward. Balodis et al. (2013) found increased activity in the ventral striatum and ventromedial prefrontal cortex in anticipation of monetary reward. This is consistent with evidence of altered structural connectivity in fronto-striatal circuits in obese individuals, and implies a general reward-processing deficit (Marqués-Iturra et al., 2015). However, other studies have failed to find an association between brain monetary processing and body mass index (BMI) (Simon et al., 2015). These inconsistencies underscore the need for a comprehensive characterization of the reward network connectivity in excess weight adults across food-related and other types of stimuli.

In this study, we used functional magnetic resonance imaging (fMRI) to map brain functional connectivity alterations in the reward system of individuals with excess weight relative to normal weight controls. Both groups performed two tasks: one assessing food-related reward processing and one assessing the processing of monetary

rewards. Functional connectivity was assessed with a data-driven graph theoretic approach to characterize whole brain network-level between-group differences during both tasks. Based on prior work (Nummenmaa et al., 2012, Stoeckel et al., 2009), we hypothesised that excess weight individuals would show disrupted functional connectivity involving frontal and striatal regions. If excess weight individuals show a general reward-processing deficit, then these disruptions should also be evident during the processing of monetary reward. Finally, we predicted that these network-level functional connectivity disruptions would be associated with personality measures of sensitivity to reward and general measures of clinical severity, such as BMI and adiposity.

2. Materials and Methods

Participants

Seventy-six healthy, right-handed adults, aged between 25 and 45 years old, participated in this study. They were classified in two groups, 39 excess weight and 37 controls, based in their Body Mass Index (BMI). The groups did not differ significantly in terms of age ($t_{(1,74)}$ = -0.40, p = 0.69), sex ($t_{(1,74)}$ = -0.02, p = 0.99), years of education ($t_{(1,74)}$ = 0.72, p=0.47), or monthly income ($t_{(1,74)}$ = -0.63, p = 0.39).

The inclusion criteria for participants were defined as follows: (i) BMI values falling within the intervals categorized as excess weight (BMI higher than 25) or lean (BMI between 19 and 25); (ii) absence of history or current evidence of neurological or psychiatric disorders or medical comorbidities associated with obesity (e.g., diabetes, hypertension); (iii) absence of significant abnormalities on structural MRI or any contraindications to MRI scanning (including claustrophobia and implanted

ferromagnetic objects). All participants had normal or corrected-to-normal vision. They were recruited through media advertisements and received a financial compensation.

The study was approved by the Human Research Ethics Committee of the University of Granada (Spain) and was conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent form certifying their voluntary participation.

Experimental paradigm

For the purpose of the study, each participant performed two tasks during the fMRI session, a food-related reward task and a monetary reward task. To assure that every subject knew all the food stimuli, participants attended a tasting session two weeks before scanning. During that session participants were allowed to try 18 different foods. These products belonged to two groups based on their palatability: highly palatable food, including sweet and fatty food (e.g., chocolate, cheese cake, hamburger) versus plain food (e.g., yoghurt, omelet). These sessions were conducted at 6:00 pm, and participants were instructed to taste each of the foods offered.

fMRI tasks

Willingness to Pay task (WtP). We used a modified version of the Willingness to pay task (Plassmann et al. 2007). Participants were presented with a photo of each of the 18 previously tasted foods. Each stimulus was presented once for two seconds followed by a four-second response period, during which time participants answered the question: "How much would you pay for it?" They could choose between four monetary options, ranging from 20 cents to 10 euros. Each selection was followed by a variable fixation period lasting between 3 and 5 seconds. Our goal in this task was to examine brain

activity and functional connectivity in high palatable food trials compared to plain food trials.

Monetary Incentive Delay task (MID). We used an adaptation of the Monetary Incentive Delay task (Nestor et al. 2010), based on the original task of Knutson (Knutson et al. 2000). At the beginning of each trial, participants were shown one of two cues indicating potential winnings or no financial outcome at the end of the trial. Cues (green or blue square) were counterbalanced across participants, and the incentive value of each trial was signaled by means of the number of horizontal lines crossing the green square (one line for 0.2€, two for 1€ and three for 5€). Each cue was presented for a fixed duration, 750msec. Subsequently, a cross-fixation was shown during a variable period of 3 to 5 sec, and after this interval participants had to perform a reaction-time task: respond to a white target star appearing for a variable length of time (150–450 ms) with a button press. Then participants received feedback (hit/miss) about the accuracy of their response for 750ms, together with the information about the amount of money won in that trial (when adequate, e.g., correct responses in reward cued trials) and their cumulative total at that point of the experiment. Finally, another fixation period (750 ms) was included before the next trial. Therefore, total trial duration ranged between 5700 and 7000 ms. Participants performed the task in two sessions of 48 trials each, yielding a total of 96 trials. Imaging analyses examined brain activity changes during two events: (1) reward-anticipation, which occurred between the presentation of the cue and the response; and (2) reward-feedback period, which occurred at the time of the feedback.

Both tasks were administrated using Presentation software (version 1.8; http://www.neurobs.com). Stimuli were presented through magnetic resonance-

compatible liquid crystal display goggles (Resonance Technology Inc), and responses were recorded through Evoke Response Pad System (Resonance Technology Inc).

Outside scanner behavioral measures

Sensitivity to Reward was measured with The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al., 2001). This questionnaire has demonstrated internal consistency, construct validity, and significant associations with reward and punishment relevant brain systems (Costumero et al., 2013).

Imaging data acquisition and preprocessing

Participants were scanned using a 3T Philips Intera Achieva System. T2*-weighted echo-planar imaging (EPI) sequences were acquired with the following parameters: repetition time (TR), 2000 ms; echo time (TE), 35ms; flip angle, 90º; field of view (FOV), 240 mm; number of slices, 21, voxel dimension, 3 x 3 x 4 mm; gap, 1mm. Specifically, we performed a 149-volume scan session for the WtP task, and two 216-volume scan sessions for the MID task. Structural images were obtained as an isotropic T1-weighted turbo-gradient-echo sequence in the sagittal plane (TR, 8.3ms; TE, 3.8 ms; flip angle, 8º; FOV 240mm; number of slices, 160; voxel dimension, 1 x 1 x 1 mm).

Image preprocessing and analysis were performed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks). Preprocessing steps included realignment to the mean image of the time series, slice timing correction, normalization, using affine and smoothly non-linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by

convolution with a 3D Gaussian kernel (full width at half maximum (FWHM) = 8 mm). Data were high-pass filtered to remove low-frequency noise (1/128 Hz) and corrected for temporal autocorrelation using an autoregressive AR model.

Statistical analyses

Behavioral analyses. Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We conducted mixed-design ANOVAs to investigate the main effect of group, main effect of task, and their interaction. Specifically, we performed a 2 (Group) x 2 (Type of Food), and a 2 (Group) x 4 (Type of Cue) ANOVAs on money paid and response time, respectively.

Task-related activation analyses. General linear models (GLM) were used to characterize task-evoked activation for each task separately. The task regressors were convolved with the SPM8 canonical hemodynamic response function. Three contrasts of interest were defined to investigate task-related activation for each subject; one in the WtP task and two in the monetary reward task. The WtP contrast tested for increased activity in High Palatable food trials compared to Plain Food trials. This contrast models brain processing of reward associated with the palatability of food, the specific reinforcer in obesity. Two contrasts were used to model brain activity during the monetary task. The first examined anticipation of monetary reward, as modeled by a linear contrast defined as: anticipation during high reward trials >Medium reward trial anticipation > low reward trial anticipation > no outcome trials. The second contrast examined feedback-related activation, and was modeled by comparing brain activity in win versus miss trials of the MID task.

Across both tasks, first-level contrast images were carried forward to second-level random-effects group analyses. Whole-brain one-sample t-tests were conducted to map main effects of task across groups for each contrast, followed by two-sample t-tests to assess between-group differences.

The results were corrected for multiple comparisons with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox (Song et al., 2011; Ward, 2013). Input parameters included a brain mask of 138884 voxels, an individual voxel threshold probability of 0.005, and a cluster connection radius of 5 mm, considering the actual smoothness of data after model estimation. A minimum cluster extent (KE) of 343, 293 and 495 voxels for contrast 1, 2, and 3 respectively, was estimated to satisfy a family-wise corrected (FWE) p value of P_{FWE} <0.05. Recent studies have pointed to the potential for false positives to arise when primary cluster-forming thresholds of p >0.001 are used (Woo et al., 2014). Here, we find no group differences at p <0.005, and the result holds for the more stringent p <0.001 threshold. We retain the more lenient p <0.005 threshold for mapping the task-related networks, as this results in a more inclusive definition of network nodes. Using this more inclusive definition ensures that we comprehensively sample the networks of interest. Note that our inclusion of more regions puts our hypothesis of localized changes in fronto-striatal systems to a more stringent test.

Task-related functional connectivity analysis

Graph analysis (Bullmore and Sporns, 2009, Rubinov and Sporns, 2010) was used to characterize brain functional connectivity during both tasks. Each brain network was

modeled as a graph composed of *N* nodes connected by *M* edges. Regions showing significant activation or deactivation in the one-sample analyses for each contrast were selected as nodes for the functional connectivity analysis. All nodes, regardless of the activation contrast used to identify them, were used in the analyses of both tasks. In this way, we were able to examine context-specific changes within a single, reward-related network. ROIs were then generated as 4 mm spheres centered on the voxel with the highest t score in each significant cluster. To prevent overlap between nodes, regions whose central points were closer than 8mm in Euclidean space were identified (n = 60) and a new node was created with a centroid that was equidistant from the two original foci. A total of 126 nodes were defined with this method. Each region-of-interest was masked by the SPM a priori probability image of grey matter in order to weight each voxel value according to its grey matter probability.

Averaged signal time courses for each of the 126 nodes were extracted from the non-smoothed images for both tasks. To measure task-related functional connectivity, we used the correlational psychophysiological interaction (cPPI) methodology (Fornito et al., 2012; http://www.nitrc.org/projects/cppi_toolbox). Separate analyses were conducted to investigate task-related functional connectivity in relation to (1) food-related reward processing; (2) anticipation of monetary reward; and (3) receipt of monetary reward. For each analysis, the BOLD signal from each node was deconvolved (Gitelman et al, 2003), multiplied by a task regressor modeling the contrast of interest [i.e., (1) high palatable food > plain food; (2) anticipation during high reward trials > medium reward trial anticipation > low reward trial anticipation > no outcome trials anticipation; and (3) win > miss trials], and then reconvolved with a canonical hemodynamic response function to generate a psychophysiological interaction (PPI)

term that quantified task-related modulations of each node's activity. These PPI terms were then correlated between every pair of regions while partialling the effects of (1) the original task regressors; (2) the raw region time courses; (3) six head motion parameters (three rotation, three translation) and their first derivatives; and (4) ten principal component time courses that captured variance related to physiological noise and residual head movement. These component time courses were estimated using the aCompCor method (Behzadi et al, 2007). Briefly, this method involves generating subject–specific tissue probability masks of white matter and CSF (thresholded at 99% probability), extracting the time-series from each voxel in each mask, excluding voxels with time courses that correlate with any of the task regressors (a threshold of $p < 0.2$ was uses for this purpose), and performing separate principal component analyses of the remaining white matter and CSF voxel time courses (Muschelli et al, 2014). The first five components from each analysis were retained as noise regressors.

The cPPI analyses resulted in three $N \times N$ functional connectivity matrices (one for each contrast of interest) per subject, where $N = 126$. Each matrix represents task-related functional connectivity between every pair of nodes. In the food reward task, a higher correlation indicated that two regions showed strong functional connectivity in the High palatable condition compared to the Plain food condition. In the monetary reward anticipation analysis, a higher correlation indicated stronger connectivity associated with the linear contrast High>Medium>Low>No Reward. In the monetary reward feedback analysis, a higher correlation indicated stronger connectivity in win compared to miss trials. Functional connectivity was measured for a total of $(N^2\text{-}N)/2 = 7875$ edges in each network, separately for each of the three task contrasts.

NBS analyses

We used the network-based statistic (NBS) to test for group differences in task-related functional connectivity in a data-driven, regionally-unbiased way (Zalesky et al, 2010). A separate analysis was conducted for each task contrast. Briefly, the NBS starts with a mass univariate analysis, in which statistical inference is performed independently at each of the 7875 connections in the network. In this case, the inferential test was a two-tailed t-test of the difference in group means between excess weight and normal weight individuals. The resulting matrix was thresholded at $p < 0.05$, uncorrected The sizes (in terms of number of edges) of the connected components of the remaining network of supra-thresholded edges were then computed, where connected components represent sets of nodes that can be linked by a set of supra-threshold edges. Group labels were then permuted and the analysis was repeated to generate an empirical null distribution of maximal component sizes. A total of 5000 permutations was used to generate this distribution. Since only the maximal component size is stored at each permutation, the resulting p-values for the observed sizes are familywise corrected at the component level (Nichols and Holmes, 2002; Zalesky et al. 2012). We retained as significant all components surviving a threshold of $p < 0.05$, component-wise corrected.

3. Results

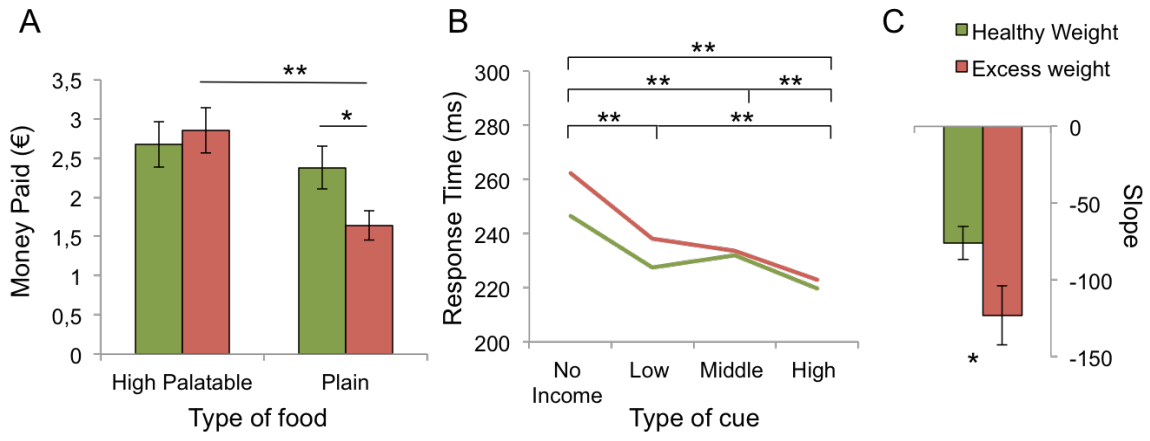
Behavioral Analyses

We found a significant "Group x Type of food" interaction ($F(1,74) = 8.57$, $p = 0.005$) in the WtP task. Within and between group comparisons showed that excess weight group paid less money for plain food than for high palatable food ($t(38) = 5.75$ $p < 0.001$), and less money than controls for plain food ($t(74) = 2.24$, $p = 0.028$). Thus, excess weight

individuals showed a higher valuation of palatable food, as indicated by a willingness to pay more money for it (Figure 1A).

In the MID task, we found a significant effect of cue type across groups on reaction time ($F(3,22) = 48{,}18$, $p < 0.001$), indicating that all participants made faster responses when they had the opportunity to win more money (Figure 1B). We found a trend-level interaction between Group and Type of cue in the reaction time ($F(3,222) = 2.76$, $p = 0.063$) (Figure 1B). A second measure to assess reward sensitivity in the MID task is the slope of the linear regression of reaction time on cue type, ordered from no income, to low, middle and high magnitude. Comparing this measure, we found significant differences between groups ($t(1,74) = 2.136$, $p = 0.037$), suggesting greater responsivity to reward in the excess weight group (Figure 1C).

Figure 1. Behavioral differences between excess and normal weight individuals during the willingness to pay and monetary incentive delay tasks. ***A***. Average money paid during the WtP task. Errors bars represent sample standard error. ***B***. Average response time for each cue type. Both groups showed the same differences as a function of cue type. ***C***. Average slope of the linear regression equation across cue type in the MID task. Errors bars represent sample standard error. * $p < 0.05$; ** $p < 0.01$.



Task-related activation

Across both groups and the three contrasts (i.e., the WtP task contrast between high palatable versus plain food and the MID contrasts of anticipation and feedback), one-sample t-tests showed significant activation in reward-related areas, including the striatum and the prefrontal cortex (i.e., middle and lateral orbitofrontal gyri), as well as in the precuneus and the occipital cortex.

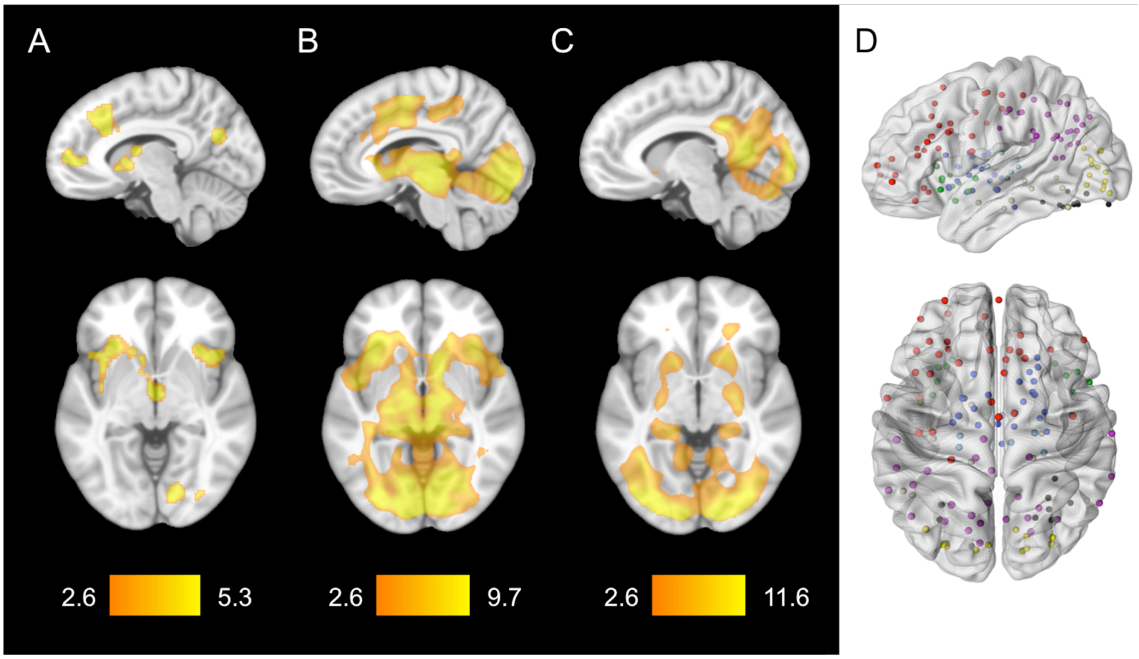
WtP task. Across both groups, processing of highly palatable versus plain food was also associated with increased activation of the midbrain, insula, anterior cingulate cortex (ACC) and supramarginal gyrus (Figure 2A).

MID task. During anticipation of monetary reward, participants across both groups activated striatal areas, as well as the midbrain, insula, ACC, supplementary motor area (SMA), precentral and postcentral gyri, thalamus, cerebellum and hippocampus. They also showed significant deactivations of the angular gyrus and posterior cingulate cortex (PCC) (Figure 2B).

During feedback (i.e., win trials versus miss trials), participants showed significant activation of the same striatal regions and the thalamus, fusiform and supramarginal gyri, hippocampus and PCC. Significant deactivation of the bilateral anterior insula was also observed (Figure 2C).

There were no significant between-groups differences in regional activation for any contrast at the selected threshold.

Figure 2: Task-related activation during the willingness to pay (***A***) and anticipatory (***B***) and feedback (***C***) contrasts of the monetary incentive delay tasks. The color bar indicates t-value. Left hemisphere is displayed on the left. ***D.*** Spatial localization of the nodes. Color node reflects anatomical divisions [i.e., Frontal (red), Insula (green), Striatum (dark blue), Thalamus (light blue), Temporal (grey), Parietal (purple), Occipital (yellow) and Cerebellum (black)]. Left hemisphere is displayed on the left.



Functional connectivity

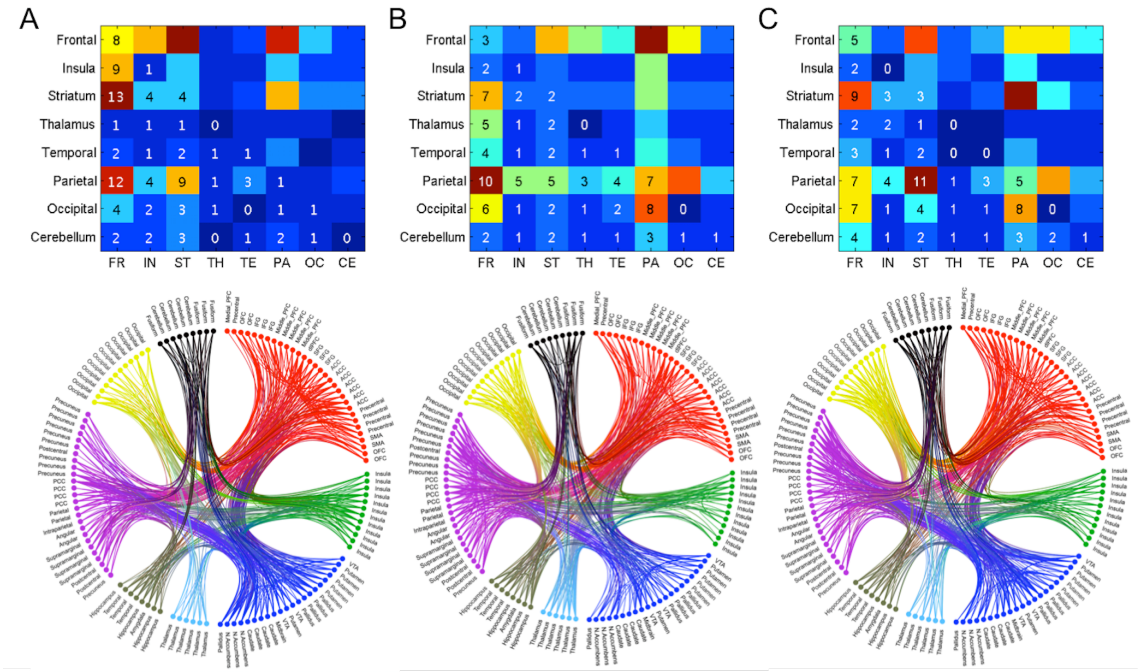
WtP task. The excess weight group showed a significant reduction of functional connectivity in the WtP task compared to controls. The network showing reduced functional connectivity comprised 544 edges and 125 nodes (p = 0.025, component-wise corrected). To better understand the anatomical distribution of this network, we categorized nodes into eight categories according to their anatomical designation:

frontal, insula, striatum, thalamus, temporal & hippocampus, parietal, occipital and cerebellum. We found that more than half of the connections in this network involved frontal cortex (50.55%). Most of these edges linked the frontal cortex with the striatum (13%) or the frontal cortex with the parietal cortex (12%). Fronto-insular (8.6%) and fronto-frontal connections (8.3%) were also frequently implicated in this network (Figure 3A). We identified no subnetworks in which excess weight individuals showed significantly increased functional connectivity during the WtP task.

MID task. During the MID task, the excess weight group showed a significant enhancement of functional connectivity, during both the anticipation and the feedback conditions, compared to controls. This pattern stood in stark contrast to the WtP task, where the excess weight group only showed evidence of reduced functional connectivity.

During reward-anticipation, one component, comprising 532 edges and 126 nodes ($p = 0.03$, component-wise corrected), showed significantly increased functional connectivity in excess weight individuals. This network largely involved frontal and parietal areas, with 10% of connections being fronto-parietal, 7.5% parieto-occipital, 7.1% intraparietal and 7% fronto-striatal (Figure 3B). During reward-feedback, a component comprising 547 edges and 125 nodes ($p = 0.005$, component-wise corrected) showed significantly increased functional connectivity in excess weight participants. This network predominantly involved frontal, striatal and parietal areas: 11% of the edges were parieto-striatal, 9 % fronto-striatal, 8% parieto-occipital and 7.5% fronto-occipital (Figure 3C).

Figure 3: Functional connectivity disruption during willingness to pay (***A***) and anticipatory (***B***) and feedback (***C***) contrasts of the monetary incentive delay tasks. Tables showed the distribution of edges based to the anatomical division they connected. Connectograms (below) showed disrupted connections for each network. Regions of interest are grouped according to anatomical divisions [i.e., FR, frontal (red), IN, insula (green), ST, striatum (dark blue), TH, thalamus (light blue), TE, temporal (grey), PA, parietal (purple), OC, occipital (yellow) and CE, cerebellum (black)].



Consistency across task conditions

To examine whether there was a common dysfunctional network across task conditions, we computed the overlap in the binary topology of the three condition-specific dysfunctional networks identified in excess weight individuals. For each task contrast, we took the sub-network showing a significant difference between groups. We then

computed the size of the intersection (in terms of number of edges) between (1) the two MID conditions (anticipation and feedback); and (2) all three conditions (i.e., monetary anticipation, monetary feedback and food related reward). The first analysis sought to identify a core dysfunctional network associated with processing monetary reward. The second sought to identify a core dysfunctional network associated with both monetary and food reward.

To test whether the overlap was significantly different to chance expectations, we generated randomized surrogates for each of the three dysfunctional networks using an established rewiring algorithm that preserves the same number of nodes, edges and degree distribution of the original networks, but which randomizes the network in all other respects (Maslov-Sneppen). We generated 5000 such networks for each of the three empirical networks and computed the size of the intersection at each of the 5000 iterations to generate empirical null distributions of network overlap.

We found that the dysfunctional networks identified during MID anticipation and feedback showed a statistically significant degree of overlap, sharing 112 edges in which task-related functional connectivity was increased in excess weight individuals ($p < 0.001$). Most of these edges were parieto-occipital (14%), fronto-occipital (8.9%) and fronto-striatal (8.9%). This network thus comprises a core dysfunctional network for the processing of monetary reward in excess weight people.

In a second analysis, we examined the consistency between the dysfunctional network identified in the WtP task and the anticipation and feedback conditions of the MID task. The degree of overlap between the dysfunctional monetary feedback and food reward networks was significantly less than expected by chance (20 edges, $p < 0.005$). A similar trend was observed for the overlap between the food and monetary anticipation

networks (24 edges, p = 0.055). These findings suggest that abnormal processing of monetary and food-related rewards in excess weight individuals is related to dysfunction in spatially and topologically segregated neural systems.

Correlations with task performance, clinical and personality measures.

We next examined how individual variations in functional connectivity with the dysfunctional networks identified for each task condition relate to task performance, clinical and personality measures. To this end, we computed the first principal component of functional connectivity measures across the edges comprising the dysfunctional network identified in each task condition and correlated each individual's component score with outcome measures: behavioral performance in the tasks, BMI, body-fat percentage and sensitivity to reward. For the WtP task, the first PC accounted for 7.16% of the variance; for anticipation it accounted for 7.60% and for feedback it accounted for 7.73%.

Correlation with task performance

We found a significant negative correlation between functional connectivity of the dysfunctional network during the WtP task and the difference score of money paid for high palatable versus plain food (r = -0.266, p = 0.020) (Figure 4A). That is, lower functional connectivity was associated with a lower valuation of plain food.

We also found a significant negative correlation between functional connectivity of the dysfunctional network during the MID contrast of anticipation to reward and the measure of reaction time change across reward magnitudes (r = -0.269, p = 0.020) (Figure 4B). According to the negative sign of the slope of the linear regression of

reaction time on cue type, this negative correlation indicates that higher functional connectivity during monetary reward anticipation was associated with greater behavioral sensitivity to reward magnitude. These correlations did not survive Bonferroni correction for twelve comparisons ($\alpha = 0.05/12 = 0.004$). These findings establish the behavioral relevance of the dysfunctional task-related functional connectivity networks identified in the group comparisons.

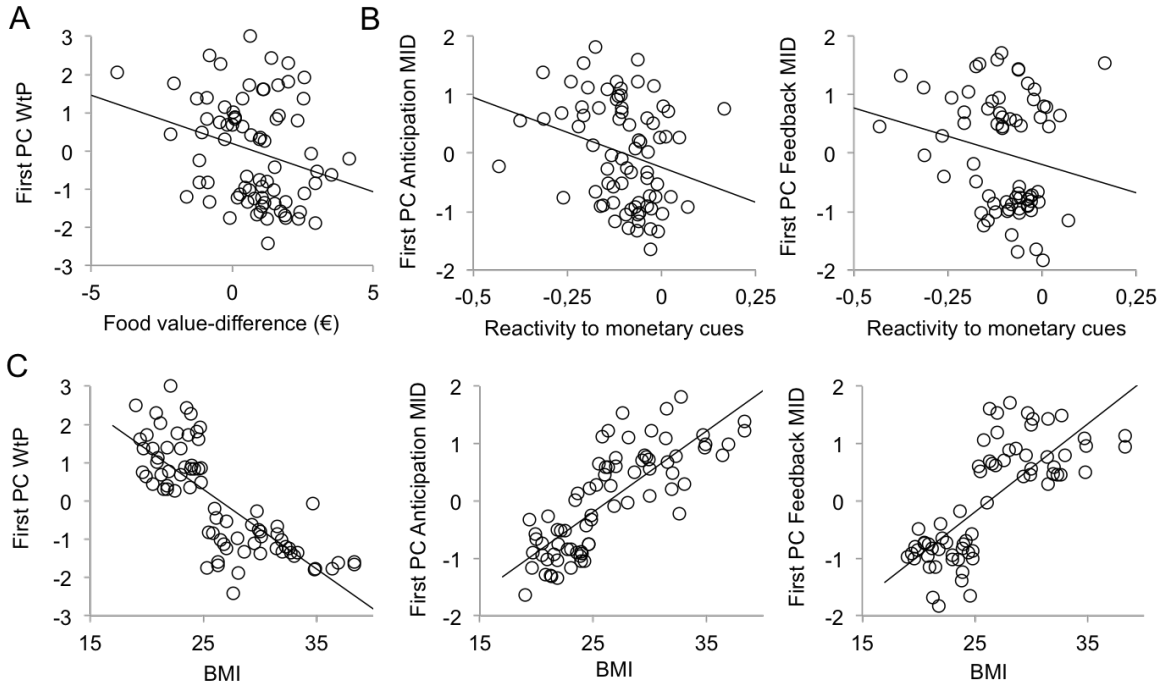
Correlations with clinical and personality measures.

There was a strong correlation between functional connectivity in the dysfunctional WtP network and BMI ($r = -0.77$, $p < 0.001$) The correlation indicates that lower functional connectivity during this task was associated with higher BMI. A similar strong correlation was found with body-fat percentage ($r = -0.53$, $p < 0.001$). The two dysfunctional MID networks also showed significant correlations with BMI and fat percentage: $r = 0.80$ and $r = 0.49$, $p < 0.001$ in the anticipatory monetary contrast and $r = 0.76$ and $r = 0.47$, $p < 0.001$, in the feedback related contrast (Figure 4C). Each of these results survived Bonferroni correction for 12 comparisons (alpha = 0.004).

We also performed partial correlations in which functional connectivity in the dysfunctional WtP network was correlated with BMI while controlling for functional connectivity in the dysfunctional MID networks. This analysis still revealed a significant negative correlation ($r = -0.304$, $p<0.013$). Similarly, the positive correlation between functional connectivity of the dysfunctional MID anticipation network and BMI remained significant when controlling for the WtP network ($r=0.368$, $p=0.002$). These results indicate that brain networks that are dysfunctional in excess weight individuals

during the processing of food and money reward are independently associated with BMI.

Figure 4. Altered networks in excess weight individuals correlate with task performance and BMI. ***A*.** Correlation between WtP network dysfunction and food value-difference measured as money paid for high palatable food minus money paid for plain food. Higher values reflect lower valuation of plain food compared to highly palatable food. ***B***. Correlation between MID network dysfunction and reactivity to monetary cues measured as the slope of the regression of response time across the reward cues. Lower values reflect higher sensitivity to reward amount. ***C.*** Correlations between altered networks and BMI.



4. Discussion

Reward processing is a primary driver of the dietary choices that lead to excess weight and obesity. A core set of regions in the striatum, the prefrontal cortex, and the midbrain are known to support the generic processing of different types of rewards, whether they be monetary, food-related, erotic, and so on. However, it is yet unclear if difficulties in reward processing among excess weight individuals are (a) specific to the context of food or generalize to other domains; and (b) are associated with dysfunction in a specific neural systems or a domain-general reward processing network. In this study we used a data-driven, connectome-wide analysis to map neural systems showing altered functional connectivity in excess weight individuals during the processing of two distinct types of reward: food-related and monetary (including the anticipation and receipt of money). We found consistent evidence for involvement of frontal, striatal and parietal areas across tasks; however, the specific neural systems identified as dysfunctional in the food and monetary contexts were different. Specifically, excess weight individuals showed reduced functional connectivity and impaired valuation of rewards during food processing, and increased functional brain connectivity and higher behavioral sensitivity to monetary rewards. The specific set of brain functional interactions that were altered in these conditions showed statistical evidence of spatial and topological segregation. During both food-related and monetary reward processing, network-level functional connectivity correlated with task performance and physical measures of weight (i.e., BMI and adiposity), providing a direct link to altered reward valuation and physical size.

Functional connections showing reduced coupling during the WtP food task in excess weight individuals predominantly linked frontal lobe nodes, which play an important

role in self-regulation (Rangel, 2013), with striatal regions involved in stimulus valuation (Montague et al., 2002), parietal regions implicated in attentional control (Hopfinger et al., 2000), and insula regions relevant to interoception (Craig, 2009). These results are consistent with a previous study that found reduced frontal cortex related functional connectivity in obese individuals during passive viewing of high palatable food images (García-García et al., 2013). Two recent studies have also reported altered white matter microstructure in fiber pathways linking frontal and subcortical areas in excess weight adults (Marqués-Iturra et al., 2015; Kullmann et al., 2015). Frontal areas play a crucial role in dietary choices. These areas code the relative value of food reward according to palatability, while also supporting behavior to achieve long-terms goal (Rangel, 2013). Reduced functional connectivity between the frontal cortex and reward-related regions has been associated with failure of top-down regulation of behavioral control (Motzkin et al, 2014). This deficit has also shown to contribute to explain dietary choices in obesity (Rangel, 2013). This conclusion is consistent with several studies that report difficulties in cognitive control and executive functions in obesity (Fitzpatrick et al., 2013). Modelling effective connectivity (e.g., Friston et al. 2003) within fronto-striatal systems may provide a useful test of the hypothesis that these circuit-level abnormalities are caused by deficient top-down signaling from the prefrontal cortex.

In the MID task, individuals with excess weight displayed enhanced functional connectivity in a similar network across reward-anticipation and reward-feedback. This network involves mainly parieto-occipital, fronto-occipital and fronto-striatal connections. Previous resting-state neuroimaging studies had demonstrated enhanced resting-state functional connectivity in individuals with obesity (Dunnelink et al. 2008;

Kullmann et al., 2012; Black et al., 2014; Lips et al., 2014; Wijngaarden et al., 2015). Therefore, in obese people the pattern of functional brain connectivity during monetary reward resembles the tonic hyper-connectivity observed in resting-state studies. Fronto-occipital networks are involved in rapid feed-forward propagation of visual inputs and direct top-down modulation of early visual processing (Forkel et al., 2014). Parieto-occipital connections have also been implicated in the orientation and maintenance of visual attention (Foxe et al, 1998). The specific involvement of visual-attentional and goal-directed networks, and the positive correlation between these networks and sensitivity to reward in our analysis, suggests that obese individuals are sensitive to monetary cues. Future studies should explore the extent to which these networks predict dietary choices driven by monetary value, such as "meal deal choices".

The non-significant overlap between the dysfunctional reward-processing networks, as well as our partial correlation analyses, indicate that different neural systems independently correlate with excess weight. Reduced functional connectivity in frontal-striatal networks during processing of food-related stimuli may relate to weakening of self-regulation skills needed to control high-calorie food choices (Hollmann et al., 2012). Money-related hyper-connectivity in visual-attentional networks may relate to excessive weight via special attention to the financial value of cheap high-calorie foods, which is linked to cues of food chains and meal deals. For example, Bruce et al. have shown parietal hyper-activation in response to fast food chains' branding logos (Bruce et al., 2014). Noteworthy, our findings are correlational and hence it is also possible that being overweight changes brain functional connectivity. Further studies are needed to better understand the relationship between these separate network alterations and clinical and societal outcomes relevant to obesity. Ultimately, different therapeutic

approaches may be needed to tackle excess weight problems, one to strengthen frontal-striatal FC in response to food stimuli, and a different one to decrease fronto-parietal-occipital FC in relation to monetary reward processing.

We did not find significant group differences in brain activation in any of the three contrasts. These results suggest that reward processing in excess weight individuals is primarily driven by dysfunction of anatomically distributed neural systems, rather than isolated dysfunction of one or a few brain regions. Other studies have reported regional activation differences between obese individuals and normal weight controls during processing of highly palatable food (Rothemund et al. 2007; Stoeckel et al., 2008), but there are few studies in overweight individuals. Most of the existing studies included participants with severe presentations of obesity (BMI>35) and other medical conditions and eating disorders (i.e., binge eating disorder), whereas our sample is free of medical conditions and mental health disorders, and spans the whole excess weight spectrum, including overweight (BMI 25-30) and obese (BMI>30) participants. In addition, we conducted regionally-unbiased, whole-brain analyses, whereas many previous studies have focused on *a priori* regions of interest.

In summary, specific functional connectivity disruption was found in excess weight individuals in response to food and money. Specifically, an enhancement in functional connectivity in a common network was found during both anticipation and reception of a monetary reward, whereas a reduction in functional connectivity was related to food reward. Our results are consistent with behavioral impaired valuation of both rewards and suggest a failure on regulation of dietary choice and food behavior. These results provide evidence of a general disruption of reward processing in excess weight adults,

but specific therapeutic approaches may be required to address specific aspects of this disruption when tackling the obesity epidemic.

Capítulo 6.

DYSFUNCTIONAL INVOLVEMENT OF EMOTION AND REWARD BRAIN REGIONS ON SOCIAL DECISION MAKING IN EXCESS WEIGHT ADOLESCENTS

Antonio Verdejo-García, Juan Verdejo-Román, Jacqueline S. Rio-Valle, Juan A. Lacomba, Francisco M. Lagos, Carles Soriano-Mas. (2014) Dysfunctional involvement of emotion and reward brain regions on social decision making in excess weight adolescents. *Human Brain Mapping*, *36* (1), 226-237.

1. Introduction

Adolescent obesity is a major public health problem that has rapidly attained epidemic levels (Gee et al. 2013; Ji, 2008; Rudolf et al. 2004; Strauss and Pollack, 2001). Neuroscience models posit that major societal changes have transferred the obesity problem to the decision-making field: in plentiful environments, decision-making is essential to prioritize what to eat (i.e. healthy-wise vs. rewarding unhealthy food) (Zheng and Berthoud, 2007). In fitting with this notion, we have shown that adolescents with excess weight have decreased activation of risk-sensitive brain regions and increased activation of reward-signaling brain regions during decisions about small safe rewards vs. high risky gains (Delgado-Rico et al. 2013). However, the relevance of decision-making to adolescent obesity goes beyond factoring personal rewards, and extends to the social evaluative domain. Adolescents with excess weight suffer significantly more peer bullying, marginalization and social isolation (Ludwig, 2007; Strauss and Pollack, 2003). These negative social experiences are the main predictor of poor psychosocial adjustment in children and adolescents with obesity (Gunnarsdottir et al., 2012). Moreover, social stress is known to decrease prosocial choices in adolescents (Youssef et al. 2012), and preclinical studies indicate that this detrimental impact is mediated by neuroadaptations in prefrontal and limbic regions (Barendse et al. 2013; McEwen, 2007). Therefore, excess weight adolescents are likely to experience social stress and social decision-making deficits, which should manifest in prefrontal-limbic neuroadaptations.

