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Función, conectividad cerebral y diferencias individuales en el procesamiento de recompensas

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BAS	Behavioral Approach System
BIS	Behavioral Inhibition System
BIS/BAS	Behavioral Inhibition/Behavioral Activation Scales
DAN	Dorsal attention network
DMN	Default mode network
FFS	Fight/Flight System
fMRI	Fuctional magnetic resonance imaging
FPN	Frontoparietal network
FS	Fun Seeking
MRI	Magnetic resonance imaging
NAcc	Núcleo Accumbens
NS	Novelty Seeking
OFC	Orbitofrontal cortex
PET	Positron emission tomography
RR	Reward Responsiveness
RST	Reinforcement Sensitivity Theory
SN	Substantia nigra
SPSRQ	Sensitivity to Punishment and Sensitivity to Reward Questionnaire
SR	Sensitivity to Reward (scale)
VTA	Ventral tegmental area

Justificación

La neurociencia es una de las disciplinas científicas que ha tenido un mayor desarrollo en los últimos años. Dentro de las neurociencias, la neurociencia cognitiva se encarga de establecer las relaciones entre el cerebro y la conducta, teniendo en cuenta como principio fundamental que toda conducta es producto de la actividad del sistema nervioso. Hoy en día, muchas de las especialidades de la psicología, entre las que se encuentra el estudio de las diferencias individuales, tratan de incorporar en sus modelos una perspectiva neurobiológica. En este sentido, el reto actual de muchos modelos de personalidad es establecer cuáles son las bases cerebrales subyacentes a las conductas que definen sus rasgos.

La Teoría de la Sensibilidad al Reforzamiento (RST, del inglés: Reinforcement Sensitivity Theory) de Jeffrey A. Gray (Gray, 1970, 1982; Gray y McNaughton, 2000) supuso una revolución en el estudio biológico de la personalidad al proponer que las diferencias individuales en los rasgos de personalidad son variaciones en la reactividad de sistemas neuroconductuales subyacentes a procesos motivacionales, emocionales y de aprendizaje (Depue y Collins, 1999). Uno de estos sistemas neuroconductuales es el sistema de aproximación conductual (BAS, del inglés: Behavioral Approach System), que estaría encargado de responder ante estímulos apetitivos y de evitación de castigo mediante la ejecución de conductas de aproximación y alejamiento, respectivamente. A nivel cerebral, este sistema se ha relacionado con las áreas pertenecientes al sistema dopaminérgico del mesencéfalo como el área tegmental ventral (VTA, del inglés: ventral tegmental area), la substantia nigra (SN), el estriado ventral, el córtex orbitofrontal (OFC, del inglés: orbitofrontal cortex) o la amígdala (Gray, 1987; Pickering y Gray, 1999, 2001; Pickering y Smillie, 2008). Según el modelo de Gray, las diferencias individuales en la reactividad del BAS darían lugar a un rasgo de personalidad de sensibilidad a la recompensa.

La idea de la existencia de un sistema de recompensa localizado en zonas dopaminérgicas no es exclusiva del modelo de Gray. Diversos modelos neuropsicológicos respaldados por una gran cantidad de evidencia empírica apoyan esta hipótesis (Haber y Knutson, 2010; Berridge, 2007; Berridge y Kringelbach, 2008; Arias-Carrión y cols., 2010; Schultz, 2010a; Wise, 2004; O'Doherty, 2004; Wise y

Rompre, 1989; McClure y cols., 2004; Hikosaka y cols., 2008). El principal desafío de la RST para validar sus hipótesis es conocer los principales mecanismos que relacionan las diferencias individuales en el funcionamiento de este sistema con la manifestación conductual del rasgo de sensibilidad a la recompensa.

El rasgo de personalidad sensibilidad a la recompensa ha sido asociado a trastornos de impulsividad, desinhibición y estado de ánimo, tales como el trastorno por déficit de atención con hiperactividad, la psicopatía, la bulimia, el trastorno bipolar, la depresión o el consumo de sustancias (Gorenstein y Newman, 1980; Bijttebier y cols., 2009). Muchos de estos trastornos a su vez han sido relacionados con disfunciones en el sistema de recompensa y alteraciones de las vías dopaminérgicas del mesencéfalo (Dichter y cols., 2012). Además el concepto de sensibilidad a la recompensa también es esencial para entender fenómenos como la adolescencia, y sus trastornos (Ernst y cols., 2006; Ernst y Fudge, 2009). Por lo tanto, establecer las relaciones entre la sensibilidad a la recompensa y el funcionamiento del sistema de recompensa es importante tanto a nivel teórico como clínico.

En la actualidad, gracias al desarrollo de las técnicas de neuroimagen es posible poner a prueba en población humana muchos de los supuestos teóricos propuestos por modelos neuropsicológicos como el de Gray. Entre las técnicas de neuroimagen destaca la resonancia magnética (MRI, del inglés: Magnetic resonance imaging) ya que permite el estudio del cerebro humano in vivo, de forma no invasiva y bajo diferentes aproximaciones. Desde que se comenzara a aplicar la MRI al estudio del cerebro humano hace poco más de 20 años, la mayoría de investigaciones se han centrado en estudiar qué áreas cerebrales subyacen a los diferentes procesos neuropsicológicos mediante el análisis de la anatomía y la respuesta funcional cerebral. En los últimos años se ha observado una proliferación de las investigaciones centradas en conceptualizar de forma multivariable la actividad cerebral, propiciada en parte por el desarrollo de los métodos de análisis de conectividad que permiten estudiar cómo interaccionan las diversa estructuras cerebrales (Friston, 2011). En la neurociencia moderna, se considera que toda función o proceso cognitivo se da gracias a la integración funcional de diversas áreas especializadas en los aspectos concretos necesarios para desarrollar dicha función (Friston, 2002). Por lo que para poder explicar de forma completa cualquier fenómeno psicológico desde una perspectiva

neuropsicológica será necesario estudiar tanto las áreas subyacentes al mismo como la conectividad entre ellas.

Existen diversos estudios que utilizan técnicas de MRI para poner a prueba las hipótesis que plantea el modelo de Gray en relación al BAS. Estos estudios aportan datos a favor de la RST encontrando una relación entre la sensibilidad a la recompensa y las diferencias individuales en la estructura y la actividad de áreas dopaminérgicas (Barrós-Loscertales y cols., 2006, 2010; Hahn y cols., 2009, 2012; Simon y cols., 2010; Beaver y cols., 2006). Sin embargo, estos estudios son escasos y todavía se requiere un mayor número de investigaciones que corroboren estos resultados y los generalicen a diferentes contextos. Además, la mayoría de estos estudios no están centrados en el análisis de la conectividad entre regiones por lo que poco se conoce sobre las diferencias individuales en la conectividad cerebral en relación a la sensibilidad a la recompensa.

El objetivo general de esta tesis es aportar datos empíricos sobre la respuesta funcional y la conectividad de las bases neurales subyacentes al rasgo de personalidad sensibilidad a la recompensa, investigando su comportamiento en diferentes situaciones de recompensa y ante diferentes reforzadores.

Capítulo 1

Introducción general

1.1 El sistema de recompensa

Una recompensa podría entenderse como cualquier objeto o meta que perseguimos o que nos esforzamos por conseguir (Arias-Carrión y cols., 2010). Otra definición más concreta podría ser aquellos objetos o eventos que generan conductas de aproximación y de consumación, influyen en el aprendizaje y se relacionan con emociones positivas (Schultz, 2010a). En general, se le llama recompensas a estímulos o eventos que son apetitivos para el individuo. Sin embargo, hay que tener en cuenta que la recompensa es un proceso psicológico producido por el cerebro o la mente en respuesta a esos estímulos, y no los estímulos en sí (Berridge y Kringelbach, 2008). En este sentido se ha propuesto que el fenómeno de la recompensa no es un proceso unitario, sino que engloba diversos componentes psicológicos que se corresponden con diferentes mecanismos neurobiológicos (Berridge y Kringelbach, 2008; Berridge y Robinson, 2003; Dickinson y Balleine 2002; Everitt y Robbins 2005; Kelley y cols., 2005; Kringelbach 2005; Leknes y Tracey 2008; Schultz 2006). De esta forma, se han distinguido tres componentes en el proceso de la recompensa cada uno de los cuales tendría elementos conscientes y no conscientes. Los componentes propuestos son: El "liking" que hace referencia al componente placentero o al impacto hedónico de la recompensa, el "wanting" que hace referencia al componente motivacional por obtener la recompensa y el "learning" que hace referencia a asociaciones (incluyendo procesos de aprendizaje Pavloviano e instrumental), representaciones y predicciones sobre las recompensas futuras en base a la experiencia previa (Berridge y Kringelbach, 2008). Teniendo en cuenta esta visión de la recompensa, podríamos definir al sistema de recompensa como el conjunto de estructuras cerebrales que subyacen a estos procesos.