The Ultimatum Game (UG) is a social decision-making task in which two parties (the proposer and the respondent) negotiate how to share a specified amount of money. The proposer makes the offer (sharing around 15%, 25% or 50% of the stake) and the

respondent chooses to either accept, in which case the money is split the way is offered, or reject, in which case none of the parties get any money. Set this way, the task raises a conflict between the cognitive choice (accepting the offer, getting the money) and the emotional response to unfairness (unfair offers elicit negative affect and increase rejection) (van't Wout et al. 2006). The typical neural network activated during unfair vs. fair offers involve the anterior insula, the dorsolateral prefrontal cortex and the anterior cingulate cortex, purportedly involved in perception of unfairness, cognitive evaluation and conflict between emotion and cognition respectively (King-Casas et al. 2008; Knoch et al. 2006; Sanfey et al. 2003). Moreover, brain regions involved in reward prediction and emotional learning further contribute to subjective feelings about the offers and behavioral decisions to accept/reject (Gospic et al. 2011; Hollmann et al. 2011). Therefore, the UG poses an interpersonal decision-making conflict in which brain regions typically involved in emotion and reward processing come into play in the social domain (Xiang et al. 2013). Further, the degree of engagement of this circuitry in response to unfair offers might be sensitive to psychological characteristics of the excess weight population that are disadvantageous in the social domain. Specifically, obesity has been associated with high maturity fears, which reflects the anxiety of facing the social-evaluative demands of adult life (Garner, 1994). These fears are the most potent determinant of social maturation during adolescence (Westenberg et al., 2004). Further obese populations typically display low sensitivity to reward and high sensitivity to punishment (Davis, 2009), which are known to impact social function specifically during adolescence (Harms et al., 2014).

In this study we aimed at mapping the activation of the social decision-making brain circuitry as measured by the UG in adolescents with excess vs. normal weight and

examining the association between separate patterns of activation (in excess vs. normal weight groups) and psychological traits including reward sensitivity and disordered eating features that are central to obesity and social decision-making behavior. On the basis of previous evidence, we expect that excess weight adolescents display blunted activation of regions involved in social decisions (i.e., anterior cingulate, insula) and social rewards (i.e., striatum, amygdala), and that these separate patterns correlate with reward sensitivity, obesity related traits, and behavioral decisions of accept/reject.

2. Materials and Methods

Participants

Eighty adolescents aged between 12 and 18 years-old participated in the study. They were classified in two groups (Normal weight [n = 44] and Excess weight [n = 36]) based on their age adjusted body mass index (BMI) percentile (Cole and Lobstein, 2012). The classification of the two groups was conducted in alignment with the guidelines of the International Obesity Task Force and the Centers for Disease Control and Prevention: Normal weight participants had age adjusted BMI percentiles in the range between the 5th and the 84th percentile, and excess weight participants had age adjusted BMI percentiles $\geq$ 85 (see Table I). Participants' socio-demographic characteristics, BMI, percentage fat and blood-count based biochemical parameters are as well displayed in Table I.

Table I: Demographic and body characteristic, scores from SPSRQ and EDI-2 and behavioral performance during the UG inside the scanner.

	Normal weight (n = 44)	Excess weight (n = 36)	p-value
Demographic variables			
Age	15.32 (1.69)	15.06 (1.88)	0.514
Gender (male/female)	19 / 25	12 / 24	0.375
BMI	20.96 (2.31)	29.11 (3.90)	<0.001
Range of BMI Percentile	9-84	85-97	
Fat (%)	18.49 (33.89)	33.89 (8.33)	<0.001
Biochemical parameters			
Insulin	33.61 (37.78)	40.26(50.91)	0.548
Basal glucose	90.61 (10.42)	90.85 (7.85)	0.910
Triglycerides	66.70 (28.63)	83.11 (35.02)	0.025
HDL	59.04 (14.86)	55.38 (12.90)	0.253
Total cholesterol	150.23 (24.52)	163.86(29.77)	0.029
Sensitivity to punishment and reward			
Sensitivity to Punishment	10.52 (5.15)	10.39 (5.03)	0.907
Sensitivity to Reward	11.84 (4.15)	9.78 (3.50)	0.020
Eating Disorders Scales			
Drive for Thinness	3.00 (4.27)	7.63 (5.81)	<0.001
Bulimia	1.33 (2.18)	1.16 (1.76)	0.716
Body Dissatisfaction	5.50 (5.97)	12.25 (7.32)	<0.001
Ineffectiveness	3.22 (3.53)	3.34 (3.82)	0.892
Perfectionism	5.25 (4.10)	5.44 (3.50)	0.841
Interpersonal Distrust	3.56 (3.00)	2.50 (2.75)	0.137
Interoceptive Awareness	4.17 (3.92)	4.09 (3.60)	0.937
Maturity Fears	5.50 (2.81)	8.31 (4.84)	0.006
Asceticism	3.64 (2.65)	3.91 (2.52)	0.672
Impulse Regulation	3.39 (3.79)	4.00 (4.17)	0.529
Social Insecurity	4.14 (3.45)	3.75 (3.62)	0.652
UG behavioral performance			
Accepted offers (%)			
All offers	58.69 (19.74)	55.90 (21.18)	0.543
Fair offers	82.36 (19.49)	83.84 (21.11)	0.870
Unfair offers	46.70 (28.41)	42.05 (29.53)	0.476
Response Time (s)			
All offers	1.010 (0.297)	1.029 (0.275)	0.777
Fair offers	0.934 (0.293)	0.971 (0.284)	0.568
Unfair offers	1.046 (0.316)	1.053 (0.279)	0.912

SD, standard deviation; BMI, body mass index; s, seconds; HDL, high-density lipoprotein

Participants were recruited from the paediatrics and endocrinology services of the Hospital "Virgen de las Nieves" in Granada (Spain), and from schools located in the same geographical area. The inclusion criteria for participants were defined as follows: (i) age range between 12 and 18 years-old; (ii) BMI percentiles falling within the intervals categorized as overweight or obesity (≥ 85: Excess weight group), or normal weight (5-84: Normal weight group); (iii) absence of history or current evidence of neurological or psychiatric disorders, assessed by participants and parents interviews and the Eating Disorder Inventory (Garner, 1994); (iv) absence of significant abnormalities on Magnetic Resonance Imaging (MRI) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects). All participants had normal or corrected-to-normal vision.

The study was approved by the Ethics Committee for Human Research of the Universidad de Granada. Both participants and parents signed an informed consent form.

Experimental task

We utilized an fMRI suitable previously validated UG task (Crockett et al. 2008) involving one proposer and one responder. Participants always played the responder's role To enhance the credibility and the interpersonal appeal of the game, participants were told that the proposer was another participant of the research project, who had left a picture of himself/herself and a list of proposals after his/her own scanning session. We told them that this proposer had been randomly selected from the pool of previous participants, and that they could see his/her picture during the game. In addition, they were told they would have the opportunity to play the role of the proposer with other

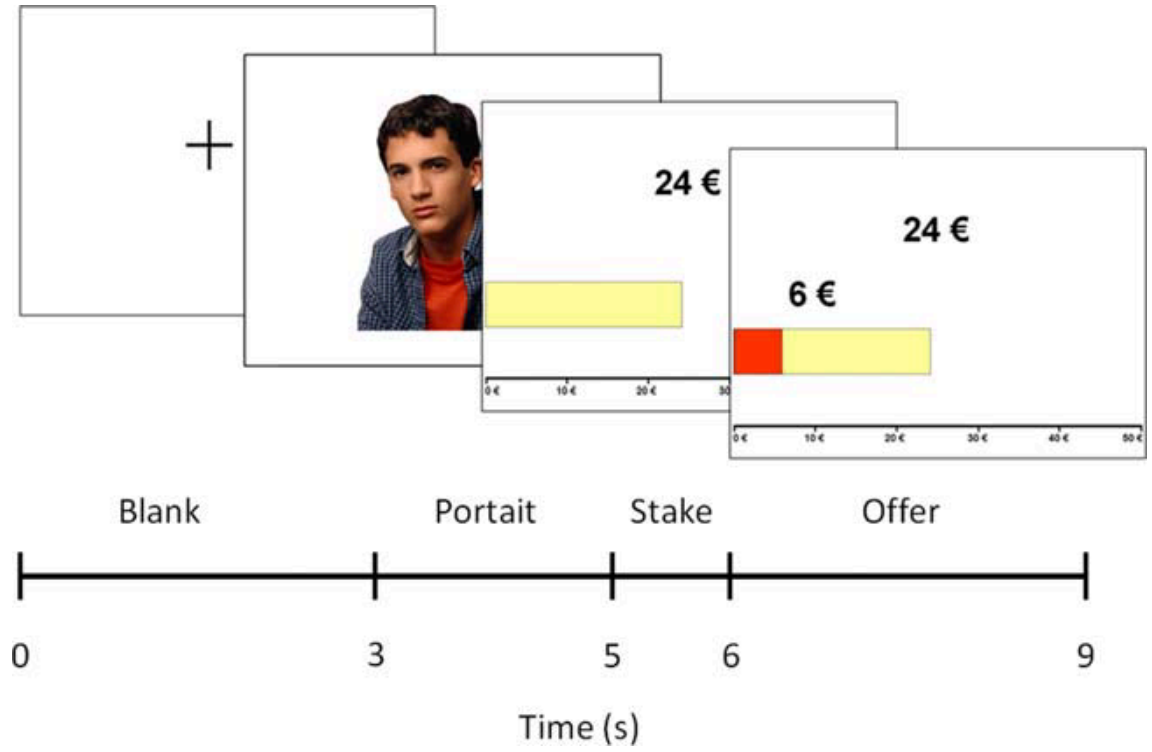
volunteers who would participate in the future, if they would allow their photograph to be taken and used in future sessions, and submit their own proposals for several stake sizes. In reality, the picture of the proposer was taken from a web pool of images and utilized with all participants to minimize potential confounders associated with social identification.

In each trial, participants were initially prompted with a picture of the proposer (2 s), followed by a graphical depiction of the money available to split in that particular trial (indicated by the number expressed in Euro and the length of a horizontal light-colored bar) and the amount of money that the proposer offered to share (indicated by the number expressed in Euro and the proportion of the above bar filled in red; 1 s). Once the offer was presented, participants had 3 s to accept or reject the offer using designated buttons in a button-box response pad. They were told that if they accepted the proposer's offer, both players were supposed to be paid in the specified way. Conversely, by rejecting the offer, none of them would get the money. After the response, each trial was followed by 3 s of baseline during which a fixation cross was presented in the screen until the next trial started, for a total trial duration of 9 s (see Figure 1). Event onsets were jittered with respect to scan onsets across trials (Henson and Mouchlianitis, 2007).

The task included two types of offers varying on degree of fairness: Fair offers, in which the proposer offered to share around 46% of the money, and Unfair offers, in which the proposer offered to share between 15 and 25% of the money. Participants were informed that payments were hypothetical. Our main interest was to contrast group differences in brain activations involved in (1) making decisions about Unfair vs. Fair offers (indexing the conflict between perception of unfairness and cognitive evaluation);

and (2) deciding to Reject vs. Accept the offers (indexing emotion-based decisions involving missing reward vs. strategic decisions).

Figure 1: Schematic representation of the UG task through depiction of one experimental trial.



Inside scanner behavioral measures:

Acceptance rates (% of offers accepted) and response times were calculated for each participant as a function of offer type.

Outside scanner behavioral measures:

The *Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)* (Torrubia et al. 2001): It is a 48 yes–no response item questionnaire that measures trait sensitivity to reward (24 items) and punishment (24 items). The SPSRQ has demonstrated sound

psychometric properties, construct validity and significant associations with biologically plausible brain systems (Costumero et al. 2013).

The *Eating Disorder Inventory* – Second Edition (EDI-2) (Garner, 1994): It is a 64-item self-report measure assessing disadvantageous psychological traits commonly associated with eating disorders. Responses are made on a 6-point Likert-type scale ranging from never to always. The EDI-2 has demonstrated sound psychometric properties, and construct validity (Elder and Grilo, 2007; Reas et al. 2006).

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). 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, 442 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, UK), running under Matlab R2009 (MathWorks, Natick, MA, USA). Preprocessing included reslicing to the first image of the time series, slice timing correction, normalization, using affine and smoothly non-linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum (FWHM) = 8 mm).

Data Analysis

Behavioral analyses:

We used the Statistical Package for the Social Sciences version 19 (SPSS 19; Chicago, IL, USA) for these analyses. We conducted independent-sample *t*-tests (two-tailed) to compare the two groups on relevant sociodemographic variables, and inside and outside scanner behavioral measures.

fMRI, main task effects:

The conditions of interest were modeled from the time at which the offer was presented to the time at which participants responded. Two contrasts of interest were defined at the first-level (single-subject) and between-group analyses: (1) 'Unfair > Fair offers', (2) 'Reject > Accept unfair offers'. The BOLD response at each voxel was convolved with the SPM8 canonical hemodynamic response function and a high-pass filter was used to remove low-frequency noise (1/128 Hz). The resulting 1st-level contrast images were then carried forward to subsequent 2nd- level random-effects (group) analyses. Main task effects were assessed with one-sample t-test, while two-sample t-tests were used to assess between-group differences. The results were corrected for multiple comparisons

with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox (Song et al. 2011; Ward, 2013). For one-sample t-tests, input parameters included a brain mask of 161,455 voxels, an individual voxel threshold probability of 0.005 and a cluster connection radius of 5 mm, considering the actual smoothness of data after model estimation. A minimum cluster extent (KE) of 436 voxels was estimated to satisfy a P_{FWE} <0.05. Significance in two-sample t-tests was assessed using the same input parameters, masking results on the basis of activation and deactivation maps derived from the one-sample t-tests. Therefore, for contrast 1 and 2, respectively, a minimum cluster extent (KE) of 54 and 87 voxels (within brain masks of 17968 and 18266 voxels), was estimated to satisfy a P_{FWE} <0.05. All analyses were conducted both including and not including age as a nuisance variable. Since in both cases we obtained the same results, we only report uncorrected effects.

Correlation analyses:

Correlation analyses were performed in SPSS. Specifically, the beta eigenvalues from the peak coordinates of each cluster of significant brain results were extracted for each participant, and then correlated with behavioral measures within each group. Correlation analyses were complemented with Structural Equation Modeling (SEM) analyses aimed at testing and estimating causal relationships between the different variables involved in our imaging and behavioral assessments. Specifically, we examined whether obesity-related psychological traits were associated with the decision of accepting or rejecting social offers through the activation/deactivation of specific brain regions. Thus, we estimated the direct effect of trait measures on the behavioral response, the effect of trait measures on brain activity (the brain-trait pathway), the

effect of brain activity on the behavioral response after controlling for trait measures (the brain-state pathway), and the indirect relationship (through activation/deactivation of specific brain regions) between trait measures and the behavioral response. The effect and statistical significance of the different paths were estimated using the mediation toolbox (http://wagerlab.colorado.edu/files/tools/mediation.html).

3. Results

Behavioral results

Independent-sample *t*-tests showed no significant between-group differences on acceptance rates or response times to any type of offer ($P > 0.1$ in all cases). Participants with excess weight showed significantly lower scores in sensitivity to reward, and significantly higher scores in drive for thinness, body dissatisfaction and maturity fears compared to normal weight peers.

Imaging results:

Unfair > Fair offers

Intra-group activations:

One-sample t-tests showed that Normal weight participants significantly activated medial wall regions (including the anterior cingulate cortex, the medial frontal gyrus and the supplementary motor area), the superior and middle fontal gyrus, the thalamus (extending to midbrain and amygdala) and the right precentral gyrus (somatosensory cortex encompassing posterior insula). Normal weight participants also showed

significant deactivations in left parietal and occipital cortices. Excess weight participants did not show significantly increased activations. However, they showed significant deactivations in a large cluster including left anterior insula, frontal operculum and superior temporal gyrus. Similar to normal weight adolescents, they also showed deactivations in bilateral parietal and occipital cortices (extending to the fusiform gyri) (Figure 2 and Table SI).

Group differences:

Excess weight adolescents showed significantly reduced activations in dorsal anterior cingulate cortex, left anterior insula/frontal operculum, superior temporal gyrus, and thalamus and midbrain (extending to the amygdala) compared to Normal weight peers (Figure 2 and Table SI).

Correlations between brain activation patterns and behavioral measures:

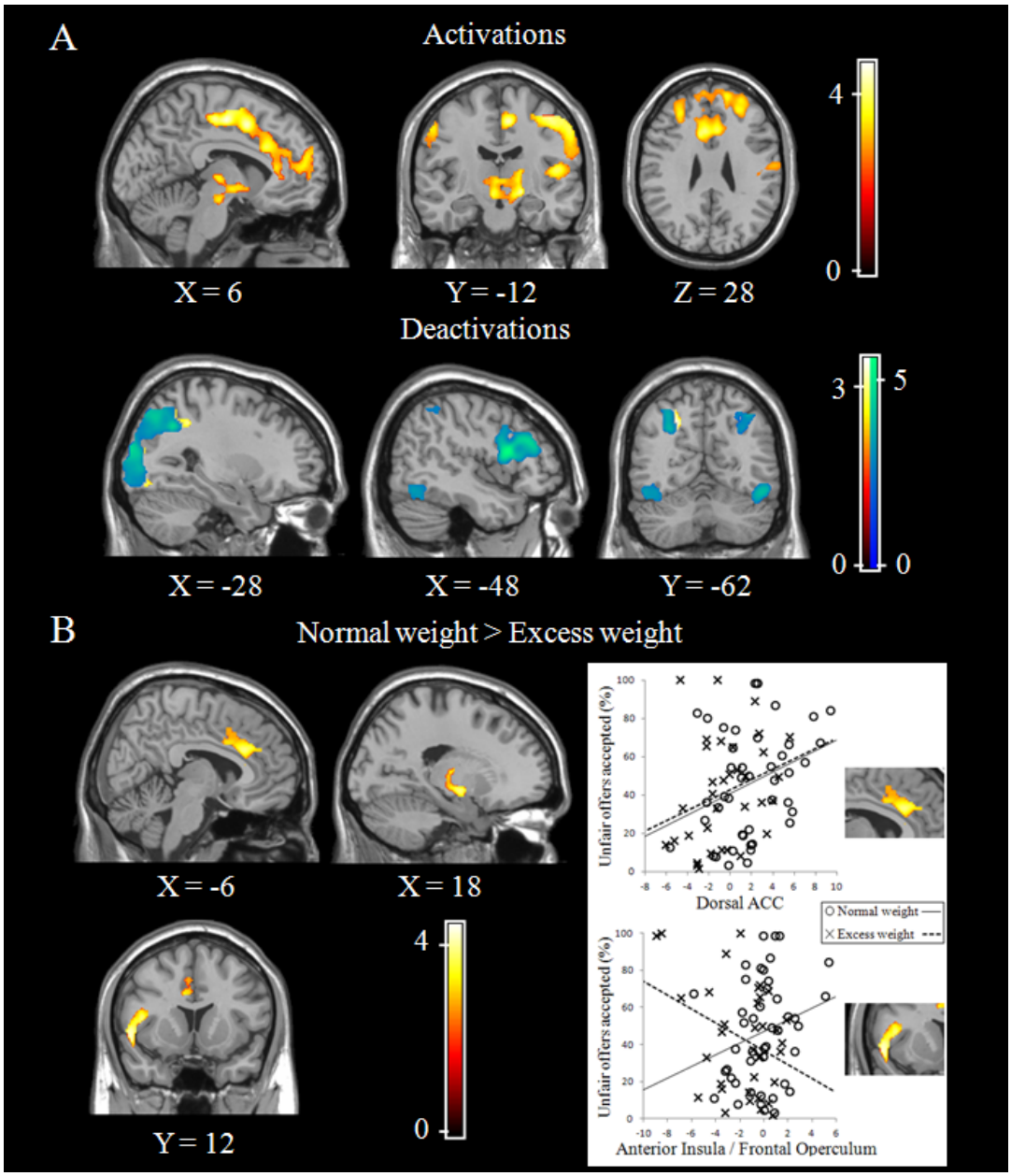
Regarding acceptance rates, the proportion of unfair offers accepted positively correlated with dorsal anterior cingulate cortex activation in normal and excess weight subjects, although such correlation was statistical significant only in the former ($r = 0.321$, $p = 0.034$, and $r = 0.283$, $p = 0.105$, respectively). By contrast, the proportion of unfair offers accepted correlated negatively with anterior insula/frontal operculum activation in Excess weight participants ($r = -0.353$, $p = 0.038$) whereas this correlation was positive and non-significant in the Normal weight group ($r = 0.241$, $p = 0.114$). The direct comparison between these correlations revealed a significant-group difference, with $z = 2.63$, $p = 0.008$ (Figure 2).

Table SI: Activations, deactivations and group differences during 'Unfair>Fair' contrast.

			MNI coordinates			Volume	
	BA	Side	X	Y	Z	(mm^3)	*t*
Activations							
Normal weight							
Thalamus		R/L	18	-20	4	11240(*)	4.68
Midbrain		R/L	-4	-12	-10	11240(*)	4.13
Amygdala		L	-18	-4	-12	11240(*)	2.82
Supplementary Motor Area	6	R/L	6	-12	50	41464(*)	4.62
Dorsal ACC	24	R/L	8	4	46	41464(*)	4.49
Rostral ACC	32	R/L	-6	20	26	41464(*)	4.33
Medial frontal gyrus	9,10	R/L	22	48	16	41464(*)	4.42
Superior frontal gyrus	9,10	R/L	-6	56	22	41464(*)	4.27
Middle frontal gyrus	9	R	24	38	32	41464(*)	4.15
Middle frontal gyrus	9	L	-30	38	28	41464(*)	3.78
Precentral Gyrus		R	42	-14	52	13456(*)	4.26
Somatosensory cortex	2,3,4	R	54	-16	50	13456(*)	4.16
Posterior Insula	13	R	46	-16	12	13456(*)	3.93
Deactivations							
Normal weight							
Middle Occipital Gyrus	19	L	-32	-88	2	11784(*)	3.95
Parietal Lobule	7	L	-28	-64	48	11784(*)	3.76
Excess weight							
Ant. Insula/Frontal operculum	13,44,45	L	-46	12	16	14176(*)	5.58
Inferior Frontal Gyrus	46	L	-48	28	26	14176(*)	4.92
Superior Temporal Gyrus	22	L	-56	12	-6	14176(*)	4.11
Parietal Lobule	7	L	-32	-58	38	23448(*)	5.17
Middle Occipital Gyrus	18,19	L	-24	-96	14	23448(*)	4.73
Fusiform Gyrus	37	L	-42	-66	-16	23448(*)	3.55
Middle Occipital Gyrus	18,19	R	32	-80	4	31976(*)	5.18
Fusiform Gyrus	37	R	48	-60	-16	31976(*)	4.26
Parietal Lobule	7	R	26	-82	44	31976(*)	4.21
Group Comparisons							
Normal weight>Excess weight							
Ant. Insula/Frontal operculum	13	L	-44	10	10	3296(*)	3.85
Inferior Frontal Gyrus	44	L	-42	24	6	3296(*)	3.05
Superior Temporal Gyrus	22	L	-54	14	-8	3296(*)	4.43
Midbrain		R	12	-10	-8	2368(*)	3.48
Thalamus		R	18	-16	4	2368(*)	3.38
ACC	24,32	R/L	-4	24	24	6864	4.04

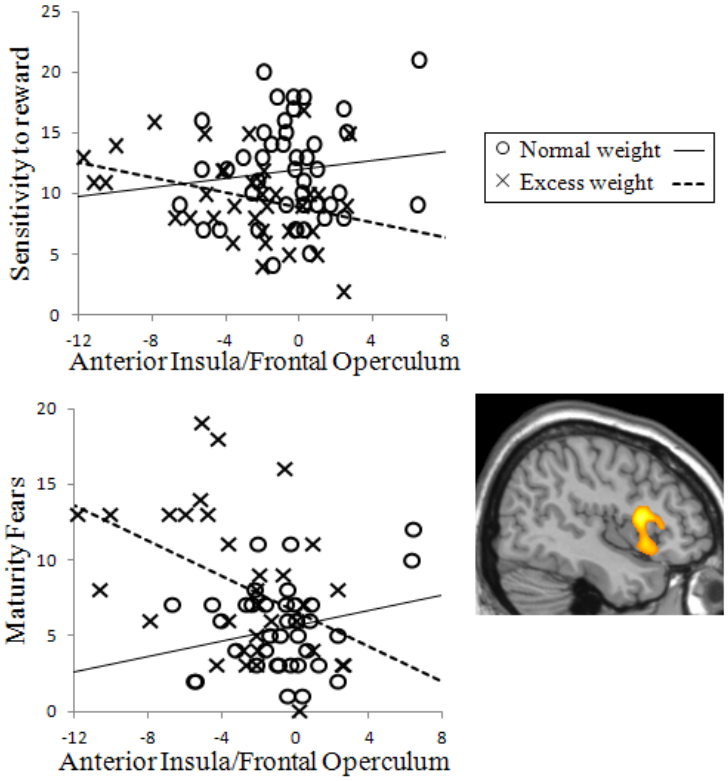
BA: Brodmann area; * part of the large cluster; ACC: Anterior Cingulate Cortex.

Figure 2: Brain activations, deactivations, and group differences during "Unfair>Fair" contrast. Note: (**A**) Top panel displays the brain regions showing activations and deactivations during "Unfair>Fair" offers in both groups. Warm colors reflect normal weight group and cold colors reflect excess weight group. (**B**) Bottom panel displays the differences between groups. Bottom-right panel displays the correlations between "Unfair offers accepted" and peaks activation at dorsal ACC and anterior insula/frontal operculum in the "Unfair>Fair" comparison. X, Y and Z denote coordinate in standard MNI space. Right hemisphere is displayed on the right. Color bar indicates T value.



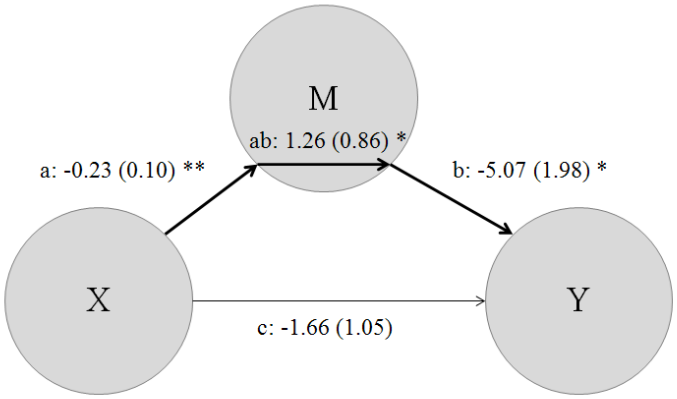
As for psychological traits, both maturity fears and sensitivity to reward scores negatively correlated with anterior insula/frontal operculum activation in excess weight participants (r = -0.443, p = 0.011 and r = -0.335, p = 0.046, respectively), whereas these correlations were positive and non-significant in normal weight group (r = 0.245, p = 0.149 and r = 0.121, p = 0.433). The direct comparison between these correlations revealed a significant group difference, with z = 2.85, p = 0.004 (for maturity fears) and z = 2.01, p = 0.044 (for sensitivity to reward; Figure 3). We found no significant correlations between drive for thinness or body dissatisfaction and brain activation patterns.

Figure 3: Scatterplots displaying the correlation between behavioral measures ("Sensitivity to Reward" and "Maturity Fears") and brain activation patterns during the "Unfair>Fair" contrast (peak activation at the anterior insula/frontal operculum region). The data of excess weight and normal weight participants are representedwith different symbols (crosses and circles, respectively) to illustrate the different direction of the correlation as a function of group.



As in excess weight participants, anterior insula/frontal operculum activation was significantly related to both the behavioral response (i.e., the proportion of unfair offers accepted) and specific trait measures (maturity fears and sensitivity to reward), in a post-hoc analysis we studied the relationships between these variables using a Structural Equation Modelling (SEM) approach. Specifically, we observed that maturity fears were indirectly and positively related to the acceptance of unfair offers through the decreased anterior insula/frontal operculum activation observed in excess weight participants ($z = 2.17$ $p = 0.03$; Figure 4). Of note, the direct correlation between maturity fears (X) and acceptance of unfair offers (Y) was negative, although non-significant (zero-order or c: $z = -0.44$, $P = 0.660$). The lack of significance of direct effects indicates that the association between maturity fears and acceptance of unfair offers is exclusively accounted for the pattern of insula activation. Moreover, the opposite signs observed between direct (c') and indirect (ab) effects further supports that the association between these behavioral variables is specifically conveyed by the pattern of insula activation. None of these effects were observed in control participants. Likewise, we did not observe any significant relationship between sensitivity to reward and behavioral responses in the task.

Figure 4: Path diagram showing the relationships between maturity fears (X), percentage of unfair offers accepted (Y), and insula activation (M) during the UG task in excess weight participants. X was inversely related to M (a, or the brain-trait pathway), while M was also inversely related to Y (b, or the brain-state pathway). X was not directly related to Y (c'), but these two measurements were indirectly related through M (a*b). *P <0.05, **P <0.01.



Reject > Accept Unfair offers

Intra-group activations:

One-sample t-test showed that during rejected offers, both groups showed significant activations in the dorsal anterior cingulate cortex, the somatosensory cortices, the insula, and the adjacent temporal cortices. However, in normal weight participants, the activation in the postcentral gyri extended to the precentral gyri and additional activations involved the supplementary motor area and the thalamus extending to putamen, midbrain and the left amygdala (Figure 5 and Table SII).

Figure 5: Brain regions activated during "Reject>Accept" unfair offers in both groups. Note: Warm colors reflect normal weight group and cold colors reflect excess weight group. X, Y, and Z denote coordinate in standard MNI space. Right hemisphere is displayed on the right. Color bar indicates T value

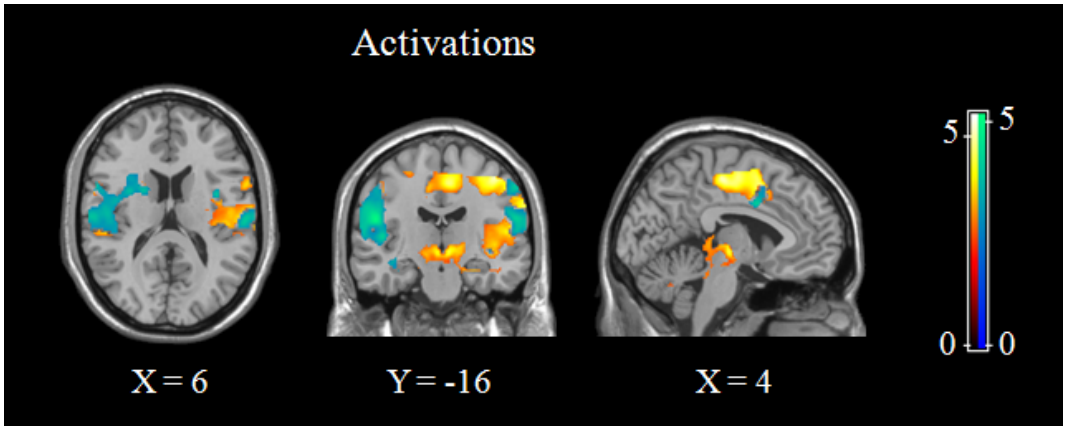


Table SII: Activations during 'Reject > Accept' unfair offers:

	BA	Side	MNI coordinates X	Y	Z	Volume (mm^3)	*t*
Activations							
Normal weight							
Supplementary Motor Area	6	R/L	8	-22	50	96408(*)	5.52
Precentral Gyrus	6	R	44	-12	54	96408(*)	5.41
Dorsal ACC	24,31,32	R/L	4	8	46	96408(*)	4.90
Somatosensory Cortex	2,3,4	R	58	-20	22	96408(*)	5.05
Somatosensory Cortex		L	-58	-26	20	96408(*)	4.40
Insula	13	R	40	-2	10	96408(*)	4.87
Midbrain		R/L	-2	-18	-6	96408(*)	4.77
Parietal Operculum		R	56	-18	12	96408(*)	4.57
Thalamus		R/L	10	-20	-2	96408(*)	4.33
Parahippocampal Gyrus		R	40	-24	-22	96408(*)	3.53
Superior Temporal Gyrus	22	R	48	-22	-2	96408(*)	3.35
Amygdala	34	L	-22	2	-22	16176(*)	4.59
Insula	13	L	-42	-4	0	16176(*)	4.53
Superior Temporal Gyrus	22	L	-54	0	-8	16176(*)	4.61
Cerebellum		L	-22	-52	-28	9440	4.41
Excess weight							
Somatosensory Cortex	2,3,4	L	-52	-16	20	27584(*)	5.17
Superior Temporal Gyrus	22	L	-40	-22	-12	27584(*)	4.71
Insula	13	L	-32	2	12	27584(*)	4.38
Insula	13	R	38	0	10	13744(*)	4.72
Somatosensory Cortex	3	R	58	-16	46	13744(*)	4.26
Superior Temporal Gyrus	22	R	48	10	-16	13744(*)	4.71
Dorsal ACC	24,32	R/L	-2	4	34	3504	5.03
Cerebellum		L	-24	-64	-20	4424	4.07
Group Comparisons							
Normal weight>Excess weight							
Supplementary Motor Area	6	R	8	-22	50	640	3.79
Precentral Gyrus	6	R	40	-14	48	592	3.17

BA: Brodmann area; * part of the large cluster; ACC: Anterior Cingulate Cortex.

Group differences:

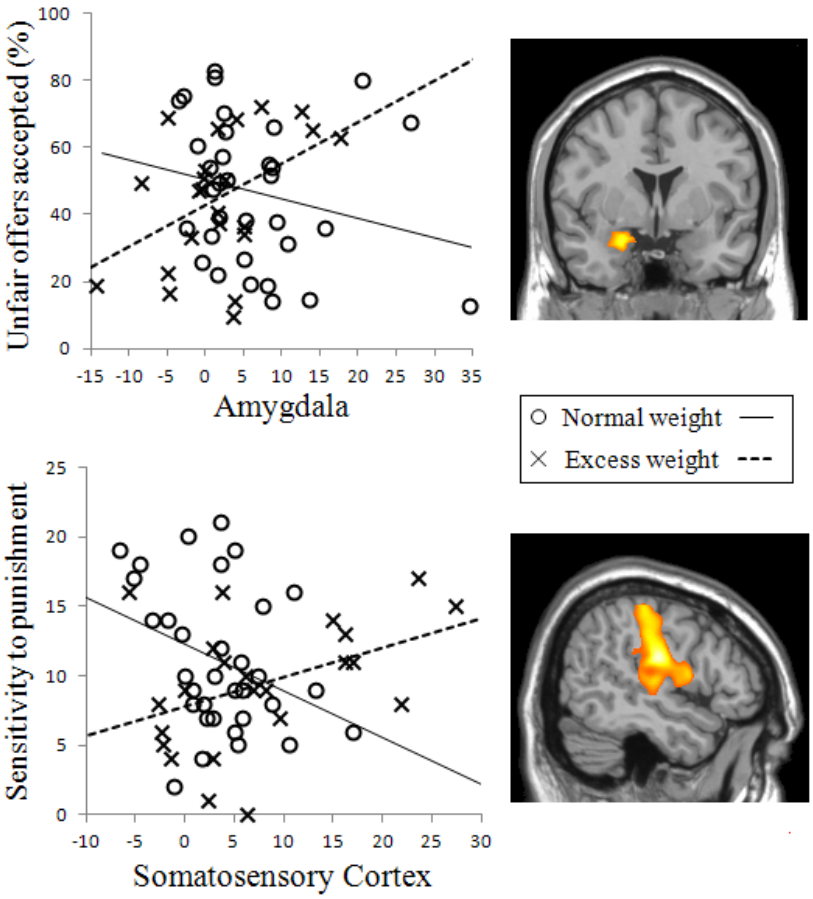
We did not observe significant differences between the groups at the selected threshold.

Correlations between brain activation patterns and behavioral decisions:

Regarding acceptance rates, the proportion of unfair offers accepted positively correlated with amygdala activation in Excess weight participants ($r = 0.448$, $p = 0.032$) whereas this correlation was negative, albeit non-significant, in the Normal weight group ($r = -0.227$, $p = 0.205$). The direct comparison between these correlations revealed a significant-group difference, with $z = 2.47$, $p = 0.013$ (Figure 6).

As for psychological traits, sensitivity to punishment positively correlated with right somatosensory cortex activation in excess weight participants ($r = 0.415$, $p = 0.049$) whereas this correlation was negative and nearly significant in the normal weight group ($r = -0.339$, $p = 0.053$). The direct comparison between these correlations revealed a significant-group difference, with $z = 2.75$, $p = 0.006$ (Figure 6). We found no significant correlations between drive for thinness or body dissatisfaction and brain activation patterns.

Figure 6: Scatterplots displaying the correlation between behavioral measures ("Unfair offers accepted" and "Sensitivity to Punishment" and brain activation patterns during the "Reject>Accept" contrast (peak activations at the amygdala and the postcentral cortex regions, respectively). The data of excess weight and normal weight participants are represented with different symbols (crosses and circles, respectively) to illustrate the different direction of the correlation as a function of group.



4. Discussion

We showed that adolescents with excess weight have reduced activation of brain regions involved in emotion and reward processing including the anterior cingulate cortex, the insula and the thalamus during social decision-making. Furthermore, we showed that deactivation of the anterior insula correlates with higher sensitivity to reward and higher maturity fears uniquely in the excess weight group, and that such deactivation accounts for an indirect relationship between maturity fears and a higher probability of accepting unfair offers. Moreover, somatosensory cortex activation during rejection of unfair offers positively correlates with sensitivity to punishment, and amygdala activation positively correlates with acceptance of unfair offers uniquely in

the excess weight group. Collectively, our findings indicate that adolescents with excess weight display blunted activation of the social decision-making circuitry, which correlates with disadvantageous traits and interpersonal decisions.

Our social decision-making task (UG) induced a reliable pattern of brain activations including the dorsal anterior cingulate cortex, the insula and thalamic/limbic regions, which is in fitting with previous evidence (Gospic et al. 2011; Sanfey et al 2003). Moreover, the activation of the anterior cingulate cortex correlated with acceptance rates in both groups, indicating goof fit between brain activation measures and behavioral decisions (Glascher et al. 2012). In this context, adolescents with excess weight exhibited significantly decreased activation of dorsal anterior cingulate cortex and thalamic regions, and concomitant deactivation of the anterior insula/frontal opercular region. The dorsal anterior cingulate and the thalamus are functionally associated with the generation of emotional responses to social stressors (Güroglu et al. 2011). The anterior insula is generally associated with perception of bodily signals and emotional awareness (Wager et al. 2009). Moreover, in the context of the UG, insula activation is specifically associated with subjective feelings of unfairness (Sanfey et al. 2003). Therefore, the decreased activation of this set of regions overly suggests decreased affective tracking of social unfairness in the excess weight group.

The central question is whether this brain activation pattern is relevant and potentially disadvantageous for the social behavior of adolescents with excess weight. Correlation analyses strongly suggest this is the case. First, insula deactivation correlated with higher acceptance rates, suggesting that reduced affective tracking of social decisions is linked to more acceptances of unfair offers. As the contribution of the affective neural circuitry is essential for adequate social functioning (Bar-On et al., 2003) this pattern is

likely to impact the real-life interpersonal decisions of obese adolescents. Moreover, the opposite pattern (positive correlations, hence more insula greater acceptance rates) has been previously demonstrated in healthy adolescents (Guroglu et al., 2011), similar to what we showed in our control group. Second, we found that insula deactivation correlated with increased maturity fears. Fears of social evaluative situations are indicative of poor social-cognitive development (Westenberg et al., 2004). Therefore, this finding is the first to demonstrate an association between poor affective tracking of social unfairness (indexed by insula deactivation) and this hindering trait of adolescent obesity. Finally, and linking the two above described relationships, we also showed that maturity fears are indirectly associated to social decision-making through blunted insula activation. Such findings demonstrate for the first time a significant association between a trait marker of eating disorder and the social decision-making behavior of excess weight adolescents conveyed by a particular pattern of brain activity. This notion agrees with developmental models that highlight the insula as a key region for the maturation of social decision-making systems during adolescence (Smith et al., 2014). At difference with maturity fears, we found no significant associations between brain activation patterns and body dissatisfaction and drive for thinness. This discrepancy is reasonable as the latter traits basically reflect the difficulties associated with physical weight gain, whereas maturity fears capture personality and interpersonal aspects of obesity (Garner, 1994). Therefore, this negative finding conceivably speaks of the specificity of the UG task as a biomarker of social disadvantage in adolescent obesity.

Moreover, insula deactivation also correlated with higher sensitivity to reward. Sensitivity to reward has been associated with higher risk-taking in social scenarios specifically during adolescence (Chein et al., 2011). Furthermore, lower insula

activations predict greater risk taking (Mohr et al., 2010) and this notion has been linked to insula-mediated sensitization of the reward system (Smith et al., 2014). More broadly, sensitivity to reward has been associated with several aspects of unhealthy eating, including binge eating patterns (Ziauddeen et al., 2012). Uncoupling of reward (i.e., wanting) from emotion (i.e., liking) processing is as well reminiscent of addictive features, in which sensitivity to rewarding stimuli increases while the hedonic quality of these stimuli decreases (Robinson and Berridge, 2003). Also in this case, the opposite pattern is typically found in healthy adolescents (Jarcho et al., 2012), consistent with what we showed in our control group. Collectively, our findings suggest that the anterior insula, which is strongly involved in the processing of highly appetizing food (Wang et al. 2004), may consequently lose control over more complex reward-related choices including social decisions.

We did not find significant group differences in brain activation as a function of type of choice (reject vs. accept). However, the relationship between behavioral responses and brain activity was again distinctive in the excess weight group. Specifically, reject-related amygdala activation correlated with greater probability of accepting unfair offers. Such finding suggests that excess weight adolescents display a paradoxically increased negative emotional reactivity in situations where they adopt a more assertive social role. Therefore, this finding suggests an abnormal role of the amygdala in directing social behavior, as greater amygdala activation is typically associated with rapid rejection of unfair offers (Gospic et al., 2011). Moreover, the pattern of somatosensory activation contingent to rejecting offers (entailing losing reward) was positively correlated with sensitivity to punishment in the excess weight group, and negatively correlated with this trait in controls. Somatosensory regions are relevant to

anticipate reinforcement outcome (Bieszczad and Weinberger, 2012), but in excess weight subjects the activation of these regions seem to reflect a trait susceptibility to reward omission or punishment. Hence, similar to those results and to the reward sensitivity-insula correlations reported above, the finding indicates that the association between reinforcement-based temperamental traits and somatosensory regions is abnormal in excess weight adolescent populations.

Our findings show that excess weight adolescents show dysfunctional engagement of brain regions involved in emotion perception and reward during social decisions. These early deficits may not only predict poor clinical prognosis (Ludwig, 2007) but also lie at the root of well-described socio-economic disadvantage in the adult obesity population, including wage penalty and hiring discrimination (Agerström and Rooth, 2011; Baum and Ford, 2004; Caliendo and Lee, 2013; Latner et al. 2012). This study has several strengths, including a large sample size, detailed medical and psychological characterization of participants, and novel use of a social decision-making paradigm in this population. Nonetheless, findings should also be assessed in the context of several limitations. First, our sample spans a 6-year adolescent period characterized by intense maturational processes, which may have impacted results. However, the psychological features addressed in the UG seem to be already optimized by the age of 9 (Güroglu et al. 2009), and analyses covaried by age showed equivalent results. Second, we used a simple version of the UG because our main interest was to raise the conflict between emotion and cognition in an interpersonal scenario. We are aware of the existence of a more specific UG literature, but the purpose of this study was not to experimentally characterize the task but to make it instrumental to understand a clinical population. Similarly, we did not detect behavioral differences between the groups in

the UG task. This is likely due to the fact that this UG task was specifically designed for fMRI experiments, seeking maximization of engagement of relevant brain circuitry, but not of potential behavioral differences. Future studies that utilize UG tasks more sensitive to behavioral profiles are warranted to reveal if our brain activation findings are mirrored by conceptually compatible behavioral group differences. Finally, future studies and longitudinal designs are warranted to address whether these deficits precede excess weight problems or arise as a consequence of weight gain or related psychosocial burden. Similarly, future studies are warranted to investigate whether these patterns can predict clinical prognosis and socio-economic disadvantage during adulthood.

5. Conclusion

We show that excess weight adolescents display impaired activation of affective brain regions during social decision-making, and that blunted activation of this circuitry accounts for the association between maturity fears and social decisions. The study yields a high translational value as the UG neural circuitry may serve as a dimensional biomarker of the risk of social disadvantage in obesity and the effectiveness of novel treatments that focus on the social burden of obesity.

IV. DISCUSIÓN GENERAL, CONCLUSIONES Y PERSPECTIVAS FUTURAS

Capítulo 7. Discusión general, conclusiones y perspectivas futuras

1. Discusión general

El estudio de los factores que han contribuido a la emergente epidemia global de la obesidad se ha convertido en uno de los principales retos del siglo XXI a nivel mundial (World Health Organization, 2014). Modelos neurocientíficos han postulado que el conocimiento de los sistemas cerebrales de recompensa y toma de decisiones puede aportar información útil para entender los procesos que conducen a la obesidad y frenar su crecimiento (Rangel, 2013). Partiendo de esta premisa, el objetivo principal de esta tesis fue investigar el funcionamiento cerebral asociado al procesamiento de distintos tipos de recompensas en personas con exceso de peso. La existencia de patrones de activación diferenciales en función del tipo de reforzador aportaría evidencia sobre la existencia de una disrupción general en el sistema de recompensa en personas con exceso de peso, que tendría un impacto más global sobre su calidad de vida. Del mismo modo consideramos interesante estudiar si las afectaciones ocurrían por igual a lo largo de todo el espectro de IMC o si eran sólo específicas de altos grados de obesidad, así como estudiar el funcionamiento de estos sistemas en adolescentes, una población con especial vulnerabilidad social y cuyos comportamientos pueden reflejarse en un aumento de la obesidad en la etapa adulta.

Nuestros resultados avalaron estas ideas. Encontramos alteraciones en la activación y en la conectividad funcional del sistema de recompensa cerebral de las personas con exceso de peso, siendo estas alteraciones específicas en función del tipo de reforzador.

En nuestro primer estudio hipotetizamos que las activaciones del sistema de recompensa cerebral durante el procesamiento de estímulos alimenticos y monetarios

mostrarían relaciones diferenciales con el índice de masa corporal, siendo lineales con la comida y cuadráticas con el dinero. Nuestros resultados confirmaron esta idea, ya que la activación de diversas regiones del sistema de recompensa cerebral (p.e., núcleo accumbens, caudado dorsal) durante el procesamiento de comida y la recepción de recompensas económicas mostró una relación lineal con el IMC. Por el contrario, la activación durante la anticipación de reforzadores monetarios y el IMC tienen una relación en forma de U invertida donde el máximo de activación, dependiendo del área estudiada, se encuentra en el rango entre el sobrepeso y valores bajos de obesidad (27-32 Kg/m^2). Además, los sujetos con sobrepeso y obesidad valoraron los alimentos apetitosos significativamente más que la comida estándar, lo que puede contribuir a sesgar sus decisiones alimentarias hacia comida más apetecible pero menos sana (Rangel, 2013). La relación lineal y positiva entre la actividad ventral y dorsal del estriado y el exceso de peso encontrada en nuestra muestra, había sido reportada en estudios anteriores (Rothemund et al., 2007, Simon et al., 2014). Estos hallazgos, concuerdan con el modelo de adicción a la comida que postula la existencia de problemas vinculados a la obesidad en el estriado ventral, ligado a incrementos en el valor asignado a la comida y el estriado dorsal relacionado con hábitos alimentarios (Tomasi & Volkow, 2013). La relación en forma de U invertida entre la activación de diversas áreas cerebrales (p.e., área suplementaria motora, corteza cingulada anterior, estriado ventral, hipocampo y amígdala) durante la anticipación de una recompensa económica y el IMC confirma los hallazgos previos en estudios sobre dopamina cerebral realizados con PET (Horstman et al., 2015) y confirman que la activación durante esta tarea es un buen indicador de la sensibilidad genérica a la recompensa (Costumero et al., 2013).

Los resultados de este primer estudio pueden tener una aplicación en el diseño de tratamientos específicos para personas con sobrepeso versus obesidad. En el caso de los primeros deberían enfocarse a reducir la hipersensibilidad general a la recompensa, mientras que en el caso de los obesos deberían buscar la estimulación del sistema de recompensa con otro tipo de reforzadores que puedan competir con la comida.

Con respecto a la conectividad funcional, el segundo estudio proponía que los adultos con exceso de peso mostrarían una disrupción en las redes cerebrales implicadas en el control de conducta y en el procesamiento de distintos tipos de recompensas.

Nuestros resultados mostraron que redes cerebrales independientes se encuentran alteradas durante el procesamiento de alimentos y dinero, involucrando principalmente regiones frontales, del estriado y del lóbulo parietal. Específicamente, los adultos con exceso de peso devaluaron subjetivamente el valor de la comida y mostraron una conectividad funcional reducida durante el procesamiento de alimentos apetitosos en comparación con alimentos estándar. Con respecto a estímulos económicos, manifestaron una mayor sensibilidad a la cantidad y una elevada conectividad funcional. Además estas disrupciones en la conectividad correlacionaron con el rendimiento durante las tareas y con los niveles de IMC y grasa. Las conexiones alteradas durante la tarea alimentaria son consistentes con literatura previa (García-García et al., 2013) e incluyen regiones frontales relacionadas con auto-regulación (Rangel, 2013), zonas del estriado relacionadas con valoración de los estímulos (Montague & Berns, 2002), áreas parietales de control atencional (Hopfinger et al., 2000) y regiones interoceptivas de la ínsula (Craig, 2009). Fundamentalmente las regiones que mostraron menor conectividad se ubican en el lóbulo frontal, una zona fundamental en las elecciones dietéticas puesto que codifica el valor relativo de los alimentos y controla el

comportamiento a largo plazo (Rangel, 2013). Además esta región juega un rol fundamental en el control cognitivo y en las funciones ejecutivas, las cuales se han encontrado consistentemente alteradas en personas obesas (Fitzpatrick et al., 2013).

El procesamiento de estímulos monetarios en adultos con exceso de peso, tanto durante su anticipación, como durante su recepción involucra a un conjunto común de conexiones. Estas redes, que se encontraron hiperconectadas en adultos obesos durante el procesamiento de estas recompensas comprenden principalmente conexiones fronto-occipitales relacionadas con procesamiento visual (Forkel et al., 2014), parieto-occipitales implicadas en orientación y mantenimiento de la atención visual (Foxe et al., 1998) y fronto-estriadas relacionadas con fallos en el control de conductas (Motzkin et al., 2014). Estas disrupciones en redes atencionales y de toma de decisiones, unida a la mayor sensibilidad a la cantidad de dinero en juego sugieren que los individuos obesos son más sensibles a señales económicas, siendo neurobiológicamente más reactivos a las ofertas de comida barata pero poco saludable, como sugiere el estudio de Bruce (2014) utilizado imágenes de marcas de comida rápida.

Los análisis de correlaciones parciales, así como la ausencia de solapado entre las redes alteradas, revelan la independencia de los procesos que se encuentran alterados ante uno y otro reforzador. Mientras que los resultados con comida parecen indicar un debilitamiento de las capacidades de autocontrol cuando se presenta delante un estimulo muy calórico, la conectividad incrementada en redes atencionales ante el dinero sugiere un sesgo atencional hacia el valor económico de comida insana y barata, relacionada por ejemplo, con ofertas de menús en cadenas de comida rápida.

Nuestro último estudio pretendía establecer los patrones cerebrales asociados a la recompensa y toma de decisiones en un contexto social. En línea con nuestra hipótesis, los adolescentes con exceso de peso evidenciaron una reducción de actividad de regiones involucradas en el procesamiento de la recompensa y emoción durante la toma de decisiones sociales. Además, la desactivación de la ínsula anterior en el grupo de exceso de peso, correlacionó con una mayor sensibilidad a la recompensa y valores de miedo a la madurez, existiendo una relación indirecta entre este rasgo y la probabilidad de aceptar ofertas injustas.

Las disminuciones de activación de los adolescentes obesos durante el procesamiento de ofertas injustas en el cíngulo anterior y el tálamo se relacionaron con problemas para generar emociones en respuesta a un estresor social (Güroglu et al., 2011) mientras que la alteración en la ínsula parece estar asociada a problemas en la percepción subjetiva de la injusticia (Sanfey et al., 2003). Estos resultados sugieren la existencia de un marcado componente emocional alterado en el procesamiento de ofertas económicas en el grupo con exceso de peso. Los análisis de correlaciones confirman esta idea, donde la tasa de ofertas injustas aceptadas, correlaciona con la desactivación de la ínsula, sugiriendo que una menor implicación emocional está relacionada con mayor aceptación de las ofertas. Esta desactivación también correlaciona con los valores de miedo a la madurez, reflejando un peor desarrollo socio-cognitivo.

Uno de los principales puntos fuertes de nuestros estudios es la metodología empleada para la selección de la muestra. Variables sociodemográficas como el sexo, la edad, los años de educación o el estatus socioeconómico se encuentran igualados entre grupos. Además, diversos trastornos metabólicos (p.e., diabetes, hipertensión, obesidad mórbida), y psicopatológicos (p.e., depresión y trastornos alimentarios como bulimia o

trastorno por atracón) fueron causas de exclusión de nuestras investigaciones, garantizando que las diferencias encontradas entre grupos se deben a la ingesta de alimentos y no a otros trastornos comorbidos.

Todos estos resultados deben entenderse en un contexto donde existen numerosas limitaciones. En primer lugar, la utilización de diferentes tareas para evocar la activación del sistema de recompensa ante cada estímulo ha impedido realizar análisis de interacción entre tipos de reforzador. Las tareas elegidas han sido utilizadas previamente en numerosos estudios para analizar la activación del sistema de recompensa pero sus diferentes características no permiten realizar comparaciones directas entre ellas. Otra posible limitación es la utilización del índice de masa corporal como variable independiente. Distintos estudios afirman que la grasa corporal está asociada con las características estructurales del cerebro (Schwartz et al., 2014), pero la limitación existente en nuestras medidas para separar grasa visceral de la grasa subcutánea y las diferencias existentes entre sexos con respecto a los porcentajes de grasa globales hacen que la utilización del índice de masa corporal sea más apropiado en este tipo de estudios donde la muestra está compuesta por participantes de ambos sexos. Finalmente la utilización de dos grupos de edad distintos también provoca que haya que ser precavidos a la hora de trasladar las conclusiones obtenidas entre los dos primeros estudios y el tercero.

2. Conclusiones

A raíz de los resultados obtenidos en los distintos estudios de esta tesis se derivan las siguientes conclusiones:

1. La activación del sistema de recompensa cerebral presenta una relación diferente con respecto al índice de masa corporal al procesar estímulos alimenticios y monetarios. Esta relación es lineal y positiva en el caso del procesamiento de alimentos y en forma de U invertida con recompensas monetarias.

2. Redes cerebrales independientes se encuentran alteradas en adultos con exceso de peso durante el procesamiento de alimentos y dinero. Específicamente presentan reducciones en conectividad funcional fronto-estriada durante el procesamiento de estímulos de comida y conectividad funcional atencional aumentada al procesar estímulos monetarios.

3. Los adultos con exceso de peso muestran alteraciones conductuales en el procesamiento de recompensas alimenticias y monetarias. Las alteraciones asociadas a recompensas alimenticias consisten en asignar menor valor a estímulos que representan comida estándar (no apetitosa). Las alteraciones asociadas a recompensas monetarias consisten en una mayor reactividad conductual (menor tiempo de reacción) asociado a estímulos más valiosos.

4. Los adolescentes con exceso de peso tienen una activación atenuada de los circuitos de toma de decisiones en un contexto de negociación económica social. Estas alteraciones correlacionan con rasgos negativos de personalidad (p.e., miedo a la madurez) y decisiones interpersonales desventajosas (p.e., aceptación de ofertas injustas).

3. Perspectivas futuras

Las conclusiones derivadas de esta tesis nos permiten generar nuevas preguntas de investigación que creemos sería interesante explorar en estudios futuros. Entre ellas podríamos destacar:

1. Confirmar si las alteraciones cerebrales encontradas durante el procesamiento de recompensas alimenticias y económicas ocurren también ante otros reforzadores naturales.

2. Profundizar en el estudio de los adultos con sobrepeso para determinar si representan un fenotipo biológicamente diferenciado de los obesos o un estado previo que puede desembocar en obesidad.

3. Comprobar, utilizando métodos de conectividad efectiva (p.e., Dynamic Causal Modelling), si las reducciones de conectividad fronto-estriada encontradas durante el procesamiento de comida se corresponden con deficiencias en los sistemas de top-down, bottom-up o de interacción entre ambos.

4. Evaluar la relación entre cada una de las redes independientes alteradas durante el procesamiento de recompensas alimenticias y económicas y sus distintas implicaciones clínicas y sociales relacionadas con la obesidad.

5. Estudios longitudinales y en población adulta pueden ayudar a confirmar la relación causal entre los déficit encontrados durante la toma de decisiones social y el exceso de peso.

V. DOCTORADO INTERNACIONAL

Capítulo 8. Summary, conclusions and future perspectives

1. Summary

The growing prevalence of obesity in modern societies has become a major global health challenge. According to the World Health Organization obesity has become a global epidemic. Recent studies posit that unhealthy habits, such as higher sedentary lifestyles, and problems to control food intake in our environments plenty of high caloric and cheap food stimuli is one of the main causes of the rising obesity problem. Currently available neuroimaging studies have shown that the processing of food stimuli evokes altered patterns of brain activity and connectivity in excess weight adults. These alterations are prominent in brain regions involved in reward processing and decision-making systems. Therefore it is crucial to investigate the functioning of the brain reward system not only when processing food, but also in relation to other types of rewards such as money and social reinforcers that could have a broader impact on excess weight peoples' quality of life.

Based in these assumptions, the main aim of this Thesis is to characterize the brain underpinnings of the processing of different types of reinforcers (i.e., food, money, social rewards) in overweight and obese adults compared to normal weight peers. To achieve this, we conducted three studies. In Study 1 we compared neural activation patterns within the brain's reward system in response to food and monetary stimuli among adults with obesity, overweight and normal weight. In Study 2 we characterized and compared functional connectivity during processing of food versus monetary rewards in excess weight versus normal weight adults. We used a novel connectivity approach based in graph theory. In Study 3 we examined patterns of brain activation during

processing of social rewards in a decision-making task. We select a special vulnerable population as excess weight adolescents.

In Study 1, we found a positive and linear relationship between BMI and brain activation during processing of food, and an inverted U-shape relationship between BMI and brain activity during monetary-processing. In Study 2, we showed specific network-level functional connectivity disruption, in excess weight adults, according to the reinforcement, particularly, a blunted functional connectivity during processing of food and an enhanced connectivity while processing monetary rewards. Finally, in study 3, we found that excess weight adolescents displayed blunted activation of the social decision-making circuitry, which correlates with disadvantageous traits and interpersonal decisions.

2. Conclusions

Based on the results from the studies reported and discussed in this thesis, we can conclude the following:

1. Brain reward system activation has a differential relation with body mass index when processing food and monetary reinforcements. This relationship is lineal and positive when processing food, and display an inverted U shape when processing monetary rewards.
2. Excess weight adults have independent brain networks disrupted while processing food and monetary reinforcements. Specifically, they have reduced fronto-striatal functional connectivity during processing of food and enhanced attentional functional connectivity while processing monetary rewards.

3. Excess weight adults show behavioral impairment during the processing of food and monetary reinforcements. The alterations associated to food reward involve lower valuation of plain food stimuli. The alterations associated to monetary rewards involve higher behavioral reactivity (less reaction time) associated to high valuable stimuli.
4. Excess weight adolescents display blunted activation of the social decision-making circuitry in a social and economic negotiation scenario. These alterations correlates with disadvantageous traits (i.e. maturity fears) and interpersonal decisions (i.e. acceptation of unfair offers).

3. Future perspectives

The results obtained in this thesis allow us to generate new research possibilities that could be tested in future studies. Among which we can highlight:

1. To determine if brain alterations linked to food and monetary rewards also apply to other natural reinforcers.
2. To establish if the reward system alterations found in overweight individuals represent a distinctive feature of this group or an "en route" state to obesity
3. To test whether fronto-striatal blunted functional connectivity during food processing are caused by deficient top-down signaling from the prefrontal cortex, by bottom-up processes or by the interaction of both systems by using effective connectivity models.
4. To examine the relationship between the neural alterations in the segregated networks associated with food and monetary rewards, and their clinical and societal outcomes relevant to obesity.

5. To conduct longitudinal designs to establish causation effects in the relationship between excess weight problems and social decision-making deficits.

GLOSARIO

Diagnostic and statistical Manual of mental Distoders (DSM): Documento publicado por la asociación estadounidense de psiquiatría que contiene la clasificación de los trastornos mentales.

Estimulación transcraneal magnética: Técnica no invasiva de estimulación de la corteza cerebral mediante pulsos magnéticos.

Exceso de peso: Según la Organización Mundial de la Salud, acumulación anormal o excesiva de grasa que puede ser perjudicial para la salud. Incluye tanto a sobrepeso como obesidad, es decir, valores de IMC superiores a 25 kg/m^2

Imagen ponderada en T1: Adquisición de resonancia magnética que se caracteriza por el tiempo que tarda la magnetización longitudinal en recuperar el 63% de su estado de equilibrio. Es el tipo de imagen más usado para estudiar la morfología del cerebro por el buen contraste que presenta entre los tejidos.

Imagen por tensor de difusión (DTI): Adquisición de resonancia magnética que es sensible a la difusión del agua a través del cerebro. Permite establecer la dirección de los axones de las neuronas que forman la materia blanca cerebral.

Índice de masa corporal (IMC): Medida antropométrica que se obtiene dividiendo el peso, medido en kilogramos entre el cuadrado de la altura, medida en metros.

Normopeso: Se consideran personas con normopeso aquellas con un valor de IMC superior a 19 kg/m^2 e inferior a 25 kg/m^2.

Obesidad: Se definen como personas obesas aquellas con un valor de IMC superior a 30 kg/m^2.

Red cerebral por defecto: Red funcional cerebral formada por las cortezas prefrontal medial y cingulada posterior, los giros angulares y la precuña. Esta red se encuentra activa "por defecto" cuando no está realizando ninguna tarea y se desactiva cuando la persona tiene alguna demanda cognitiva.

Red de saliencia: Red funcional cerebral principalmente formada por las ínsulas anteriores y la parte dorsal de la corteza cingulada anterior. Su función se ha relacionado con la integración de información sensorial, emocional y cognitiva.

Sobrepeso: Se considera sobrepeso valores de IMC superiores a 25 kg/m^2, pero inferiores a 30 kg/m^2

Teoría de grafos: Rama de las matemáticas que estudia redes de elementos interconectados.

REFERENCIAS

Acosta, M. C., Manubay, J., & Levin, F. R. (2008). Pediatric obesity: Parallels with addiction and treatment recommendations. *Harvard Review of Psychiatry*, *16*(2), 80–96. doi:10.1080/10673220802069764

Aertsen, A. M., Gerstein, G. L., Habib, M. K., & Palm, G. (1989). Dynamics of neuronal firing correlation: modulation of "effective connectivity." *Journal of Neurophysiology*, *61*(5), 900–917.

Agerström, J., & Rooth, D.O. (2011). The role of automatic obesity stereotypes in real hiring discrimination. *Journal of Applied Psychology*, *96*(4), 790–805. doi.org/10.1037/a0021594

Albayrak, Ö., Wölfle, S. M., & Hebebrand, J. (2012). Does food addiction exist? a phenomenological discussion based on the psychiatric classification of substance-related disorders and addiction. *Obesity Facts*, *5*(2), 165–179. doi.org/10.1159/000338310

Arana, F. S., Parkinson, J. A., Hinton, E., Holland, A. J., Owen, A. M., & Roberts, A. C. (2003). Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. *The Journal of Neuroscience*, *23*(29), 9632–9638.

Baarendse, P. J. J., Counotte, D. S., O'Donnell, P., & Vanderschuren, L. J. M. J. (2013). Early social experience is critical for the development of cognitive control and dopamine modulation of prefrontal cortex function. *Neuropsychopharmacology*, *38*(8), 1485–1494. doi.org/10.1038/npp.2013.47

Babbs, R. K., Sun, X., Felsted, J., Chouinard-Decorte, F., Veldhuizen, M. G., & Small, D. M. (2013). Decreased caudate response to milkshake is associated with higher body mass index and greater impulsivity. *Physiology & Behavior*, *121*, 103–111. doi:10.1016/j.physbeh.2013.03.025

Ball, K., Crawford, D., & Kenardy, J. (2004). Longitudinal relationships among overweight, life satisfaction, and aspirations in young women. *Obesity Research*, *12*(6), 1019–1030. doi:10.1038/oby.2004.125

Balodis, I. M., Kober, H., Worhunsky, P. D., White, M. A., Stevens, M. C., Pearlson, G. D., … Potenza, M. N. (2013). Monetary reward processing in obese individuals with and without binge eating disorder. *Biological Psychiatry*, *73*(9), 877–886. doi:10.1016/j.biopsych.2013.01.014

Balodis, I. M., Molina, N. D., Kober, H., Worhunsky, P. D., White, M. A., Rajita Sinha, … Potenza, M. N. (2013). Divergent neural substrates of inhibitory control in binge eating disorder relative to other manifestations of obesity. *Obesity*, *21*(2), 367–377. doi:10.1002/oby.20068

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., … Van Essen, D. C. (2013). Function in the human connectome: Task-fMRI and individual differences in behavior. *NeuroImage*, *80*, 169–189. doi:10.1016/j.neuroimage.2013.05.033

Bar-On, R., Tranel, D., Denburg, N. L., & Bechara, A. (2003). Exploring the neurological substrate of emotional and social intelligence. *Brain*, *126*(8), 1790–1800. doi.org/10.1093/brain/awg177

Batterink, L., Yokum, S., & Stice, E. (2010). Body mass correlates inversely with inhibitory control in response to food among adolescent girls: An fMRI study. *NeuroImage*, *52*(4), 1696–1703. doi:10.1016/j.neuroimage.2010.05.059

Baum, C. L., & Ford, W. F. (2004). The wage effects of obesity: a longitudinal study. *Health Economics*, *13*(9), 885–899. doi.org/10.1002/hec.881

Beaver, J. D., Lawrence, A. D., Ditzhuijzen, J. van, Davis, M. H., Woods, A., & Calder, A. J. (2006). Individual differences in reward drive predict neural responses to images

of food. *The Journal of Neuroscience*, *26*(19), 5160–5166. doi:10.1523/JNEUROSCI.0350-06.2006

Benton, D. (2010). The plausibility of sugar addiction and its role in obesity and eating disorders. *Clinical Nutrition*, *29*(3), 288–303. doi.org/10.1016/j.clnu.2009.12.001

Benton, D., & Young, H. A. (2016). A meta-analysis of the relationship between brain dopamine receptors and obesity: a matter of changes in behavior rather than food addiction? *International Journal of Obesity*, *40*(S1), S12–S21. doi:10.1038/ijo.2016.9

Berridge, K. C., Ho, C.-Y., Richard, J. M., & DiFeliceantonio, A. G. (2010). The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Research*, *1350*, 43–64. doi.org/10.1016/j.brainres.2010.04.003

Berthoud, H.-R. (2007). Interactions between the "cognitive" and "metabolic" brain in the control of food intake. *Physiology & Behavior*, *91*(5), 486–498. doi:10.1016/j.physbeh.2006.12.016

Besson, P., Dinkelacker, V., Valabregue, R., Thivard, L., Leclerc, X., Baulac, M., … Dupont, S. (2014). Structural connectivity differences in left and right temporal lobe epilepsy. *NeuroImage*, *100*, 135–144. doi:10.1016/j.neuroimage.2014.04.071

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. doi.org/10.1016/j.neuroimage.2007.04.042

Bieszczad, K. M., & Weinberger, N. M. (2012). Extinction reveals that primary sensory cortex predicts reinforcement outcome. *European Journal of Neuroscience*, *35*(4), 598–613. doi.org/10.1111/j.1460-9568.2011.07974.x

Birch, L. L., & Davison, K. K. (2001). Family environmental factors influencing the developing behavioral controls of food intake and childhood overweight. *Pediatric Clinics of North America*, *48*(4), 893–907.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537–541.

Black, W. R., Lepping, R. J., Bruce, A. S., Powell, J. N., Bruce, J. M., Martin, L. E., … Simmons, W. K. (2014). Tonic hyper-connectivity of reward neurocircuitry in obese children. *Obesity*, *22*(7), 1590–1593. doi:10.1002/oby.20741

Bobb, J. F., Schwartz, B. S., Davatzikos, C., & Caffo, B. (2014). Cross-sectional and longitudinal association of body mass index and brain volume. *Human Brain Mapping*, *35*(1). doi:10.1002/hbm.22159

Bonato, D. P., & Boland, F. J. (1983). Delay of gratification in obese children. *Addictive Behaviors*, *8*(1), 71–74. doi:10.1016/0306-4603(83)90059-X

Braet, C., Claus, L., Verbeken, S., & Vlierberghe, L. V. (2007). Impulsivity in overweight children. *European Child & Adolescent Psychiatry*, *16*(8), 473–483. doi:10.1007/s00787-007-0623-2

Bressler, S. L. (1995). Large-scale cortical networks and cognition. *Brain Research Reviews*, *20*(3), 288–304. doi.org/10.1016/0165-0173(94)00016-I

Brooks, S. J., Benedict, C., Burgos, J., Kempton, M. J., Kullberg, J., Nordenskjöld, R., … Schiöth, H. B. (2013). Late-life obesity is associated with smaller global and regional gray matter volumes: a voxel-based morphometric study. *International Journal of Obesity*, *37*(2), 230–236. doi:10.1038/ijo.2012.13

Bruce, A. S., Bruce, J. M., Black, W. R., Lepping, R. J., Henry, J. M., Cherry, J. B. C., … Savage, C. R. (2014). Branding and a child's brain: an fMRI study of neural responses to

logos. *Social Cognitive and Affective Neuroscience*, *9*(1), 118–122. doi:10.1093/scan/nss109

Bruce, A. S., Holsen, L. M., Chambers, R. J., Martin, L. E., Brooks, W. M., Zarcone, J. R., … Savage, C. R. (2010). Obese children show hyperactivation to food pictures in brain networks linked to motivation, reward and cognitive control. *International Journal of Obesity*, *34*(10), 1494–1500. doi:10.1038/ijo.2010.84

Brunello, G., & D'Hombres, B. (2007). Does body weight affect wages?: Evidence from Europe. *Economics & Human Biology*, *5*(1), 1–19. doi:10.1016/j.ehb.2006.11.002

Buckner, R. L., & Vincent, J. L. (2007). Unrest at rest: Default activity and spontaneous network correlations. *NeuroImage*, *37*(4), 1091–1096. doi:10.1016/j.neuroimage.2007.01.010

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, *10*(3), 186–198. doi:10.1038/nrn2575

Burger, K. S., & Stice, E. (2011). Variability in reward responsivity and obesity: evidence from brain imaging studies. *Current Drug Abuse Reviews*, *4*(3), 182–189.

Bustamante, J.-C., Barrós-Loscertales, A., Costumero, V., Fuentes-Claramonte, P., Rosell-Negre, P., Ventura-Campos, N., … Ávila, C. (2014). Abstinence duration modulates striatal functioning during monetary reward processing in cocaine patients. *Addiction Biology*, *19*(5), 885–894. doi.org/10.1111/adb.12041

Cajal, S. R. (1995). *Histology of the Nervous System of Man and Vertebrates.* New York: Oxford Univ. Press.

Calhoun, V. D., Adali, T., Pearlson, G. D., & Pekar, J. J. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping*, *14*(3), 140–151.

Caliendo, M., & Lee, W.-S. (2013). Fat chance! Obesity and the transition from unemployment to employment. *Economics & Human Biology*, *11*(2), 121–133. doi.org/10.1016/j.ehb.2012.02.002

Carnell, S., Benson, L., Pantazatos, S. P., Hirsch, J., & Geliebter, A. (2014). Amodal brain activation and functional connectivity in response to high-energy-density food cues in obesity. *Obesity*, *22*(11), 2370–2378. doi:10.1002/oby.20859

Carter, A., Hendrikse, J., Lee, N., Yucel, M., Verdejo-Garcia, A., Andrews, Z., & Hall, W. (2016). The neurobiology of "food addiction" and its implications for obesity treatment and policy. *Annual Review of Nutrition*, *36*(1), null. doi:10.1146/annurev-nutr-071715-050909

Chein, J., Albert, D., O'Brien, L., Uckert, K., & Steinberg, L. (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. *Developmental Science*, *14*(2), F1–F10. doi.org/10.1111/j.1467-7687.2010.01035.x

Christakou, A., Brammer, M., & Rubia, K. (2011). Maturation of limbic corticostriatal activation and connectivity associated with developmental changes in temporal discounting. *NeuroImage*, *54*(2), 1344–1354. doi:10.1016/j.neuroimage.2010.08.067

Cocores, J. A., & Gold, M. S. (2009). The Salted Food Addiction Hypothesis may explain overeating and the obesity epidemic. *Medical Hypotheses*, *73*(6), 892–899. doi.org/10.1016/j.mehy.2009.06.049

Cole, T. J., & Lobstein, T. (2012). Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatric Obesity*, *7*(4), 284–294. doi:10.1111/j.2047-6310.2012.00064.x

Comings, D. E., & Blum, K. (2000). Reward deficiency syndrome: genetic aspects of behavioral disorders. *Progress in Brain Research*, *126*, 325–341. doi:10.1016/S0079-6123(00)26022-6

Contreras-Rodríguez, O., Albein-Urios, N., Vilar-López, R., Perales, J. C., Martínez-Gonzalez, J. M., Fernández-Serrano, M. J., … Verdejo-García, A. (2016). Increased corticolimbic connectivity in cocaine dependence versus pathological gambling is associated with drug severity and emotion-related impulsivity. *Addiction Biology*, *21*(3), 709–718. doi.org/10.1111/adb.12242

Costa, L. da C. F., Silva, D. A. S., Alvarenga, M. dos S., & de Vasconcelos, F. de A. G. (2016). Association between body image dissatisfaction and obesity among schoolchildren aged 7–10 years. *Physiology & Behavior*, *160*, 6–11. doi:10.1016/j.physbeh.2016.03.022

Costumero, V., Barrós-Loscertales, A., Bustamante, J. C., Ventura-Campos, N., Fuentes, P., & Ávila, C. (2013). Reward sensitivity modulates connectivity among reward brain areas during processing of anticipatory reward cues. *European Journal of Neuroscience*, *38*(3), 2399–2407. doi:10.1111/ejn.12234

Craig, A. D. (2009). How do you feel — now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*(1), 59–70. doi:10.1038/nrn2555

Crockett, M. J., Clark, L., Tabibnia, G., Lieberman, M. D., & Robbins, T. W. (2008). Serotonin modulates behavioral reactions to unfairness. *Science*, *320*(5884), 1739–1739. doi:10.1126/science.1155577

Damoiseaux, J. S., Rombouts, S. a. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*, *103*(37), 13848–13853. doi:10.1073/pnas.0601417103

Davids, S., Lauffer, H., Thoms, K., Jagdhuhn, M., Hirschfeld, H., Domin, M., … Lotze, M. (2009). Increased dorsolateral prefrontal cortex activation in obese children during observation of food stimuli. *International Journal of Obesity*, *34*(1), 94–104. doi:10.1038/ijo.2009.193

Davis, C. (2009). Psychobiological traits in the risk profile for overeating and weight gain. *International Journal of Obesity*, *33*(S2), S49–S53. doi.org/10.1038/ijo.2009.72

Davis, C., & Fox, J. (2008). Sensitivity to reward and body mass index (BMI): Evidence for a non-linear relationship. *Appetite*, *50*(1), 43–49. doi:10.1016/j.appet.2007.05.007

Delgado-Rico, E., Soriano-Mas, C., Verdejo-Román, J., S. Río-Valle, J., & Verdejo-García, A. (2013). Decreased insular and increased midbrain activations during decision-making under risk in adolescents with excess weight. *Obesity*, *21*(8), 1662–1668. doi:10.1002/oby.20375

Deng, X.-D., Jiang, H., Ma, Y., Gao, Q., Zhang, B., Mu, B., … Liu, Y. (2015). Association between DRD2/ANKK1 TaqIA polymorphism and common illicit drug dependence: Evidence from a meta-analysis. *Human Immunology*, *76*(1), 42–51. doi:10.1016/j.humimm.2014.12.005

Dietrich, A., Federbusch, M., Grellmann, C., Villringer, A., & Horstmann, A. (2014). Body weight status, eating behavior, sensitivity to reward/punishment, and gender: relationships and interdependencies. *Eating Behavior*, *5*, 1073. doi:10.3389/fpsyg.2014.01073

Dimitropoulos, A., Tkach, J., Ho, A., & Kennedy, J. (2012). Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. *Appetite*, *58*(1), 303–312. doi:10.1016/j.appet.2011.10.014

Dubbelink, K. T. E. O., Felius, A., Verbunt, J. P. A., Dijk, B. W. van, Berendse, H. W., Stam, C. J., & Waal, H. A. D. de. (2008). Increased resting-state functional connectivity in obese adolescents; a magnetoencephalographic pilot study. *PLOS ONE*, *3*(7), e2827. doi.org/10.1371/journal.pone.0002827

Elder, K. A., & Grilo, C. M. (2007). The spanish language version of the Eating Disorder Examination Questionnaire: Comparison with the spanish language version of the eating disorder examination and test–retest reliability. *Behaviour Research and Therapy*, *45*(6), 1369–1377. doi.org/10.1016/j.brat.2006.08.012

Fagundo, A. B., Torre, R. de la, Jiménez-Murcia, S., Agüera, Z., Granero, R., Tárrega, S., … Fernández-Aranda, F. (2012). Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. *PLOS ONE*, *7*(8), e43382. doi:10.1371/journal.pone.0043382

Farooqi, I. S., Bullmore, E., Keogh, J., Gillard, J., O'Rahilly, S., & Fletcher, P. C. (2007). Leptin regulates striatal regions and human eating behavior. *Science*, *317*(5843), 1355–1355. doi:10.1126/science.1144599

Fellows, L. K., & Farah, M. J. (2005). Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cerebral Cortex*, *15*(1), 58–63. doi:10.1093/cercor/bhh108

Figlewicz, D. P., & Sipols, A. J. (2010). Energy regulatory signals and food reward. *Pharmacology Biochemistry and Behavior*, *97*(1), 15–24. doi:10.1016/j.pbb.2010.03.002

Finkelstein, E. A., Ruhm, C. J., & Kosa, K. M. (2005). Economic causes and consequences of obesity. *Annual Review of Public Health*, *26*(1), 239–257. doi:10.1146/annurev.publhealth.26.021304.144628

Fitzpatrick, S., Gilbert, S., & Serpell, L. (2013). Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? *Neuropsychology Review*, *23*(2), 138–156. doi:10.1007/s11065-013-9224-7

Flegal K. M., Graubard B. I., Williamson D. F., & Gail M. H. (2005). Excess deaths associated with underweight, overweight, and obesity. *JAMA*, *293*(15), 1861–1867. doi:10.1001/jama.293.15.1861

Flegal K. M., Kit B. K., Orpana H., & Graubard B. I. (2013). Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. *JAMA*, *309*(1), 71–82. doi:10.1001/jama.2012.113905

Fletcher, P. C., Napolitano, A., Skeggs, A., Miller, S. R., Delafont, B., Cambridge, V. C., … Bullmore, E. T. (2010). Distinct modulatory effects of satiety and sibutramine on brain responses to food images in humans: A double dissociation across hypothalamus, amygdala, and ventral striatum. *The Journal of Neuroscience*, *30*(43), 14346–14355. doi.org/10.1523/JNEUROSCI.3323-10.2010

Forkel, S. J., Thiebaut de Schotten, M., Kawadler, J. M., Dell'Acqua, F., Danek, A., & Catani, M. (2014). The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. *Cortex*, *56*, 73–84. doi:10.1016/j.cortex.2012.09.005

Fornito, A., Harrison, B. J., Zalesky, A., & Simons, J. S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proceedings of the National Academy of Sciences*, *109*(31), 12788–12793. doi.org/10.1073/pnas.1204185109

Fornito, A., Yoon, J., Zalesky, A., Bullmore, E. T., & Carter, C. S. (2011). General and specific functional connectivity disturbances in first-episode schizophrenia during

cognitive control performance. *Biological Psychiatry*, *70*(1), 64–72. doi:10.1016/j.biopsych.2011.02.019

Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Reviews Neuroscience*, *16*(3), 159–172. doi:10.1038/nrn3901

Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport*, *9*(17), 3929–3933.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–711. doi:10.1038/nrn2201

Frank, S., Lee, S., Preissl, H., Schultes, B., Birbaumer, N., & Veit, R. (2012). The obese brain athlete: self-regulation of the anterior insula in adiposity. *PLoS ONE*, *7*(8). doi:10.1371/journal.pone.0042570

Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F. A. M., Nitsche, M. A., … Boggio, P. S. (2008). Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite*, *51*(1), 34–41. doi:10.1016/j.appet.2007.09.016

Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1993). Functional connectivity: the principal-component analysis of large (pet) data sets. *Journal of Cerebral Blood Flow & Metabolism*, *13*(1), 5–14. doi:10.1038/jcbfm.1993.4

Friston, K. J., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *NeuroImage*, *19*(4), 1273–1302. doi.org/10.1016/S1053-8119(03)00202-7

Gabay, A. S., Radua, J., Kempton, M. J., & Mehta, M. A. (2014). The Ultimatum Game and the brain: A meta-analysis of neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *47*, 549–558. doi:10.1016/j.neubiorev.2014.10.014

García-García, I., Jurado, M. A., Garolera, M., Segura, B., Marqués-Iturria, I., Pueyo, R., … Junqué, C. (2013). Functional connectivity in obesity during reward processing. *NeuroImage*, *66*, 232–239. doi.org/10.1016/j.neuroimage.2012.10.035

García-García, I., Jurado, M. Á., Garolera, M., Segura, B., Sala-Llonch, R., Marqués-Iturria, I., … Junqué, C. (2013). Alterations of the salience network in obesity: A resting-state fMRI study. *Human Brain Mapping*, *34*(11), 2786–2797. doi:10.1002/hbm.22104

García-García, I., Narberhaus, A., Marqués-Iturria, I., Garolera, M., Rădoi, A., Segura, B., … Jurado, M. A. (2013). Neural responses to visual food cues: insights from functional magnetic resonance imaging. *European Eating Disorders Review*, *21*(2), 89–98. doi:10.1002/erv.2216

Garner D.M. 1994: Eating Disorders Inventory-2. Odessa, FL: Psychological Assessment Resources.