Desde que Olds y Milner observaron en 1954 que la estimulación de determinadas zonas del cerebro de la rata producía efectos conductuales similares a los producidos por la entrega de un reforzador primario, un gran número de investigaciones han ayudado a definir las bases neurobiológicas relacionadas con el sistema de la

recompensa. En general, se ha propuesto que el circuito dopaminérgico y las áreas cerebrales relacionadas con este neurotransmisor forman la parte principal de este sistema (Haber y Knutson, 2010; Berridge y Robinson, 1998; Berridge, 2007: Berridge y Kringelbach, 2008; Arias-Carrión y cols., 2010; Ikemoto, 2007; Schultz, 2010a; Wise, 2004; Kassubek y cols., 2011; Cools, 2008; O'Doherty, 2004; Wise y Rompre, 1989; McClure y cols., 2004). Estas áreas incluirían zonas del mesencéfalo como el VTA o la SN, zonas del sistema límbico como los ganglios basales o la amígdala, y zonas de la corteza prefrontal como el cingulado anterior o el OFC (Haber y Knutson, 2010; O'Doherty, 2004). Numerosas investigaciones tanto en animales como en humanos apoyan la idea de que la dopamina tiene un papel importante en el procesamiento de la recompensa. Por ejemplo, estudios animales han mostrado una relación entre la dopamina y diversos reforzadores primarios como comida (Hernandez y Hoebel, 1988; McCullough y Salamone, 1992; Radhakishun y cols., 1988; Blackburn y cols., 1989; Ljungberg y cols., 1992; Kiyatkin y Gratton, 1994; Bassareo y Di Chiara, 1999), bebida (Young y cols., 1992; Mirenowicz y Schultz, 1994; Richardson y Gratton, 1996) o sexo (Damsma y cols., 1992; Mas y cols., 1990; Pfaus y cols.,1995; Pleim y cols., 1990; Fiorino y cols., 1997; Wang y cols., 1995). Además, se ha visto que el bloqueo de los receptores de dopamina reduce conductas tanto instrumentales como consumatorias de recompensa (Bailey y cols., 1986; Ettenberg y Camp, 1986; Ettenberg, 1989), mientras que la destrucción de las vías dopaminérgicas produce que los animales se vuelvan insensibles a la comida y otros reforzadores, sin que estos déficits se expliquen por la pérdida de la capacidad de caminar, masticar, tragar o realizar otros movimientos necesarios para comer (Marshall y cols., 1974; Ungerstedt y cols., 1971; Zigmond y cols., 1972). Por otra parte, estudios en humanos han mostrado que agonistas dopaminérgicos incrementan la respuesta en el estriado ante recompensas inesperadas (Pessiglione y cols., 2006) y ante la anticipación de recompensas (Ye y cols., 2011), además de incrementar la elección de recompensas inmediatas en tareas de toma de decisiones (Pine y cols., 2010). Del mismo modo, estudios de tomografía por emisión de positrones (PET, del inglés: positron emission tomography) han mostrado una relación entre la disposición a realizar esfuerzo por la obtención de recompensas y la actividad dopaminérgica en el estriado y el córtex prefrontal medial (Treadway y cols., 2012), así como un incremento de la dopamina en estas mismas áreas en respuesta a recompensas monetarias (Pappata y cols., 2002; Zald y cols., 2004; Ceccarini y cols., 2012) y a la presencia de comidas apetitivas (Volkow y cols., 2002). Finalmente, otros

estudios de neuroimagen encontraron incrementos en la actividad de áreas dopaminérgicas durante el procesamiento de estímulos apetitivos como comida (O'Doherty y cols., 2002; Small y cols., 2001), dinero (Breiter y cols., 2001; Delgado y cols., 2000; Elliott y cols., 2000b; Knutson y cols., 2000, 2001, 2003; O'Doherty y cols., 2001) estímulos sexuales (Bühler y cols., 2008; Kühn y cols., 2011; Redouté y cols., 2000; Stoléru y cols., 2012; Karama y cols., 2002; walter y cols., 2008; Sescousse y cols., 2010), chistes (Mobbs y cols., 2003) o la presentación de caras atractivas (Aharon cols., 2001).

En resumen, podemos afirmar que la dopamina desempeña un papel central que en el procesamiento de la recompensa. Sin embargo, es necesario tener en cuenta que las áreas relacionadas con el sistema de recompensa reciben influencia de muchos otros neurotransmisores como la serotonina, el glutamato, la acetilcolina, el GABA, los endocanabinoides o la orexina (Mark y cols., 2011; Hayes y Greenshawa, 2011; Kranz y cols., 2010; Stuber y cols., 2012; Barrot y cols., 2012; Pattij y Vanderschuren, 2008; Calipari y España, 2012; El Khoury y cols., 2012), por lo que la actividad de estas zonas dependerá de la interacción de todos ellos.

1.1.1 Principales estructuras del sistema de recompensa

1.1.1.1 El mesencéfalo y las vías dopaminérgicas

Las neuronas dopaminérgicas están topográficamente organizadas en pequeños grupos de somas distribuidos por diversas zonas del cerebro que proyectan hacia otras áreas cerebrales formado tractos anatómicos. Se han distinguido hasta siete circuitos dopaminérgicos, de los cuales el sistema eferente del mesencéfalo es el que se ha relacionado con el procesamiento de la recompensa. Este sistema, comienza en el mesencéfalo y proyecta a diversas zonas del sistema límbico y cortical.

El mesencéfalo es una estructura importante dentro del sistema de recompensa porque alberga los núcleos de las neuronas dopaminérgicas relacionadas con la recompensa. En este sentido se han distinguido principalmente tres núcleos dopaminérgicos que se localizan en el área retrorubral, en la SN y en el VTA (Hökfelt, 1984; Albanese y cols., 1986). Desde estos núcleos surgen diversas proyecciones, de las cuales, se han distinguido principalmente tres (ver figura 1): La vía nigroestriatal, que se origina en la SN y proyecta hacia zonas del estriado como el caudado o el putamen. La

vía mesolímbica, que se origina en el VTA y proyecta principalmente hacia el núcleo accumbens (NAcc), el tubérculo olfatorio, el septum, la amígdala y el hipocampo. Y la vía mesocortical, que se origina también en el VTA y proyecta hacia la corteza prefrontal, el cingulado y el córtex perirrinal (Arias-Carrión y cols., 2010). Estas dos últimas vías se encuentran anatómicamente superpuestas por lo que se les ha denominado conjuntamente como la vía mesocorticolímbica (Arias-Carrión y cols., 2010; Wise, 2004). Generalmente, se ha relacionado a la vía nigroestriatal con la conducta motora, mientras que la vía mesocorticolímbica se ha relacionado principalmente con la motivación, el aprendizaje por incentivos y la conducta dirigida a metas (Iversen y Iversen, 2007).

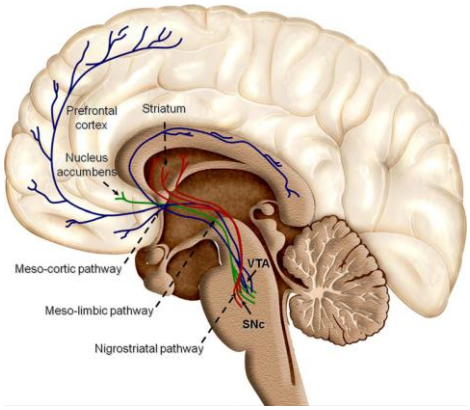

Figura 1: Sistema dopaminérgico del mesencéfalo. Extraído de Arias-Carrión y cols., 2010.

La mayor parte de la investigación que apoya este tipo de organización de las estructuras dopaminérgicas del mesencéfalo se ha basado principalmente en el estudio de ratas. Sin embargo, estudios en humanos y primates no humanos han mostrado que existen determinadas diferencias entre especies que se deben tener en cuenta (Björklund y Dunnett, 2007; Düzel y cols., 2009). Por ejemplo, se ha visto que en humanos el número y complejidad de las neuronas dopaminérgicas en el mesencéfalo es mayor que en ratas (Björklund y Dunnett, 2007). Además, se ha observado que existen diferencias en su distribución, de modo que en humanos y primates aproximadamente un 75% de las neuronas dopaminérgicas se encuentran en la SN, un 15% en el VTA y un 10% en el área retrorubral (Hirsch y cols., 1992; François y cols., 1999), mientras que en ratas su distribución es similar en el VTA y la SN con un 45% cada una, por un 10% en el área retrorubral (German y Manaye, 1993). Por otra parte, en humanos y primates los límites entre el VTA y la SN son más difusos, de modo que en estas especies los núcleos

dopaminérgicos se diferencian mejor dividiéndolos entre niveles dorsal, que incluye la SN dorsal y la parte contigua del VTA, y ventral, que incluye la parte ventral de la SN (Düzel y cols., 2009; Lynd-Balta y Haber, 1994; Haber y Knutson, 2010; Björklund y Dunnett, 2007). Por último, también hay diferencias en las proyecciones de los núcleos dopaminérgicos hacia otras zonas del cerebro. Por un lado, estas proyecciones están más distribuidas en humanos, de modo que las proyecciones hacia la corteza prefrontal se originan tanto en el VTA como en la SN, y no solo en el VTA como ocurre en ratas (Düzel y cols., 2009; Williams y Goldman-Rakic, 1998; Haber y cols., 2000; Björklund y Dunnett, 2007). Por otro lado, en el cerebro de la rata las proyecciones corticales están restringidas a determinadas zonas del córtex prefrontal, el cingulado y el córtex entorrinal, mientras que en primates estas conexiones se extienden a amplias zonas de la corteza con especial énfasis en zonas parietales (Björklund y Dunnett, 2007; Lewis y cols., 1998). A nivel funcional, se ha sugerido que hasta ahora, no se pueden atribuir funciones diferenciadas para cada una de las estructuras dopaminérgicas del mesencéfalo en los primates, al menos de una forma cualitativa, de modo que las diferencias a nivel funcional entre el VTA y la SN y el área retrorubral, en caso de haberlas, serian en cuanto al grado de implicación de cada una de estas estructuras en la función (Düzel y cols., 2009).

1.1.1.1.1 Funciones dopaminérgicas

Principalmente, se han atribuido dos funciones a las neuronas dopaminérgicas del mesencéfalo en relación a la recompensa. Por un lado, se han asociado con el aprendizaje (Wise, 2004; Schultz y cols., 1997; Montague y cols., 1996), mientras que por otro lado, se han asociado con la motivación (Berridge and Robinson, 1998; Depue y Collins, 1999; Alcaro y cols., 2007).