Gearhardt, A. N., Grilo, C. M., DiLeone, R. J., Brownell, K. D., & Potenza, M. N. (2011). Can food be addictive? Public health and policy implications. *Addiction*, *106*(7), 1208–1212. doi.org/10.1111/j.1360-0443.2010.03301.x

Gearhardt A. N., Yokum S., Orr P. T., Stice E., Corbin W. R., & Brownell K. D. (2011). Neural correlates of food addiction. *Archives of General Psychiatry*, *68*(8), 808–816. doi:10.1001/archgenpsychiatry.2011.32

Gee, S., Chin, D., Ackerson, L., Woo, D., & Howell, A. (2013). Prevalence of childhood and adolescent overweight and obesity from 2003 to 2010 in an integrated health care delivery system. *Journal of Obesity*, *2013*. doi.org/10.1155/2013/417907

Geier, C. F. (2013). Adolescent cognitive control and reward processing: Implications for risk taking and substance use. *Hormones and Behavior*, *64*(2), 333–342. doi:10.1016/j.yhbeh.2013.02.008

Gitelman, D. R., Penny, W. D., Ashburner, J., & Friston, K. J. (2003). Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. *NeuroImage*, *19*(1), 200–207.

Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., … Tranel, D. (2012). Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(36), 14681–14686. doi.org/10.1073/pnas.1206608109

Gonzales, M. M., Tarumi, T., Miles, S. C., Tanaka, H., Shah, F., & Haley, A. P. (2010). Insulin sensitivity as a mediator of the relationship between BMI and working memory-related brain activation. *Obesity*, *18*(11), 2131–2137. doi:10.1038/oby.2010.183

Gospic, K., Mohlin, E., Fransson, P., Petrovic, P., Johannesson, M., & Ingvar, M. (2011). Limbic justice—amygdala involvement in immediate rejection in the Ultimatum Game. *PLoS Biology*, *9*(5). doi.org/10.1371/journal.pbio.1001054

Griffiths, L. J., Wolke, D., Page, A. S., & Horwood, J. P. (2006). Obesity and bullying: different effects for boys and girls. *Archives of Disease in Childhood*, *91*(2), 121–125. doi:10.1136/adc.2005.072314

Grosshans M., Vollmert C., Vollstädt-Klein S., Tost H. T., Leber S., Bach P., … Kiefer F. (2012). Association of leptin with food cue–induced activation in human reward pathways. *Archives of General Psychiatry*, *69*(5), 529–537. doi:10.1001/archgenpsychiatry.2011.1586

Guerrieri, R., Nederkoorn, C., & Jansen, A. (2007). How impulsiveness and variety influence food intake in a sample of healthy women. *Appetite*, *48*(1), 119–122. doi:10.1016/j.appet.2006.06.004

Guerrieri, R., Nederkoorn, C., Stankiewicz, K., Alberts, H., Geschwind, N., Martijn, C., & Jansen, A. (2007). The influence of trait and induced state impulsivity on food

intake in normal-weight healthy women. *Appetite*, *49*(1), 66–73. doi:10.1016/j.appet.2006.11.008

Gunnarsdottir, T., Njardvik, U., Olafsdottir, A. S., Craighead, L. W., & Bjarnason, R. (2012). Teasing and social rejection among obese children enrolling in family-based behavioural treatment: effects on psychological adjustment and academic competencies. *International Journal of Obesity*, *36*(1), 35–44. doi.org/10.1038/ijo.2011.181

Gunstad, J., Paul, R. H., Cohen, R. A., Tate, D. F., Spitznagel, M. B., Grieve, S., & Gordon, E. (2008). Relationship between body mass index and brain volume in healthy adults. *International Journal of Neuroscience*, *118*(11), 1582–1593. doi:10.1080/00207450701392282

Guo, J., Simmons, W. K., Herscovitch, P., Martin, A., & Hall, K. D. (2014). Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. *Molecular Psychiatry*, *19*(10), 1078–1084. doi.org/10.1038/mp.2014.102

Güroğlu, B., van den Bos, W., & Crone, E. A. (2009). Fairness considerations: Increasing understanding of intentionality during adolescence. *Journal of Experimental Child Psychology*, *104*(4), 398–409. doi.org/10.1016/j.jecp.2009.07.002

Güroğlu, B., van den Bos, W., van Dijk, E., Rombouts, S. A. R. B., & Crone, E. A. (2011). Dissociable brain networks involved in development of fairness considerations: Understanding intentionality behind unfairness. *NeuroImage*, *57*(2), 634–641. doi:10.1016/j.neuroimage.2011.04.032

Haber, S. N., & Knutson, B. (2009). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, *35*(1), 4–26. doi:10.1038/npp.2009.129

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-making involves modulation of the vmpfc valuation system. *Science*, *324*(5927), 646–648. doi:10.1126/science.1168450

Hariri, A. R., Brown, S. M., Williamson, D. E., Flory, J. D., Wit, H. de, & Manuck, S. B. (2006). Preference for immediate over delayed rewards is associated with magnitude of ventral striatal activity. *The Journal of Neuroscience*, *26*(51), 13213–13217. doi:10.1523/JNEUROSCI.3446-06.2006

Harms, M. B., Zayas, V., Meltzoff, A. N., & Carlson, S. M. (2014). Stability of executive function and predictions to adaptive behavior from middle childhood to pre-adolescence. *Frontiers in Psychology*, *5*. doi.org/10.3389/fpsyg.2014.00331

Hassenstab, J. J., Sweet, L. H., Del Parigi, A., McCaffery, J. M., Haley, A. P., Demos, K. E., … Wing, R. R. (2012). Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: A preliminary MRI study. *Psychiatry Research*, *202*(1), 77–79. doi:10.1016/j.pscychresns.2011.09.008

Hebebrand, J., & Herpertz-Dahlmann, B. (2009). Psychological and psychiatric aspects of pediatric obesity. *Child and Adolescent Psychiatric Clinics of North America*, *18*(1), 49–65. doi:10.1016/j.chc.2008.08.002

Henson, R. N., & Mouchlianitis, E. (2007). Effect of spatial attention on stimulus-specific haemodynamic repetition effects. *NeuroImage*, *35*(3), 1317–1329. doi.org/10.1016/j.neuroimage.2007.01.019

Hinkle, W., Cordell, M., Leibel, R., Rosenbaum, M., & Hirsch, J. (2013). Effects of reduced weight maintenance and leptin repletion on functional connectivity of the hypothalamus in obese humans. *PLoS ONE*, *8*(3). doi:10.1371/journal.pone.0059114

Hollmann, M., Hellrung, L., Pleger, B., Schlögl, H., Kabisch, S., Stumvoll, M., … Horstmann, A. (2012). Neural correlates of the volitional regulation of the desire for food. *International Journal of Obesity*, *36*(5), 648–655. doi.org/10.1038/ijo.2011.125

Hollmann, M., Rieger, J. W., Baecke, S., Lützkendorf, R., Müller, C., Adolf, D., & Bernarding, J. (2011). Predicting decisions in human social interactions using real-time fMRI and pattern classification. *PLoS ONE*, *6*(10).doi.org/10.1371/journal.pone.0025304

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*, *3*(3), 284–291. doi:10.1038/72999

Horstmann, A., Fenske, W. K., & Hankir, M. K. (2015). Argument for a non-linear relationship between severity of human obesity and dopaminergic tone. *Obesity Reviews*, *16*(10), 821–830. doi:10.1111/obr.12303

Horvath, T. L. (2005). The hardship of obesity: a soft-wired hypothalamus. *Nature Neuroscience*, *8*(5), 561–565. doi:10.1038/nn1453

Ifland, J. R., Preuss, H. G., Marcus, M. T., Rourke, K. M., Taylor, W. C., Burau, K., … Manso, G. (2009). Refined food addiction: A classic substance use disorder. *Medical Hypotheses*, *72*(5), 518–526. doi.org/10.1016/j.mehy.2008.11.035

Jarcho, J. M., Benson, B. E., Plate, R. C., Guyer, A. E., Detloff, A. M., Pine, D. S., … Ernst, M. (2012). Developmental effects of decision-making on sensitivity to reward: An fMRI study. *Developmental Cognitive Neuroscience*, *2*(4), 437–447. doi.org/10.1016/j.dcn.2012.04.002

Jastreboff, A. M., Sinha, R., Lacadie, C., Small, D. M., Sherwin, R. S., & Potenza, M. N. (2013). Neural correlates of stress- and food cue–induced food craving in obesity association with insulin levels. *Diabetes Care*, *36*(2), 394–402. doi:10.2337/dc12-1112

Jensen, C. D., & Kirwan, C. B. (2015). Functional brain response to food images in successful adolescent weight losers compared with normal-weight and overweight controls. *Obesity*, *23*(3), 630–636. doi:10.1002/oby.21004

Ji, C.-Y., & Cooperative Study on Childhood Obesity: Working Group on Obesity in China (WGOC). (2008). The prevalence of childhood overweight/obesity and the epidemic changes in 1985–2000 for Chinese school-age children and adolescents. *Obesity Reviews*, *9*, 78–81. doi.org/10.1111/j.1467-789X.2007.00443.x

Jia, Z., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., Stevens, M. C., Pearlson, G. D., & Potenza, M. N. (2011). An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. *Biological Psychiatry*, *70*(6), 553–560. doi.org/10.1016/j.biopsych.2011.05.008

Karlsson, H. K., Tuulari, J. J., Hirvonen, J., Lepomäki, V., Parkkola, R., Hiltunen, J., … Nummenmaa, L. (2013). Obesity is associated with white matter atrophy: a combined diffusion tensor imaging and voxel-based morphometric study. *Obesity (Silver Spring, Md.)*, *21*(12), 2530–2537. doi:10.1002/oby.20386

Kenny, P. J. (2011). Reward mechanisms in obesity: new insights and future directions. *Neuron*, *69*(4), 664–679. doi.org/10.1016/j.neuron.2011.02.016

King-Casas, B., Sharp, C., Lomax-Bream, L., Lohrenz, T., Fonagy, P., & Montague, P. R. (2008). The rupture and repair of cooperation in borderline personality disorder. *Science (New York, N.Y.)*, *321*(5890), 806–810. doi.org/10.1126/science.1156902

Kishinevsky, F. I., Cox, J. E., Murdaugh, D. L., Stoeckel, L. E., Cook III, E. W., & Weller, R. E. (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite*, *58*(2), 582–592. doi:10.1016/j.appet.2011.11.029

Knoch, D., Pascual-Leone, A., Meyer, K., Treyer, V., & Fehr, E. (2006). Diminishing reciprocal fairness by disrupting the right prefrontal cortex. *Science*, *314*(5800), 829–832. doi.org/10.1126/science.1129156

Knutson, B., Fong, G., Adams, C., Varner, J., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, *12*(17), 3683–3687.

Knutson, B., Westdorp, A., Kaiser, E., & Hommer, D. (2000). FMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage*, *12*(1), 20–27. doi.org/10.1006/nimg.2000.0593

Koritzky, G., Dieterle, C., Rice, C., Jordan, K., & Bechara, A. (2014). Decision-making, sensitivity to reward and attrition in weight management. *Obesity*, *22*(8), 1904–1909. doi.org/10.1002/oby.20770

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews Neuroscience*, *6*(9), 691–702. doi:10.1038/nrn1747

Kringelbach, M. L., O'Doherty, J., Rolls, E. T., & Andrews, C. (2003). Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cerebral Cortex*, *13*(10), 1064–1071. doi:10.1093/cercor/13.10.1064

Kullmann, S., Callaghan, M. F., Heni, M., Weiskopf, N., Scheffler, K., Häring, H.-U., … Preissl, H. (2015). Specific white matter tissue microstructure changes associated with obesity. *NeuroImage*, *125*, 36–44. doi.org/10.1016/j.neuroimage.2015.10.006

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H.-U., … Preissl, H. (2012). The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. *Human Brain Mapping*, *33*(5), 1052–1061. doi:10.1002/hbm.21268

Kullmann, S., Pape, A.-A., Heni, M., Ketterer, C., Schick, F., Häring, H.-U., … Veit, R. (2013). Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults. *Cerebral Cortex*, *23*(5), 1247–1256. doi:10.1093/cercor/bhs124

Kurth, F., Levitt, J. G., Phillips, O. R., Luders, E., Woods, R. P., Mazziotta, J. C., … Narr, K. L. (2013). Relationships between gray matter, body mass index, and waist circumference in healthy adults. *Human Brain Mapping*, *34*(7), 1737–1746. doi:10.1002/hbm.22021

Latner, J. D., Ebneter, D. S., & O'Brien, K. S. (2012). Residual obesity stigma: an experimental investigation of bias against obese and lean targets differing in weight-loss history. *Obesity*, *20*(10), 2035–2038. doi.org/10.1038/oby.2012.55

Lawrence, N. S., Hinton, E. C., Parkinson, J. A., & Lawrence, A. D. (2012). Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. *NeuroImage*, *63*(1), 415–422. doi:10.1016/j.neuroimage.2012.06.070

Lips, M. A., Wijngaarden, M. A., van der Grond, J., van Buchem, M. A., de Groot, G. H., Rombouts, S. A., … Veer, I. M. (2014). Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. *The American Journal of Clinical Nutrition*, *100*(2), 524–531. doi:10.3945/ajcn.113.080671

Logan, G. D., Schachar, R. J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science*, *8*(1), 60–64. doi:10.1111/j.1467-9280.1997.tb00545.x

Ludwig, D. S. (2007). Childhood obesity--the shape of things to come. *The New England Journal of Medicine*, *357*(23), 2325–2327. doi.org/10.1056/NEJMp0706538

Lutter, M., & Nestler, E. J. (2009). Homeostatic and hedonic signals interact in the regulation of food intake. *The Journal of Nutrition*, *139*(3), 629–632. doi:10.3945/jn.108.097618

Maayan, L., Hoogendoorn, C., Sweat, V., & Convit, A. (2011). Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity*, *19*(7), 1382–1387. doi:10.1038/oby.2011.15

Margules, D. L., & Olds, J. (1962). Identical "feeding" and "rewarding" systems in the lateral hypothalamus of rats. *Science*, *135*(3501), 374–375. doi:10.1126/science.135.3501.374

Marks, B. L., Katz, L. M., Styner, M., & Smith, J. K. (2011). Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. *British Journal of Sports Medicine*, *45*(15), 1208–1215. doi.org/10.1136/bjsm.2009.068114

Marqués-Iturria, I., Pueyo, R., Garolera, M., Segura, B., Junqué, C., García-García, I., … Jurado, M. Á. (2013). Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. *Psychiatry Research: Neuroimaging*, *214*(2), 109–115. doi:10.1016/j.pscychresns.2013.06.004

Marqués-Iturria, I., Scholtens, L. H., Garolera, M., Pueyo, R., García-García, I., González-Tartiere, P., … van den Heuvel, M. P. (2015). Affected connectivity organization of the reward system structure in obesity. *NeuroImage*, *111*, 100–106. doi.org/10.1016/j.neuroimage.2015.02.012

Martin, L. E., Holsen, L. M., Chambers, R. J., Bruce, A. S., Brooks, W. M., Zarcone, J. R., … Savage, C. R. (2010). Neural mechanisms associated with food motivation in obese and healthy weight adults. *Obesity*, *18*(2), 254–260. doi:10.1038/oby.2009.220

Mayer, J., & Marshall, N. B. (1956). Specificity of gold thioglucose for ventromedial hypothalamic lesions and hyperphagia. *Nature*, *178*(4547), 1399–1400. doi.org/10.1038/1781399a0

McElroy, S. L., Kotwal, R., Malhotra, S., Nelson, E. B., Keck, P. E., & Nemeroff, C. B. (2004). Are mood disorders and obesity related? A review for the mental health professional. *The Journal of Clinical Psychiatry*, *65*(5), 634–651.

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews*, *87*(3), 873–904. doi.org/10.1152/physrev.00041.2006

Medic, N., Ziauddeen, H., Vestergaard, M. D., Henning, E., Schultz, W., Farooqi, I. S., & Fletcher, P. C. (2014). Dopamine modulates the neural representation of subjective value of food in hungry subjects. *The Journal of Neuroscience*, *34*(50), 16856–16864. doi:10.1523/JNEUROSCI.2051-14.2014

Mestre, Z. L., Melhorn, S. J., Askren, M. K., Tyagi, V., Gatenby, C., Young, L., … Schur, E. A. (2016). Effects of anxiety on caloric intake and satiety-related brain activation in women and men. *Psychosomatic Medicine*. doi:10.1097/PSY.0000000000000299

Mohr, P. N. C., Biele, G., & Heekeren, H. R. (2010). Neural processing of risk. *The Journal of Neuroscience*, *30*(19), 6613–6619. doi.org/10.1523/JNEUROSCI.0003-10.2010

Montague, P. R., & Berns, G. S. (2002). Neural economics and the biological substrates of valuation. *Neuron*, *36*(2), 265–284. doi:10.1016/S0896-6273(02)00974-1

Moreno-López, L., Soriano-Mas, C., Delgado-Rico, E., Rio-Valle, J. S., & Verdejo-García, A. (2012). Brain structural correlates of reward sensitivity and impulsivity in adolescents with normal and excess weight. *PLOS ONE*, *7*(11), e49185. doi:10.1371/journal.pone.0049185

Motzkin, J. C., Baskin-Sommers, A., Newman, J. P., Kiehl, K. A., & Koenigs, M. (2014). Neural correlates of substance abuse: Reduced functional connectivity between areas underlying reward and cognitive control. *Human Brain Mapping*, *35*(9), 4282–4292. doi.org/10.1002/hbm.22474

Mueller, K., Anwander, A., Möller, H. E., Horstmann, A., Lepsien, J., Busse, F., … Pleger, B. (2011). Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. *PLoS ONE*, *6*(4). doi.org/10.1371/journal.pone.0018544

Munafò, M. R., Matheson, I. J., & Flint, J. (2007). Association of the DRD2 gene Taq1A polymorphism and alcoholism: a meta-analysis of case–control studies and evidence of publication bias. *Molecular Psychiatry*, *12*(5), 454–461. doi:10.1038/sj.mp.4001938

Munafò, M. R., Timpson, N. J., David, S. P., Ebrahim, S., & Lawlor, D. A. (2009). Association of the DRD2 gene Taq1A polymorphism and smoking behavior: A meta-analysis and new data. *Nicotine & Tobacco Research*, *11*(1), 64–76. doi:10.1093/ntr/ntn012

Murdaugh, D. L., Cox, J. E., Cook, E. W., & Weller, R. E. (2012). fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage*, *59*(3), 2709–2721.

Muschelli, J., Nebel, M. B., Caffo, B. S., Barber, A. D., Pekar, J. J., & Mostofsky, S. H. (2014). Reduction of motion-related artifacts in resting state fMRI using aCompCor. *NeuroImage*, *96*, 22-35. doi.org/10.1016/j.neuroimage.2014.03.028

Nederkoorn, C., Jansen, E., Mulkens, S., & Jansen, A. (2007). Impulsivity predicts treatment outcome in obese children. *Behaviour Research and Therapy*, *45*(5), 1071–1075. doi:10.1016/j.brat.2006.05.009

Nederkoorn, C., Smulders, F. T. Y., Havermans, R. C., Roefs, A., & Jansen, A. (2006). Impulsivity in obese women. *Appetite*, *47*(2), 253–256. doi:10.1016/j.appet.2006.05.008

Needham, B. L., & Crosnoe, R. (2005). Overweight status and depressive symptoms during adolescence. *Journal of Adolescent Health*, *36*(1), 48–55. doi:10.1016/j.jadohealth.2003.12.015

Nestor, L., Hester, R., & Garavan, H. (2010). Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *NeuroImage*, *49*(1), 1133–1143. doi.org/10.1016/j.neuroimage.2009.07.022

Ng, J., Stice, E., Yokum, S., & Bohon, C. (2011). An fMRI study of obesity, food reward, and perceived caloric density. Does a low-fat label make food less appealing? *Appetite*, *57*(1), 65–72. doi:10.1016/j.appet.2011.03.017

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., … Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, *384*(9945), 766–781. doi:10.1016/S0140-6736(14)60460-8

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, *15*(1), 1–25. doi.org/10.1002/hbm.1058

Nummenmaa, L., Hirvonen, J., Hannukainen, J. C., Immonen, H., Lindroos, M. M., Salminen, P., & Nuutila, P. (2012). Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. *PLOS ONE*, *7*(2), e31089. doi:10.1371/journal.pone.0031089

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron*, *33*(5), 815–826. doi:10.1016/S0896-6273(02)00603-7

Ogawa, S., Menon, R. S., Tank, D. W., Kim, S. G., Merkle, H., Ellermann, J. M., & Ugurbil, K. (1993). Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophysical Journal*, *64*(3), 803–812. doi:10.1016/S0006-3495(93)81441-3

Opel, N., Redlich, R., Grotegerd, D., Dohm, K., Haupenthal, C., Heindel, W., … Dannlowski, U. (2015). Enhanced neural responsiveness to reward associated with obesity in the absence of food-related stimuli. *Human Brain Mapping*, *36*(6), 2330–2337. doi:10.1002/hbm.22773

Opel, N., Redlich, R., Grotegerd, D., Dohm, K., Heindel, W., Kugel, H., … Dannlowski, U. (2015). Obesity and major depression: Body-mass index (BMI) is associated with a severe course of disease and specific neurostructural alterations. *Psychoneuroendocrinology*, *51*, 219–226. doi:10.1016/j.psyneuen.2014.10.001

Pannacciulli, N., Del Parigi, A., Chen, K., Le, D. S. N. T., Reiman, E. M., & Tataranni, P. A. (2006). Brain abnormalities in human obesity: A voxel-based morphometric study. *NeuroImage*, *31*(4), 1419–1425. doi:10.1016/j.neuroimage.2006.01.047

Passamonti, L., Rowe, J. B., Schwarzbauer, C., Ewbank, M. P., Hagen, E. von dem, & Calder, A. J. (2009). Personality predicts the brain's response to viewing appetizing foods: the neural basis of a risk factor for overeating. *The Journal of Neuroscience*, *29*(1), 43–51. doi:10.1523/JNEUROSCI.4966-08.2009

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768–774.

Peng, D., Shi, F., Shen, T., Peng, Z., Zhang, C., Liu, X., … Shen, D. (2014). Altered brain network modules induce helplessness in major depressive disorder. *Journal of Affective Disorders*, *168*, 21–29. doi:10.1016/j.jad.2014.05.061

Plassmann, H., O'Doherty, J., & Rangel, A. (2007). Orbitofrontal cortex encodes willingness to pay in everyday economic transactions. *The Journal of Neuroscience*, *27*(37), 9984–9988. doi.org/10.1523/JNEUROSCI.2131-07.2007

Pohjalainen, T., Rinne, J. O., Någren, K., Lehikoinen, P., Anttila, K., Syvälahti, E. K., & Hietala, J. (1998). The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Molecular Psychiatry*, *3*(3), 256–260.

Puhl, R., & Brownell, K. D. (2001). Bias, discrimination, and obesity. *Obesity Research*, *9*(12), 788–805.

Puhl, R. M., & Heuer, C. A. (2009). The stigma of obesity: a review and update. *Obesity*, *17*(5), 941–964. doi.org/10.1038/oby.2008.636

Raji, C. A., Ho, A. J., Parikshak, N. N., Becker, J. T., Lopez, O. L., Kuller, L. H., … Thompson, P. M. (2010). Brain structure and obesity. *Human Brain Mapping*, *31*(3), 353–364. doi:10.1002/hbm.20870

Rangel, A. (2013). Regulation of dietary choice by the decision-making circuitry. *Nature Neuroscience*, *16*(12), 1717–1724. doi:10.1038/nn.3561

Reas, D. L., Grilo, C. M., & Masheb, R. M. (2006). Reliability of the Eating Disorder Examination-Questionnaire in patients with binge eating disorder. *Behaviour Research and Therapy*, *44*(1), 43–51. doi.org/10.1016/j.brat.2005.01.004

Reinert, K. R. S., Po'e, E. K., & Barkin, S. L. (2013). The Relationship between Executive Function and Obesity in Children and Adolescents: A Systematic Literature Review. *Journal of Obesity*, *2013*. doi:10.1155/2013/820956

Robinson, T. E., & Berridge, K. C. (2003). Addiction. *Annual Review of Psychology*, *54*, 25–53. doi.org/10.1146/annurev.psych.54.101601.145237

Rolls, E. (2008). Functions of the orbitofrontal and pregenual cingulate cortex in taste, olfaction, appetite and emotion. *Acta Physiologica Hungarica*, *95*(2), 131–164. doi:10.1556/APhysiol.95.2008.2.1

Rolls, E. T. (2011). Taste, olfactory and food texture reward processing in the brain and obesity. *International Journal of Obesity*, *35*(4), 550–561. doi.org/10.1038/ijo.2010.155

Rosenbaum, D. L., & White, K. S. (2015). The relation of anxiety, depression, and stress to binge eating behavior. *Journal of Health Psychology*, *20*(6), 887–898. doi:10.1177/1359105315580212

Rothemund, Y., Preuschhof, C., Bohner, G., Bauknecht, H.-C., Klingebiel, R., Flor, H., & Klapp, B. F. (2007). Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *NeuroImage*, *37*(2), 410–421. doi:10.1016/j.neuroimage.2007.05.008

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, *52*(3), 1059–1069. doi:10.1016/j.neuroimage.2009.10.003

Rudolf, M., Greenwood, D., Cole, T., Levine, R., Sahota, P., Walker, J., … Truscott, J. (2004). Rising obesity and expanding waistlines in schoolchildren: a cohort study. *Archives of Disease in Childhood*, *89*(3), 235–237. doi.org/10.1136/adc.2002.020552

Rydén, A., Sullivan, M., Torgerson, J. S., Karlsson, J., Lindroos, A.-K., & Taft, C. (2003). Severe obesity and personality: a comparative controlled study of personality traits. *International Journal of Obesity and Related Metabolic Disorders: Journal of*

the International Association for the Study of Obesity, *27*(12), 1534–1540. doi:10.1038/sj.ijo.0802460

Sánchez-Cruz, J.-J., Jiménez-Moleón, J. J., Fernández-Quesada, F., & Sánchez, M. J. (2013). Prevalencia de obesidad infantil y juvenil en España en 2012. *Revista Española de Cardiología*, *66*(5), 371–376. doi:10.1016/j.recesp.2012.10.016

Sanfey, A. G., Rilling, J. K., Aronson, J. A., Nystrom, L. E., & Cohen, J. D. (2003). The neural basis of economic decision-making in the Ultimatum Game. *Science*, *300*(5626), 1755–1758. doi:10.1126/science.1082976

Sardinha, L. B., Santos, D. A., Silva, A. M., Grøntved, A., Andersen, L. B., & Ekelund, U. (2016). A comparison between BMI, waist circumference, and waist-to-height ratio for identifying cardio-metabolic risk in children and adolescents. *PLOS ONE*, *11*(2), e0149351. doi:10.1371/journal.pone.0149351

Scaglioni, S., Arrizza, C., Vecchi, F., & Tedeschi, S. (2011). Determinants of children's eating behavior. *The American Journal of Clinical Nutrition*, *94*(6 Suppl), 2006S–2011S. doi:10.3945/ajcn.110.001685

Schaeffer, D. J., Krafft, C. E., Schwarz, N. F., Chi, L., Rodrigue, A. L., Pierce, J. E., … McDowell, J. E. (2014). An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. *Psychophysiology*, *51*(8), 728–733. doi.org/10.1111/psyp.12227

Schwartz, D. H., Dickie, E., Pangelinan, M. M., Leonard, G., Perron, M., Pike, G. B., … Paus, T. (2014). Adiposity is associated with structural properties of the adolescent brain. *NeuroImage*, *103*, 192–201. doi.org/10.1016/j.neuroimage.2014.09.030

Sescousse, G., Caldú, X., Segura, B., & Jean-Claude Dreher. (2013). Processing of primary and secondary rewards: A quantitative meta-analysis and review of human

functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *37*(4), 681–696. doi:10.1016/j.neubiorev.2013.02.002

Sharkey, R. J., Karama, S., & Dagher, A. (2015). Overweight is not associated with cortical thickness alterations in children. *Frontiers in Neuroscience*, *9*. doi:10.3389/fnins.2015.00024

Simon, J. J., Skunde, M., Hamze Sinno, M., Brockmeyer, T., Herpertz, S. C., Bendszus, M., … Friederich, H.-C. (2014). Impaired cross-talk between mesolimbic food reward processing and metabolic signaling predicts body mass index. *Frontiers in Behavioral Neuroscience*, *8*, 359. doi:10.3389/fnbeh.2014.00359

Simon, J. J., Skunde, M., Wu, M., Schnell, K., Herpertz, S. C., Bendszus, M., … Friederich, H.-C. (2015). Neural dissociation of food- and money-related reward processing using an abstract incentive delay task. *Social Cognitive and Affective Neuroscience*, *10*(8), 1113–1120. doi.org/10.1093/scan/nsu162

Small, D. M., Jones-Gotman, M., & Dagher, A. (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *NeuroImage*, *19*(4), 1709–1715. doi:10.1016/S1053-8119(03)00253-2

Small, D. M., Zatorre, R. J., Dagher, A., Evans, A. C., & Jones-Gotman, M. (2001). Changes in brain activity related to eating chocolate. *Brain*, *124*(9), 1720–1733. doi:10.1093/brain/124.9.1720

Smith, A. R., Steinberg, L., & Chein, J. (2014). The role of the anterior insula in adolescent decision making. *Developmental Neuroscience*, *36*(3-4), 196–209. doi.org/10.1159/000358918

Song, X.-W., Dong, Z.-Y., Long, X.-Y., Li, S.-F., Zuo, X.-N., Zhu, C.-Z., … Zang, Y.-F. (2011). REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PloS One*, *6*(9), e25031. doi.org/10.1371/journal.pone.0025031

Stanek, K. M., Grieve, S. M., Brickman, A. M., Korgaonkar, M. S., Paul, R. H., Cohen, R. A., & Gunstad, J. J. (2011). Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity*, *19*(3), 500–504. doi.org/10.1038/oby.2010.312

Stice, E., Figlewicz, D. P., Gosnell, B. A., Levine, A. S., & Pratt, W. E. (2013). The contribution of brain reward circuits to the obesity epidemic. *Neuroscience & Biobehavioral Reviews*, *37*(9, Part A), 2047–2058. doi:10.1016/j.neubiorev.2012.12.001

Stice, E., Spoor, S., Bohon, C., Veldhuizen, M., & Small, D. (2008). Relation of reward from food intake and anticipated food intake to obesity: A functional magnetic resonance imaging study. *Journal of Abnormal Psychology*, *117*(4), 924–935. doi:10.1037/a0013600

Stice, E., Yokum, S., Blum, K., & Bohon, C. (2010). Weight gain is associated with reduced striatal response to palatable food. *The Journal of Neuroscience*, *30*(39), 13105–13109. doi:10.1523/JNEUROSCI.2105-10.2010

Stice, E., Yokum, S., Bohon, C., Marti, N., & Smolen, A. (2010). Reward circuitry responsivity to food predicts future increases in body mass: Moderating effects of DRD2 and DRD4. *NeuroImage*, *50*(4), 1618–1625. doi:10.1016/j.neuroimage.2010.01.081

Stice, E., Yokum, S., & Burger, K. S. (2013). Elevated reward region responsivity predicts future substance use onset but not overweight/obesity onset. *Biological Psychiatry*, *73*(9), 869–876. doi:10.1016/j.biopsych.2012.11.019

Stice, E., Yokum, S., Burger, K. S., Epstein, L. H., & Small, D. M. (2011). Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. *The Journal of Neuroscience*, *31*(12), 4360–4366. doi:10.1523/JNEUROSCI.6604-10.2011

Stoeckel, L. E., Kim, J., Weller, R. E., Cox, J. E., Cook III, E. W., & Horwitz, B. (2009). Effective connectivity of a reward network in obese women. *Brain Research Bulletin*, *79*(6), 388–395. doi:10.1016/j.brainresbull.2009.05.016

Stoeckel, L. E., Murdaugh, D. L., Cox, J. E., Iii, E. W. C., & Weller, R. E. (2013). Greater impulsivity is associated with decreased brain activation in obese women during a delay discounting task. *Brain Imaging and Behavior*, *7*(2), 116–128. doi:10.1007/s11682-012-9201-4

Stoeckel, L. E., Weller, R. E., Cook III, E. W., Twieg, D. B., Knowlton, R. C., & Cox, J. E. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *NeuroImage*, *41*(2), 636–647. doi:10.1016/j.neuroimage.2008.02.031

Strauss R.S., & Pollack H.A. (2001). Epidemic increase in childhood overweight, 1986-1998. *JAMA*, *286*(22), 2845–2848. doi.org/10.1001/jama.286.22.2845

Strauss RS, & Pollack HA. (2003). Social marginalization of overweight children. *Archives of Pediatrics & Adolescent Medicine*, *157*(8), 746–752. doi.org/10.1001/archpedi.157.8.746

Taki, Y., Kinomura, S., Sato, K., Inoue, K., Goto, R., Okada, K., … Fukuda, H. (2008). Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity*, *16*(1), 119–124. doi:10.1038/oby.2007.4

Thamotharan, S., Lange, K., Zale, E. L., Huffhines, L., & Fields, S. (2013). The role of impulsivity in pediatric obesity and weight status: A meta-analytic review. *Clinical Psychology Review*, *33*(2), 253–262. doi:10.1016/j.cpr.2012.12.001

Thanos, P. K., Ramalhete, R. C., Michaelides, M., Piyis, Y. K., Wang, G.-J., & Volkow, N. D. (2008). Leptin receptor deficiency is associated with upregulation of cannabinoid

1 receptors in limbic brain regions. *Synapse*, *62*(9), 637–642. doi:10.1002/syn.20531

Tomasi, D., & Volkow, N. D. (2013). Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. *Critical Reviews in Biochemistry and Molecular Biology*, *48*(1), 1–19. doi:10.3109/10409238.2012.735642

Torrubia, R., Ávila, C., Moltó, J., & Caseras, X. (2001). The sensitivity to punishment and sensitivity to reward questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. *Personality and Individual Differences*, *31*(6), 837–862. doi:10.1016/S0191-8869(00)00183-5

Tregellas, J. R., Wylie, K. P., Rojas, D. C., Tanabe, J., Martin, J., Kronberg, E., … Cornier, M.-A. (2011). Altered default network activity in obesity. *Obesity*, *19*(12), 2316–2321. doi:10.1038/oby.2011.119

Tryon, M. S., Carter, C. S., DeCant, R., & Laugero, K. D. (2013). Chronic stress exposure may affect the brain's response to high calorie food cues and predispose to obesogenic eating habits. *Physiology & Behavior*, *120*, 233–242. doi:10.1016/j.physbeh.2013.08.010

van den Berg, L., Pieterse, K., Malik, J. A., Luman, M., Willems van Dijk, K., Oosterlaan, J., & Delemarre-van de Waal, H. A. (2011). Association between impulsivity, reward responsiveness and body mass index in children. *International Journal of Obesity*, *35*(10), 1301–1307. doi:10.1038/ijo.2011.116

van den Bos, W., & Güroğlu, B. (2009). The role of the ventral medial prefrontal cortex in social decision making. *The Journal of Neuroscience*, *29*(24), 7631–7632. doi:10.1523/JNEUROSCI.1821-09.2009

van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*, *20*(8), 519–534. doi:10.1016/j.euroneuro.2010.03.008

van den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*, *30*(10), 3127–3141. doi:10.1002/hbm.20737

van Jaarsveld, C. H. M., Fidler, J. A., Steptoe, A., Boniface, D., & Wardle, J. (2009). Perceived stress and weight gain in adolescence: A longitudinal analysis. *Obesity*, *17*(12), 2155–2161. doi:10.1038/oby.2009.183

van 't Wout, M., Kahn, R. S., Sanfey, A. G., & Aleman, A. (2006). Affective state and decision-making in the Ultimatum Game. *Experimental Brain Research*, *169*(4), 564–568. doi.org/10.1007/s00221-006-0346-5

Veit, R., Kullmann, S., Heni, M., Machann, J., Häring, H.-U., Fritsche, A., & Preissl, H. (2014). Reduced cortical thickness associated with visceral fat and BMI. *NeuroImage : Clinical*, *6*, 307–311. doi:10.1016/j.nicl.2014.09.013

Verbeken, S., Braet, C., Lammertyn, J., Goossens, L., & Moens, E. (2012). How is reward sensitivity related to bodyweight in children? *Appetite*, *58*(2), 478–483. doi:10.1016/j.appet.2011.11.018

Verdejo-García, A., & Bechara, A. (2009). A somatic marker theory of addiction. *Neuropharmacology*, *56, Supplement 1*, 48–62. doi:10.1016/j.neuropharm.2008.07.035

Verdejo-Garcia, A., Clark, L., Verdejo-Román, J., Albein-Urios, N., Martinez-Gonzalez, J. M., Gutierrez, B., & Soriano-Mas, C. (2015). Neural substrates of cognitive flexibility in

cocaine and gambling addictions. *The British Journal of Psychiatry*, bjp.bp.114.152223. doi:10.1192/bjp.bp.114.152223

Verdejo-García, A., Pérez-Expósito, M., Schmidt-Río-Valle, J., Fernández-Serrano, M. J., Cruz, F., Pérez-García, M., … Campoy, C. (2010). Selective alterations within executive functions in adolescents with excess weight. *Obesity*, *18*(8), 1572–1578. doi:10.1038/oby.2009.475

Verstynen, T. D., Weinstein, A., Erickson, K. I., Sheu, L. K., Marsland, A. L., & Gianaros, P. J. (2013). Competing physiological pathways link individual differences in weight and abdominal adiposity to white matter microstructure. *NeuroImage*, *79*, 129–137. doi.org/10.1016/j.neuroimage.2013.04.075

Volkow, N. D., & Baler, R. D. (2015). NOW vs LATER brain circuits: implications for obesity and addiction. *Trends in Neurosciences*, *38*(6), 345–352. doi:10.1016/j.tins.2015.04.002

Volkow, N. D., & O'Brien, C. P. (2007). Issues for DSM-V: should obesity be included as a brain disorder? *American Journal of Psychiatry*, *164*(5), 708–710. doi:10.1176/ajp.2007.164.5.708

Volkow, N. D., Wang, G.-J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: implications for obesity. *Trends in Cognitive Sciences*, *15*(1), 37–46. doi:10.1016/j.tics.2010.11.001

Volkow, N. D., Wang, G.-J., Fowler, J. S., & Telang, F. (2008). Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *363*(1507), 3191–3200. doi:10.1098/rstb.2008.0107

Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Goldstein, R. Z., Alia-Klein, N., … Pradhan, K. (2009). Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity*, *17*(1), 60–65. doi:10.1038/oby.2008.469

Volkow, N. D., Wang, G.-J., Telang, F., Fowler, J. S., Thanos, P. K., Logan, J., … Pradhan, K. (2008). Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: Possible contributing factors. *NeuroImage*, *42*(4), 1537–1543. doi:10.1016/j.neuroimage.2008.06.002

Volkow, N. D., Wang, G.-J., Tomasi, D., & Baler, R. D. (2013). Obesity and addiction: neurobiological overlaps. *Obesity Reviews*, *14*(1), 2–18. doi.org/10.1111/j.1467-789X.2012.01031.x

Volkow, N. D., Wang, G.-J., Tomasi, D., & Baler, R. D. (2013). The addictive dimensionality of obesity. *Biological Psychiatry*, *73*(9), 811–818. doi:10.1016/j.biopsych.2012.12.020

Wager, T. D., van Ast, V. A., Hughes, B. L., Davidson, M. L., Lindquist, M. A., & Ochsner, K. N. (2009). Brain mediators of cardiovascular responses to social threat, Part II: Prefrontal-subcortical pathways and relationship with anxiety. *NeuroImage*, *47*(3), 836–851. doi.org/10.1016/j.neuroimage.2009.05.044

Walther, K., Birdsill, A. C., Glisky, E. L., & Ryan, L. (2010). Structural brain differences and cognitive functioning related to body mass index in older females. *Human Brain Mapping*, *31*(7), 1052–1064. doi:10.1002/hbm.20916

Wang, G.-J., Volkow, N. D., Logan, J., Pappas, N. R., Wong, C. T., Zhu, W., … Fowler, J. S. (2001). Brain dopamine and obesity. *The Lancet*, *357*(9253), 354–357. doi:10.1016/S0140-6736(00)03643-6

Wang, G.-J., Volkow, N. D., Telang, F., Jayne, M., Ma, J., Rao, M., … Fowler, J. S. (2004). Exposure to appetitive food stimuli markedly activates the human brain. *NeuroImage*, *21*(4), 1790–1797. doi.org/10.1016/j.neuroimage.2003.11.026

Ward BD (2013) AFNI and NIFTI server at NIMH in Bethesda, MD USA. Simultaneous inference for FMRI data. Consultado Septiembre 2013 en http://afni.nimh.nih.gov/pub/dist/756 doc/manual/AlphaSim.pdf

Westenberg, P. M., Drewes, M. J., Goedhart, A. W., Siebelink, B. M., & Treffers, P. D. A. (2004). A developmental analysis of self-reported fears in late childhood through mid-adolescence: social-evaluative fears on the rise? *Journal of Child Psychology and Psychiatry*, *45*(3), 481–495. doi.org/10.1111/j.1469-7610.2004.00239.x

Weygandt, M., Mai, K., Dommes, E., Leupelt, V., Hackmack, K., Kahnt, T., … Haynes, J.-D. (2013). The role of neural impulse control mechanisms for dietary success in obesity. *NeuroImage*, *83*, 669–678. doi:10.1016/j.neuroimage.2013.07.028

Whiteside, S. P., & Lynam, D. R. (2001). The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Personality and Individual Differences*, *30*(4), 669–689. doi:10.1016/S0191-8869(00)00064-7

Wijngaarden, M. A., Veer, I. M., Rombouts, S. A. R. B., van Buchem, M. A., Willems van Dijk, K., Pijl, H., & van der Grond, J. (2015). Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. *Behavioural Brain Research*, *287*, 127–134. doi:10.1016/j.bbr.2015.03.016

Woo, C.-W., Krishnan, A., & Wager, T. D. (2014). Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. *NeuroImage*, *91*, 412–419. doi.org/10.1016/j.neuroimage.2013.12.058

World Health Organization. (1997). *Obesity: preventing and managing the global epidemic*. Geneva, Switzerland: World Health Organization

World Health Organization. (2009). *Global health risks: mortality and burden of disease attributable to selected major risks.* Geneva, Switzerland: World Health Organization.

World Health Organization. (2014). *Global status report on noncommunicable diseases 2014*. Geneva, Switzerland: World Health Organization.

Xiang, T., Lohrenz, T., & Montague, P. R. (2013). Computational substrates of norms and their violations during social exchange. *The Journal of Neuroscience*, *33*(3), 1099–1108. doi.org/10.1523/JNEUROSCI.1642-12.2013

Xu, J., Li, Y., Lin, H., Sinha, R., & Potenza, M. N. (2013). Body mass index correlates negatively with white matter integrity in the fornix and corpus callosum: a diffusion tensor imaging study. *Human Brain Mapping*, *34*(5), 1044–1052. doi.org/10.1002/hbm.21491

Yokum, S., Ng, J., & Stice, E. (2011). Attentional bias to food images associated with elevated weight and future weight gain: An fMRI Study. *Obesity (Silver Spring, Md.)*, *19*(9), 1775–1783. doi:10.1038/oby.2011.168

Yokum, S., Ng, J., & Stice, E. (2012). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. *International Journal of Obesity*, *36*(5), 656–664. doi:10.1038/ijo.2011.175

Youssef, F. F., Dookeeram, K., Basdeo, V., Francis, E., Doman, M., Mamed, D., … Legall, G. (2012). Stress alters personal moral decision making. *Psychoneuroendocrinology*, *37*(4), 491–498. doi.org/10.1016/j.psyneuen.2011.07.017

Zalesky, A., Cocchi, L., Fornito, A., Murray, M. M., & Bullmore, E. (2012). Connectivity differences in brain networks. *NeuroImage*, *60*(2), 1055–1062. doi.org/10.1016/j.neuroimage.2012.01.068

Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. *NeuroImage*, *53*(4), 1197–1207. doi.org/10.1016/j.neuroimage.2010.06.041

Zheng, H., & Berthoud, H.-R. (2007). Eating for pleasure or calories. *Current Opinion in Pharmacology*, *7*(6), 607–612. doi:10.1016/j.coph.2007.10.011

Ziauddeen, H., Farooqi, I. S., & Fletcher, P. C. (2012). Obesity and the brain: how convincing is the addiction model? *Nature Reviews Neuroscience*, *13*(4), 279–286. doi:10.1038/nrn3212

Ziauddeen, H., & Fletcher, P. C. (2013). Is food addiction a valid and useful concept? *Obesity Reviews*, *14*(1), 19–28. doi:10.1111/j.1467-789X.2012.01046.x

ANEXOS ARTÍCULOS PUBLICADOS Y EN REVISIÓN

ANEXO I

BRAIN REWARD SYSTEM'S ALTERATIONS IN RESPONSE TO FOOD AND MONETARY STIMULI IN OVERWEIGHT AND OBESE INDIVIDUALS

Juan Verdejo-Román, Raquel Vilar-López, Juan F. Navas, Carles Soriano-Mas, Antonio Verdejo-García. (Under review) Brain reward system's alterations in response to food and monetary stimuli in overweight and obese individuals. *International Journal of Obesity.*

Title Page

Short title: Food and monetary processing in overweight and obesity

Brain reward system's alterations in response to food and monetary stimuli in overweight and obese individuals

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The authors report no biomedical financial interests or potential conflicts of interests.

Abstract

Background: The brain reward system is crucial to understand obesity in modern society, as increased neural responsivity to reward can fuel the unhealthy food choices that are driving the growing obesity epidemic. We tested brain's reward system responsivity to food and monetary rewards in individuals with excessive weight (overweight and obese) versus normal weight controls, along with the relationship between this responsivity and body mass index (BMI).

Methods: The sample comprised 21 adults with obesity (BMI>30), 21 with overweight (BMI between 25 and 30) and 39 with normal weight (BMI<25). Participants underwent a functional magnetic resonance imaging (fMRI) scanner while performing two tasks that involve the processing of food (Willing to Pay) and monetary rewards (Monetary Incentive Delay). Neural activations within the brain reward system were compared across the three groups. Curve fit analyses were conducted to establish the association between BMI and brain reward system's response.

Results: Individuals with obesity had greater food-evoked responsivity in the dorsal and ventral striatum compared to overweight and normal weight groups. There was an inverted U-shape association between BMI and monetary-evoked responsivity in the ventral striatum, medial frontal cortex and amygdala; that is, individuals with BMIs between 27 and 32 had greater responsivity to monetary stimuli.

Conclusions: Obesity is associated with greater food-evoked responsivity, and overweight is associated with greater monetary-evoked responsivity in the brain's reward system. Group differences in neural response to reward suggest the need to implement different strategies to regulate excess weight in overweight versus obesity.

Introduction

Between 1980 and 2013 the prevalence of overweight and obesity has increased from 857 million to 2.1 billion people worldwide, becoming a major global health challenge.[1] Specifically, overweight and obesity are associated with increased risk of cardiovascular disease, stroke, type II diabetes and different types of cancer, being a consistent risk factor for these conditions when Body Mass Index (BMI) is above 23 kg/m^2.[1] In Western societies, cheap availability of high palatable foods is a primary driver of the growing obesity epidemic.[2] Foods rich in sugar and fat stimulate the brain reward network, bypassing the homeostatic mechanisms that control food intake, and hence fostering eating, even in the absence of energetic needs.[3-4]

Current neurobiological theories are advocating for a "food addiction model" of obesity, given overlapping neurobiological alterations between individuals with obesity and substance addictions.[5-8] Specifically, this model posits that individuals with overweight and obesity display increased responsivity of the brain's reward system to food stimuli, leading to a loss of control over food intake.[9] In spite of the growing influence of this food addiction model, overweight and obesity are heterogeneous conditions, and more neurobiological research is needed to establish if this notion is relevant across the different manifestations of excessive weight, or to particular phenotypes.[10] Currently available functional magnetic resonance imaging (fMRI) studies have shown that sensory cues of high-palatable food evoke increased neural activation in the striatum and related regions of the brain reward network in both overweight and obese individuals versus normal weight controls.[11-16] Positron Emission Tomography (PET) studies have also shown reduced striatal dopamine D2 binding potential in severely obese individuals (BMI≥40).[17] However, striatal dopamine D2 binding potential is

increased in individuals with more moderate degree of excess weight for height.[18] Altogether, PET studies suggest that overweight and obesity may have unique neural underpinnings, and it has been proposed that the association between BMI and dopaminergic/reward network activity follows an inverted U-shape curve; that is, the association is positive in overweight individuals, but negative in obese individuals.[19] This proposed model is clinically significant and needs to be formally tested. If individuals with overweight versus obesity value food and other rewards via different brain mechanisms, delineation of these mechanisms would lead to better understanding of the underlying neurobiology of these disorders and, potentially, to more specific interventions for overweight and/or obesity.

General reward sensitivity has been customarily indexed in neuroimaging studies with the Monetary Incentive Delay (MID) task.[20] In normal weight individuals, MID-evoked brain activations in the midbrain, striatum and orbitofrontal cortex have been associated with trait reward sensitivity,[20] and the food addiction model would predict a stronger involvement of these regions in people with excess weight. However, currently available studies have yielded contradictory findings. Balodis et al.[21] showed increased reward system activation during the MID task in obese individuals versus controls, although no differences were found during reward feedback. Conversely, Simon[22] did not found a significant association between BMI and MID-evoked neural activation. Therefore, existing studies have not yet clearly ascertained the association between excess weight and brain responses to monetary stimuli, or overlapping and/or unique patterns of brain activation related to monetary versus food stimuli. The latter is relevant because the low prices of highly palatable foods have contributed to increase their subjective value, and thus to food choices leading to the obesity epidemic.[23]

In this study, we aimed to compare brain activations evoked by food and monetary rewards in individuals with obesity, overweight and normal weight; and to determine the association between reward-evoked brain activations and BMI. We hypothesized that, in response to high palatable foods, excess weight participants, would display increased activation of key regions of the brain reward system, and particularly the striatum.[22] We also hypothesized that in response to monetary rewards, which is a biological index of generalized sensitivity to reward, there would be an inverted U-shape association between brain's reward system activation and BMI.[19]

Methods and Materials

Participants

Eighty-one healthy adults, aged between 25 and 45 years old were recruited for this study. They were classified in three groups on the basis of BMI: 39 Normal weights (NW); 21 Overweight (OW) and 21 Obese (OB). Participants' sociodemographic characteristics, and BMI and fat percentage data are displayed in Table 1. The inclusion criteria were defined as follows: (i) BMI falling within the intervals categorized as overweight (BMI between 25 and 30 kg/m^2), obesity (BMI over 30 kg/m^2) or normal weight (BMI between 19 and 25 kg/m^2); (ii) right-handedness. The exclusion criteria were: (i) history or current evidence of medical or psychiatric disorders that co-occur with obesity (e.g., diabetes, hypertension, binge eating, bulimia nervosa, depression) indicated with clinical assessments conducted by professional nurses and psychologists; (ii) abnormalities on Magnetic Resonance Imaging (MRI) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects).

All participants had normal or corrected-to-normal vision. They were recruited through media advertisements and received a financial compensation. The study was approved by the Ethics Committee for Research in Humans of the University of Granada (Spain) and was conducted in accordance with the Declaration of Helsinki. All participants signed written informed consent.

Experimental Procedure

Participants underwent two reward related tasks during an fMRI session. Each of these tasks involved the processing of different rewards: food and money.

To ensure that every subject knew all the food stimuli to be used in the food reward fMRI task, two weeks before scanning participants attended to a catered tasting session. During that session subjects were gathered in a room and allowed to eat 18 different foods. These products had been previously classified based in their palatability: high palatable food, including sweet and fatty food (e.g., chocolate, cheese cake, burger) and plain food (e.g., yoghurt, omelet, orange). These sessions were conducted at 6:00 pm, and each participant should taste each food.

All the fMRI sessions were conducted between one and three hours after lunch. At the beginning of this session BMI and fat percentage were obtained using a body composition analyzer TANITA BC-420 (GP Supplies Ltd., London, UK). To control the satiety level, participants rated their subjective degree of appetite on a 10-cm visual analog scale (VAS) three times along the fMRI session: prior to scan, immediately before the food-stimuli task and immediately after leaving the MRI room.

fMRI Tasks

Food reward: We used a modified version of the Willingness to pay task.[24] Participants watched each of the 18 previously tasted foods once. Each stimulus was presented in the screen for 2 seconds and after that, they had 4 seconds to answer: "How much would you pay for it?" They could choose between four prices, ranging from 20 cents to 10 euros. Each selection was followed by a variable time between 3 and 5 seconds of baseline during which a cross fixation was presented on the screen. Our main interest was to contrast group differences between high palatable and plain food trials.

Monetary reward: We used an adaptation of the Monetary Incentive Delay task,[25] based on the original task employed by Knutson.[26] At the beginning of each trial, participants were shown one of two cues (green or blue square) indicating potential winnings or no financial outcome at the end of the trial. The incentive value of each trial was signaled by means of the number of horizontal lines crossing the square (one line for 0.2€, two for 1€ and three for 5€). Each cue was presented for a fixed duration of 750msec. Subsequently, a cross-fixation was shown during a variable period of 3 to 5 sec, and after this interval participants had to perform a reaction-time task: respond to a white target star appearing for a variable length of time (150–450 ms) with a button press. Then participants received feedback (hit/miss) about the accuracy of their response for 750ms, together with the information about the amount of money won in that trial (when adequate, i.e., correct responses in reward cued trials) and their cumulative total at that point of the experiment. Finally, another fixation period (750 ms) was included before the next trial. Therefore, total trial duration ranged between 5700 and 7000 ms. Participants performed 24 trials of each type of cue yielding a total of 96 trials.

Imaging analyses explored brain activity changes during two periods, the reward-anticipatory period, which included the cue presentation, the variable waiting delay and the actual response period, and the reward-feedback period, involving the presentation

of visual feedback (hit/miss). Specifically, a linear contrast (High reward > Medium reward > Low reward > No outcome trials) was defined at the first level (within-subject) to explore brain activation during reward-anticipation, while a Win > Miss contrast was used for the reward-feedback period. Therefore, this task yields two main conditions of interest: reward anticipation (High vs. Medium vs. Low vs. No reward) and reward feedback (Win vs. Miss).

Imaging data acquisition and preprocessing

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). During task performance, three T2*-weighted echo-planar imaging (EPI) sequences were acquired according to the following parameters: 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, and a total of 21 axial slices of 4 mm with a 1 mm gap). Specifically, we collected 149 scans for the food reward task and 432 scans for the monetary reward task. 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 also 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). The functional images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks, Natick, MA, USA). Preprocessing included re-slicing to the mean image of the time series, slice timing correction, normalization, using affine and smoothly non-

linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum (FWHM) = 8 mm). Data were high-pass filtered to remove low-frequency noise (1/128 Hz) and corrected for temporal autocorrelation using an autoregressive AR model.

Outside scanner behavioral measures

Sensitivity to Reward was measured with The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ).[27] This questionnaire has demonstrated internal consistency; construct validity, and significant associations with reward and punishment relevant brain systems.[20]

Statistical analyses

Behavioral analyses:

Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We tested between-group differences in demographic, body composition and sensitivity to reward variables with one-way ANOVAs, followed by post-hoc two sample t-tests. We conducted a series of mixed-design ANOVAs to analyze putative interactions between study groups and variables of interest (i.e., fMRI tasks conditions), followed by post-hoc within- and between-group analyses.

Neuroimaging analyses:

Task regressors were convolved with the SPM8 canonical hemodynamic response function. To prevent motion artifacts, six head motion parameters were entered as

regressors of no interest in all first-level analyses. One-sample t-tests were conducted on the resulting first-level contrast images to assess across-group activations in each of the contrasts. Next, we conducted a series of three-group ANOVAs to assess between-group differences using the same first-level contrast images.

Due to the existence of an *a priori* hypothesis about changes in brain activity within the reward system, all statistical analyses were spatially restricted to such region of interest. Such mask was defined empirically according to the results obtained from a large series of previous studies assessing reward system function by means of fMRI examination. Specifically, similar to other studies,[28] we used the reward system mask provided by Neurosynth (www.neurosynth.org). This mask includes brain regions that have shown to be associated with reward processing via meta-analytic research (i.e., striatum, anterior and posterior cingulate cortices, supplementary motor area, prefrontal cortices, insula, dopaminergic midbrain, hippocampus, amygdala and intraparietal cortices). Statistical significance threshold was corrected for multiple comparisons using a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1,000 Monte Carlo simulations, using the AlphaSim algorithm as implemented in the SPM REST toolbox.[29] Input parameters included a brain mask of 51517 voxels (the reward system mask), an individual voxel threshold probability of 0.005 and a cluster connection radius of 5 mm. At 11.0 and 9.2 mm FWHM smoothness for the food and monetary task contrasts, respectively, corresponded to a minimum cluster extent (KE) of 220 and 154 voxels to satisfy a Family-wise error (FWE) corrected P value of $P_{FWE} < 0.05$.

To exclude potential confounds linked to sex differences, we replicated all contrasts of interest controlling for sex. Results were equivalent, and hence we only report results

for the non-covaried analyses. We also performed specific men vs. female analysis and did not find significant between-group differences.

To examine the association between brain activations and BMI, we conducted curve fit analyses in SPSS. The peak beta eigenvalues from each cluster of significant between-group differences was extracted and related with BMI values.

Results

Behavioral measures

Appetite and Sensitivity to Reward measurements:

We found no significant between-group differences or interactions between Group and Time for subjective measures of appetite ($F(4,146) = 0.638$, $P = 0.599$). Likewise, we did not found any significant between-group differences in sensitivity to reward scores. The relationship between BMI and sensitivity to reward scores followed a non-significant inverted U-shape curve ($R^2 = 0.040$, $P = 0.204$).

fMRI behavioral measures

Food reward task

We found a significant "Group x Food Type" interaction ($F(2,77) = 4.162$, $P = 0.019$). Paired within-group contrasts showed that OB and OW groups paid more money for high-palatable food than for plain food ($P = 0.002$ and $p < 0.001$), unlike the NW group ($P = 0.220$). Paired between-group contrasts showed that OB paid significantly less

money for plain food compared to NW ($t(58) = 2.24$, $P = 0.020$). We found no group differences for high palatable food.

Monetary reward

We found a significant "Group x Reward" interaction ($F(6,231) = 2.67$, $P = 0.030$). Within-group analyses showed a significant effect of cue type ($F(2,7) = 4,608$, $P = 0.013$), indicating that all participants made faster responses in high incentive trials. Between groups comparisons showed that OB had significant slower reaction time in neutral ($t(57) = 2.315$, $P = 0.028$) and low incentive trials ($t(57) = 2.160$, $P = 0.035$) compared to NW. Behavioral results are summarized in Table 2.

Neuroimaging

Food reward task

During high-palatable versus plain food participants significantly activated bilaterally the dorsal caudate, the nucleus accumbens, the ventral putamen, the ventral tegmental area, the intraparietal, ventromedial and dorsolateral prefrontal and anterior cingulate cortices, and the anterior insula extending to the lateral orbitofrontal gyrus (Table S1 and Figure 1).

Group comparisons showed that OB subjects displayed significantly increased activations bilaterally in the dorsal caudate and nucleus accumbens compared to both NW and OW participants. In addition, OB group had significantly increased activation in the anterior cingulate cortex compared to the NW group (Table S1 and Figure 1).

Post hoc analyses showed a linear and positive correlation between BMI and bilaterally activation in the dorsal caudate (Right: $r = 0.408$, $R^2 = 0.166$, $P < 0.001$; Left: $r = 0.299$,

R^2 = 0.089, P = 0.007), the nucleus accumbens (Right: r = 0.333, R^2 = 0.111, P = 0.003; Left: r = 0.312, R^2 = 0.097, P = 0.005) and the dorsal anterior cingulate gyrus (r = 0.351, R^2 =0.123, P = 0.002).

Monetary reward

Reward anticipation contrast

Parametric increases in reward magnitude cues were associated with higher activations in bilateral dorsal and ventral striatum, midbrain (including ventral tegmental area), thalamus, amygdala-hippocampal complex, orbitofrontal cortex, middle frontal gyrus, anterior insula, and anterior and posterior cingulate and intraparietal and cortices (Table S2, Figure 2).

Group comparisons showed that OW individuals displayed significantly increased activation in the anterior cingulate cortex/supplementary motor area in comparison with both OB and NW groups. Likewise, OW individuals (but not OB individuals) showed a significantly increased activation in the ventral tegmental area, the ventral putamen, the lateral orbitofrontal cortex and the hippocampus-amygdala complex in comparison with NW participants (Table S2, Figure 2).

Curve fit analyses of the association between BMI and peak activations from the above analyses showed inverted-U associations for the supplementary motor area (R^2 = 0.240, P < 0.001), dorsal anterior cingulate (R^2 = 0.144, P = 0.003), ventral tegmental area (R^2 = 0.103, P = 0.016), ventral putamen (right: R^2 = 0.137, P = 0.004; left: R^2 = 0.079, P = 0.043), hippocampus (R^2 = 0.135, P = 0.004) and amygdala (R^2 = 0.115, P = 0.009). Post-hoc analyses showed that the peaks of the inverted U ranged between 27 and 32 Kg/m^2.

Reward feedback contrast

In win versus miss trials participants significantly activated the bilateral ventral and dorsal striatum, the amygdala-hippocampal complex, the orbitofrontal cortex, the middle frontal gyrus, the posterior cingulate, and the intraparietal cortices. Miss compared to win trials evoked activations including the anterior insula, the dorsal anterior cingulate cortex and the supplementary motor area. (Table S3, Figure 3).

Group comparisons in Win versus Miss trials showed that OB individuals compared to NW had increased activation in the rostral-ventral pons. Likewise, OB individuals compared to OW had increased activation in the nucleus accumbens. Curve fit analyses showed a linear and positive association between nucleus accumbens and pons activations and BMI scores ($r = 0.363$, $R^2 = 0.132$, $P = 0.001$, $r = 0.276$, $R^2 = 0.076$, $P = 0.014$). (Table S3, Figure 3).

Discussion

We found that individuals with obesity and overweight have unique patterns of brain activation in response to food and monetary rewards. Specifically, individuals with obesity display enhanced food-evoked ventral and dorsal striatal activations compared to individuals with overweight and normal weight. Conversely, individuals with overweight display increased monetary-reward anticipation activations in widespread regions across the brain reward network. Monetary reward feedback, however, evoked greater responses in the rostral-ventral pons and nucleus accumbens in obese individuals versus normal weight and overweight subjects, respectively. Food and monetary-feedback evoked neural activations showed a linear positive relationship with BMI,

whereas monetary-reward-anticipation evoked neural activations showed an inverted U-shape association with BMI.

The increased responsivity of the ventral and dorsal striatum to high-palatable food in obese individuals is consistent with previous fMRI studies showing increased striatal activation in response to food cues.[11,30] Critically, we show that these alterations are specific to individuals with obesity (relative to overweight), and therefore they may reflect severity related neuroadaptations. This notion is consistent with food addiction models of obesity, which propose that this disorder is associated with ventral striatal neuroadaptations leading to incentive sensitization of food, and dorsal striatal neuroadaptations leading to food-related habits.[31] Our findings also extend available evidence by showing alterations in a food choice task, with greater ecological validity than passive observation of food cues.[13] In fact, imaging findings were paralleled by behavioral results, which show that obese individuals assign less value to standard food, which may bias their food choices towards highly palatable unhealthy food.[23]

The increased responsivity of the VTA/striatum, amygdala, orbitofrontal cortex, and medial prefrontal cortex in overweight individuals to anticipation of monetary rewards, and the inverted U-shaped relationship between activation of these regions and BMI is consistent with findings of dopamine-PET studies.[19] Indeed, brain activation in the MID task is regarded as a biological index of general sensitivity of the brain reward system.[20] Our findings clearly indicate that brain response to monetary-reward anticipation is increased in individuals with overweight, and comparatively decreased in individuals with obesity. This finding is relevant, as it indicates that strategies to prevent overweight might need to focus on downplaying general hyper-reactivity of the brain reward system, whereas strategies to prevent obesity might need to stimulate the brain reward system's responsivity to alternative reinforcers that can compete with food. It

remains to be determined if overweight-specific reward system hyper-reactivity represents a different biological phenotype, or an "en-route" state leading to obesity. In any case, our results have theoretical implications for the understanding and prevention of overweight versus obesity.

The increased responsivity of the nucleus accumbens to monetary reward feedback in obese individuals is also consistent with the incentive sensitization model, although in this case with the "liking" or hedonic aspects of reward (and not the "wanting" or anticipation aspects).[32] The nucleus accumbens is the key "liking" hotspot of the brain, which is involved among other functions in amplifying the taste of food.[33] Likewise, our finding is similar to previous results in cocaine dependent users, which have greater activation of the nucleus accumbens during feedback processing in the MID task.[34,35] Therefore, our findings indicate that obese individuals have similar alterations in reward feedback processing to those observed among addiction populations.

This study has important strengths. The groups were well matched in key sociodemographic characteristics, such as age, years of education and socioeconomic status. We also applied strict eligibility criteria, which ruled out the presence of obesity related comorbid conditions, including medical comorbidities (i.e., diabetes, hypertension) and mental health problems (i.e., depression or eating disorders, such as binge eating or bulimia nervosa). We also maximized the ecological validity of assessments by pre-exposing participants to the food products of the neuroimaging task in a pre-scanner buffet session. Nevertheless, our findings also need to be understood in the context of some limitations. First, we used different tasks to assess food-related reward (Willingness to Pay) and monetary reward (Monetary Incentive Delay), and therefore we could not analyze interaction effects of food and monetary rewards on the brain reward system. Nonetheless, both tasks are well-validated measures of reward

processing in relation to food and money stimuli. Moreover, the number of participants in each group was unequal: Obese and overweight groups were smaller than the normal weight group. We addressed this limitation by performing post-hoc tests of homogeneity of variance for all significant findings, which showed non-significant results (i.e., homogenous variances across groups) in all cases. Another potential limitation is the use of BMI as the main independent variable. Recent evidence has shown that measures of body fat, and particularly visceral fat, are more sensitive to brain health specifically among adolescents.[36] We chose BMI over body fat because our measure of fat (bioelectrical impedance) does not allow reliable estimations of visceral versus subcutaneous fat, and BMI was more adequate than total body fat to classify adult participants of both sexes. Furthermore, BMI is regarded as a reliable index of weight-to-height ratio and is the key indicator of overweight and obesity in population-based studies.[1] An additional limitation is the non-significant curvilinear relationship between BMI and the behavioral measure of sensitivity to reward (SPSRQ). This negative finding can be explained by methodological differences between self-report and biological (neuroimaging) measures –the latter more objective and sensitive, and/or by the strict inclusion/exclusion criteria, which resulted in a narrow BMI range. This relationship has been previously demonstrated in a behavioral study with a broader BMI range (17 to 51 kg/m^2) relative to ours (19 to 38 kg/m^2).[37] Finally, we analyzed neuroimaging activations within discrete regions of the brain reward system, although these regions are known to be part of an integrated network. Therefore, future studies performing functional connectivity assessments of the reward system during food and monetary reward processing will probably be a relevant add-on to present findings.

In conclusion, our results support the food addiction model and previous evidence showing an increased food-cue reactivity in striatal areas and a greater subjective value

of high palatable foods in excess weight adults. Conversely, a different pattern of activation was found during monetary reward anticipation, with an inverted U-shape relationship between brain reward system activation and BMI. These reinforcement-dependent differential processing should be confirmed using other natural reinforces, and further studies in overweight populations should also investigate whether overweight-specific reward system alterations represents a distinctive feature of this group or an "en route" state to obesity.

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References

1 Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet* 2014; **384**: 766–781.

2 Finkelstein EA, Ruhm CJ, Kosa KM. Economic Causes and Consequences of Obesity. *Ann Rev Pub Health* 2005; **26**: 239–257.

3 Volkow ND, Wang G-J, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* 2011; **15**: 37–46.

4 Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE. The contribution of brain reward circuits to the obesity epidemic. *Neurosci Biobehav Rev* 2013; **37**: 2047–2058.

5 Volkow ND, O'Brien CP. Issues for DSM-V: Should Obesity Be Included as a Brain Disorder? *Am J Psych* 2007; **164**: 708–710.

6 Burger KS, Stice E. Variability in Reward Responsivity and Obesity: Evidence from Brain Imaging Studies. *Curr Drug Abuse Rev* 2011; **4**: 182–189.

7 Kenny PJ. Reward Mechanisms in Obesity: New Insights and Future Directions. *Neuron* 2011; **69**: 664–679.

8 Volkow ND, Wang G-J, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. *Obes Rev* 2013; **14**: 2–18.

9 Volkow ND, Wang G-J, Tomasi D, Baler RD. The Addictive Dimensionality of Obesity. *Biol Psych* 2013; **73**: 811–818.

10 Carter A, Hendrikse J, Lee N, Yucel M, Verdejo-Garcia A, Andrews Z *et al*. The Neurobiology of "Food Addiction" and Its Implications for Obesity Treatment and Policy. *Ann Rev Nutr* 2016; **36**: (in press).

11 Rothemund Y, Preuschhof C, Bohner G, Bauknecht H-C, Klingebiel R, Flor H *et al.* Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. *NeuroImage* 2007; **37**: 410–421.

12 Stoeckel LE, Weller RE, Cook III EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *NeuroImage* 2008; **41**: 636–647.

13 Fletcher PC, Napolitano A, Skeggs A, Miller SR, Delafont B, Cambridge VC *et al.* Distinct Modulatory Effects of Satiety and Sibutramine on Brain Responses to Food Images in Humans: A Double Dissociation across Hypothalamus, Amygdala, and Ventral Striatum. *J Neurosci* 2010; **30**: 14346–14355.

14 Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR *et al.* Neural Mechanisms Associated With Food Motivation in Obese and Healthy Weight Adults. *Obesity* 2010; **18**: 254–260.

15 Jastreboff AM, Sinha R, Lacadie C, Small DM, Sherwin RS, Potenza MN. Neural Correlates of Stress- and Food Cue–Induced Food Craving in Obesity Association with insulin levels. *Diab Care* 2013; **36**: 394–402.

16 Carnell S, Benson L, Pantazatos SP, Hirsch J, Geliebter A. Amodal brain activation and functional connectivity in response to high-energy-density food cues in obesity. *Obesity* 2014; **22**: 2370–2378.

17 Wang G-J, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W *et al.* Brain dopamine and obesity. *The Lancet* 2001; **357**: 354–357.

18 Guo J, Simons WK, Herscovitch P, Martin A, Hall KD. Striatal dopamine D2-like receptor correlation patterns with human obesity and opportunistic eating behavior. *Mol Psych* 2014; **19**: 1078–1084.

19 Horstman A, Fenkse WK, Hankir MK. Argument for a non-linear relationship between severity of human obesity and dopaminergic tone. *Obesity Rev* 2015; **16**: 821–830.

20 Costumero V, Barrós-Loscertales A, Bustamante JC, Ventura-Campos N, Fuentes P, Ávila C. Reward sensitivity modulates connectivity among reward brain areas during processing of anticipatory reward cues. *Eur J Neurosci* 2013; **38**: 2399–2407.

21 Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD *et al.* Monetary Reward Processing in Obese Individuals With and Without Binge Eating Disorder. *Biol Psych* 2013; **73**: 877–886.

22 Simon JJ, Skunde M, Wu M, Schnell K, Herpertz SC, Bendszus M *et al.* Neural dissociation of food- and money-related reward processing using an abstract incentive delay task. *Soc Cogn Affect Neurosci* 2015; **10**: 1113–1120.

23 Rangel A. Regulation of dietary choice by the decision-making circuitry. *Nat Neurosci* 2013; **16**: 1717–1724.

24 Plassmann H, O'Doherty J, Rangel A. Orbitofrontal Cortex Encodes Willingness to Pay in Everyday Economic Transactions. *J Neurosci* 2007; **27**: 9984–9988.

25 Nestor L, Hester R, Garavan H. Increased ventral striatal BOLD activity during non-drug reward anticipation in cannabis users. *NeuroImage* 2010; **49**: 1133–1143.

26 Knutson B 1, Fong G, Adams C, Varner J, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 2001; **12**: 3683–3687.

27 Torrubia R, Ávila C, Moltó J, Caseras X. The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. *Pers Indiv Diff* 2001; **31**: 837–862.

28 Contreras-Rodríguez O, Albein-Urios N, Vilar-López R, Perales JC, Martínez-Gonzalez JM, Fernández-Serrano MJ *et al.* Increased corticolimbic connectivity in cocaine dependence versus pathological gambling is associated with drug severity and emotion-related impulsivity. *Addict Biol* 2015; e-pub ahead of print 29 March 2015; doi:10.1111/adb.12242

29 Song X-W, Dong Z-Y, Long X-Y, Li S-F, Zuo X-N, Zhu C-Z *et al.* REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS ONE* 2011; **6**: e25031.

30 Simon JJ, Skunde M, Hamze Sinno M, Brockmeyer T, Herpertz SC, Bendszus M *et al.* Impaired cross-talk between mesolimbic food reward processing and metabolic signaling predicts body mass index. *Front Behav Neurosci* 2014; **8**: 359.

31 Tomasi D, Volkow ND. Striatocortical pathway dysfunction in addiction and obesity: differences and similarities. *Crit Rev Biochem Mol Biol* 2013; **48**: 1–19.

32 Robinson TE, Berridge KC. Addiction. *Ann Rev Psychol* 2003; **54**: 25–53.

33 Berridge KC, Ho C-Y, Richard JM, DiFeliceantonio AG. The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Res* 2010; **1350**: 43–64.

34 Jia Z, Worhunsky PD, Carroll KM, Rounsaville BJ, Stevens MC, Pearlson GD *et al.* An Initial Study of Neural Responses to Monetary Incentives as Related to Treatment Outcome in Cocaine Dependence. *Biol Psych* 2011; **70**: 553–560.

35 Bustamante J-C, Barrós-Loscertales A, Costumero V, Fuentes-Claramonte P, Rosell-Negre P, Ventura-Campos N *et al.* Abstinence duration modulates striatal functioning during monetary reward processing in cocaine patients. *Addict Biol* 2014; **19**: 885–894.

36 Schwartz DH, Dickie E, Pangelinan MM, Leonard G, Perron M, Pike GB, Richer L, Veillette S, Pausova Z, Paus T. Adiposity is associated with structural properties of the adolescent brain. *NeuroImage* 2014; **103**:192-201.