- Hipótesis del aprendizaje:

Una de las hipótesis que relaciona a la dopamina con el aprendizaje propone que este neurotransmisor facilitaría las asociaciones estímulo-estímulo o estímulo-respuesta siempre que estas vayan seguidas de recompensa (Wise, 2004, 2008). Según esta hipótesis, el aprendizaje se produciría mediante mecanismos de potenciación a largo plazo, es decir, incrementos en la trasmisión sináptica entre neuronas, y depresión a largo plazo, es decir, decrementos en la transmisión sináptica entre neuronas. Así por ejemplo, la presencia de dopamina en una sinapsis produciría cambios duraderos de

forma que la neurona postsináptica fuera más reactiva a la neurona presináptica en las siguientes descargas. A favor de esta hipótesis se ha observado que la potenciación a largo plazo y la depresión a largo plazo están relacionadas con la dopamina en áreas como el hipocampo (ver Hansen y Manahan-Vaughan 2012 para revisión), el estriado dorsal (Calabresi y cols., 1992; Centonze y cols., 2001), la amígdala (Bissière y cols., 2003; Li y cols., 2011; Krishnan y cols., 2010), el córtex prefrontal (Huang y cols., 2004; Otani y cols., 2003; Law-Tho y cols., 1995; Xu y Yao, 2010; Kolomiets y cols., 2009) o el VTA (Overton y cols., 1999). Además, la infusión de dopamina en determinadas zonas del cerebro incrementa la consolidación de determinadas conductas o aprendizajes (Wise y cols., 2004).

Otra de las hipótesis que han relacionado a la dopamina con el aprendizaje sugiere que las neuronas dopaminérgicas del mesencéfalo codificarían la predicción del error de recompensa (Schultz y cols., 1997). La predicción del error está relacionada con el impacto que tiene una recompensa en función de la expectativa previa, de modo que si la recompensa es mayor de lo esperado la predicción de error es positiva, mientras que si la recompensa es menor de lo esperado la predicción de error es negativa. Según esta hipótesis la respuesta de las neuronas dopaminérgicas aumentaría ante la predicción de error positiva, mientras que disminuiría ante la predicción de error negativa (ver Schultz, 2002, 2006, 2007, 2010b para revisión). Esta propuesta se podría expresar con la siguiente formula:

Respuesta dopaminérgica = Recompensa ocurrida – Recompensa esperada

Esta hipótesis planteada por Wolfram Schultz, se basa en el modelo de Rescorla-Wagner, donde se explicaba el incremento el en aprendizaje que se produce en un ensayo de un condicionamiento pavloviano en función de la intensidad de los estímulos condicionado e incondicionado y de los emparejamientos anteriores entre esos estímulos (Rescorla y Wagner, 1972). Los datos empíricos que apoyan esta hipótesis provienen principalmente de estudios fisiológicos donde se utilizaban electrodos para medir la actividad neuronal en el cerebro de primates durante procedimientos de condicionamiento clásico o instrumental. En estos estudios se observó que las neuronas dopaminérgicas respondían tanto a reforzadores primarios como a estímulos condicionados a estos, de forma que a medida que aumentaban los emparejamientos entre estímulos, cada vez respondían más al estímulo condicionado y menos al

reforzador primario hasta que al final dejaban de responder a este. Sin embargo, si se presentaba el reforzador primario de forma espontánea sin estar precedido por el estímulo condicionado, las neuronas dopaminérgicas respondían de nuevo (Ljungberg y cols., 1992; Romo y Schultz, 1990; Mirenowicz y Schultz, 1994; Hollerman y Schultz, 1998). Este fenómeno se atribuyó a la predictibilidad del estímulo, de modo que cuanto menos predecible era el reforzador, mayor respuesta dopaminérgica. Además, se observó que cuando se presentaba un estímulo condicionado sin ir seguido de su correspondiente reforzador primario (omisión de reforzador), la actividad dopaminérgica mostraba un decremento de su actividad normal en el momento en que normalmente se solía presentar el reforzador primario (Ljungberg y cols., 1991; Schultz y cols., 1993; Hollerman y Schultz, 1998). Así, la actividad dopaminérgica parecía codificar la predicción del error de un modo similar al propuesto por las teorías del condicionamiento (Rescorla y Wagner, 1972; Mackintosh, 1975), aumentando ante reforzadores inesperados y disminuyendo ante la omisión del reforzador. Finalmente, esta hipótesis fue probada mediante un procedimiento de bloqueo donde se observó que la actividad dopaminérgica no respondía simplemente a asociaciones estímulo-recompensa sino que respondía a la predicción del error (Waelti y cols., 2001). Posteriormente, estudios de neuroimagen en humanos en los cuales se manipulaba la expectativa de recompensa mediante la presentación de recompensas inesperadas, la omisión de recompensas esperadas o la modificación del tiempo entre el estímulo condicionado y el reforzador, mostraron que la actividad de áreas dopaminérgicas como el estriado ventral o el córtex prefrontal medial seguía un patrón acorde con la predicción del error (McClure y cols., 2003; O'Doherty y cols., 2003; Berns y cols., 2001).

- Hipótesis motivacionales:

La dopamina también se ha relacionado con aspectos motivacionales. En este sentido se ha propuesto que las vías dopaminérgicas del mesencéfalo responden ante la saliencia del incentivo (Berridge y Robinson, 1998; Berridge, 2007). La saliencia de incentivo hace referencia a un estado motivacional asociado a estímulos, produciendo que estos sean deseados ("wanted") por el organismo. Este estado motivacional produciría la atracción del organismo hacia el objeto deseado. La saliencia de incentivo de un objeto dependerá tanto de la experiencia previa con ese objeto como de los estados fisiológicos actuales del organismo (hambre, sed, etc.). La saliencia de incentivo

es producida principalmente por reforzadores primarios, pero por mecanismos de condicionamiento clásico puede ser transferida a estímulos condicionados haciendo que estos produzcan reacciones similares a los reforzadores primarios. Una consecuencia de esta transferencia sería el automoldeamiento, donde los animales producen respuestas consumatorias ante estímulos condicionados (Berridge, 2007). Según el modelo, las sensaciones placenteras ("liking") generadas por los reforzadores primarios, producirían activación de la saliencia de incentivo ("wanting") y de los mecanismos de aprendizaje ("learning"), de modo que el componente hedónico del reforzador produce por mecanismos de condicionamiento clásico que se atribuya saliencia de incentivo a los estímulos que lo predicen. La dopamina, estaría relacionada exclusivamente con el componente de deseo ("wanting"). A favor de esta hipótesis, se ha visto que agonistas dopaminérgicos incrementan la respuesta conductual en presencia del estímulo condicionado en tareas de transferencia pavloviana-instrumental (Wyvell y Berridge, 2000, 2001), en las cuales se aísla el componente motivacional de los otros componentes de la recompensa. Además, se ha visto que un incremento producido por agonistas dopaminérgicos en la respuesta del globo pálido ventral, un área donde se cree que converge información de los diferentes componentes de la recompensa (Berridge, 2007), se explicaba por la saliencia de incentivo (Tindell y cols., 2005). Por último, se ha visto que ratones manipulados genéticamente para que produzcan un exceso de dopamina, muestran un aumento motivacional hacia estímulos de recompensa pero no un mayor aprendizaje de recompensas ni mayores respuestas hedónicas (Cagniard y cols., 2006; Peciña y cols., 2003; Yin y cols., 2006).

- Otras funciones dopaminérgicas:

Además de su función motivacional y de aprendizaje en la recompensa, las vías dopaminérgicas del mesencéfalo han sido relacionadas con otras funciones como el procesamiento de estímulos relevantes en general (apetitivos, aversivos, dolorosos, novedosos, etc.) y con respuestas de orientación hacia ellos (Horvitz, 2000; Redgrave y cols., 1999; Redgrave y Gurney, 2006; Lisman y Grace, 2005; Knutson y Cooper, 2006; Bunzeck y Düzel, 2006). Recientemente, se ha propuesto un modelo según el cual existirían dos tipos de poblaciones neuronales dopaminérgicas en el mesencéfalo; una que codificaría el valor motivacional del estímulo, mostrando activación ante estímulos apetitivos e inhibición ante estímulos aversivos (de acuerdo con las teorías expuestas anteriormente que relacionan la dopamina con la recompensa), y otra que respondería a

la saliencia del estímulo, mostrando mayor activación para estímulos relevantes (positivos y negativos) que para estímulos neutros (Bromberg-Martin y cols., 2010). Además, según este modelo ambos grupos neuronales responderían a señales de alerta, que serían aquellos estímulos inesperados que por su localización, tamaño o modalidad sensorial requirieran una focalización de la atención por su posible relevancia para el organismo (Bromberg-Martin y cols., 2010). Por último, existe una implicación clara de la dopamina en el control del movimiento, lo cual se demuestra por su relación con la enfermedad de Parkinson (Smith y Villalba, 2008; Cenci 2007; Brooks, 2001).

1.1.1.2 El Estriado Ventral

El estriado ventral hace referencia a un área cerebral compuesta por diversas estructuras que incluyen principalmente al NAcc, al tubérculo olfatorio y la zonas adyacentes al NAcc del caudado y del putamen (Haber y Knutson, 2010; Friedman y cols., 2002). El NAcc a su vez se ha dividido en dos zonas: el "core" que se ha relacionado con la generación de respuestas condicionadas en función de las asociaciones estímulo-consecuencia y el "shell" que se ha relacionado con el aprendizaje de asociaciones estímulo-consecuencia (Ikemoto, 2007). Las principales áreas de destino donde proyectan las neuronas del estriado ventral son el globo pálido ventral y estructuras del mesencéfalo (como VTA o SN). El "shell" proyecta además hacia el hipotálamo lateral y el área gris periacueductal, un área relacionada con conductas de lucha y escape (Gray y McNaughton, 2000). Finalmente la parte medial del estriado ventral proyecta hacia el núcleo del lecho de la estría terminal, indicando una influencia directa en la "extended amígdala", mientras que la parte ventral del estriado ventral proyecta hacia el nucleus basalis, mediante el cual el estriado ventral puede conectarse con la corteza cerebral de forma directa sin utilizar el circuito pálido-talámico (Haber y Knutson, 2010). Por otro lado, el estriado ventral recibe aferencias corticales desde el OFC, el córtex prefrontal medial, la ínsula y el cingulado anterior, y desde zonas subcorticales como el tálamo, el hipocampo y distintos núcleos de la amígdala como el núcleo basolateral, que proyecta a varias partes del estriado ventral aunque principalmente sobre el NAcc, y el núcleo central, que proyecta sobre el "shell" (Haber y Knutson, 2010). Además, como se ha comentado anteriormente el estriado ventral es uno de los principales objetivos de la vía dopaminérgica mesolímbica (Albanese y cols., 1986; Björklund y Dunnett, 2007; Haber y knutson, 2010; Arias-Carrión y cols., 2010; Iversen y Iversen, 2007).

Generalmente, se considera que el estriado ventral integra la información procedente de la vía mesolímbica, por lo que se le ha relacionado tanto con aspectos motivacionales (Depue y Collins, 1999) como con la predicción del error (McClure y cols., 2004; McClure y cols., 2003; O'Doherty y cols., 2003; Berns y cols., 2001). Estudios de neuroimagen han mostrado una activación del estriado ventral durante la presentación de una gran variedad de estímulos apetitivos como olores agradables (Gottfried y cols., 2002), chistes (Mobbs y cols., 2003) caras y cuerpos atractivos (Aharon cols., 2001; Spicer y Platek, 2010), dinero (Breiter y cols., 2001, Elliott y cols., 2003; Sescousse y cols., 2010) o estímulos sexuales (Redouté y cols., 2000, Stoléru y cols., 2012; Karama y cols., 2002; walter y cols., 2008). El estriado ventral se ha relacionado también con la anticipación de la recompensa (Knutson y Cooper, 2005). En este sentido, se ha visto activación de esta área en respuesta a señales que anticipaban diferentes recompensas como comida o dinero (O'Doherty y cols., 2002, Knutson y cols., 2000, 2001). Además, se ha visto que la actividad de esta zona esta modulada por diferentes aspectos de la anticipación a la recompensa como la magnitud (Knutson y cols., 2001; Yacubian y cols., 2006) o la probabilidad (Abler y cols., 2006). Por otro lado, en un meta-análisis realizado por Liu y cols. (2011) donde se utilizaron 142 artículos de toma de decisiones con recompensa, se observó que el estriado ventral aparecía comúnmente activado a través de diferentes fases del procesamiento de la recompensa incluyendo anticipación pero también evaluación o reactividad, por lo que este autor concluyó que el estriado ventral está implicado en el procesamiento de la recompensa en general y que todavía se necesita más investigación para poder atribuirle un rol concreto. Por último, diversos estudios han mostrado activación de esta zona ante la anticipación de posibles castigos y ante estímulos inesperados (Carter y cols., 2009; Zink y cols., 2006), por lo que es posible que el estriado ventral también procese información sobre la saliencia de los estímulos en general, además de la información relacionada con la recompensa (Bromberg-Martin y cols., 2010).

1.1.1.3 La amígdala

La amígdala es un conjunto heterogéneo de núcleos neuronales situados en el sistema límbico. Los núcleos de la amígdala se pueden agrupar en tres zonas, la amígdala basolateral, la amígdala central y la amígdala superficial (Amunts y cols., 2005). De estas zonas, la amígdala basolateral y la amígdala central son las más relacionadas con el sistema de recompensa. La amígdala recibe inputs de todas las

modalidades sensoriales (olfativa, gustativa, visual, auditiva, somatosensorial y visceral) y proyecta hacia la mayoría de ellas principalmente a través de la amígdala basolateral. Además, también tiene conexiones recíprocas con la corteza entorrinal e hipocampo, y recibe aferencias desde el córtex prefrontal (principalmente de sus partes orbital y medial) y de la vía dopaminérgica mesolímbica (Sah y cols., 2003; Price, 2003; McDonald, 1998). Se han distinguido principalmente dos tractos eferentes desde la amígdala, la estría terminal, que proyecta hacia: hipotálamo lateral, núcleo del lecho, estriado ventral y núcleos septales. Y el tracto amigdalofugal ventral, que proyecta hacia: núcleo dorsomedial del tálamo, hipotálamo, estriado ventral, OFC, cingulado anterior, área periacueductal gris, SN, VTA, formación reticular, núcleo dorsal del vago y núcleo del tracto solitario (Price, 2003; Redolar, 2008). Estas conexiones muestran que la amígdala está asociada tanto con áreas relacionadas con la recompensa como con áreas relacionadas con emociones negativas, además de proyectar sobre núcleos troncoencefálicos involucrados en el control del sistema autónomo. Diversos estudios han mostrado que las proyecciones desde la amígdala al NAcc son importantes para el componente motivacional de la recompensa (Stuber y cols., 2011; Chang y cols., 2012). Por otro lado, se ha propuesto que las conexiones entre la amígdala y el OFC son importantes para la formación y la actualización de expectativas acerca del valor de la recompensa (Holland y Gallagher, 2004; Murray, 2007).

En general, la amígdala se considera asociada tanto al procesamiento de estímulos apetitivos como aversivos (Murray, 2007; Cardinal y cols., 2002; Haber y Knutson, 2010; O'Doherty, 2004; McClure y cols., 2004), lo cual es congruente con sus conexiones anatómicas. Estudios en animales y humanos han mostrado que esta zona está relacionada con la intensidad de los estímulos emocionales y con la codificación del valor de las recompensas (Gottfried y cols., 2003; Anderson y cols., 2003; Small y cols., 2003; Corbit y Balleine, 2005). Concretamente, se ha propuesto que la amígdala basolateral enlaza las propiedades sensoriales de los estímulos con la emoción, lo cual es importante para la representación del valor de la recompensa, mientras que la amígdala central está relacionada con el control del arousal o la intensidad de las emociones (Murray, 2007; Cardinal y cols., 2002).

1.1.1.4 El córtex orbitofrontal

La corteza orbitofrontal hace referencia a la parte más ventral del córtex prefrontal. Esta área está especialmente desarrollada en humanos y primates, y se localiza principalmente en las áreas 10, 11 y 47 de la división de Brodmann (Elliott, 2000a; Kringelbach, 2005). El OFC recibe información gustativa desde la ínsula, olfativa desde el área piriforme, visual desde el córtex temporal inferior y el polo temporal, auditiva desde el córtex temporal superior y somatosensiorial desde el córtex somatosensorial primario y secundario, además de recibir también información visceral (Rolls, 2000). El OFC también recibe proyecciones desde la amígdala, el tálamo medio-dorsal, la corteza entorrinal, el hipocampo, el mesencéfalo, el cingulado anterior y el córtex prefrontal dorsolateral. Por otra parte, el OFC proyecta hacia áreas del córtex temporal inferior, corteza entorrinal, amígdala, diversas zonas del estriado (incluyendo el NAcc), hipotálamo, área gris periacueductal, cingulado anterior y córtex prefrontal dorsolateral (Ongür y Price, 2000; Elliott, 2000a). Además, también se ha visto que el OFC modula la actividad de las vías dopaminérgicas del mesencéfalo (Lodge, 2011), siendo estas conexiones importantes para el aprendizaje (Takahashi y cols., 2009)

Al igual que el estriado ventral, el OFC es un área que suele aparecer activa en los estudios de neuroimagen que utilizan tareas de recompensa (Liu y cols., 2011). Pacientes con daño cerebral en esta zona muestran conductas desinhibidas, euforia, irresponsabilidad y falta de afecto (Elliott, 2000a; Rolls, 2000). El OFC ha sido propuesto como una zona importante para la integración sensorial y la representación del valor de la recompensa (Kringelbach, 2005; Rolls, 2000). Se ha observado que la información de cada modalidad sensorial está representada en áreas específicas dentro del OFC las cuales contienen neuronas especializadas en responder ante diferentes sensaciones (gustos, olores, texturas, etc.) ya sean positivas o negativas (Kringelbach, 2005; Rolls, 2000). Esta representación sensorial ocuparía las zonas posteriores del OFC, mientras que en zonas más anteriores se integraría la información entre diversas modalidades produciendo representaciones de los estímulos (Kringelbach, 2005). Por ejemplo, se ha visto que existen neuronas en el OFC que responden tanto a la información gustativa de un alimento determinado como a su olor o a su percepción visual (Rolls y Baylis, 1994). Además, diversos estudios han mostrado que el OFC no solo integra la información de diferentes modalidades sensoriales, sino que además responde en función del valor de la recompensa. Diversos estudios en humanos y