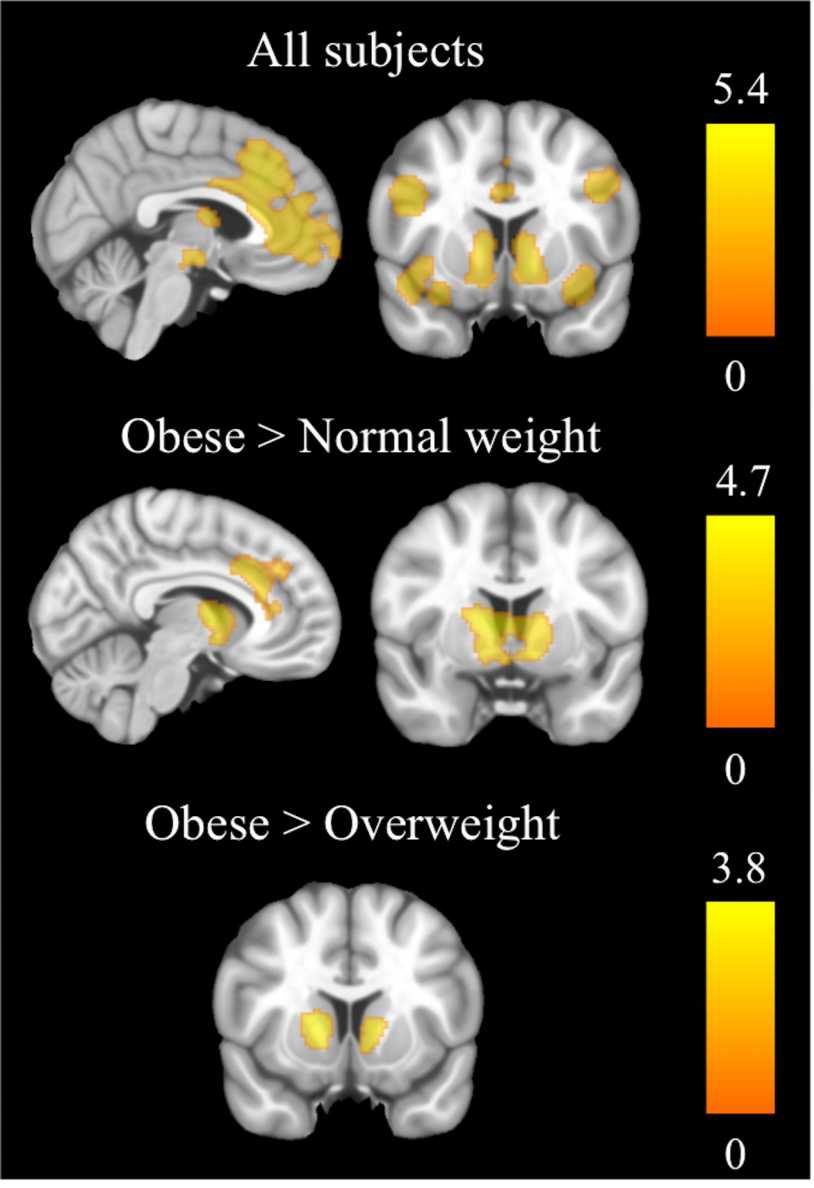
37 Davis C, Fox J. Sensitivity to reward and body mass index (BMI): evidence for a non-linear relationship. *Appetite* 2008; **50**: 43-49.

Figure Captions

Figure 1: Left panel: Brain evoked activation and between-group differences during the food reward task. Right hemisphere is displayed on the right. The color bar indicates t-value. Right panel: Scatter plots showing a linear relationship between BMI and the peak activations from regions showing significant between-group differences.

Figure 2: Left panel: Brain evoked activation and between-group differences during monetary anticipation contrast. Right hemisphere is displayed on the right. The color bar indicates t-value. Right panel: Scatter plots showing a quadratic relationship (inverted U-shape) between BMI and the peak activations from regions showing significant between-group differences.

Figure 3: Left panel: Brain evoked activation and between-group differences during monetary feedback contrast. Right hemisphere is displayed on the right. The color bar indicates t-value (hot colors for the win vs. miss contrast and cold colors for the miss vs. win contrast). Right panel: Scatter plots showing a linear relationship between BMI and the peak activations from regions showing significant between-group differences.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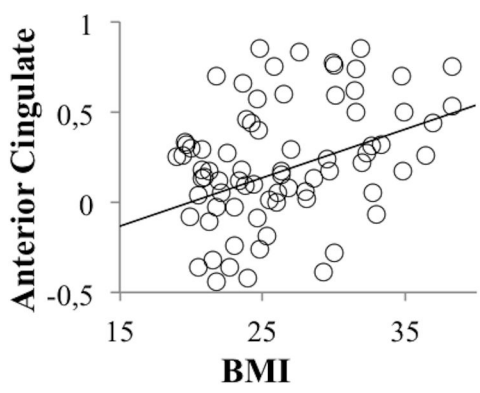
Obese > Normal weight
4.7
0
Obese > Overweight
3.8
0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0
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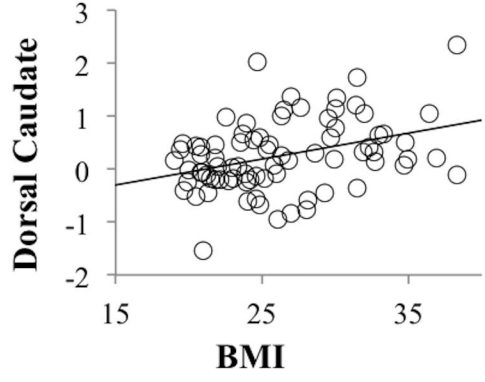
15
25
35
BMI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0
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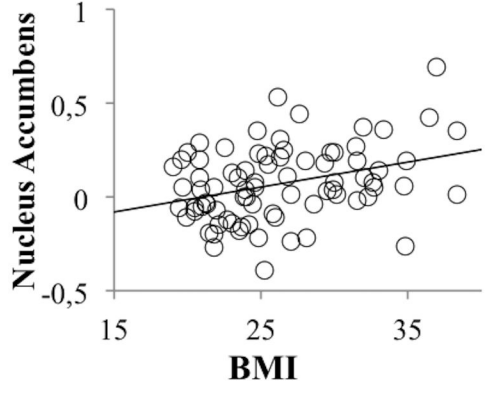
15
25
35
BMI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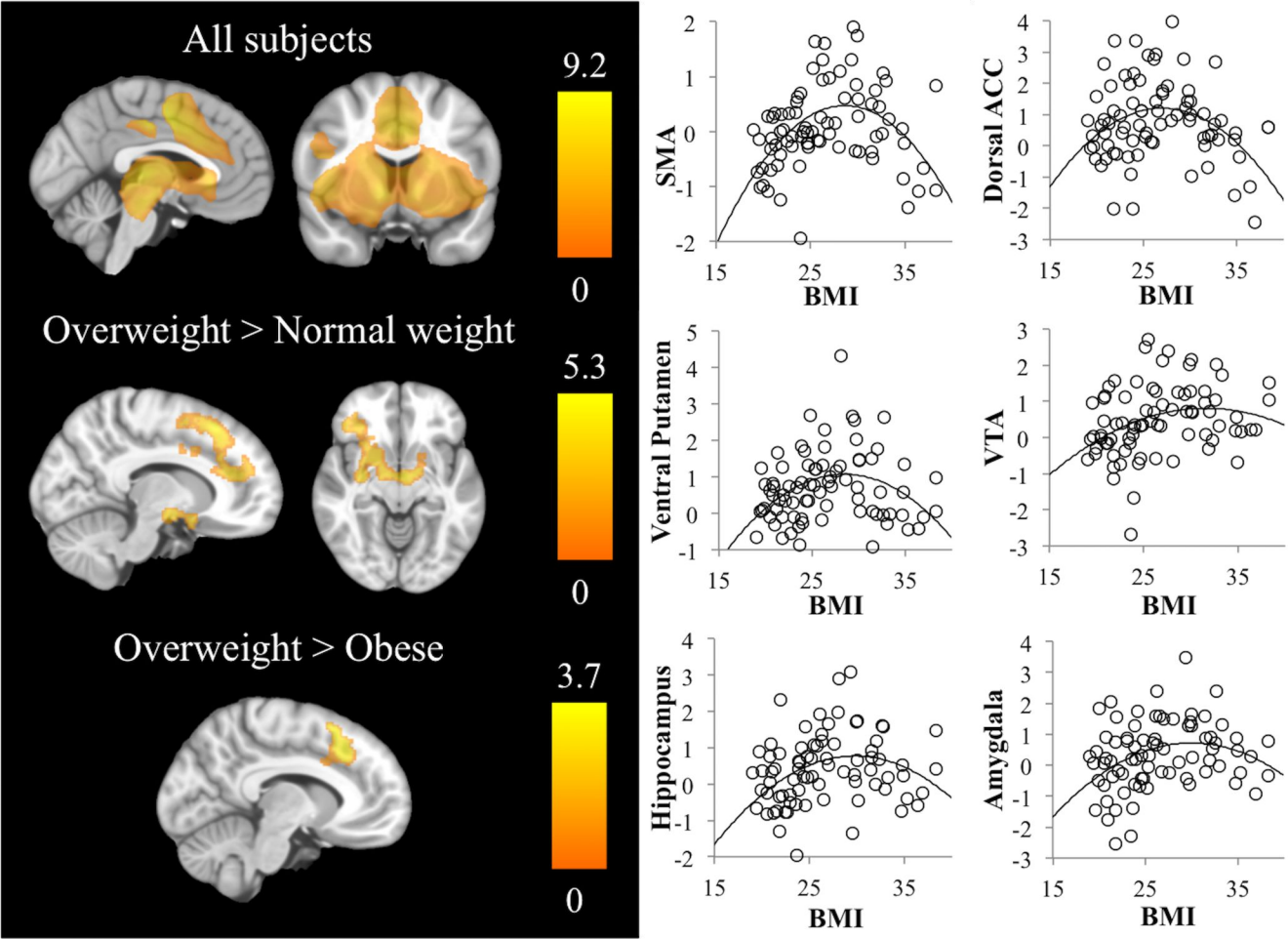
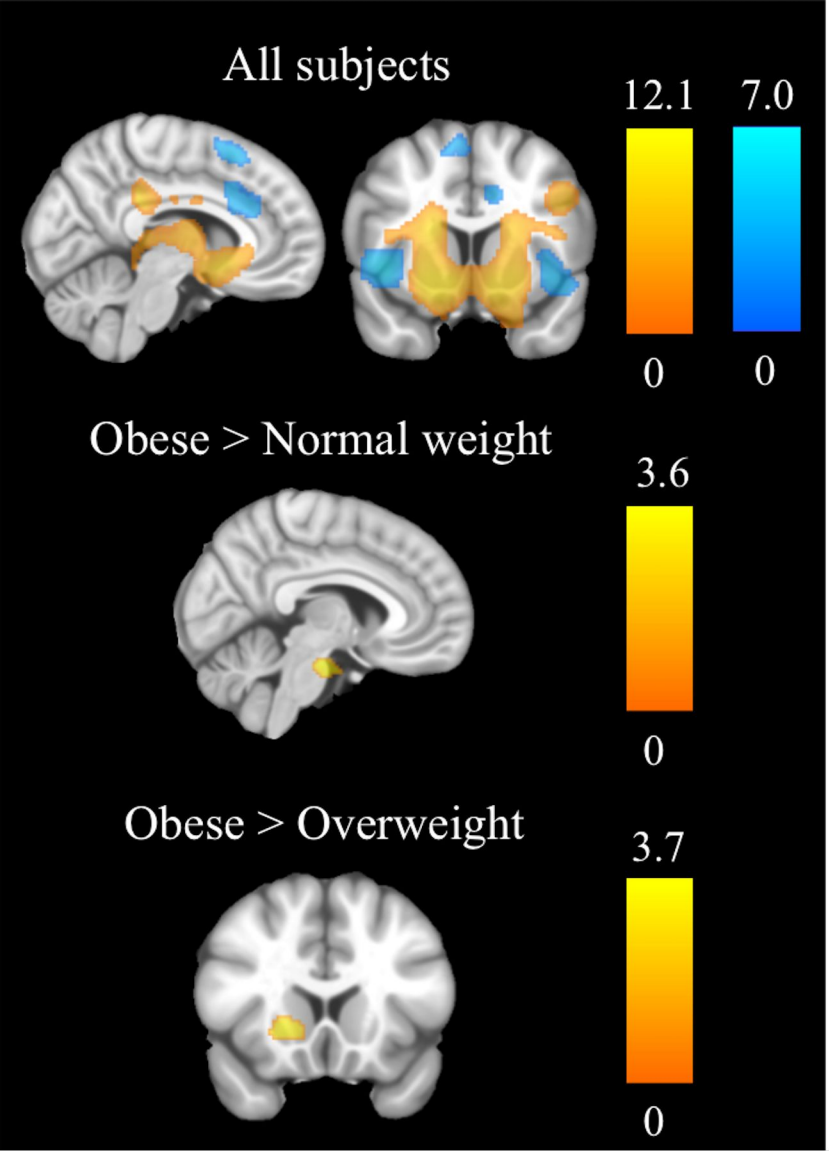
0
-0,5
15
25
35
BMI


All subjects
9.2
0
Overweight > Normal weight
5.3
0
Overweight > Obese
3.7
0
SMA
Dorsal ACC
Ventral Putamen
VTA
Hippocampus
Amygdala
BMI


All subjects
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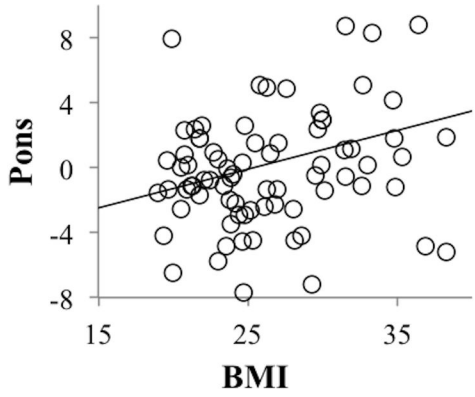
0
Obese > Normal weight
3.6
0
Obese > Overweight
3.7
0


Pons
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4
0
-4
-8
15
25
35
BMI

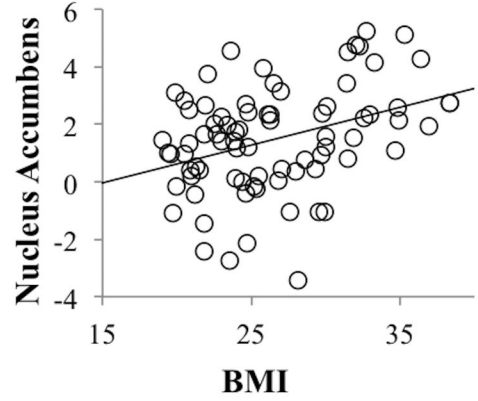
Nucleus Accumbens
6
4
2
0
-2
-4
15
25
35
BMI

Table 1: Sociodemographic characteristics and body composition by group.

No	rmal weight (n=39) Mean (SD)	Overweight (n=21) Mean (SD)	Obese (n=21) Mean (SD)	P-value
Age	33.08 (6.73)	35.00 (6.31)	32.19 (5.81)	0.345
Sex (male/female)	18 / 21	10 / 11	10 / 11	0.992
Years of education	18.18 (3.75)	17.86 (3.58)	17.14 (3.75)	0.599
Monthly income				
<600€ 2	0.5%	9.5%	10.0%	
601-1000€ 10.3	%	9.5%	15.0%	
1001-1500€ 2	0.5%	28.6%	25.0%	0.650
1501-2000€ 1	7.9%	14.3%	15.0%	
2001-2499€ 1	0.3%	9.5%	30.0%	
>2500€ 2	0.5%	28.6%	5%	
BMI (kg/m^2)	22.20 (1.76)	27.35* (1.59)	33.43* (2.56)	<0.001
Fat (%)	19.66 (5.96)	28.23* (7.56)	33.99* (8.97)	<0.001

BMI, Body mass index; *P<0.05 compared to the Normal Weight group.

Table 2: Behavioral data on trait sensitivity to reward and performance on fMRI tasks.

	Normal weight (n=39) Mean (SD)	Overweight (n=21) Mean (SD)	Obese (n=21) Mean (SD)	ANOVA P-value
Sensitivity to reward	10.31 (3.89)	10.14 (3.81)	9.76 (4.00)	0.875
Willingness to Pay: Money paid (€)				
High-palatable food	2.63 (1.75)	3.03 (2.26)	2.49 (1.25)	0.605
Plain food	2.36 (1.63)	1.81 (1.27)	1.42* (1.01)	0.045
Monetary Incentive Delay: Response Time (s)				
Neutral	0.246 (0.038)	0.252 (0.052)	0.279* (0.059)	0.042
Low	0.227 (0.033)	0.233 (0.048)	0.249* (0.046)	0.137
Medium	0.231 (0.037)	0.234 (0.043)	0.242 (0.047)	0.612
High	0.219 (0.032)	0.222 (0.036)	0.230 (0.040)	0.507

*P<0.05 in relation to Normal Weight group.

ANEXO II

INDEPENDENT FUNCTIONAL CONNECTIVITY NETWORKS UNDERPIN FOOD AND MONETARY REWARD SENSITIVITY IN OBESITY

Juan Verdejo-Román, Alex Fornito, Carles Soriano-Mas, Raquel Vilar-López, Antonio Verdejo-García. (Under review) independent functional connectivity networks underpin food and monetary reward sensitivity in obesity. *The Journal of Neuroscience.*

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Independent functional connectivity networks underpin food and monetary reward sensitivity in obesity

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Commercial Interest:

Title Page

Independent functional connectivity networks underpin food and monetary reward sensitivity in obesity

Abbreviated title: Disrupted reward-related brain connectivity in obesity

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Abstract:

The over-valuation of highly palatable food is a primary driver of excess weight problems, and is associated with activation of brain regions involved in reward processing. However, it remains unclear if these brain regions act as an integrated network, and if this network is specialized in food reward, or generally involved in reward processing. We used functional magnetic resonance imaging (fMRI) to characterize functional connectivity during processing of food and monetary rewards in excess and healthy weight adults. Seventy-six healthy adults, 37 with normal weight (BMI<25) and 39 with excess weight (BMI>25) performed two reward tasks in the fMRI scanner, one involving food-related rewards (Willingness to Pay for food) and one involving monetary rewards (Monetary Incentive Delay). A data-driven graph approach was applied to compare whole-brain, task-related functional connectivity between groups. We found that excess weight individuals showed a higher valuation of highly palatable food and greater sensitivity to monetary rewards. They also exhibited decreased functional connectivity during the processing of food rewards in a network that principally involved frontal and striatal areas, and increased functional connectivity of frontal and parietal areas during the processing of monetary rewards. These two networks were topologically and anatomically distinct, were correlated with task performance, and were independently associated with BMI. Our findings suggest that the processing of food-related and monetary rewards are both altered in excess weight individuals, and that these alterations have distinct neural underpinnings that are independently related to adiposity.

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Significance Statement

High valuation of energy dense and cheap food rewards (e.g., meal deals) is a primary driver of the dietary choices that lead to obesity. Here, we map the brain networks involved in the processing of food and monetary rewards in excess weight individuals using functional magnetic resonance imaging. We found that excess weight people show a higher valuation of both food and monetary rewards, and that these behavioural changes are associated with domain-specific alterations in brain network functional connectivity. Disrupted connectivity in these two networks independently correlated with body mass index, suggesting that they uniquely contribute to obesity. These results may shed light on why people with excess weight are more attracted to high calorie food that is cheap but unhealthy.

Introduction

Obesity is currently the most important health problem in developed countries, as it is linked to some of the leading causes of mortality (i.e., cardiovascular disease or diabetes) (Flegal et al., 2013). In recent decades, the prevalence of obesity has reached worldwide epidemic proportions (Ng et al., 2014) and this growth has been linked to the availability of highly processed food rich in sugar and fat (Stice et al, 2013). Obesity is increasingly conceptualized as a disorder of reward-based decision-making, according to cognitive neuroscience and neuroimaging evidence showing that obese people predominantly make food choices based on the rewarding aspects of food products, instead of their homeostatic or health properties (Volkow et al., 2011; Burger & Stice, 2011; Kenny, 2011).

Value-based choices rely on the function of a well-defined network of brain regions central to reward processing, including the anterior cingulate, orbitofrontal and dorsal prefrontal cortices, the ventral striatum, the dopaminergic midbrain and the amygdala and hippocampal complex (Haber & Knutson, 2010). Individuals with excess weight show significantly increased activation in these areas in response to high caloric food cues (Rothemund et al. 2007; Stoeckel et al., 2008; Martin et al., 2010; Dimitropoulos et al., 2012; Simon et al., 2014). However, despite evidence that these reward-related regions behave as an integrated network, it is as yet unclear how network-level disturbances relate to altered brain reward processing in obesity. Functional connectivity studies have examined discrete elements of the brain's reward-processing system (i.e., striatum, midbrain, amygdala, orbitofrontal cortex), but these studies have reported contradictory findings. While some studies in excess weight adults have found enhanced functional connectivity of striatal areas during processing of highly palatable food (Stoeckel et al., 2009; Nummenmaa et al., 2012; Carnell et al., 2014) other studies

found reduced functional connectivity mainly involving frontal areas (Stoeckel et al., 2009; Kullmann et al., 2013; García-García et al., 2013).

In addition, it remains unclear whether disruptions of the neural systems supporting reward-based decision-making in this population are specific to the processing of food-related stimuli or represent a general sensitization of reward processes. The existence of a general deficit of reward-processing, (i.e., independent of the specific stimulus), predicts that obese people will have generic problems in evaluating natural reinforcers, which will, in turn, have a broad impact on obese peoples' choices and quality of life (Rangel, 2013). Nevertheless, few studies have examined the brain's reward system activity in excess weight individuals during the processing of generic stimuli, such as monetary reward. Balodis et al. (2013) found increased activity in the ventral striatum and ventromedial prefrontal cortex in anticipation of monetary reward. This is consistent with evidence of altered structural connectivity in fronto-striatal circuits in obese individuals, and implies a general reward-processing deficit (Marqués-Iturra et al., 2015). However, other studies have failed to find an association between brain monetary processing and body mass index (BMI) (Simon et al., 2015). These inconsistencies underscore the need for a comprehensive characterization of the reward network connectivity in excess weight adults across food-related and other types of stimuli.

In this study, we used functional magnetic resonance imaging (fMRI) to map brain functional connectivity alterations in the reward system of individuals with excess weight relative to normal weight controls. Both groups performed two tasks: one assessing food-related reward processing and one assessing the processing of monetary rewards. Functional connectivity was assessed with a data-driven graph theoretic approach to characterize whole brain network-level between-group differences during

both tasks. Based on prior work (Nummenmaa et al., 2012, Stoeckel et al., 2009), we hypothesised that excess weight individuals would show disrupted functional connectivity involving frontal and striatal regions. If excess weight individuals show a general reward-processing deficit, then these disruptions should also be evident during the processing of monetary reward. Finally, we predicted that these network-level functional connectivity disruptions would be associated with personality measures of sensitivity to reward and general measures of clinical severity, such as BMI and adiposity.

Materials and Methods

Participants

Seventy-six healthy, right-handed adults, aged between 25 and 45 years old, participated in this study. They were classified in two groups, 39 excess weight and 37 controls, based in their Body Mass Index (BMI). The groups did not differ significantly in terms of age ($t_{(1,74)}$=-0.40, p=0.69), sex ($t_{(1,74)}$=-0.02, p=0.99), years of education ($t_{(1,74)}$=0.72, p=0.47), or monthly income ($t_{(1,74)}$=-0.63, p=0.39).

The inclusion criteria for participants were defined as follows: (i) BMI values falling within the intervals categorized as excess weight (BMI higher than 25) or lean (BMI between 19 and 25); (ii) absence of history or current evidence of neurological or psychiatric disorders or medical comorbidities associated with obesity (e.g., diabetes, hypertension); (iii) absence of significant abnormalities on structural MRI or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects). All participants had normal or corrected-to-normal vision. They were recruited through media advertisements and received a financial compensation.

The study was approved by the Human Research Ethics Committee of the University of Granada (Spain) and was conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent form certifying their voluntary participation.

Experimental paradigm

For the purpose of the study, each participant performed two tasks during the fMRI session, a food-related reward task and a monetary reward task. To assure that every subject knew all the food stimuli, participants attended a tasting session two weeks before scanning. During that session participants were allowed to try 18 different foods. These products belonged to two groups based on their palatability: highly palatable food, including sweet and fatty food (e.g., chocolate, cheese cake, hamburger) versus plain food (e.g., yoghurt, omelet). These sessions were conducted at 6:00 pm, and participants were instructed to taste each of the foods offered.

fMRI tasks

Willingness to Pay task (WtP). We used a modified version of the Willingness to pay task (Plassmann et al. 2007). Participants were presented with a photo of each of the 18 previously tasted foods. Each stimulus was presented once for two seconds followed by a four-second response period, during which time participants answered the question: "How much would you pay for it?" They could choose between four monetary options, ranging from 20 cents to 10 euros. Each selection was followed by a variable fixation period lasting between 3 and 5 seconds. Our goal in this task was to examine brain activity and functional connectivity in high palatable food trials compared to plain food trials.

Monetary Incentive Delay task (MID). We used an adaptation of the Monetary Incentive Delay task (Nestor et al. 2010), based on the original task of Knutson (Knutson et al. 2000). At the beginning of each trial, participants were shown one of two cues indicating potential winnings or no financial outcome at the end of the trial. Cues (green or blue square) were counterbalanced across participants, and the incentive value of each trial was signaled by means of the number of horizontal lines crossing the green square (one line for 0.2€, two for 1€ and three for 5€). Each cue was presented for a fixed duration, 750msec. Subsequently, a cross-fixation was shown during a variable period of 3 to 5 sec, and after this interval participants had to perform a reaction-time task: respond to a white target star appearing for a variable length of time (150–450 ms) with a button press. Then participants received feedback (hit/miss) about the accuracy of their response for 750ms, together with the information about the amount of money won in that trial (when adequate, e.g., correct responses in reward cued trials) and their cumulative total at that point of the experiment. Finally, another fixation period (750 ms) was included before the next trial. Therefore, total trial duration ranged between 5700 and 7000 ms. Participants performed the task in two sessions of 48 trials each, yielding a total of 96 trials. Imaging analyses examined brain activity changes during two events: (1) reward-anticipation, which occurred between the presentation of the cue and the response; and (2) reward-feedback period, which occurred at the time of the feedback.

Both tasks were administrated using Presentation software (version 1.8; http://www.neurobs.com). Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology Inc), and responses were recorded through Evoke Response Pad System (Resonance Technology Inc).

Outside scanner behavioral measures

Sensitivity to Reward was measured with The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al., 2001). This questionnaire has demonstrated internal consistency, construct validity, and significant associations with reward and punishment relevant brain systems (Costumero et al., 2013).

Imaging data acquisition and preprocessing

Participants were scanned using a 3T Philips Intera Achieva System. T2*-weighted echo-planar imaging (EPI) sequences were acquired with the following parameters: repetition time (TR), 2000 ms; echo time (TE), 35ms; flip angle, 90º; field of view (FOV), 240 mm; number of slices, 21, voxel dimension, 3 x 3 x 4 mm; gap, 1mm. Specifically, we performed a 149-volume scan session for the WtP task, and two 216-volume scan sessions for the MID task. Structural images were obtained as an isotropic T1-weighted turbo-gradient-echo sequence in the sagittal plane (TR, 8.3ms; TE, 3.8 ms; flip angle, 8º; FOV 240mm; number of slices, 160; voxel dimension, 1 x 1 x 1 mm).

Image preprocessing and analysis were performed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, UK), running under Matlab R2009 (MathWorks). Preprocessing steps included realignment to the mean image of the time series, slice timing correction, normalization, using affine and smoothly non-linear transformations, to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum (FWHM) = 8 mm). Data were high-pass filtered to remove low-frequency noise (1/128 Hz) and corrected for temporal autocorrelation using an autoregressive AR model.

Statistical analyses

Behavioral analyses. Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA). We conducted mixed-design ANOVAs to investigate the main effect of group, main effect of task, and their interaction. Specifically, we performed a 2 (Group) x 2 (Type of Food), and a 2 (Group) x 4 (Type of Cue) ANOVAs on money paid and response time, respectively.

Task-related activation analyses. General linear models (GLM) were used to characterize task-evoked activation for each task separately. The task regressors were convolved with the SPM8 canonical hemodynamic response function. Three contrasts of interest were defined to investigate task-related activation for each subject; one in the WtP task and two in the monetary reward task. The WtP contrast tested for increased activity in High Palatable food trials compared to Plain Food trials. This contrast models brain processing of reward associated with the palatability of food, the specific reinforcer in obesity. Two contrasts were used to model brain activity during the monetary task. The first examined anticipation of monetary reward, as modeled by a linear contrast defined as: anticipation during high reward trials >Medium reward trial anticipation > low reward trial anticipation > no outcome trials. The second contrast examined feedback-related activation, and was modeled by comparing brain activity in win versus miss trials of the MID task.

Across both tasks, first-level contrast images were carried forward to second-level random-effects group analyses. Whole-brain one-sample t-tests were conducted to map main effects of task across groups for each contrast, followed by two-sample t-tests to assess between-group differences.

The results were corrected for multiple comparisons with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox (Song et al., 2011; Ward, 2013). Input parameters included a brain mask of 138884 voxels, an individual voxel threshold probability of 0.005, and a cluster connection radius of 5 mm, considering the actual smoothness of data after model estimation. A minimum cluster extent (KE) of 343, 293 and 495 voxels for contrast 1, 2, and 3 respectively, was estimated to satisfy a family-wise corrected (FWE) p value of $P_{FWE} < 0.05$. Recent studies have pointed to the potential for false positives to arise when primary cluster-forming thresholds of p>.001 are used (Woo et al., 2014). Here, we find no group differences at p<.005, and the result holds for the more stringent p<.001 threshold. We retain the more lenient p <.005 threshold for mapping the task-related networks, as this results in a more inclusive definition of network nodes. Using this more inclusive definition ensures that we comprehensively sample the networks of interest. Note that our inclusion of more regions puts our hypothesis of localized changes in fronto-striatal systems to a more stringent test.

Task-related functional connectivity analysis

Graph analysis (Bullmore and Sporns, 2009, Rubinov and Sporns, 2010) was used to characterize brain functional connectivity during both tasks. Each brain network was modeled as a graph composed of *N* nodes connected by *M* edges. Regions showing significant activation or deactivation in the one-sample analyses for each contrast were selected as nodes for the functional connectivity analysis. All nodes, regardless of the activation contrast used to identify them, were used in the analyses of both tasks. In this way, we were able to examine context-specific changes within a single, reward-related

network. ROIs were then generated as 4 mm spheres centered on the voxel with the highest t score in each significant cluster. To prevent overlap between nodes, regions whose central points were closer than 8mm in Euclidean space were identified (n = 60) and a new node was created with a centroid that was equidistant from the two original foci. A total of 126 nodes were defined with this method. Each region-of-interest was masked by the SPM a priori probability image of grey matter in order to weight each voxel value according to its grey matter probability.

Averaged signal time courses for each of the 126 nodes were extracted from the non-smoothed images for both tasks. To measure task-related functional connectivity, we used the correlational psychophysiological interaction (cPPI) methodology (Fornito et al., 2012; http://www.nitrc.org/projects/cppi_toolbox). Separate analyses were conducted to investigate task-related functional connectivity in relation to (1) food-related reward processing; (2) anticipation of monetary reward; and (3) receipt of monetary reward. For each analysis, the BOLD signal from each node was deconvolved (Gitelman et al, 2003), multiplied by a task regressor modeling the contrast of interest [i.e., (1) high palatable food > plain food; (2) anticipation during high reward trials > medium reward trial anticipation > low reward trial anticipation > no outcome trials anticipation; and (3) win > miss trials], and then reconvolved with a canonical hemodynamic response function to generate a psychophysiological interaction (PPI) term that quantified task-related modulations of each node's activity. These PPI terms were then correlated between every pair of regions while partialling the effects of (1) the original task regressors; (2) the raw region time courses; (3) six head motion parameters (three rotation, three translation) and their first derivatives; and (4) ten principal component time courses that captured variance related to physiological noise

and residual head movement. These component time courses were estimated using the aCompCor method (Behzadi et al, 2007). Briefly, this method involves generating subject–specific tissue probability masks of white matter and CSF (thresholded at 99% probability), extracting the time-series from each voxel in each mask, excluding voxels with time courses that correlate with any of the task regressors (a threshold of $p<0.2$ was uses for this purpose), and performing separate principal component analyses of the remaining white matter and CSF voxel time courses (Muschelli et al, 2014). The first five components from each analysis were retained as noise regressors.

The cPPI analyses resulted in three $N \times N$ functional connectivity matrices (one for each contrast of interest) per subject, where $N = 126$. Each matrix represents task-related functional connectivity between every pair of nodes. In the food reward task, a higher correlation indicated that two regions showed strong functional connectivity in the High palatable condition compared to the Plain food condition. In the monetary reward anticipation analysis, a higher correlation indicated stronger connectivity associated with the linear contrast High>Medium>Low>No Reward. In the monetary reward feedback analysis, a higher correlation indicated stronger connectivity in win compared to miss trials. Functional connectivity was measured for a total of $(N^2-N)/2=7875$ edges in each network, separately for each of the three task contrasts.

NBS analyses

We used the network-based statistic (NBS) to test for group differences in task-related functional connectivity in a data-driven, regionally-unbiased way (Zalesky et al, 2010). A separate analysis was conducted for each task contrast. Briefly, the NBS starts with a mass univariate analysis, in which statistical inference is performed independently at

each of the 7875 connections in the network. In this case, the inferential test was a two-tailed t-test of the difference in group means between excess weight and normal weight individuals. The resulting matrix was thresholded at $p<.05$, uncorrected The sizes (in terms of number of edges) of the connected components of the remaining network of supra-thresholded edges were then computed, where connected components represent sets of nodes that can be linked by a set of supra-threshold edges. Group labels were then permuted and the analysis was repeated to generate an empirical null distribution of maximal component sizes. A total of 5000 permutations was used to generate this distribution. Since only the maximal component size is stored at each permutation, the resulting p-values for the observed sizes are familywise corrected at the component level (Nichols and Holmes, 2002; Zalesky et al. 2012). We retained as significant all components surviving a threshold of $p<.05$, component-wise corrected.

Results

Behavioral Analyses

We found a significant "Group x Type of food" interaction ($F(1,74)=8.57$, $p=0.005$) in the WtP task. Within and between group comparisons showed that excess weight group paid less money for plain food than for high palatable food ($t(38)=5.75$ $p<0.001$), and less money than controls for plain food ($t(74)=2.24$, $p=0.028$). Thus, excess weight individuals showed a higher valuation of palatable food, as indicated by a willingness to pay more money for it (Figure 1A).

In the MID task, we found a significant effect of cue type across groups on reaction time ($F(3,22)=48,18$, $p<0.001$), indicating that all participants made faster responses when they had the opportunity to win more money (Figure 1B). We found a trend-level

interaction between Group and Type of cue in the reaction time ($F(3,222)=2.76$, $p=0.063$) (Figure 1B). A second measure to assess reward sensitivity in the MID task is the slope of the linear regression of reaction time on cue type, ordered from no income, to low, middle and high magnitude. Comparing this measure, we found significant differences between groups ($t(1,74)=2.136$, $p=0.037$), suggesting greater responsivity to reward in the excess weight group (Figure 1C).

Task-related activation

Across both groups and the three contrasts (i.e., the WtP task contrast between high palatable versus plain food and the MID contrasts of anticipation and feedback), one-sample t-tests showed significant activation in reward-related areas, including the striatum and the prefrontal cortex (i.e., middle and lateral orbitofrontal gyri), as well as in the precuneus and the occipital cortex.

WtP task. Across both groups, processing of highly palatable versus plain food was also associated with increased activation of the midbrain, insula, anterior cingulate cortex (ACC) and supramarginal gyrus.

MID task. During anticipation of monetary reward, participants across both groups activated striatal areas, as well as the midbrain, insula, ACC, supplementary motor area (SMA), precentral and postcentral gyri, thalamus, cerebellum and hippocampus. They also showed significant deactivations of the angular gyrus and posterior cingulate cortex (PCC).

During feedback (i.e., win trials versus miss trials), participants showed significant activation of the same striatal regions and the thalamus, fusiform and supramarginal gyri, hippocampus and PCC. Significant deactivation of the bilateral anterior insula was also observed.

There were no significant between-groups differences in regional activation for any contrast at the selected threshold.

Functional connectivity

WtP task. The excess weight group showed a significant reduction of functional connectivity in the WtP task compared to controls. The network showing reduced functional connectivity comprised 544 edges and 125 nodes (p=0.025, component-wise corrected). To better understand the anatomical distribution of this network, we categorized nodes into eight categories according to their anatomical designation: frontal, insula, striatum, thalamus, temporal & hippocampus, parietal, occipital and cerebellum. We found that more than half of the connections in this network involved frontal cortex (50.55%). Most of these edges linked the frontal cortex with the striatum (13%) or the frontal cortex with the parietal cortex (12%). Fronto-insular (8.6%) and fronto-frontal connections (8.3%) were also frequently implicated in this network (Figure 3A). We identified no subnetworks in which excess weight individuals showed significantly increased functional connectivity during the WtP task.

MID task. During the MID task, the excess weight group showed a significant enhancement of functional connectivity, during both the anticipation and the feedback conditions, compared to controls. This pattern stood in stark contrast to the WtP task,

where the excess weight group only showed evidence of reduced functional connectivity.

During reward-anticipation, one component, comprising 532 edges and 126 nodes ($p=0.03$, component-wise corrected), showed significantly increased functional connectivity in excess weight individuals. This network largely involved frontal and parietal areas, with 10% of connections being fronto-parietal, 7.5% parieto-occipital, 7.1% intraparietal and 7% fronto-striatal (Figure 3B). During reward-feedback, a component comprising 547 edges and 125 nodes ($p=0.005$, component-wise corrected) showed significantly increased functional connectivity in excess weight participants. This network predominantly involved frontal, striatal and parietal areas: 11% of the edges were parieto-striatal, 9 % fronto-striatal, 8% parieto-occipital and 7.5% fronto-occipital (Figure 3C).

Consistency across task conditions

To examine whether there was a common dysfunctional network across task conditions, we computed the overlap in the binary topology of the three condition-specific dysfunctional networks identified in excess weight individuals. For each task contrast, we took the sub-network showing a significant difference between groups. We then computed the size of the intersection (in terms of number of edges) between (1) the two MID conditions (anticipation and feedback); and (2) all three conditions (i.e., monetary anticipation, monetary feedback and food related reward). The first analysis sought to identify a core dysfunctional network associated with processing monetary reward. The second sought to identify a core dysfunctional network associated with both monetary and food reward.

To test whether the overlap was significantly different to chance expectations, we generated randomized surrogates for each of the three dysfunctional networks using an established rewiring algorithm that preserves the same number of nodes, edges and degree distribution of the original networks, but which randomizes the network in all other respects (Maslov-Sneppen). We generated 5000 such networks for each of the three empirical networks and computed the size of the intersection at each of the 5000 iterations to generate empirical null distributions of network overlap.

We found that the dysfunctional networks identified during MID anticipation and feedback showed a statistically significant degree of overlap, sharing 112 edges in which task-related functional connectivity was increased in excess weight individuals ($p<0.001$). Most of these edges were parieto-occipital (14%), fronto-occipital (8.9%) and fronto-striatal (8.9%). This network thus comprises a core dysfunctional network for the processing of monetary reward in excess weight people.

In a second analysis, we examined the consistency between the dysfunctional network identified in the WtP task and the anticipation and feedback conditions of the MID task. The degree of overlap between the dysfunctional monetary feedback and food reward networks was significantly less than expected by chance (20 edges, $p<0.005$). A similar trend was observed for the overlap between the food and monetary anticipation networks (24 edges, $p = 0.055$). These findings suggest that abnormal processing of monetary and food-related rewards in excess weight individuals is related to dysfunction in spatially and topologically segregated neural systems.

Correlations with task performance, clinical and personality measures.

We next examined how individual variations in functional connectivity with the dysfunctional networks identified for each task condition relate to task performance, clinical and personality measures. To this end, we computed the first principal component of functional connectivity measures across the edges comprising the dysfunctional network identified in each task condition and correlated each individual's component score with outcome measures: behavioral performance in the tasks, BMI, body-fat percentage and sensitivity to reward. For the WtP task, the first PC accounted for 7.16% of the variance; for anticipation it accounted for 7.60% and for feedback it accounted for 7.73%.