animales han mostrado que el OFC responde a la presentación de alimentos o estímulos asociados a ellos cuando los sujetos tienen hambre pero deja de responder a ese alimento (y no a otros) una vez se ha comido (O'Doherty y cols., 2000; Gottfried y cols., 2003, Rolls y cols., 1989; Critchley y Rolls, 1996). Así el OFC responde selectivamente al valor de la recompensa y no a la simple presentación del estímulo como las zonas sensoriales primarias. Por otro lado, el OFC se ha relacionado con la toma de decisiones y la monitorización del valor actual de la recompensa (Kringelbach, 2005; Elliott, 2000a; Wallis, 2007). En este sentido, se ha visto que la lesión del OFC produce dificultades para cambiar la conducta en función de la contingencia (Gallagher y cols., 1999; Baxter y cols., 2000) y una mayor disposición a la elección de recompensas inmediatas en lugar de respuestas que den un mayor beneficio final (Bechara y cols., 1994; Mobini y cols., 2002). Además, estudios de neuroimagen han mostrado activación del OFC en tareas donde se requería la selección de respuestas en función del valor de la recompensa (Elliott, 2000a). En un meta-análisis realizado recientemente sobre 87 estudios de diversa índole como estudios de recompensa, castigo, memoria o estimulación sensorial, en los cuales se encontraban activaciones en el OFC, se llegó a la conclusión que la zona medial de este área cerebral estaba relacionada con la monitorización del valor de la recompensa mientras que las zonas laterales estaban relacionadas con la evaluación de los castigos que pueden llevar a un cambio en la conducta. Por otro lado se vio que las zonas posteriores del OFC se relacionaban con el procesamiento de los estímulos sensoriales para su posterior integración, mientras que las zonas más anteriores se relacionaba con la atribución del valor de recompensa y con la respuesta a recompensas abstractas como el dinero (Kringelbach y Rolls, 2004). Por último, se ha sugerido que el OFC está implicado en la representación consciente del "liking" o placer subjetivo (Kringelbach, 2005; Berridge y Kringelbach, 2008). A favor de esta propuesta estudios de neuroimagen han mostrado que la actividad del OFC en respuesta a recompensas correlaciona con valoraciones subjetivas de placer (Kringelbach y cols., 2003; Small y cols., 2001; De Araujo y cols., 2003; Anderson y cols., 2003; Rolls y cols., 2003).

1.1.1.5 Otras áreas del sistema de recompensa

El mesencéfalo, el estriado ventral, la amígdala y el OFC son las regiones cerebrales que mayor investigación han suscitado en relación al sistema de la recompensa y que generalmente se consideran como sus principales áreas (Haber y

Knutson, 2010; O'Doherty, 2004; McClure y cols., 2004). Sin embargo, existen otras áreas que también pueden tener un papel importante dentro de este sistema.

Aunque el estriado dorsal se ha relacionado tradicionalmente con el control del movimiento (Iversen y Iversen, 2007), estudios recientes han mostrado que juega un papel importante en la selección e iniciación de la conducta motivada y en el aprendizaje de asociaciones respuesta-consecuencia (Balleine y cols., 2007; Hikosaka y cols., 2008). Concretamente se ha relacionado la zona medial del estriado dorsal con el aprendizaje de nuevas asociaciones respuesta-consecuencia y en la selección de las conductas apropiadas en función del valor de la recompensa actual, mientras que las zonas laterales del estriado dorsal se han relacionado con las conductas guiadas por estímulos, automáticas o habituadas (Balleine y cols., 2007).

El globo pálido ventral conecta con un gran número de estructuras relacionadas con el sistema de la recompensa, incluyendo el NAcc y las zonas dopaminérgicas del mesencéfalo (Haber y Knutson, 2010). Debido a sus conexiones se ha propuesto como un área donde convergen los tres elementos de la recompensa, "wanting", "liking" y "learning" (Berridge, 2007). Se ha mostrado que la activación de esta zona se relaciona con las reacciones hedónicas ("liking") producidas por reforzadores (Tindell y cols., 2006; Smith y Berridge, 2007) por lo que se ha propuesto como uno de los núcleos subcorticales del procesamiento del placer junto con el NAcc (Berridge y Kringelbach, 2008).

La habénula lateral es un área que se asocia con la regulación de la señal dopaminérgica de recompensa (Haber y Knutson, 2010; Hikosaka y cols., 2008). Esta zona responde de forma inversa a la dopamina en relación a los estímulos de recompensa, inhibiéndose ante estímulos que predicen recompensa y respondiendo ante estímulos predictivos de no recompensa y ante la omisión de recompensas esperadas (Matsumoto y Hikosaka, 2007). Además, se ha visto que la estimulación eléctrica de esta zona produce inhibición dopaminérgica (Ji y Shepard, 2007).

El tálamo es una estructura que conecta las estructuras corticales con las subcorticales. Concretamente el tálamo dorsal-medial es el área donde proyectan las estructuras relacionadas con la recompensa. Generalmente, las conexiones entre el tálamo y la corteza son recíprocas. Sin embargo, se ha visto que existen diversas conexiones desde el córtex prefrontal hacia el tálamo dorsal-medial que no tienen su

correspondiente feedback, por lo que se cree que esta zona puede integrar algún tipo de información procedente de las áreas de asociación frontales relacionada con la recompensa (Haber y Knutson, 2010).

El hipotálamo lateral se ha relacionado con el sistema de recompensa porque contiene orexina, un neurotransmisor importante para la conducta alimentaria y el arousal general (Willie y cols., 2001). Recientemente, se ha visto que la orexina del hipotálamo lateral influye en la conducta motivada mediante la activación de la vía mesolímbica (Calipari y España, 2012; Aston-Jones y cols., 2010; Harris y cols., 2005; Narita y cols., 2006).

Los núcleos del rafe y sus proyecciones serotonérgicas también se han relacionado con la recompensa (Hayes y Greenshawa, 2011; Kranz y cols., 2010). Esta zona recibe proyecciones de otras zonas del sistema de recompensa como OFC, SN, amígdala y habénula lateral (Haber y Knutson, 2010). Recientemente, se ha visto que esta zona responde ante la presentación de recompensas y señales asociadas a estas, a diferencia de las neuronas dopaminérgicas que responden solo si la recompensa es inesperada (Nakamura y cols., 2008).

La ínsula se ha asociado con el procesamiento emocional y se ha sugerido que puede estar implicada en la experiencia emocional subjetiva (Craig, 2009). Esta zona se ha visto activada tanto para la anticipación de recompensas como castigos y su actividad correlaciona con el arousal positivo y negativo (Knutson y Greer, 2008). Estudios recientes han mostrado que la ínsula esta funcionalmente conectada con el NAcc (Camara y cols., 2008) y se ha propuesto que estas conexiones forman parte de una red relacionada con la anticipación de recompensas (Camara y cols., 2009).

El cingulado anterior se ha relacionado generalmente con el control cognitivo y la monitorización de la conducta (Botvinick, 2007; van Veen y Carter, 2002; Ridderinkhof y cols., 2004). Además, se cree que esta zona junto con el OFC tienen un papel importante para la toma de decisiones (Wallis y Kennerley, 2011; Walton y Mars, 2007). En este sentido se ha propuesto que la interacción entre el cingulado anterior y OFC lateral se relaciona con la monitorización del proceso la recompensa favoreciendo el cambio conductual en caso de que se alteren las contingencias (Kringelbach, 2005). Concretamente, el cingulado anterior se asociaría principalmente con la evaluación de las consecuencias del cambio (Wallis y Kennerley, 2011).

Finalmente, el córtex prefrontal medial se ha relacionado con la predicción del error de recompensa (Knutson y Cooper, 2005). Concretamente se ha visto que la actividad de esta zona aumenta cuando se recibe una recompensa esperada y disminuye cuando se omite la recompensa (Knutson y cols., 2003). Además, sea visto que esta zona procesa diversos componentes de la anticipación a la recompensa como su probabilidad o magnitud (Knutson y cols., 2005). En base a estos y otros resultados se ha sugerido que el córtex prefrontal medial puede integrar el valor de la recompensa a través de diferentes estímulos y sus dimensiones (Haber y Knutson, 2010).

1.2 Teoría de sensibilidad al reforzamiento

Hoy en día se conoce a la teoría neuropsicológica de la personalidad de Jeffrey A. Gray (1970, 1982) como la teoría de la sensibilidad al reforzamiento (Pickering y cols., 1995). Esta teoría comenzó su desarrollo en los años 70 a partir de la investigación animal y fue evolucionando durante los años posteriores a su aparición hasta su última revisión en el año 2000 (Gray y McNaughton, 2000). La RST postula la existencia de diversos sistemas neurales especializados en detectar, procesar y responder ante determinados estímulos, donde la presencia de uno de estos estímulos pondrá en marcha un determinado sistema neural que podrá producir estados motivacionales, emocionales, respuestas conductuales y procesos de aprendizaje (ver Corr, 2008a para revisión). De este modo, Gray desarrolla un modelo conceptual del funcionamiento del sistema nervioso donde propone la existencia de tres sistemas neurales; el BAS, el sistema de inhibición conductual (BIS, del inglés: Behavioral Inhibition System) y el sistema de lucha-huida (FFS, del inglés: Fight/Flight System). En su modelo, Gray muestra las relaciones entre los diferentes sistemas neurales relacionando cada uno de estos sistemas con un substrato biológico cerebral.

Una de las principales propuestas de la RST es que describe la personalidad como diferencias individuales en la sensibilidad/reactividad de los diferentes sistemas neurales ante los estímulos a los que responden (Gray, 1970, 1982; Gray y McNaughton, 2000). Así, en la RST se relacionan factores motivacionales y emocionales que estarían asociados a respuestas a corto plazo de los sistemas neurales con la personalidad, que se asociaría a una disposición de respuesta de estos sistemas a largo plazo (Corr, 2008b). Por tanto, la RST propone un modelo biológico de la

personalidad donde las diferencias individuales observables a nivel conductual que dan lugar a los diferentes rasgos de personalidad son el resultado de diferencias individuales en la reactividad de determinados sistemas cerebrales.

1.2.1 La RST: inicios y evolución

Segun Corr (2004) el nacimiento oficial de la RST surgió con la publicación de una teoría psicofisiológica alternativa a la teoría de Hans Eysenck sobre la introversión-extraversión (Gray, 1970). Eysenck antes que Gray, ya propuso un modelo biológico de la personalidad según el cual existirían dos sistemas cerebrales principales (Eysenck, 1967; Eysenck y Eysenck, 1985). Uno de estos sistemas, cuya base biológica la encontraríamos en el Sistema de Activación Reticular Ascendente, estaría encargado de controlar el arousal cortical producido por la estimulación entrante y se asociaría con la dimensión de personalidad Extraversión-Introversión, de modo que los sujetos introvertidos tendrían un menor umbral de activación de este sistema que los extravertidos y por consiguiente, tendrían generalmente un mayor estado de arousal. El otro sistema se encargaría de controlar las respuestas hacia estímulos emocionales y su base biológica se encontraría en la activación del sistema límbico, este sistema estaría asociado con la dimensión de personalidad Neuroticismo-Estabilidad. Además de estos dos sistemas principales, Eysenck propuso también la existencia de un tercer sistema asociado a la dimensión de Psicoticismo que se relacionaría con la función dopaminérgica. Las diferencias individuales que darían lugar a los diferentes rasgos tendrían su origen en los niveles de arousal/activación de estos sistemas (Matthews y Gilliland, 1999).

Gray propuso dos grandes cambios sobre el modelo de Eysenck. En primer lugar, propuso una rotación de 30º del neuroticismo y la extraversión respecto de su posición en el eje de coordenadas para dar lugar a dos nuevos ejes causalmente más eficientes de sensibilidad a la recompensa y de sensibilidad al castigo (ver figura 2). En segundo lugar, propuso un cambio en las bases neuropsicológicas de estas dos dimensiones de la personalidad proponiendo al BAS como base neurobiológica de la sensibilidad a la recompensa y al BIS como base biológica para la sensibilidad al castigo (Pickering y cols., 1999).

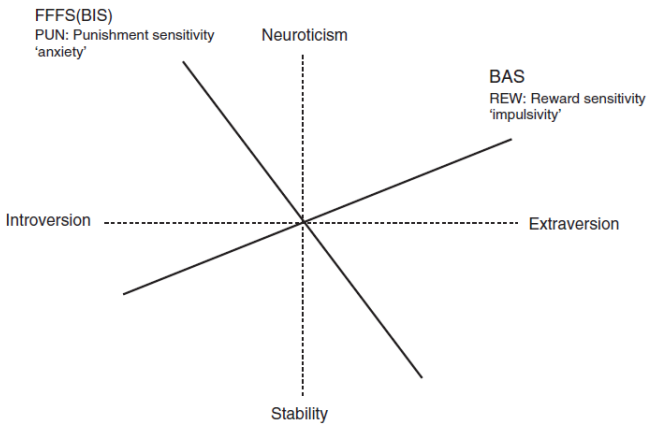

Figura 2: Esquema de la relación entre las dimensiones de los modelos de Eysenck y Gray. Extraído de Pickering y Corr, 2008

En el año 2000, el propio Gray junto con Neil McNaughton, propusieron una revisión de la teoría con el objetivo de actualizarla en base a la investigación empírica que se había desarrollado en los años anteriores. En esta revisión de la teoría se mantienen los mismos sistemas neurales propuestos en la versión antigua (BIS, BAS y FFS) pero cambian las funciones de algunos de ellos y las interacciones entre los mismos, siendo ahora el FFS y el BAS los encargados de responder ante estímulos aversivos y apetitivos respectivamente, quedando el BIS como un sistema encargado de la resolución de conflictos. Por otra parte, se propone al FFS junto con el BIS para explicar las bases neurobiológicas de la sensibilidad al castigo, permaneciendo el BAS como base biológica de la sensibilidad a la recompensa. En general, en esta revisión se intentó clarificar determinados aspectos de la antigua teoría a la vez que se modificaron antiguos supuestos y se introdujeron nuevos conceptos. El resultado de esta revisión es la nueva RST que en la actualidad, sigue siendo un marco de referencia para numerosas investigaciones científicas.

1.2.2 Los sistemas neuroconductuales propuestos por la RST

- El sistema de aproximación conductual (BAS):

En la versión más reciente de la RST, el BAS es un sistema cerebral encargado de responder ante estímulos condicionados e incondicionados apetitivos y de omisión de castigos. Cuando uno de estos estímulos está presente se dan dos efectos en la conducta que están mediados por el BAS, un efecto motivacional, debido un incremento en el arousal que estimula y redirige la conducta hacia la fuente de reforzamiento, y un efecto

en el aprendizaje, debido a que se redirige la atención sobre el estímulo de recompensa facilitando el procesamiento de la información y el aprendizaje de relaciones estímulo-estímulo y estímulo-respuesta (Pickering y Gray, 2001; Smillie y cols., 2007; Pickering y Smillie, 2008). Además, el BAS también se ha relacionado con el afecto positivo y las emociones de esperanza, en relación con los estímulos de recompensa, y alivio, en relación con los estímulos de evitación activa de estímulos aversivos (Fowles, 2002); pero también con emociones y afecto negativo (Carver, 2004). Clínicamente, el BAS estaría asociado con la predisposición a trastornos como las conductas adictivas, los trastornos de impulsividad, la manía y la depresión (Pickering y Corr, 2008). Un hecho a tener en cuenta según la RST es que el BAS no está implicado en las respuestas consumatorias ante los reforzadores biológicos (como comer, beber, copular, etc.), cada uno de los cuales estaría mediado por sistemas cerebrales diferentes, sino que su función principal es la reducción de la distancia espacio-temporal entre las metas actuales y el reforzador biológico final.

A nivel neurobiológico se ha relacionado al BAS principalmente con estructuras cerebrales pertenecientes al sistema dopaminérgico (Pickering y Gray, 1999; 2001). Según McNaughton y Corr, (2008), las estructuras del sistema dopaminérgico que más se relacionan con el BAS serían el VTA, el estriado ventral, el globo pálido ventral, y el córtex prefrontal.

- El sistema de lucha huida (FFS):

El FFS es un sistema cerebral encargado de responder ante estímulos condicionados e incondicionados aversivos. Ante un estímulo amenazante, el FFS produciría una respuesta defensiva con el objetivo de evitar o escapar de dicho estímulo. Así, la función principal de este sistema sería reducir la discrepancia producida por el estímulo amenazante hasta lograr un estado de seguridad. Para ello, el FFS utiliza diferentes tipos de respuestas defensivas en función de la proximidad con el estímulo amenazante. De esta forma, en distancias cortas puede producir una respuesta defensiva de lucha, mientras que en distancias intermedias puede producir respuestas de escape; o de congelación en los casos en que no sea posible el escape (McNaughton y Corr, 2004). La respuesta del FFS varía en función de lo que se conoce como distancia de defensa (Blanchard y Blanchard, 1990), que es un constructo que representa la intensidad percibida por parte del sujeto del estímulo amenazante. Así por ejemplo, un

estímulo amenazante de alta intensidad podrá producir una determinada respuesta defensiva a mayor distancia real de la que requeriría un estímulo amenazante de menor intensidad. En este sentido, se ha observado que las diferencias individuales en la sensibilidad al castigo modulan la distancia de defensa (McNaughton y Corr, 2004).

El FFS estaría asociado con la emoción de miedo, el cual, no solo sería diferente de la ansiedad sino que se darían en condiciones opuestas. Esta relación opuesta entre el miedo y la ansiedad se explica mediante un constructo denominado dirección de la defensa (Gray y McNaughton, 2000). De esta forma, el miedo estaría relacionado con situaciones en las que se requieren respuestas defensivas de escape o evitación de la amenaza (por ejemplo ante la presencia de un depredador). Por el contrario, la ansiedad (que está asociada al BIS) estaría relacionada con situaciones en las que se requiere una aproximación defensiva a la amenaza (por ejemplo un examen). Clínicamente, el FFS se relacionaría con las crisis de pánico y las fobias (Pickering y Corr, 2008).

Como substrato biológico del FFS se han propuesto diversas áreas cerebrales que incluyen zonas del mesencéfalo, como el área gris periacueductal, del sistema límbico, como el hipotálamo medial o la amígdala, y zonas frontales como el cingulado anterior y el córtex prefrontal ventral (Corr y McNaughton, 2008).

- El sistema de inhibición conductual (BIS):

El BIS es un sistema cerebral implicado en la resolución de conflictos. Este sistema entra en funcionamiento cuando se genera algún conflicto en el BAS, en el FFS o entre ambos. Así, su función principal es devolver al organismo a un estado de no conflicto. Según McNaughton y Corr (2004) los tipos de conflictos que puede haber son: conflictos de aproximación-evitación (por una activación simultánea del BAS y del FFS), conflictos de aproximación-aproximación (por ejemplo, por la existencia de dos posibles recompensas) y conflictos de evitación-evitación (por ejemplo, por la existencia de dos posibles castigos). El tipo de conflicto más paradigmático es el de aproximación-evitación, en el cual el sujeto debe de aproximarse a un estímulo amenazante (aproximación defensiva). Durante este tipo de conflictos se han diferenciado diversas respuestas conductuales en función de la distancia de la amenaza, de forma que en distancias intermedias serán más probables conductas de evaluación de riesgos mientras que en distancias cortas se producirían con mayor probabilidad conductas de inactividad defensiva (McNaughton y Corr, 2008). Al igual que ocurría

con el FFS, la respuesta del BIS varía en función de la distancia de defensa. En general, como resultado de la activación de este sistema se produce una interrupción de la conducta actual, un aumento del afecto negativo, una focalización de la atención hacia la fuente de conflicto y un incremento del arousal. De esta forma el BIS facilita la resolución del conflicto mediante la evaluación de la potencial amenaza evitando las conductas que puedan poner al sujeto en contacto con esta (Gray y McNaughton, 2000). Como se ha comentado anteriormente, el BIS está asociado con la ansiedad y subjetivamente su activación se experimenta como preocupación y rumiación. Clínicamente se ha asociado con los trastornos de ansiedad generalizada y obsesivo-compulsivo (Corr, 2008b).