Correlation with task performance

We found a significant negative correlation between functional connectivity of the dysfunctional network during the WtP task and the difference score of money paid for high palatable versus plain food ($r = -0.266$, $p = 0.020$) (Figure 4A). That is, lower functional connectivity was associated with a lower valuation of plain food.

We also found a significant negative correlation between functional connectivity of the dysfunctional network during the MID contrast of anticipation to reward and the measure of reaction time change across reward magnitudes ($r = -0.269$, $p=0.020$) (Figure 4B). According to the negative sign of the slope of the linear regression of reaction time on cue type, this negative correlation indicates that higher functional connectivity during monetary reward anticipation was associated with greater behavioral sensitivity to reward magnitude. These correlations did not survive Bonferroni correction for twelve comparisons ($\alpha=0.05/12=0.004$). These findings

establish the behavioral relevance of the dysfunctional task-related functional connectivity networks identified in the group comparisons.

Correlations with clinical and personality measures.

There was a strong correlation between functional connectivity in the dysfunctional WtP network and BMI ($r = -0.77$, $p<0.001$) The correlation indicates that lower functional connectivity during this task was associated with higher BMI. A similar strong correlation was found with body-fat percentage ($r = -0.53$, $p<0.001$). The two dysfunctional MID networks also showed significant correlations with BMI and fat percentage: $r = 0.80$ and $r = 0.49$, $p<0.001$ in the anticipatory monetary contrast and $r = 0.76$ and $r = 0.47$, $p<0.001$, in the feedback related contrast (Figure 4C). Each of these results survived Bonferroni correction for 12 comparisons (alpha = 0.004).

We also performed partial correlations in which functional connectivity in the dysfunctional WtP network was correlated with BMI while controlling for functional connectivity in the dysfunctional MID networks. This analysis still revealed a significant negative correlation ($r = -0.304$, $p<0.013$). Similarly, the positive correlation between functional connectivity of the dysfunctional MID anticipation network and BMI remained significant when controlling for the WtP network ($r=0.368$, $p=0.002$). These results indicate that brain networks that are dysfunctional in excess weight individuals during the processing of food and money reward are independently associated with BMI.

Discussion

Reward processing is a primary driver of the dietary choices that lead to excess weight and obesity. A core set of regions in the striatum, the prefrontal cortex, and the midbrain are known to support the generic processing of different types of rewards, whether they be monetary, food-related, erotic, and so on. However, it is yet unclear if difficulties in reward processing among excess weight individuals are (a) specific to the context of food or generalize to other domains; and (b) are associated with dysfunction in a specific neural systems or a domain-general reward processing network. In this study we used a data-driven, connectome-wide analysis to map neural systems showing altered functional connectivity in excess weight individuals during the processing of two distinct types of reward: food-related and monetary (including the anticipation and receipt of money). We found consistent evidence for involvement of frontal, striatal and parietal areas across tasks; however, the specific neural systems identified as dysfunctional in the food and monetary contexts were different. Specifically, excess weight individuals showed reduced functional connectivity and impaired valuation of rewards during food processing, and increased functional brain connectivity and higher behavioral sensitivity to monetary rewards. The specific set of brain functional interactions that were altered in these conditions showed statistical evidence of spatial and topological segregation. During both food-related and monetary reward processing, network-level functional connectivity correlated with task performance and physical measures of weight (i.e., BMI and adiposity), providing a direct link to altered reward valuation and physical size.

Functional connections showing reduced coupling during the WtP food task in excess weight individuals predominantly linked frontal lobe nodes, which play an important role in self-regulation (Rangel, 2013), with striatal regions involved in stimulus

valuation (Montague et al., 2002), parietal regions implicated in attentional control (Hopfinger et al., 2000), and insula regions relevant to interoception (Craig, 2009). These results are consistent with a previous study that found reduced frontal cortex related functional connectivity in obese individuals during passive viewing of high palatable food images (García-García et al., 2013). Two recent studies have also reported altered white matter microstructure in fiber pathways linking frontal and subcortical areas in excess weight adults (Marqués-Iturra et al., 2015; Kullmann et al., 2015). Frontal areas play a crucial role in dietary choices. These areas code the relative value of food reward according to palatability, while also supporting behavior to achieve long-terms goal (Rangel, 2013). Reduced functional connectivity between the frontal cortex and reward-related regions has been associated with failure of top-down regulation of behavioral control (Motzkin et al, 2014). This deficit has also shown to contribute to explain dietary choices in obesity (Rangel, 2013). This conclusion is consistent with several studies that report difficulties in cognitive control and executive functions in obesity (Fitzpatrick et al., 2013). Modelling effective connectivity (e.g., Friston et al. 2003) within fronto-striatal systems may provide a useful test of the hypothesis that these circuit-level abnormalities are caused by deficient top-down signaling from the prefrontal cortex.

In the MID task, individuals with excess weight displayed enhanced functional connectivity in a similar network across reward-anticipation and reward-feedback. This network involves mainly parieto-occipital, fronto-occipital and fronto-striatal connections. Previous resting-state neuroimaging studies had demonstrated enhanced resting-state functional connectivity in individuals with obesity (Dunnelink et al. 2008; Kullmann et al., 2012; Black et al., 2014; Lips et al., 2014; Wijngaarden et al., 2015).

Therefore, in obese people the pattern of functional brain connectivity during monetary reward resembles the tonic hyper-connectivity observed in resting-state studies. Fronto-occipital networks are involved in rapid feed-forward propagation of visual inputs and direct top-down modulation of early visual processing (Forkel et al., 2014). Parieto-occipital connections have also been implicated in the orientation and maintenance of visual attention (Foxe et al, 1998). The specific involvement of visual-attentional and goal-directed networks, and the positive correlation between these networks and sensitivity to reward in our analysis, suggests that obese individuals are sensitive to monetary cues. Future studies should explore the extent to which these networks predict dietary choices driven by monetary value, such as "meal deal choices".

The non-significant overlap between the dysfunctional reward-processing networks, as well as our partial correlation analyses, indicate that different neural systems independently correlate with excess weight. Reduced functional connectivity in frontal-striatal networks during processing of food-related stimuli may relate to weakening of self-regulation skills needed to control high-calorie food choices (Hollmann et al., 2012). Money-related hyper-connectivity in visual-attentional networks may relate to excessive weight via special attention to the financial value of cheap high-calorie foods, which is linked to cues of food chains and meal deals. For example, Bruce et al. have shown parietal hyper-activation in response to fast food chains' branding logos (Bruce et al., 2014). Noteworthy, our findings are correlational and hence it is also possible that being overweight changes brain functional connectivity. Further studies are needed to better understand the relationship between these separate network alterations and clinical and societal outcomes relevant to obesity. Ultimately, different therapeutic approaches may be needed to tackle excess weight problems, one to strengthen frontal-striatal FC in

response to food stimuli, and a different one to decrease fronto-parietal-occipital FC in relation to monetary reward processing.

We did not find significant group differences in brain activation in any of the three contrasts. These results suggest that reward processing in excess weight individuals is primarily driven by dysfunction of anatomically distributed neural systems, rather than isolated dysfunction of one or a few brain regions. Other studies have reported regional activation differences between obese individuals and normal weight controls during processing of highly palatable food (Rothemund et al. 2007; Stoeckel et al., 2008), but there are few studies in overweight individuals. Most of the existing studies included participants with severe presentations of obesity (BMI>35) and other medical conditions and eating disorders (i.e., binge eating disorder), whereas our sample is free of medical conditions and mental health disorders, and spans the whole excess weight spectrum, including overweight (BMI 25-30) and obese (BMI>30) participants. In addition, we conducted regionally-unbiased, whole-brain analyses, whereas many previous studies have focused on *a priori* regions of interest.

In summary, specific functional connectivity disruption was found in excess weight individuals in response to food and money. Specifically, an enhancement in functional connectivity in a common network was found during both anticipation and reception of a monetary reward, whereas a reduction in functional connectivity was related to food reward. Our results are consistent with behavioral impaired valuation of both rewards and suggest a failure on regulation of dietary choice and food behavior. These results provide evidence of a general disruption of reward processing in excess weight adults,

610 but specific therapeutic approaches may be required to address specific aspects of this
611 disruption when tackling the obesity epidemic.

612

613 **References**

614 Balodis IM, Kober H, Worhunsky PD, White MA, Stevens MC, Pearlson GD, Sinha R,
615 Grilo CM, Potenza MN (2013) Monetary Reward Processing in Obese Individuals
616 With and Without Binge Eating Disorder. Biological Psychiatry 73:877–886.

617 Behzadi Y, Restom K, Liau J, Liu TT (2007) A component based noise correction
618 method (CompCor) for BOLD and perfusion based fMRI. NeuroImage 37:90–101.

619 Black WR, Lepping RJ, Bruce AS, Powell JN, Bruce JM, Martin LE, Davis AM,
620 Brooks WM, Savage CR, Simmons WK (2014) Tonic hyper-connectivity of
621 reward neurocircuitry in obese children. Obesity 22:1590–1593.

622 Bruce AS, Bruce JM, Black WR, Lepping RJ, Henry JM, Cherry JBC, Martin LE, Papa
623 VB, Davis AM, Brooks WM, Savage CR (2014) Branding and a child's brain: an
624 fMRI study of neural responses to logos. Soc Cogn Affect Neurosci 9:118–122.

625 Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of
626 structural and functional systems. Nat Rev Neurosci 10:186–198.

627 Burger KS, Stice E (2011) Variability in Reward Responsivity and Obesity: Evidence
628 from Brain Imaging Studies. Curr Drug Abuse Rev 4:182–189.

629 Carnell S, Benson L, Pantazatos SP, Hirsch J, Geliebter A (2014) Amodal brain
630 activation and functional connectivity in response to high energy-density food
631 cues in obesity. Obesity 22:2370-2378.

632 Costumero V, Barrós-Loscertales A, Bustamante JC, Ventura-Campos N, Fuentes P,
633 Ávila C (2013) Reward sensitivity modulates connectivity among reward brain

areas during processing of anticipatory reward cues. Eur J Neurosci 38:2399–2407.

Craig AD (2009) How do you feel — now? The anterior insula and human awareness. Nat Rev Neurosci 10:59–70.

Dimitropoulos A, Tkach J, Ho A, Kennedy J (2012) Greater corticolimbic activation to high-calorie food cues after eating in obese vs. normal-weight adults. Appetite 58:303–312.

Dubbelink KTEO, Felius A, Verbunt JPA, Dijk BW van, Berendse HW, Stam CJ, Waal HAD de (2008) Increased Resting-State Functional Connectivity in Obese Adolescents; A Magnetoencephalographic Pilot Study. PLOS ONE 3:e2827.

Flegal KM, Kit BK, Orpana H, Graubard BI (2013) Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. JAMA 309:71–82.

Fitzpatrick S, Gilbert S, Serpell L (2013) Systematic review: are overweight and obese individuals impaired on behavioural tasks of executive functioning? Neuropsychol Rev 23:138–156.

Forkel SJ, Thiebaut de Schotten M, Kawadler JM, Dell'Acqua F, Danek A, Catani M (2014) The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. Cortex 56:73–84.

Fornito A, Harrison BJ, Zalesky A, Simons JS (2012) Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. PNAS 109:12788–12793.

Foxe JJ, Simpson GV, Ahlfors SP (1998) Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. Neuroreport 9:3929–3933.

Friston KJ, Harrison L, Penny W (2003) Dynamic causal modelling. NeuroImage 19:1273–1302.

García-García I, Jurado MA, Garolera M, Segura B, Marqués-Iturria I, Pueyo R, Vernet-Vernet M, Sender-Palacios MJ, Sala-Llonch R, Ariza M, Narberhaus A, Junqué C (2013) Functional connectivity in obesity during reward processing. NeuroImage 66:232–239.

Gitelman DR, Penny WD, Ashburner J, Friston KJ (2003) Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. Neuroimage 19:200–207.

Haber SN, Knutson B (2010) The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacology 35:4–26.

Hollmann M, Hellrung L, Pleger B, Schlögl H, Kabisch S, Stumvoll M, Villringer A, Horstmann A (2012) Neural correlates of the volitional regulation of the desire for food. Int J Obes 36:648–655.

Hopfinger JB, Buonocore MH, Mangun GR (2000) The neural mechanisms of top-down attentional control. Nature Neuroscience 3:284–291.

Kenny PJ (2011) Reward Mechanisms in Obesity: New Insights and Future Directions. Neuron 69:664–679.

Knutson B, Westdorp A, Kaiser E, Hommer D (2000) FMRI Visualization of Brain Activity during a Monetary Incentive Delay Task. NeuroImage 12:20–27.

Kullmann S, Heni M, Veit R, Ketterer C, Schick F, Häring H-U, Fritsche A, Preissl H (2012) The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum Brain Mapp 33:1052–1061.

683 Kullmann S, Pape A-A, Heni M, Ketterer C, Schick F, Häring H-U, Fritsche A, Preissl
684 H, Veit R (2013) Functional Network Connectivity Underlying Food Processing:
685 Disturbed Salience and Visual Processing in Overweight and Obese Adults. Cereb
686 Cortex 23:1247–1256.
687 Kullmann S, Callaghan MF, Heni M, Weiskopf N, Scheffler K, Häring H-U, Fritsche A,
688 Veit R, Preissl H (2015) Specific white matter tissue microstructure changes
689 associated with obesity. Neuroimage 125:36–44.
690 Lips MA, Wijngaarden MA, van der Grond J, van Buchem MA, de Groot GH,
691 Rombouts SA, Pijl H, Veer IM (2014) Resting-state functional connectivity of
692 brain regions involved in cognitive control, motivation, and reward is enhanced in
693 obese females. Am J Clin Nutr 100:524–531.
694 Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR, Butler MG,
695 Savage CR (2010) Neural Mechanisms Associated With Food Motivation in
696 Obese and Healthy Weight Adults. Obesity 18:254–260.
697 Marqués-Iturria I, Scholtens LH, Garolera M, Pueyo R, García-García I, González-
698 Tartiere P, Segura B, Junqué C, Sender-Palacios MJ, Vernet-Vernet M, Sánchez-
699 Garre C, de Reus MA, Jurado MA, van den Heuvel MP (2015) Affected
700 connectivity organization of the reward system structure in obesity. NeuroImage
701 111:100–106.
702 Montague PR, Berns GS (2002) Neural economics and the biological substrates of
703 valuation. Neuron 36:265–284.
704 Motzkin JC, Baskin-Sommers A, Newman JP, Kiehl KA, Koenigs M (2014) Neural
705 correlates of substance abuse: Reduced functional connectivity between areas
706 underlying reward and cognitive control. Hum Brain Mapp 35:4282–4292.

707 Muschelli J, Nebel MB, Caffo BS, Barber AD, Pekar JJ, Mostofsky SH (2014)
708 Reduction of motion-related artifacts in resting state fMRI using aCompCor.
709 NeuroImage 96:22–35.
710 Nestor L, Hester R, Garavan H (2010) Increased ventral striatal BOLD activity during
711 non-drug reward anticipation in cannabis users. Neuroimage 49:1133–1143.
712 Ng M et al. (2014) Global, regional, and national prevalence of overweight and obesity
713 in children and adults during 1980–2013: a systematic analysis for the Global
714 Burden of Disease Study 2013. The Lancet 384:766–781.
715 Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional
716 neuroimaging: A primer with examples. Hum Brain Mapp 15:1–25.
717 Nummenmaa L, Hirvonen J, Hannukainen JC, Immonen H, Lindroos MM, Salminen P,
718 Nuutila P (2012) Dorsal Striatum and Its Limbic Connectivity Mediate Abnormal
719 Anticipatory Reward Processing in Obesity. PLOS ONE 7:e31089.
720 Plassmann H, O'Doherty J, Rangel A (2007) Orbitofrontal Cortex Encodes Willingness
721 to Pay in Everyday Economic Transactions. J Neurosci 27:9984–9988.
722 Rangel A (2013) Regulation of dietary choice by the decision-making circuitry. Nat
723 Neurosci 16:1717–1724.
724 Rothemund Y, Preuschhof C, Bohner G, Bauknecht H-C, Klingebiel R, Flor H, Klapp
725 BF (2007) Differential activation of the dorsal striatum by high-calorie visual
726 food stimuli in obese individuals. NeuroImage 37:410–421.
727 Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: Uses
728 and interpretations. NeuroImage 52:1059–1069.
729 Simon JJ, Skunde M, Hamze Sinno M, Brockmeyer T, Herpertz SC, Bendszus M,
730 Herzog W, Friederich H-C (2014) Impaired cross-talk between mesolimbic food

reward processing and metabolic signaling predicts body mass index. Front Behav Neurosci 8:359.

Simon JJ, Skunde M, Wu M, Schnell K, Herpertz SC, Bendszus M, Herzog W, Friederich H-C (2015) Neural dissociation of food- and money-related reward processing using an abstract incentive delay task. Soc Cogn Affect Neurosci 10:1113-1120.

Song X-W, Dong Z-Y, Long X-Y, Li S-F, Zuo X-N, Zhu C-Z, He Y, Yan C-G, Zang Y-F (2011) REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS ONE 6:e25031.

Stice E, Figlewicz DP, Gosnell BA, Levine AS, Pratt WE (2013) The contribution of brain reward circuits to the obesity epidemic. Neuroscience & Biobehavioral Reviews 37:2047–2058.

Stoeckel LE, Weller RE, Cook III EW, Twieg DB, Knowlton RC, Cox JE (2008) Widespread reward-system activation in obese women in response to pictures of high-calorie foods. NeuroImage 41:636–647.

Stoeckel LE, Kim J, Weller RE, Cox JE, Cook III EW, Horwitz B (2009) Effective connectivity of a reward network in obese women. Brain Research Bulletin 79:388–395.

Torrubia R, Ávila C, Moltó J, Caseras X (2001) The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Personality and Individual Differences 31:837–862.

Volkow ND, Wang G-J, Baler RD (2011) Reward, dopamine and the control of food intake: implications for obesity. Trends in Cognitive Sciences 15:37–46.

Ward BD (2013) AFNI and NIFTI server at NIMH in Bethesda, MD USA. Simultaneous inference for FMRI data. Available

at:http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim. pdf, accessed on September 2013.

Wijngaarden MA, Veer IM, Rombouts SARB, van Buchem MA, Willems van Dijk K, Pijl H, van der Grond J (2015) Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behavioural Brain Research 287:127–134.

Woo C-W, Krishnan A, Wager TD (2014) Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. NeuroImage 91:412–419.

Zalesky A, Fornito A, Bullmore ET (2010) Network-based statistic: Identifying differences in brain networks. NeuroImage 53:1197–1207.

Zalesky A, Cocchi L, Fornito A, Murray MM, Bullmore E (2012) Connectivity differences in brain networks. NeuroImage 60:1055–1062.

Figure Legends

Figure 1. Behavioral differences between excess and normal weight individuals during the willingness to pay and monetary incentive delay tasks. ***A***. Average money paid during the WtP task. Errors bars represent sample standard error. ***B***. Average response time for each cue type. Both groups showed the same differences as a function of cue type. ***C***. Average slope of the linear regression equation across cue type in the MID task. Errors bars represent sample standard error. ***** $p<0.05$; ** $p<.01$.

Figure 2: Task-related activation during the willingness to pay (***A***) and anticipatory (***B***) and feedback (***C***) contrasts of the monetary incentive delay tasks. The color bar indicates t-value. Left hemisphere is displayed on the left. ***D.*** Spatial localization of the nodes. Color node reflects anatomical divisions [i.e., Frontal (red), Insula (green),

781 Striatum (dark blue), Thalamus (light blue), Temporal (grey), Parietal (purple),
782 Occipital (yellow) and Cerebellum (black)]. Left hemisphere is displayed on the left.
783
784 **Figure 3:** Functional connectivity disruption during willingness to pay (***A***) and
785 anticipatory (***B***) and feedback (***C***) contrasts of the monetary incentive delay tasks.
786 Tables showed the distribution of edges based to the anatomical division they connected.
787 Connectograms (below) showed disrupted connections for each network. Regions of
788 interest are grouped according to anatomical divisions [i.e., FR, frontal (red), IN, insula
789 (green), ST, striatum (dark blue), TH, thalamus (light blue), TE, temporal (grey), PA,
790 parietal (purple), OC, occipital (yellow) and CE, cerebellum (black)].
791
792 **Figure 4.** Altered networks in excess weight individuals correlate with task
793 performance and BMI. ***A.*** Correlation between WtP network dysfunction and food
794 value-difference measured as money paid for high palatable food minus money paid for
795 plain food. Higher values reflect lower valuation of plain food compared to highly
796 palatable food. ***B***. Correlation between MID network dysfunction and reactivity to
797 monetary cues measured as the slope of the regression of response time across the
798 reward cues. Lower values reflect higher sensitivity to reward amount. ***C.*** Correlations
799 between altered networks and BMI.
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Figures

Figure 1:

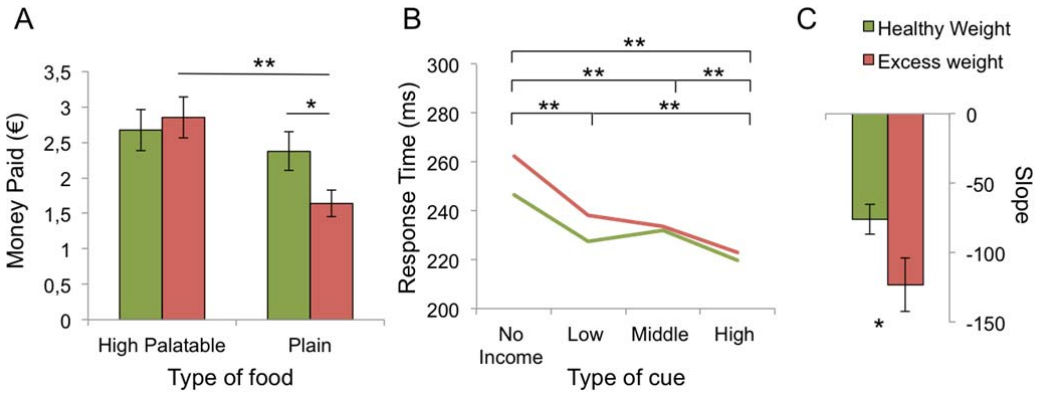
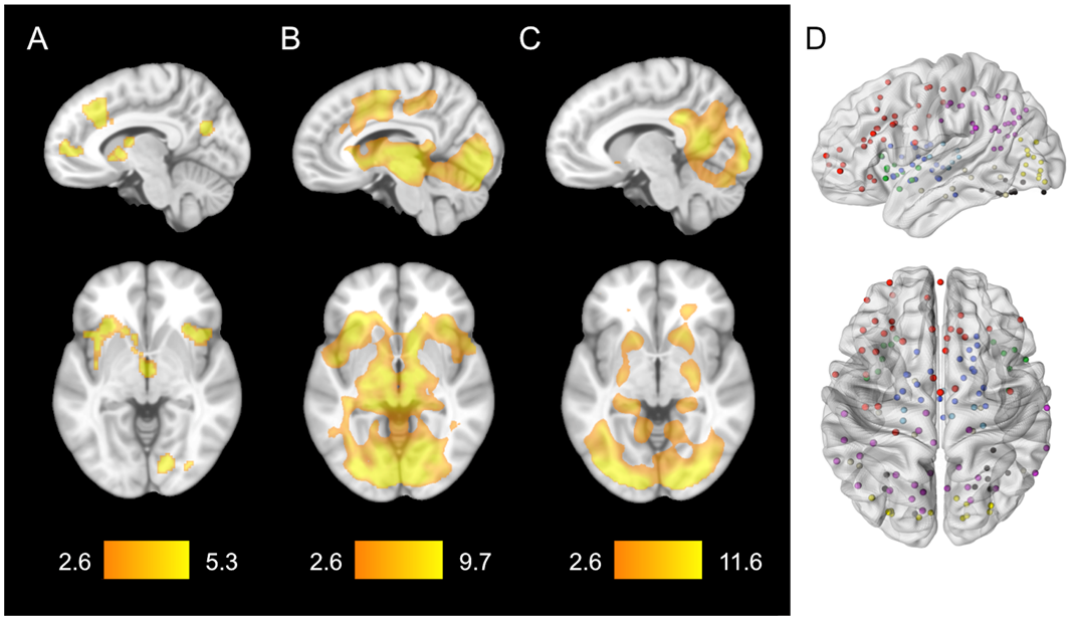
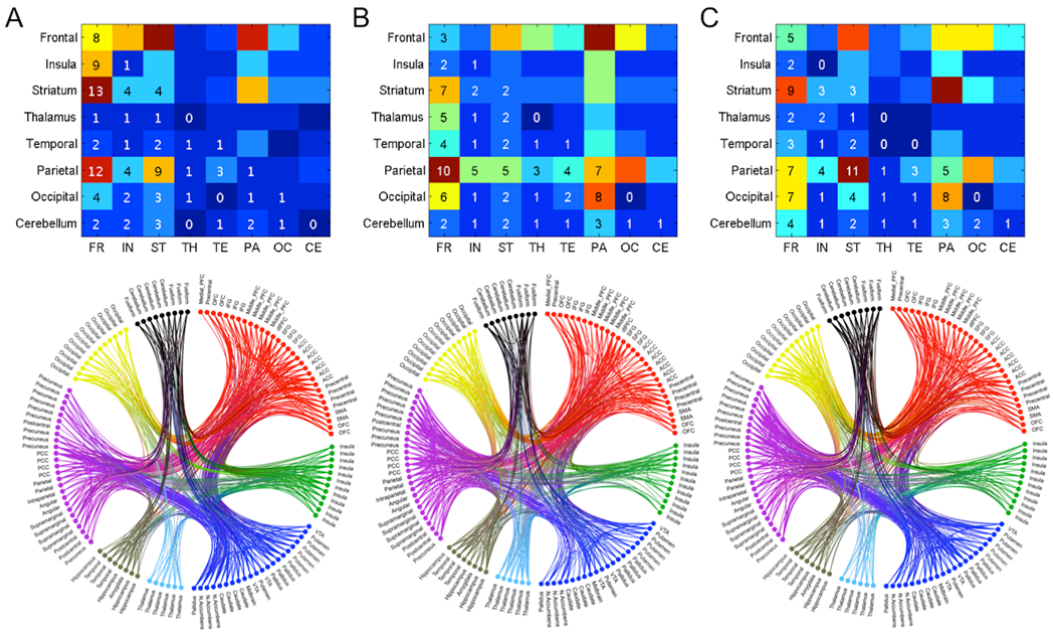


Figure 2:



819 Figure 3:



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822 Figure 4:

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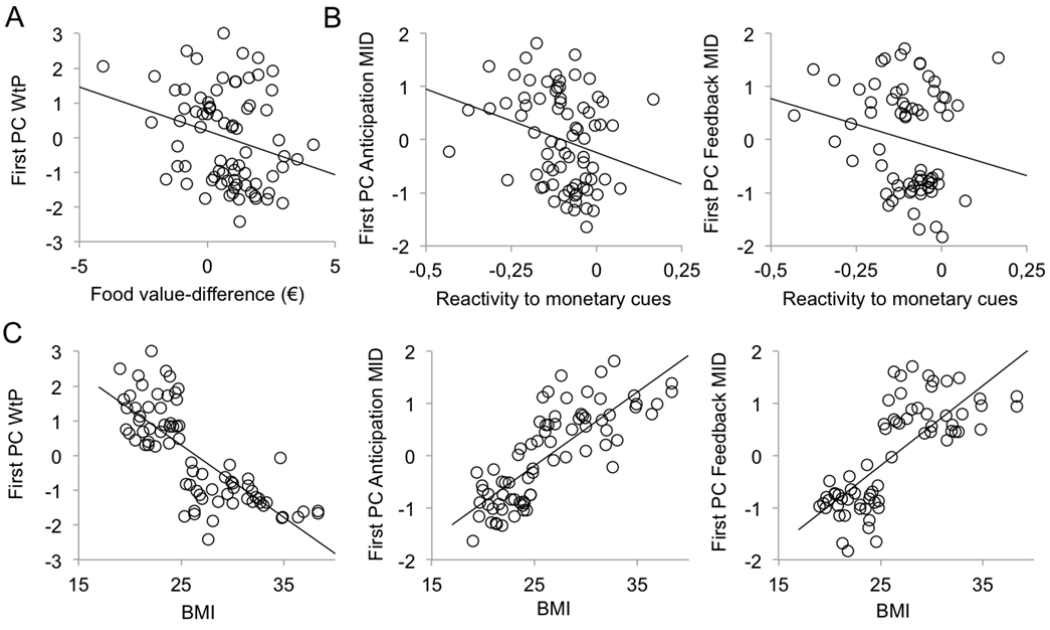

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ANEXO III

DYSFUNCTIONAL INVOLVEMENT OF EMOTION AND REWARD BRAIN REGIONS ON SOCIAL DECISION MAKING IN EXCESS WEIGHT ADOLESCENTS

Antonio Verdejo-García, Juan Verdejo-Román, Jacqueline S. Rio-Valle, Juan A. Lacomba, Francisco M. Lagos, Carles Soriano-Mas. (2014) Dysfunctional involvement of emotion and reward brain regions on social decision making in excess weight adolescents. *Human Brain Mapping, 36* (1), 226-237.

◆ Human Brain Mapping 36:226–237 (2015) ◆

Dysfunctional Involvement of Emotion and Reward Brain Regions on Social Decision Making in Excess Weight Adolescents

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Abstract: Obese adolescents suffer negative social experiences, but no studies have examined whether obesity is associated with dysfunction of the social brain or whether social brain abnormalities relate to disadvantageous traits and social decisions. We aimed at mapping functional activation differences in the brain circuitry of social decision making in adolescents with excess versus normal weight, and at examining whether these separate patterns correlate with reward/punishment sensitivity, disordered eating features, and behavioral decisions. In this fMRI study, 80 adolescents aged 12 to 18 years old were classified in two groups based on age adjusted body mass index (BMI) percentiles: normal weight ($n = 44$, BMI percentiles 5th–84th) and excess weight ($n = 36$, BMI percentile $\geq$ 85th). Participants were scanned while performing a social decision-making task (ultimatum game) in which they chose to "accept" or "reject" offers to split monetary stakes made by another peer. Offers varied in fairness (Fair vs. Unfair) but in all cases "accepting" meant both players win the money, whereas "rejecting" meant both lose it. We showed that adolescents with excess weight compared to controls display significantly decreased activation of anterior insula, anterior cingulate, and midbrain during decisions about Unfair versus Fair offers. Moreover, excess weight subjects show lower sensitivity to reward and more maturity fears, which correlate with insula activation. Indeed, blunted insula activation accounted for the relationship between maturity fears and acceptance of unfair offers. Excess weight adolescents have diminished activation of brain

Additional Supporting Information may be found in the online version of this article.

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Conflict of interest: The authors declare not having competing financial interests in relation to the work described.

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regions essential for affective tracking of social decision making, which accounts for the association between maturity fears and social decisions. *Hum Brain Mapp 36:226–237, 2015.*

Key words: obesity; social decision making; anterior insula; fMRI

INTRODUCTION

Adolescent obesity is a major public health problem that has rapidly attained epidemic levels [Gee et al., 2013; Ji, 2008; Rudolf et al., 2004; Strauss and Pollack, 2001]. Neuroscience models posit that major societal changes have transferred the obesity problem to the decision-making field: in plentiful environments, decision making is essential to prioritize what to eat (i.e., health-wise versus rewarding unhealthy food) [Zheng and Berthoud, 2007]. In fitting with this notion, we have shown that adolescents with excess weight have decreased activation of risk-sensitive brain regions and increased activation of reward-signaling brain regions during decisions about small safe rewards versus high risky gains [Delgado-Rico et al., 2013]. However, the relevance of decision making to adolescent obesity goes beyond factoring personal rewards, and extends to the social-evaluative domain. Adolescents with excess weight suffer significantly more peer bullying, marginalization, and social isolation [Ludwig, 2007; Strauss and Pollack, 2003]. These negative social experiences are the main predictor of poor psychosocial adjustment in children and adolescents with obesity [Gunnarsdottir et al., 2012]. Moreover, social stress is known to decrease prosocial choices in adolescents [Youssef et al., 2012], and preclinical studies indicate that this detrimental impact is mediated by neuroadaptations in prefrontal and limbic regions [Baarendse et al., 2013; McEwen, 2007]. Therefore, excess weight adolescents are likely to experience social stress and social decision-making deficits, which should manifest in prefrontal-limbic neuroadaptations.

The ultimatum game (UG) is a social decision-making task in which two parties (the proposer and the respondent) negotiate how to share a specified amount of money. The proposer makes the offer (sharing around 15, 25, or 50% of the stake) and the respondent chooses to either accept, in which case the money is split the way is offered, or reject, in which case none of the parties get any money. Set this way, the task raises a conflict between the cognitive choice (accepting the offer, getting the money) and the emotional response to unfairness (unfair offers elicit negative affect and increase rejection) [van't Wout et al., 2006]. The typical neural network activated during unfair versus fair offers involve the anterior insula, the dorsolateral prefrontal cortex and the anterior cingulate cortex, purportedly involved in perception of unfairness, cognitive evaluation, and conflict between emotion and cognition, respectively, [King-Casas et al., 2008; Knoch et al., 2006; Sanfey et al., 2003]. Moreover, brain regions involved in reward prediction and emotional learning further contribute to subjective feelings about the offers and behavioral decisions to accept/reject [Gospic et al., 2011; Hollmann et al., 2011]. Therefore, the UG poses an interpersonal decision-making conflict in which brain regions typically involved in emotion and reward processing come into play in the social domain [Xiang et al., 2013]. Further, the degree of engagement of this circuitry in response to unfair offers might be sensitive to psychological characteristics of the excess weight population that are disadvantageous in the social domain. Specifically, obesity has been associated with high maturity fears, which reflects the anxiety of facing the social-evaluative demands of adult life [Garner, 1994]. These fears are the most potent determinant of social maturation during adolescence [Westenberg et al., 2004]. Further, obese populations typically display low sensitivity to reward and high sensitivity to punishment [Davis, 2009], which are known to impact social function specifically during adolescence [Harms et al., 2014].

In this study, we aimed at mapping the activation of the social decision-making brain circuitry as measured by the UG in adolescents with excess versus normal weight and examining the association between separate patterns of activation (in excess vs. normal weight groups) and psychological traits including reward sensitivity and disordered eating features that are central to obesity and social decision-making behavior. On the basis of previous evidence, we expect that excess weight adolescents display blunted activation of regions involved in social decisions (i.e., anterior cingulate, insula) and social rewards (i.e., striatum, amygdala), and that these separate patterns correlate with reward sensitivity, obesity-related traits, and behavioral decisions of accept/reject.

MATERIALS AND METHODS

Participants

Eighty adolescents aged between 12 and 18 years participated in the study. They were classified in two groups (normal weight [$n = 44$] and excess weight [$n = 36$]) based on their age adjusted body mass index (BMI) percentile [Cole and Lobstein, 2012]. The classification of the two groups was conducted in alignment with the guidelines of the International Obesity Task Force and the Centers for Disease Control and Prevention: Normal weight participants had age adjusted BMI percentiles in the range between the 5th and the 84th percentile, and excess weight participants had age adjusted BMI percentiles ≥ 85 (see

TABLE I. Demographic and body characteristic, scores from SPSRQ and EDI-2 and behavioral performance during the UG inside the scanner

	Normal weight (n =44) mean (SD)	Excess weight (n = 36) mean (SD)	P-value
Demographic variables			
Age	15.32 (1.69)	15.06 (1.88)	0.514
Gender (male/female)	19/25	12/24	0.375
BMI	20.96 (2.31)	29.11 (3.90)	<0.001
Range of BMI percentiles	9–84	85–97	
Fat (%)	18.49 (33.89)	33.89 (8.33)	<0.001
Biochemical parameters			
Insulin	33.61 (37.78)	40.26(50.91)	0.548
Basal glucose	90.61 (10.42)	90.85 (7.85)	0.910
Triglycerides	66.70 (28.63)	83.11 (35.02)	0.025
HDL	59.04 (14.86)	55.38 (12.90)	0.253
Total cholesterol	150.23 (24.52)	163.86 (29.77)	0.029
Sensitivity to punishment and reward			
Sensitivity to punishment	10.52 (5.15)	10.39 (5.03)	0.907
Sensitivity to reward	11.84 (4.15)	9.78 (3.50)	0.020
Eating disorders scales			
Drive for thinness	3.00 (4.27)	7.63 (5.81)	<0.001
Bulimia	1.33 (2.18)	1.16 (1.76)	0.716
Body dissatisfaction	5.50 (5.97)	12.25 (7.32)	<0.001
Ineffectiveness	3.22 (3.53)	3.34 (3.82)	0.892
Perfectionism	5.25 (4.10)	5.44 (3.50)	0.841
Interpersonal distrust	3.56 (3.00)	2.50 (2.75)	0.137
Interoceptive awareness	4.17 (3.92)	4.09 (3.60)	0.937
Maturity fears	5.50 (2.81)	8.31 (4.84)	0.006
Asceticism	3.64 (2.65)	3.91 (2.52)	0.672
Impulse regulation	3.39 (3.79)	4.00 (4.17)	0.529
Social insecurity	4.14 (3.45)	3.75 (3.62)	0.652
UG behavioral performance			
Accepted offers (%)			
All offers	58.69 (19.74)	55.90 (21.18)	0.543
Fair offers	82.36 (19.49)	83.84 (21.11)	0.870
Unfair offers	46.70 (28.41)	42.05 (29.53)	0.476
Response time (s)			
All offers	1.010 (0.297)	1.029 (0.275)	0.777
Fair offers	0.934 (0.293)	0.971 (0.284)	0.568
Unfair offers	1.046 (0.316)	1.053 (0.279)	0.912

SD, standard deviation; BMI, body mass index; s, seconds; HDL, high-density lipoprotein.

Table I). Participants' sociodemographic characteristics, BMIs, percentage fat, and blood count-based biochemical parameters are as well displayed in Table I. Participants were recruited from the paediatrics and endocrinology services of the Hospital "Virgen de las Nieves" in Granada (Spain), and from schools located in the same geographical area. The inclusion criteria for participants were defined as follows: (i) age range between 12 and 18 years; (ii) BMI percentiles falling within the intervals categorized as overweight or obesity (≥85: Excess weight group), or normal weight (5–84: Normal weight group); (iii) absence of history or current evidence of neurological or psychiatric disorders, assessed by participants and parents interviews and the Eating Disorder Inventory [Garner, 1994]; (iv) absence of significant abnormalities on magnetic resonance imaging (MRI) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects). All participants had normal or corrected-to-normal vision.

The study was approved by the Ethics Committee for Human Research of the Universidad de Granada. Both participants and parents signed an informed consent form.

Experimental Task

We utilized an fMRI suitable previously validated UG task [Crockett et al., 2008] involving one proposer and one

responder. Participants always played the responder's role. To enhance the credibility and the interpersonal appeal of the game, participants were told that the proposer was another participant of the research project, who had left a picture of himself/herself and a list of proposals after his/her own scanning session. We told them that this proposer had been randomly selected from the pool of previous participants, and that they could see his/her picture during the game. In addition, they were told they would have the opportunity to play the role of the proposer with other volunteers who would participate in the future, if they would allow their photograph to be taken and used in future sessions, and submit their own proposals for several stake sizes. In reality, the picture of the proposer was taken from a web pool of images and utilized with all participants to minimize potential confounders associated with social identification.