Aunque las reacciones descritas del BIS están basadas principalmente en estudios de conflictos de aproximación-evitación, la teoría sugiere que las mismas reacciones se dan para los conflictos de evitación-evitación y conflictos de aproximación-aproximación. Por tanto, la teoría sugiere que cualquier tipo de conflicto que se produzca entre las diferentes alternativas de respuesta podrá generar ansiedad independientemente de cuál sea su origen. Un aspecto importante a tener en cuenta es que la activación del BIS no está restringida solamente a situaciones concretas o a reacciones ante estímulos específicos, sino que el término conflicto al que se refiere la teoría abarca también conflictos entre metas u objetivos generales que pueda tener el individuo.

Como base biológica del BIS se han propuesto áreas del mesencéfalo como el área periacueductal gris, zonas límbicas como el hipotálamo medial, la amígdala y el sistema septo-hipocampal y zonas frontales como el cingulado posterior y el córtex prefrontal dorsal (McNaughton y Corr, 2008).

- Interacción entre los sistemas:

La figura 3 muestra el modelo conceptual del sistema nervioso propuesto por la RST. Según este modelo, la presencia de un estímulo pondrá en marcha un determinado sistema neural que podrá producir estados motivacionales, emocionales y respuestas conductuales. Como se observa en la figura, en el centro del modelo se encuentran el BAS y el FFS, que responden ante estímulos apetitivos y aversivos respectivamente. La activación de uno de estos sistemas produce la inhibición del otro en referencia a la toma de decisiones, lo cual facilita la conducta mediada por dicho sistema (Corr,

2008b). Cuando estos dos sistemas se activan simultáneamente se incrementa el arousal. Si la activación de los sistemas es desigual, entonces no hay conflicto y la conducta final dependerá de cuál de los sistemas está más activo. Por el contrario, si la activación de los sistemas es similar, entonces se genera un conflicto produciendo activación del BIS. La activación del BIS, incrementa aún más el arousal, produce una focalización de la atención hacia los estímulos que generan el conflicto e inhibe cualquier respuesta que se esté produciendo en ese momento por parte del BAS o del FFS. La activación del BIS es asimétrica de forma que favorece la activación del FFS. Por lo tanto, la activación del BIS ante una situación de conflicto producirá una tendencia a evitar la posible amenaza. Por último, el modelo propone que la fuerza de la conducta final que se produzca, bien sea de aproximación o de evitación, estará modulada por la interacción de los sistemas que se hayan activado en ese momento. Así por ejemplo, una respuesta de aproximación será menos vigorosa ante la presencia de un estímulo amenazante que sin él.

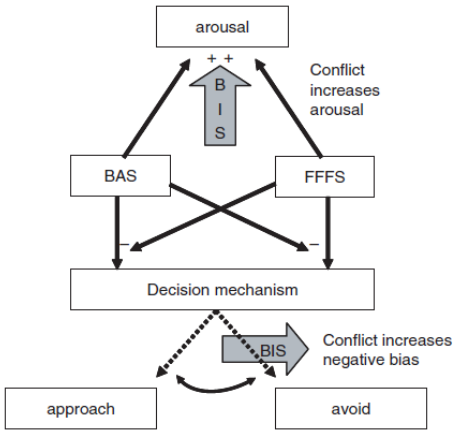

Figura 3: Sistema nervioso conceptual según el modelo de Gray. Extraído de Corr, 2008a.

1.2.3 La personalidad en la RST

Según Corr (2008b), la RST plantea un modelo por el cual diversos sistemas cerebrales específicos se encargarían de controlar conductas (por ejemplo, escape, lucha, o congelación) y emociones concretas (pánico, miedo), que podrían asociarse a determinadas percepciones o cogniciones (“voy a morir”). Estos sistemas locales estarían asociados entre sí para controlar funciones más generales (defensa) en

contextos más amplios (presencia de amenaza). Al mismo tiempo, estos sistemas interaccionarían con otros sistemas (BAS, BIS) y estarían modulados por sistemas generales (como los de arousal y atención). Cada uno de estos niveles de organización neural podría estudiarse desde el punto de su activación en un determinado momento (estado) o de su reactividad general ante diversas situaciones (rasgo). El estudio de la personalidad atiende a este segundo nivel de análisis. De este modo, la personalidad podría entenderse como el resultado de las diferencias individuales en la reactividad de diferentes sistemas neurales. Así por ejemplo, se esperaría que los sujetos con una alta reactividad del BAS fueran más optimistas, buscadores de recompensas e impulsivos que los sujetos con baja reactividad del BAS. Por otra parte, se esperaría que los sujetos con una alta reactividad del FFS tuvieran una mayor propensión al miedo y a la evitación que los sujetos con una baja reactividad del FFS. Por último, se esperaría que los sujetos con una alta reactividad del BIS tuvieran una mayor propensión a la preocupación, a la ansiedad y a la rumiación que los sujetos con una baja sensibilidad del BIS.

En general, la RST postula la existencia de dos grandes rasgos de personalidad: Un rasgo de sensibilidad a la recompensa, el cual estaría asociado principalmente al BAS y representaría diferencias individuales a largo plazo en la reactividad de este sistema, y un rasgo de sensibilidad al castigo, el cual estaría asociado al FFS y al BIS, y representaría diferencias individuales a largo plazo en la percepción de amenaza (Corr, 2004; McNaughton y Corr, 2008)

1.3 El sistema de recompensa como base biológica del BAS: Evidencia desde la neuroimagen.

Las bases biológicas del BAS han sido estudiadas utilizando diferentes metodologías de investigación (Corr, 2008a). De todas ellas, técnicas de neuroimagen como MRI o PET proporcionan una perspectiva única gracias a que permiten el estudio del cerebro humano in vivo con una gran resolución espacial, una buena resolución temporal y con acceso a estructuras profundas como los ganglios basales. Mediante estas técnicas es posible abordar el estudio biológico del BAS desde diferentes niveles de análisis incluyendo morfología, respuesta funcional y conectividad. Aunque no muchos, existen algunos estudios que han encontrado diferencias individuales en rasgos

de personalidad relacionados con el BAS utilizando estas técnicas. Generalmente, el procedimiento utilizado por estos estudios consiste en dividir a los sujetos en grupos a partir sus características de personalidad para luego comparar los datos obtenidos mediante la técnica de neuroimagen, o como alternativa, en correlacionar los datos de neuroimagen con las puntuaciones obtenidas por los sujetos en escalas de personalidad. A continuación se mostraran algunos de estos estudios, tanto los que han utilizado escalas diseñadas específicamente para medir la reactividad del BAS, como la escala "Sensitivity to Reward" (SR) del "Sensitivity to Punishment and Sensitivity to Reward Questionnaire" (SPSRQ; Torrubia y cols., 2001) o las escalas "Reward Responsiveness" (RR), "Drive" y "Fun Seeking" (FS) del cuestionario "Behavioral Inhibition/Behavioral Activation Scales" (BIS/BAS; Carver y White, 1994), como los que han utilizado escalas de otros modelos de personalidad que miden rasgos que comparten características conceptuales con el BAS como la escala "Novelty Seeking" (NS) del "Temperament and Character Inventory" (Cloninger y cols., 1993) o la escala "Sensation Seeking" del "Zuckerman–Kuhlman Personality Questionnaire" (Zuckerman, 2002).

1.3.1 Estudios morfológicos

Mediante estudios de morfología se ha observado que el volumen del estriado ventral correlaciona negativamente con las puntuaciones en SR (Barrós-Loscertales y cols., 2006). Además, se ha visto que las puntuaciones en NS correlacionan positivamente con el volumen del giro frontal medio izquierdo, giro precentral izquierdo, córtex prefrontal medial superior y córtex cingulado posterior, mientras que correlaciona negativamente con el volumen del giro frontal inferior izquierdo, claustrum izquierdo y cerebelo (Gardini y cols., 2009; Iidaka y cols., 2006; Van Schuerbeek y cols., 2011). Estos estudios muestran diferencias morfológicas en áreas principales del sistema de recompensa como el estriado ventral o el córtex prefrontal, pero también en otras zonas que no se habían relacionado específicamente con este sistema.

1.3.2 Estudios de neuroimagen funcional

Diversos estudios de neuroimagen funcional han mostrado relación entre las diferencias individuales en la actividad cerebral durante tareas de recompensa y las puntuaciones obtenidas por los sujetos en las escalas asociadas al BAS. Por ejemplo, se ha visto que los sujetos con puntuaciones altas en escalas asociadas al BAS muestran

una mayor activación del mesencéfalo y el estriado ventral durante la anticipación de recompensas monetarias (Carter y cols., 2009; Hahn y cols., 2009), así como una mayor activación del estriado ventral, ínsula y OFC durante la recepción de recompensas monetarias (Camara y cols., 2010b; Simon y cols., 2010; Cservenka y cols., 2012). Además, una alta reactividad del BAS se ha asociado con una mayor activación del mesencéfalo, estriado ventral y córtex prefrontal ante la presentación de imágenes de comidas apetitivas (Beaver y cols., 2006) y del córtex prefrontal ante la presentación de imágenes eróticas (Barrós-Loscertales y cols., 2010). En un estudio reciente, se vio que la relación entre las puntuaciones en SR y la actividad del córtex prefrontal inferior durante una tarea de control cognitivo estaba modulada por la posibilidad de obtener recompensas (Jimura y cols., 2010).