In each trial, participants were initially prompted with a picture of the proposer (2 s), followed by a graphical depiction of the money available to split in that particular trial (indicated by the number expressed in Euro and the length of a horizontal light-colored bar) and the amount of money that the proposer offered to share (indicated by the number expressed in Euro and the proportion of the above bar filled in red; 1 s). Once the offer was presented, participants had 3 s to accept or reject the offer using designated buttons in a button-box response pad. They were told that if they accepted the proposer's offer, both players were supposed to be paid in the specified way. Conversely, by rejecting the offer, none of them would get the money. After the response, each trial was followed by 3 s of baseline during which a fixation cross was presented in the screen until the next trial started, for a total trial duration of 9 s (see Fig. 1). Event onsets were jittered with respect to scan onsets across trials [Henson and Mouchlianitis, 2007].

The task included two types of offers varying on degree of fairness: Fair offers, in which the proposer offered to share around 46% of the money, and Unfair offers, in which the proposer offered to share between 15 and 25% of the money. Participants were informed that payments were hypothetical. Our main interest was to contrast group differences in brain activations involved in (1) making decisions about Unfair versus Fair offers (indexing the conflict between perception of unfairness and cognitive evaluation); and (2) deciding to Reject versus Accept the offers (indexing emotion-based decisions involving missing reward vs. strategic decisions).

Inside scanner behavioral measures

Acceptance rates (% of offers accepted) and response times were calculated for each participant as a function of offer type.

Outside scanner behavioral measures

The Sensitivity to Punishment and Sensitivity to Reward Questionnaire* (SPSRQ) *[Torrubia et al., 2001]. It is a 48 yes–no response item questionnaire that measures trait sensitivity to reward (24 items) and punishment (24 items). The SPSRQ has demonstrated sound psychometric properties, construct validity, and significant associations with biologically plausible brain systems [Costumero et al., 2013].

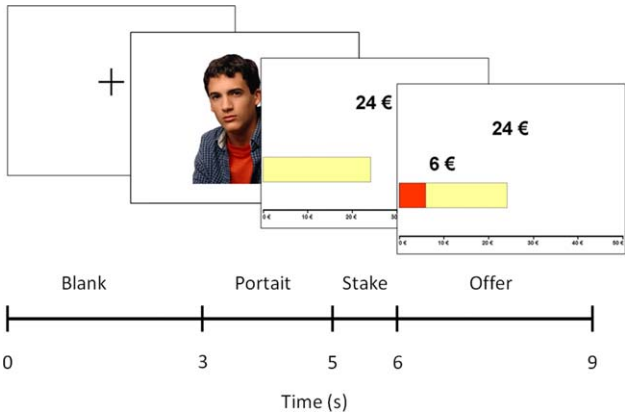

Figure 1.
Schematic representation of the UG task through depiction of one experimental trial. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The Eating Disorder Inventory—Second Edition (EDI-2) [Garner, 1994]. It is a 64-item self-report measure assessing disadvantageous psychological traits commonly associated with eating disorders. Responses are made on a 6-point Likert-type scale ranging from never to always. The EDI-2 has demonstrated sound psychometric properties and construct validity [Elder and Grilo, 2007; Reas et al., 2006].

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). 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 × 230 mm, 96 × 96 matrix, flip angle = 90°, 21 4 mm axial slices, 1-mm gap, 442 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 × 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, Northridge, CA) and responses were recorded through Evoke Response Pad System (Resonance Technology).

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, UK), running under MATLAB R2009 (MathWorks, Natick, MA). Preprocessing included reslicing to the first image of the time series, slice timing correction, 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 Analysis

Behavioral analyses

We used the Statistical Package for the Social Sciences version 19 (SPSS 19; Chicago, IL) for these analyses. We conducted independent-sample *t*-tests (two-tailed) to compare the two groups on relevant sociodemographic variables and inside and outside scanner behavioral measures.

fMRI, main task effects

The conditions of interest were modeled from the time at which the offer was presented to the time at which participants responded. Two contrasts of interest were defined at the first-level (single-subject) and between-group analyses: (1) "Unfair > Fair offers," (2) "Reject > Accept unfair offers." The BOLD response at each voxel was convolved with the SPM8 canonical hemodynamic response function and a high-pass filter was used to remove low-frequency noise (1/128 Hz). The resulting first-level contrast images were then carried forward to subsequent second-level random-effect (group) analyses. Main task effects were assessed with one-sample *t*-test while two-sample *t*-tests were used to assess between-group differences. The results were corrected for multiple comparisons with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox [Song et al., 2011; Ward, 2013]. For one-sample *t*-tests, input parameters included a brain mask of 161,455 voxels, an individual voxel threshold probability of 0.005, and a cluster connection radius of 5 mm, considering the actual smoothness of data after model estimation. A minimum cluster extent (KE) of 436 voxels was estimated to satisfy a $P_{FWE} < 0.05$. Significance in two-sample *t*-tests was assessed using the same input parameters, masking results on the basis of activation and deactivation maps derived from the one-sample *t*-tests. Therefore, for contrasts 1 and 2, respectively, a minimum cluster extent (KE) of 54 and 87 voxels (within brain masks of 17,968 and 18,266 voxels), was estimated to satisfy a $P_{FWE} < 0.05$. All analyses were conducted both including and not including age as a nuisance variable. As in both cases we obtained the same results, we only report uncorrected effects.

Correlation analyses

Correlation analyses were performed in SPSS. Specifically, the beta eigenvalues from the peak coordinates of each cluster of significant brain results were extracted for each participant, and then correlated with behavioral measures within each group. Correlation analyses were complemented with structural equation modeling (SEM) analyses aimed at testing and estimating causal relationships between the different variables involved in our imaging and behavioral assessments. Specifically, we examined whether obesity-related psychological traits were associated with the decision of accepting or rejecting social offers through the activation/deactivation of specific brain regions. Thus, we estimated the direct effect of trait measures on the behavioral response, the effect of trait measures on brain activity (the brain-trait pathway), the effect of brain activity on the behavioral response after controlling for trait measures (the brain-state pathway), and the indirect relationship (through activation/deactivation of specific brain regions) between trait measures and the behavioral response. The effect and statistical significance of the different paths were estimated using the mediation toolbox (http://wagerlab.colorado.edu/files/tools/mediation.html).

RESULTS

Behavioral Results

Independent-sample *t*-tests showed no significant between-group differences on acceptance rates or response times to any type of offer ($P > 0.1$ in all cases). Participants with excess weight showed significantly lower scores in sensitivity to reward, and significantly higher scores in drive for thinness, body dissatisfaction, and maturity fears compared to normal weight peers.

Imaging Results

Unfair > Fair offers.

Intra-group activations

One-sample *t*-tests showed that Normal weight participants significantly activated medial wall regions (including the anterior cingulate cortex, the medial frontal gyrus, and the supplementary motor area), the superior and middle fontal gyrus, the thalamus (extending to midbrain and amygdala), and the right precentral gyrus (somatosensory cortex encompassing posterior insula). Normal weight participants also showed significant deactivations in left parietal and occipital cortices. Excess weight participants did not show significantly increased activations. However, they showed significant deactivations in a large cluster including left anterior insula, frontal operculum, and superior temporal gyrus. Similar to normal weight adolescents, they also showed deactivations in bilateral parietal and occipital cortices (extending to the fusiform gyri; Fig. 2 and Supporting Information Table SI).

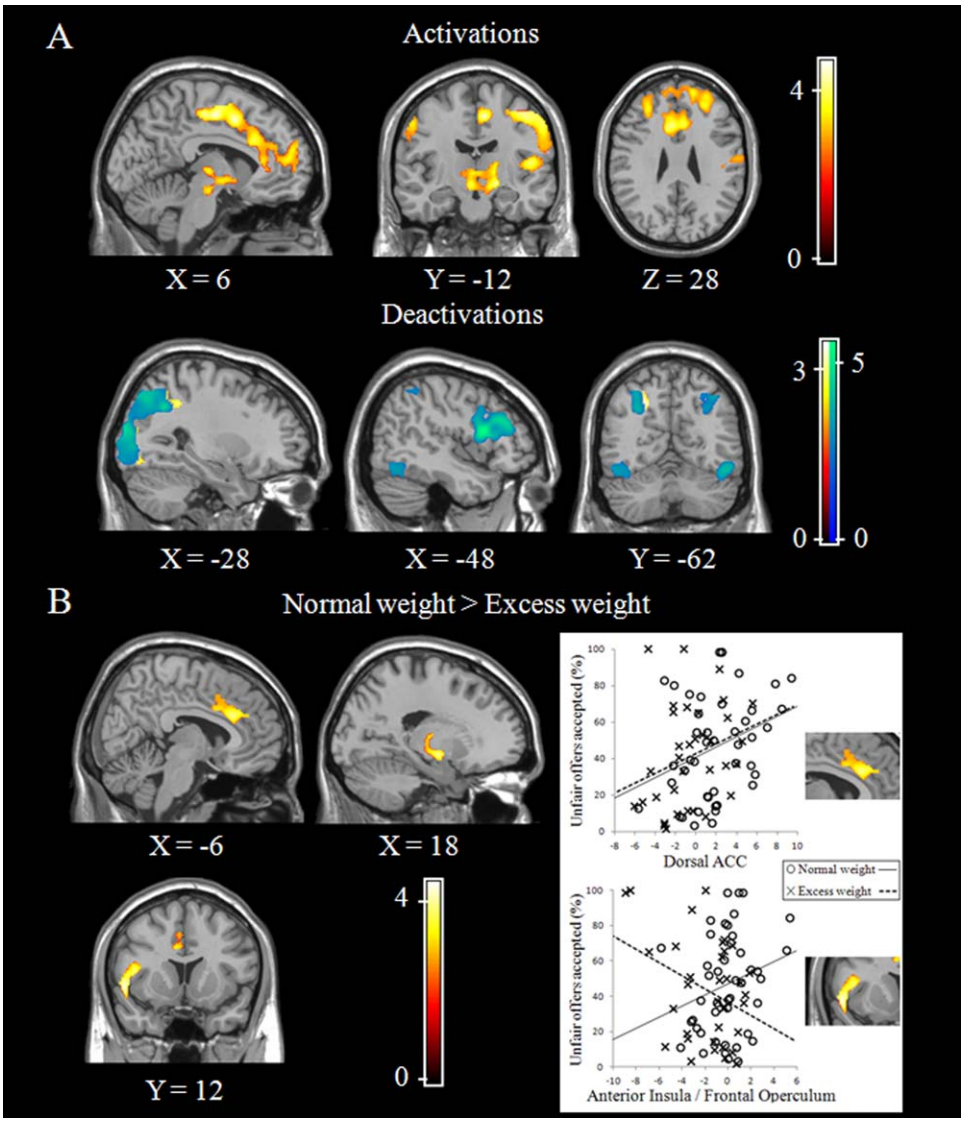

Figure 2.

Brain activations, deactivations, and group differences during "Unfair > Fair" contrast. Note: (**A**) Top panel displays the brain regions showing activations and deactivations during "Unfair > Fair" offers in both groups. Warm colors reflect normal weight group and cold colors reflect excess weight group. (**B**) Bottom panel displays the differences between groups. Bottom-right panel displays the correlations between "Unfair offers accepted" and peaks activation at dorsal ACC and anterior insula/frontal operculum in the "Unfair > Fair" comparison. *X*, *Y* and *Z* denote coordinate in standard MNI space. Right hemisphere is displayed on the right. Color bar indicates *T* value. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Group differences

Excess weight adolescents showed significantly reduced activations in dorsal anterior cingulate cortex, left anterior insula/frontal operculum, superior temporal gyrus, and thalamus and midbrain (extending to the amygdala) compared to normal weight peers (Fig. 2 and Supporting Information Table SI).

Correlations between brain activation patterns and behavioral measures

Regarding acceptance rates, the proportion of unfair offers accepted positively correlated with dorsal anterior cingulate cortex activation in normal and excess weight subjects, although such correlation was statistical significant only in the former ($r = 0.321$, $P = 0.034$, and $r = 0.283$,

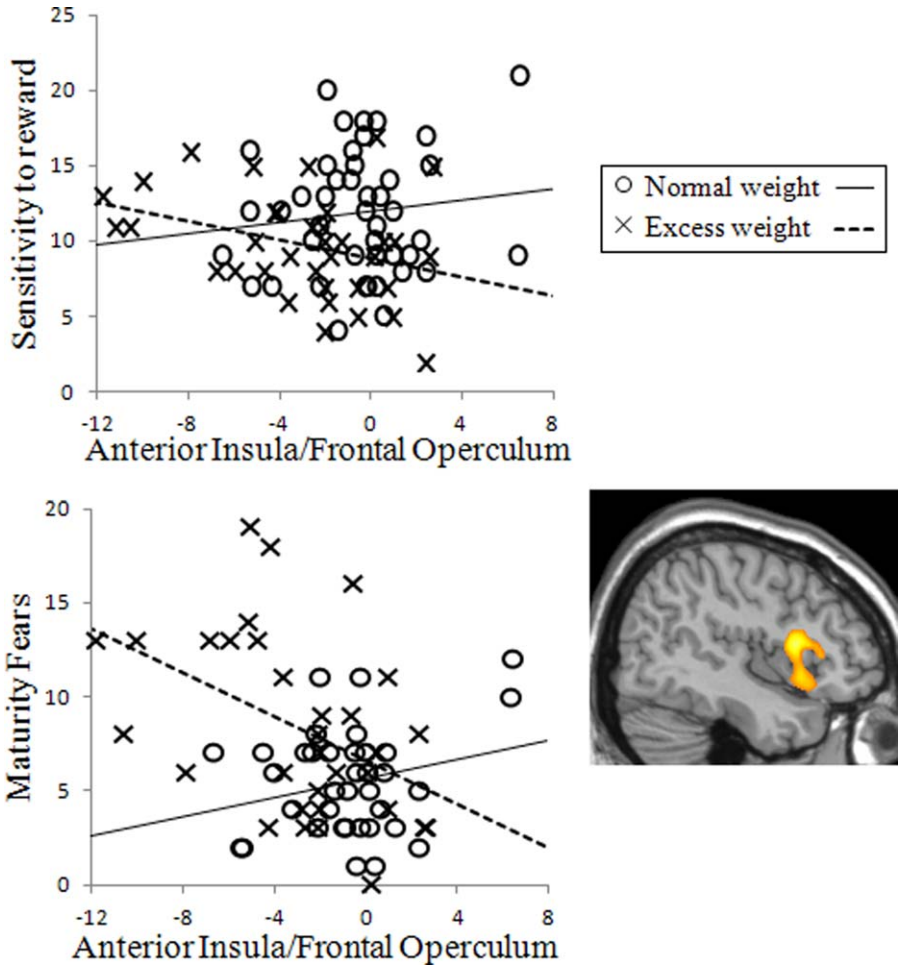

Figure 3.

Scatterplots displaying the correlation between behavioral measures ("Sensitivity to Reward" and "Maturity Fears") and brain activation patterns during the "Unfair > Fair" contrast (peak activation at the anterior insula/frontal operculum region). The data of excess weight and normal weight participants are represented with different symbols (crosses and circles, respectively) to illustrate the different direction of the correlation as a function of group. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$P = 0.105$, respectively). By contrast, the proportion of unfair offers accepted correlated negatively with anterior insula/frontal operculum activation in excess weight participants ($r = -0.353$, $P = 0.038$), whereas this correlation was positive and nonsignificant in the normal weight group ($r = 0.241$, $P = 0.114$). The direct comparison between these correlations revealed a significant group difference, with $z = 2.63$, $P = 0.008$ (Fig. 2).

As for psychological traits, both maturity fears and sensitivity to reward scores negatively correlated with anterior insula/frontal operculum activation in excess weight participants ($r = -0.443$, $P = 0.011$ and $r = -0.335$, $P = 0.046$, respectively), whereas these correlations were positive and nonsignificant in the normal weight group ($r = 0.245$, $P = 0.149$ and $r = 0.121$, $P = 0.433$). The direct comparison between these correlations revealed a significant group difference, with $z = 2.85$, $P = 0.004$ (for maturity fears) and $z = 2.01$, $P = 0.044$ (for sensitivity to reward; Fig. 3). We found no significant correlations between drive for thinness or body dissatisfaction and brain activation patterns.

As in excess weight participants, anterior insula/frontal operculum activation was significantly related to both the behavioral response (i.e., the proportion of unfair offers accepted) and specific trait measures (maturity fears and sensitivity to reward); in a post hoc analysis, we studied the relationships between these variables using a SEM approach. Specifically, we observed that maturity fears were indirectly and positively associated with the acceptance of unfair offers through the decreased anterior insula/frontal operculum activation observed in excess

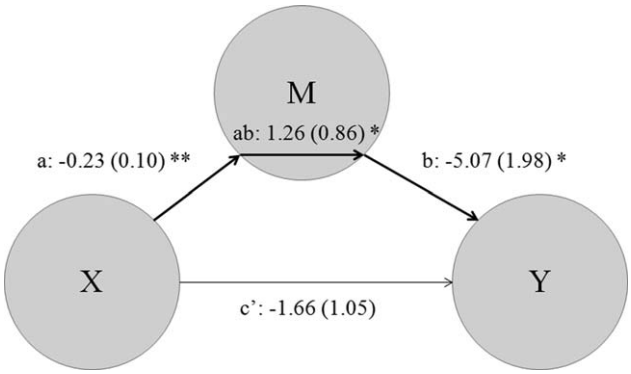

Figure 4.

Path diagram showing the relationships between maturity fears (*X*), percentage of unfair offers accepted (*Y*), and insula activation (*M*) during the UG task in excess weight participants. *X* was inversely related to *M* (*a*, or the brain-trait pathway), while *M* was also inversely related to *Y* (*b*, or the brain-state pathway). *X* was not directly related to *Y* (*c'*), but these two measurements were indirectly related through *M* (*a***b*). **P* < 0.05, ***P* < 0.01.

weight participants ($z = 2.17$, $P = 0.03$; Fig. 4). Of note, the direct correlation between maturity fears (*X*) and acceptance of unfair offers (*Y*) was negative, although nonsignificant (zero-order or *c*: $z = -0.44$, $P = 0.660$). The lack of significance of direct effects indicates that the association between maturity fears and acceptance of unfair offers is exclusively accounted for the pattern of insula activation. Moreover, the opposite signs observed between direct (*c'*) and indirect (*ab*) effects further supports that the association between these behavioral variables is specifically conveyed by the pattern of insula activation. None of these effects were observed in control participants. Likewise, we did not observe any significant relationship between sensitivity to reward and behavioral responses in the task.

REJECT > ACCEPT UNFAIR OFFERS

Intra-group activations

One-sample *t*-test showed that during rejected offers, both groups showed significant activations in the dorsal anterior cingulate cortex, the somatosensory cortices, the insula, and the adjacent temporal cortices. However, in normal weight participants, the activation in the postcentral gyri extended to the precentral gyri and additional activations involved the supplementary motor area and the thalamus extending to putamen, midbrain, and the left amygdala (Fig. 5 and Supporting Information Table SII).

Group differences

We did not observe significant differences between the groups at the selected threshold.

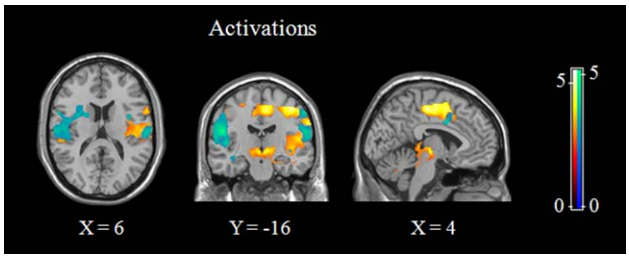

Figure 5.

Brain regions activated during "Reject > Accept" unfair offers in both groups. Note: Warm colors reflect normal weight group and cold colors reflect excess weight group. *X*, *Y*, and *Z* denote coordinate in standard MNI space. Right hemisphere is displayed on the right. Color bar indicates *T* value. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Correlations between brain activation patterns and behavioral decisions

Regarding acceptance rates, the proportion of unfair offers accepted positively correlated with amygdala activation in excess weight participants ($r = 0.448$, $P = 0.032$), whereas this correlation was negative, albeit nonsignificant, in the normal weight group ($r = -0.227$, $P = 0.205$). The direct comparison between these correlations revealed a significant group difference, with $z = 2.47$, $P = 0.013$ (Fig. 6).

As for psychological traits, sensitivity to punishment positively correlated with right somatosensory cortex activation in excess weight participants ($r = 0.415$, $P = 0.049$), whereas this correlation was negative and nearly significant in the normal weight group ($r = -0.339$, $P = 0.053$). The direct comparison between these correlations revealed a significant group difference, with $z = 2.75$, $P = 0.006$ (Fig. 6). We found no significant correlations between drive for thinness or body dissatisfaction and brain activation patterns.

DISCUSSION

We showed that adolescents with excess weight have reduced activation of brain regions involved in emotion and reward processing including the anterior cingulate cortex, the insula, and the thalamus during social decision making. Furthermore, we showed that deactivation of the anterior insula correlates with higher sensitivity to reward and higher maturity fears uniquely in the excess weight group and that such deactivation accounts for an indirect relationship between maturity fears and a higher probability of accepting unfair offers. Moreover, somatosensory cortex activation during rejection of unfair offers positively correlates with sensitivity to punishment, and amygdala activation positively correlates with acceptance of unfair offers uniquely in the excess weight group. Collectively, our findings indicate that adolescents with excess weight display blunted activation of the social decision-making

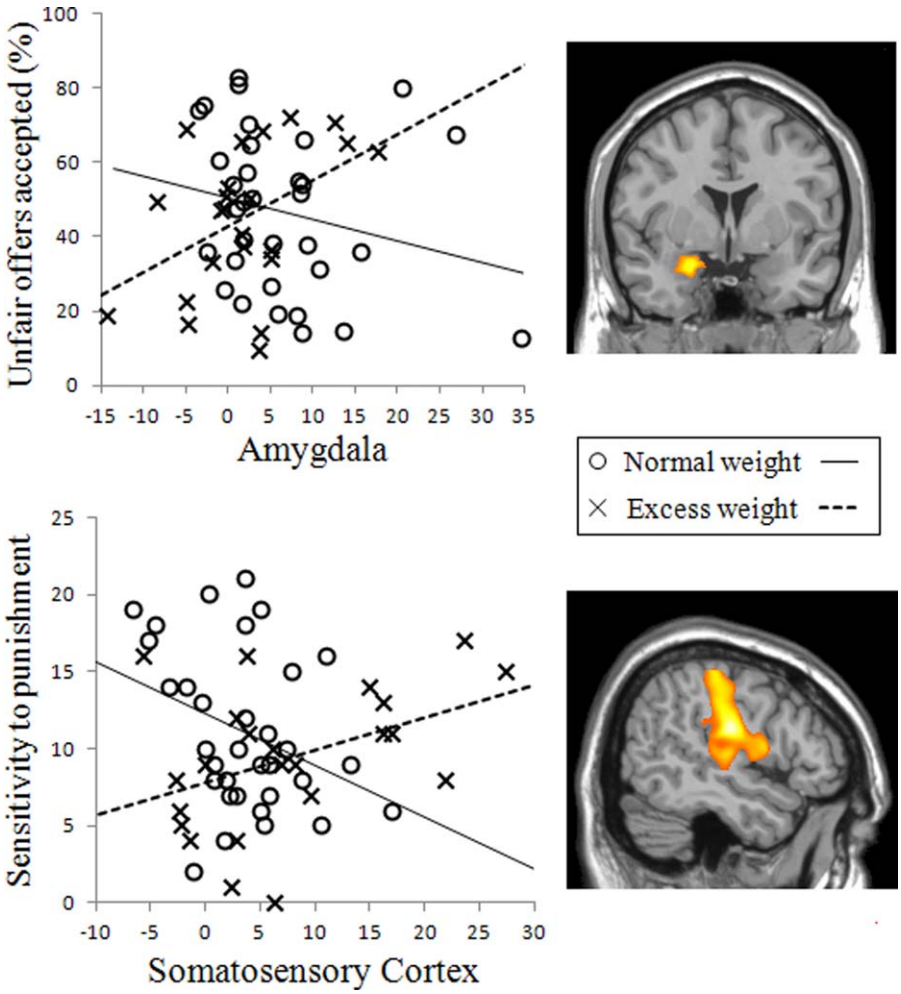

Figure 6.

Scatterplots displaying the correlation between behavioral measures ("Unfair offers accepted" and "Sensitivity to Punishment" and brain activation patterns during the "Reject > Accept" contrast (peak activations at the amygdala and the postcentral cortex regions, respectively). The data of excess weight and normal weight participants are represented with different symbols (crosses and circles, respectively) to illustrate the different direction of the correlation as a function of group. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

circuitry, which correlates with disadvantageous traits and interpersonal decisions.

Our social decision-making task (UG) induced a reliable pattern of brain activations including the dorsal anterior cingulate cortex, the insula and thalamic/limbic regions, which is in fitting with previous evidence [Gospic et al., 2011; Sanfey et al., 2003]. Moreover, the activation of the anterior cingulate cortex correlated with acceptance rates in both groups, indicating good fit between brain activation measures and behavioral decisions [Glascher et al., 2012]. In this context, adolescents with excess weight exhibited significantly decreased activation of dorsal anterior cingulate cortex and thalamic regions and concomitant deactivation of the anterior insula/frontal opercular region. The dorsal anterior cingulate and the thalamus are functionally associated with the generation of emotional responses to social stressors [Güroglu et al., 2011]. The anterior insula is generally associated with perception of bodily signals and emotional awareness [Wager et al., 2009]. Moreover, in the context of the UG, insula activation is specifically associated with subjective feelings of unfairness [Sanfey et al., 2003]. Therefore, the decreased activation of this set of regions suggests decreased affective tracking of social unfairness in the excess weight group.

The central question is whether this brain activation pattern is relevant and potentially disadvantageous for the social behavior of adolescents with excess weight. Correlation analyses strongly suggest this is the case. First, insula

deactivation correlated with higher acceptance rates, suggesting that reduced affective tracking of social unfairness is linked to more acceptances of unfair offers. As the contribution of the affective neural circuitry is essential for adequate social functioning [Bar-On et al., 2003], this pattern is likely to impact the real-life interpersonal decisions of obese adolescents. Moreover, the opposite pattern (positive correlations, hence more insula greater acceptance rates) has been previously demonstrated in healthy adolescents [Güroglu et al., 2011], similar to what we showed in our control group. Second, we found that insula deactivation correlated with increased maturity fears. Fears of social-evaluative situations are indicative of poor social-cognitive development [Westenberg et al., 2004]. Therefore, this finding is the first to demonstrate an association between poor affective tracking of social unfairness (indexed by insula deactivation) and this hindering trait of adolescent obesity. Finally, and linking the two above described relationships, we also showed that maturity fears are indirectly associated to social decision making through blunted insula activation. Such findings demonstrate for the first time a significant association between a trait marker of eating disorders and the social decision-making behavior of excess weight adolescents conveyed by a particular pattern of brain activity. This notion agrees with developmental models that highlight the insula as a key region for the maturation of social decision-making systems during adolescence [Smith et al., 2014]. At difference with maturity fears, we found no significant associations between brain activation patterns and body dissatisfaction and drive for thinness. This discrepancy is reasonable as the latter traits basically reflect the difficulties associated with physical weight gain, whereas maturity fears capture personality and interpersonal aspects of obesity [Garner, 1994]. Therefore, this negative finding conceivably speaks of the specificity of the UG task as a biomarker of social disadvantage in adolescent obesity.

Moreover, insula deactivation also correlated with higher sensitivity to reward. Sensitivity to reward has been associated with higher risk-taking in social scenarios specifically during adolescence [Chein et al., 2011]. Furthermore, lower insula activations predict greater risk taking [Mohr et al., 2010] and this notion has been linked to insula-mediated sensitization of the reward system [Smith et al., 2014]. More broadly, sensitivity to reward has been associated with several aspects of unhealthy eating, including binge eating patterns [Ziauddeen et al., 2012]. Uncoupling of reward (i.e., wanting) from emotion (i.e., liking) processing is as well reminiscent of addictive features, in which sensitivity to rewarding stimuli increases while the hedonic quality of these stimuli decreases [Robinson and Berridge, 2003]. Also in this case, the opposite pattern is typically found in healthy adolescents [Jarcho et al., 2012], consistent with what we showed in our control group. Collectively, our findings suggest that the anterior insula, which is strongly involved in the processing of highly appetizing food [Wang et al., 2004], may consequently lose control over more complex reward-related choices including social decisions.

We did not find significant group differences in brain activation as a function of type of choice (reject vs. accept). However, the relationship between behavioral responses and brain activity was again distinctive in the excess weight group. Specifically, reject-related amygdala activation correlated with greater probability of accepting unfair offers. Such finding suggests that excess weight adolescents display a paradoxically increased negative emotional reactivity in situations where they adopt a more assertive social role. Therefore, this finding suggests an abnormal role of the amygdala in directing social behavior, as greater amygdala activation is typically associated with rapid rejection of unfair offers [Gospic et al., 2011]. Moreover, the pattern of somatosensory activation contingent to rejecting offers (entailing losing reward) was positively correlated with sensitivity to punishment in the excess weight group, and negatively correlated with this trait in controls. Somatosensory regions are relevant to anticipate reinforcement outcome [Bieszczad and Weinberger, 2012], but in excess weight subjects the activation of these regions seem to reflect a trait susceptibility to reward omission or punishment. Hence, similar to those results and to the reward sensitivity-insula correlations reported above, this finding indicates that the association between reinforcement-based temperamental traits and somatosensory regions is abnormal in excess weight adolescent populations.

Our findings show that excess weight adolescents show dysfunctional engagement of brain regions involved in emotion perception and reward during social decisions. These early deficits may not only predict poor clinical prognosis [Ludwig, 2007] but also lie at the root of well-described socioeconomic disadvantage in the adult obesity population, including wage penalty and hiring discrimination [Agerström and Rooth, 2011; Baum and Ford, 2004; Caliendo and Lee, 2013; Latner et al., 2012]. This study has several strengths, including a large sample size, detailed medical and psychological characterization of participants, and novel use of a social decision-making paradigm in this population. Nonetheless, findings should also be assessed in the context of several limitations. First, our sample spans a 6-year adolescent period characterized by intense maturational processes, which may have impacted results. However, the psychological features addressed in the UG seem to be already optimized by the age of 9 [Güroglu et al., 2009], and analyses covaried by age showed equivalent results. Second, we used a simple version of the UG because our main interest was to raise the conflict between emotion and cognition in an interpersonal scenario. We are aware of the existence of a more specific UG literature; however, the purpose of this study was not to experimentally characterize the task but to make it instrumental to understand a clinical population. Similarly, we did not detect behavioral differences between the groups in the UG task. This is likely due to the fact that

this UG task was specifically designed for fMRI experiments, seeking maximization of engagement of relevant brain circuitry but not of potential behavioral differences. Future studies that utilize UG tasks more sensitive to behavioral profiles are warranted to reveal if our brain activation findings are mirrored by conceptually compatible behavioral group differences. Finally, future studies and longitudinal designs are warranted to address whether these deficits precede excess weight problems or arise as a consequence of weight gain or related psychosocial burden. Similarly, future studies are warranted to investigate whether these patterns can predict clinical prognosis and socioeconomic disadvantage during adulthood.

CONCLUSION

We show that excess weight adolescents display impaired activation of affective brain regions during social decision making, and that blunted activation of this circuitry accounts for the association between maturity fears and social decisions. The study yields a high translational value as the UG neural circuitry may serve as a dimensional biomarker of the risk of social disadvantage in obesity and of the effectiveness of novel treatments that focus on the social burden of obesity.

ACKNOWLEDGEMENTS

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REFERENCES

Agerström J, Rooth DO (2011): The role of automatic obesity stereotypes in real hiring discrimination. J Appl Psychol 96:790–805.

Baarendse PJ, Counotte DS, O'Donnell P, Vanderschuren LJ (2013): Early social experience is critical for the development of cognitive control and dopamine modulation of prefrontal cortex function. Neuropsychopharmacology 38:1485–1494.

Bar-On R, Tranel D, Denburg NL, Bechara A (2003): Exploring the neurological substrate of emotional and social intelligence. Brain 126:1790–1800.

Baum CL, Ford WF (2004): The wage effects of obesity: A longitudinal study. Health Econ 13:885–899.

Bieszczad KM, Weinberger NM (2012): Extinction reveals that primary sensory cortex predicts reinforcement outcome. Eur J Neurosci 35:598–613.

Caliendo M, Lee WS (2013): Fat chance! Obesity and the transition from unemployment to employment. Econ Hum Biol 11:121–133.

Chein J, Albert D, O'Brien L, Uckert K, Steinberg L (2011): Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. Dev Sci 14:F1–F10.

Cole TJ, Lobstein T (2012): Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes 7:284–294.

Costumero V, Barros-Loscertales A, Bustamante JC, Ventura-Campos N, Fuentes P, Ávila C (2013): Reward sensitivity modulates connectivity among reward brain areas during processing of anticipatory reward cues. Eur J Neurosci 38: 2399–2407.

Crockett MJ, Clark L, Tabibnia G, Lieberman MD, Robbins TW (2008): Serotonin modulates behavioral reactions to unfairness. Science 320:1739.

Davis C (2009): Psychobiological traits in the risk profile for overeating and weight gain. Int J Obes 33(Suppl 2):S49–S53.

Delgado-Rico E, Soriano-Mas C, Verdejo-Roman J, Schmidt Rio-Valle J, Verdejo-Garcia A (2013): Decreased insular and increased midbrain activations during decision-making under risk in adolescents with excess weight. Obesity 21: 1662–1668.

Elder KA, Grilo CM (2007): The Spanish language version of the Eating Disorder Examination Questionnaire: Comparison with the Spanish language version of the eating disorder examination and test-retest reliability. Behav Res Ther 45:1369–1377.

Garner DM. 1994: Eating Disorders Inventory-2. Odessa, FL: Psychological Assessment Resources.

Gee S, Chin D, Ackerson L, Woo D, Howell A (2013): Prevalence of childhood and adolescent overweight and obesity from 2003 to 2010 in an integrated health care delivery system. J Obes 2013:417907.

Glascher J, Adolphs R, Damasio H, Bechara A, Rudrauf D, Calamia M, Paul LK, Tranel D (2012): Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. Proc Natl Acad Sci USA 109:14681–14686.

Gospic K, Mohlin E, Fransson P, Petrovic P, Johannesson M, Ingvar M (2011): Limbic justice–amygdala involvement in immediate rejection in the Ultimatum Game. PLoS Biol 9: e1001054.

Gunnarsdottir T, Njardvik U, Olafsdottir AS, Craighead LW, Bjarnason R (2012): Teasing and social rejection among obese children enrolling in family-based behavioural treatment: Effects on psychological adjustment and academic competencies. Int J Obes 36:35–44.

Güroglu B, van den Bos W, Crone EA (2009): Fairness considerations: Increasing understanding of intentionality during adolescence. J Exp Child Psychol 104:398–409.

Güroglu B, van den Bos W, van Dijk E, Rombouts SA, Crone EA (2011): Dissociable brain networks involved in development of fairness considerations: Understanding intentionality behind unfairness. NeuroImage 57:634–641.

Harms MB, Zayas V, Meltzoff AN, Carlson SM (2014): Stability of executive function and predictions to adaptive behavior from middle childhood to pre-adolescence. Front Psychol 5:331.

Henson RN, Mouchlianitis E (2007): Effect of spatial attention on stimulus-specific haemodynamic repetition effects. NeuroImage 35:1317–1329.

Hollmann M, Rieger JW, Baecke S, Lützkendorf R, Müller C, Adolf D, Bernarding J (2011): Predicting decisions in human social interactions using real-time fMRI and pattern classification. PloS One 6:e25304.

Jarcho JM, Benson BE, Plate RC, Guyer AE, Detloff AM, Pine DS, Leibenluft E, Ernst M (2012): Developmental effects of decision-making on sensitivity to reward: An fMRI study. Dev Cogn Neurosci 2:437–447.

Ji CY (2008): The prevalence of childhood overweight/obesity and the epidemic changes in 1985-2000 for Chinese school-age children and adolescents. Obes Rev 9:78–81.

King-Casas B, Sharp C, Lomax-Bream L, Lohrenz T, Fonagy P, Montague PR (2008): The rupture and repair of cooperation in borderline personality disorder. Science 321:806–810.

Knoch D, Pascual-Leone A, Meyer K, Treyer V, Fehr E (2006): Diminishing reciprocal fairness by disrupting the right prefrontal cortex. Science 314:829–832.

Latner JD, Ebneter DS, O'Brien KS (2012): Residual obesity stigma: An experimental investigation of bias against obese and lean targets differing in weight-loss history. Obesity 20:2035–2038.

Ludwig DS (2007): Childhood obesity—The shape of things to come. N Engl J Med 357:2325–2327.

McEwen BS (2007): Physiology and neurobiology of stress and adaptation: Central role of the brain. Physiol Rev 87:873–904.

Mohr PN, Biele G, Heekeren HR (2010): Neural processing of risk. J Neurosci 30:6613–6619.

Reas DL, Grilo CM, Masheb RM (2006): Reliability of the Eating Disorder Examination-Questionnaire in patients with binge eating disorder. Behav Res Ther 44:43–51.

Robinson TE, Berridge KC (2003): Addiction. Annu Rev Psychol 54:25–53.

Rudolf MC, Greenwood DC, Cole TJ, Levine R, Sahota P, Walker J, Holland P, Cade J, Truscott J (2004): Rising obesity and expanding waistlines in schoolchildren: A cohort study. Arch Dis Child 89:235–237.

Sanfey AG, Rilling JK, Aronson JA, Nystrom LE, Cohen JD (2003): The neural basis of economic decision-making in the Ultimatum Game. Science 300:1755–1758.

Smith AR, Steinberg L, Chein J (2014): The role of the anterior insula in adolescent decision making. Dev Neurosci 36:196–209.

Song XW, Dong ZY, Long XY, Li SF, Zuo XN, Zhu CZ, He Y, Yan CG, Zang YF (2011): REST: A toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6:e25031.

Strauss RS, Pollack HA (2001): Epidemic increase in childhood overweight, 1986–1998. JAMA 286:2845–2848.

Strauss RS, Pollack HA (2003): Social marginalization of overweight children. Arch Pediatr Adolesc Med 157:746–752.

Torrubia R, Avila C, Molto J, Caseras X (2001): The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Pers Individ Dif 31:837–862.

van't Wout M, Kahn RS, Sanfey AG, Aleman A (2006): Affective state and decision-making in the Ultimatum Game. Exp Brain Res 169:564–568.

Wager TD, van Ast VA, Hughes BL, Davidson ML, Lindquist MA, Ochsner KN (2009): Brain mediators of cardiovascular responses to social threat, part II: Prefrontal subcortical pathways and relationship with anxiety. Neuroimage 47: 836–851.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR, Geliebter A, Fowler JS (2004): Exposure to appetitive food stimuli markedly activates the human brain. NeuroImage 21:1790–1797.

Ward BD (2013) AFNI and NIFTI server at NIMH in Bethesda, MD USA. Simultaneous inference for FMRI data. Available at:http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf, accessed on September 2013.

Westenberg PM, Drewes MJ, Goedhart AW, Siebelink BM, Treffers PD (2004): A developmental analysis of self-reported fears in late childhood through mid-adolescence: Social-evaluative fears on the rise? J Child Psychol Psychiatry 45:481–495.

Xiang T, Lohrenz T, Montague PR (2013): Computational substrates of norms and their violations during social exchange. J Neurosci 33:1099–1108a.

Youssef FF, Dookeeram K, Basdeo V, Francis E, Doman M, Mamed D, Maloo S, Deganner J, Dobo L, Ditshotlo P, Legall G (2012): Stress alters personal moral decision making. Psychoneuroendocrinology 37:491–498.

Zheng H, Berthoud HR (2007): Eating for pleasure or calories. Curr Opin Pharmacol 7:607–612.

Ziauddeen H, Farooqi IS, Fletcher PC (2012): Obesity and the brain: How convincing is the addiction model? Nat Rev Neurosci 13:279–286.