Por otra parte, las escalas asociadas al BAS se han relacionado con la activación cerebral en condiciones que no implicaban recompensa. Por ejemplo se ha visto que las puntuaciones en NS correlacionan positivamente con la actividad del mesencéfalo durante la presentación de estímulos novedosos (Krebs y cols., 2009) y con la actividad del córtex prefrontal medial ante señales que predecían estímulos emocionales tanto positivos como negativos (Bermpohl y cols., 2008), mientras que correlacionan negativamente con la activación de la ínsula y el cingulado anterior durante estímulos personalmente relevantes para los sujetos (Enzi y cols., 2009). Además, se ha visto una correlación negativa entre las puntuaciones en las escalas del BAS y la activación de áreas frontales, parietales y del cingulado anterior durante una tarea de control cognitivo (Gray y cols., 2005). En tareas de "go/no go", se han visto que los sujetos con puntuaciones altas en "Sensation Seeking" muestran una mayor respuesta en el cingulado anterior, el córtex parietal, la ínsula, el córtex occipital y el precuneus durante la iniciación de respuesta (Collins y cols., 2012). Por otro lado, la SR se ha asociado positivamente con la actividad del estriado ventral y el córtex prefrontal inferior, y negativamente con la actividad del precuneus y del cingulado anterior rostral durante una tarea de cambio cognitivo (Avila y cols., 2012). Por último, otros estudios han mostrado una relación entre las puntuaciones de NS y la actividad en áreas auditivas en respuesta a sonidos (Röhl y Uppenkamp, 2010) y una mayor aleatoriedad de las series temporales del estriado ventral y el OFC medidas durante resting en sujetos con alta SR (Hahn y cols., 2012).

1.3.3 Estudios de conectividad

En estudios de tractografía en los cuales se analiza la cantidad de sustancia blanca entre regiones, se observó que los sujetos que puntuaban alto en NS presentaban mayor conectividad entre el estriado y la amígdala, lo que se propuso como un posible mecanismo mediante el cual la amígdala podía modular la actividad del estriado en contextos novedosos o de codificación de estímulos emocionales (Cohen y cols., 2008). En un estudio más reciente, se ha visto además una mayor conectividad entre el estriado y el OFC en los sujeto con alta NS (Lei y cols., en prensa).

Por otro lado, mediante un análisis de conectividad efectiva se observó que el patrón de conectividad cerebral mostrado durante una tarea de toma de decisiones era acorde con los supuestos de la RST. En este procedimiento, los participantes debían tomar una decisión que podía ser de riesgo o no riesgo (conflicto), la cual era recompensada o castigada. Los resultados mostraron mayor conectividad entre el estriado ventral y el córtex prefrontal durante la recompensa, mayor conectividad entre la amígdala, el cingulado anterior y el hipotálamo durante el castigo y mayor conectividad entre el hipocampo y el córtex prefrontal durante el conflicto (Gonen y cols., 2012).

Por último, otros estudios han mostrado que las puntuaciones en NS modulan la conectividad entre el estriado ventral y el córtex prefrontal medial durante la toma de decisiones relacionadas con recompensas (Diekhof y Gruber, 2010), mientras que las puntuaciones en la escala "drive" modulan la conectividad entre el estriado ventral y el córtex parietal inferior durante la presentación de señales que indicaban la posibilidad de obtener recompensas en tareas de interacciones cognitivo-motivacionales (Padmala y Pessoa, 2011).

1.3.4 Conclusiones

En general, los estudios de neuroimagen muestran diferencias individuales en áreas del sistema de recompensa relacionadas con los rasgos de personalidad asociados al BAS. Los estudios de morfometría muestran diferencias de volumen principalmente en el estriado y en el córtex prefrontal. Por otro lado, los estudios de neuroimagen funcional muestran diferencias de actividad en las principales áreas del sistema de recompensa tanto en tareas que implican procesamiento de recompensa como en otro

tipo de tareas, indicando que estas diferencias se manifiestan a través de diversos contextos. Por último, los escasos estudios de conectividad muestran diferencias en la conectividad entre regiones del sistema de recompensa, sobre todo en lo que respecta a conexiones cortico-subcorticales. Todos estos estudios ponen de manifiesto que las bases neurales del BAS están representadas, al menos en parte, por zonas del sistema dopaminérgico y que las técnicas de neuroimagen son una herramienta de gran utilidad para el estudio biológico de la personalidad.

Capítulo 2

Marco experimental

2.1 Planteamiento de la investigación

Diversas líneas de investigación apoyan la existencia de un sistema de recompensa localizado principalmente en las áreas cerebrales pertenecientes al sistema dopaminérgico del mesencéfalo (Haber y Knutson, 2010; Berridge y Robinson, 1998; Berridge, 2007; Berridge y Kringelbach, 2008; Arias-Carrión y cols., 2010; Ikemoto, 2007; Schultz, 2010a; Wise, 2004; Kassubek y cols., 2011; Cools, 2008; O'Doherty, 2004; Wise y Rompre, 1989; McClure y cols., 2004). La RST de Gray incorpora este sistema como sustrato neurobiológico del BAS en su modelo conceptual del sistema nervioso. El BAS sería un sistema encargado de responder ante estímulos condicionados e incondicionados de recompensa y omisión de castigo. Según el modelo biológico de la personalidad que plantea la RST, las diferencias individuales estables a largo plazo en la reactividad del BAS, es decir, en las respuestas de las áreas cerebrales de recompensa interconectadas entre sí, darían lugar a un rasgo de personalidad de sensibilidad a la recompensa (Gray, 1970, 1982; Gray y McNaughton, 2000). Por lo tanto, mediante el estudio de la relación entre las diferencias individuales en el funcionamiento cerebral durante el procesamiento de la recompensa y los patrones conductuales asociados a la sensibilidad a la recompensa será posible definir cuáles son bases neurales de este rasgo.

Una de las técnicas capaces de medir y cuantificar la reactividad de las zonas cerebrales del BAS es la resonancia magnética funcional (fMRI del inglés: functional magnetic resonance imaging). Esta técnica es una de las más utilizadas para el estudio del funcionamiento cerebral gracias a que posee una gran resolución espacial y una buena resolución temporal. La fMRI permite el estudio in vivo de procesos perceptivos, cognitivos, emocionales y motores. Además, su carácter no invasivo la hace preferible a otras técnicas de neuroimagen, como el PET o la tomografía computarizada por emisión de fotones individuales, para el estudio con seres humanos. La fMRI no solo es una técnica óptima para el estudio de los substratos neurales del BAS sino también para el estudio de las bases cerebrales de cualquier modelo neuropsicológico.

A partir de la literatura en referencia al BAS, son diversas las cuestiones que faltan por dilucidar, algunas de las cuales pueden ser abordadas mediante el uso de fMRI. Una primera cuestión es si las diferencias en función de la reactividad del BAS se observan en procedimientos de condicionamiento clásico. La RST propone que el BAS es un sistema que responde ante estímulos condicionados e incondicionados apetitivos (Pickering y Gray, 2001). Sin embargo, en las primeras formulaciones del modelo de Gray, se consideraba que el BAS no respondía ante estímulos incondicionados apetitivos mientras que sí hipotetizaba un mayor aprendizaje pavloviano en los sujetos con alta impulsividad (Gray, 1975). Este hecho, produjo que hubiera cierta controversia sobre el papel del BAS en el condicionamiento clásico (Matthews y Gilliland, 1999; Corr, 2001). Algunos estudios han encontrado diferencias individuales en la actividad cerebral relacionadas con la sensibilidad a la recompensa utilizando procedimientos de condicionamiento instrumental (Hanh y cols., 2009; Carter y cols., 2000), pero no se conoce si la modulación de la respuesta cerebral en función de la personalidad se observa en procedimientos de condicionamiento clásico. En los estudios presentados en esta tesis, se utilizaron paradigmas tanto de condicionamiento clásico (primer estudio) como instrumental (segundo y tercer estudio) adaptados al contexto de MRI con el fin de estudiar la respuesta del BAS ante las señales condicionadas mediante ambos procedimientos.

Una segunda cuestión es si el tipo de estímulo reforzador puede modificar los resultados. Aunque estudios previos de neuroimagen han mostrado que tanto las recompensas monetarias como los estímulos sexuales son capaces de activar áreas del circuito de recompensa (Liu y cols., 2011; Stoléru y cols., 2012), el uso de recompensas monetarias como reforzador en las investigaciones donde se pone a prueba el modelo de Gray está más extendido (Carter y cols., 2009; Hahn y cols., 2009; Camara y cols., 2010b; Simon y cols., 2010; Cservenka y cols., 2012). En los estudios incluidos en esta tesis se han utilizado tanto recompensas monetarias como estímulos sexuales para estudiar la actividad del BAS. Concretamente, en el primer estudio utilizaron estímulos sexuales como recompensa para estudiar la respuesta del BAS ante este tipo de reforzadores. Por otra parte, en el segundo estudio se utilizaron recompensas monetarias como reforzador para obtener diferencias individuales en la actividad de las zonas cerebrales asociadas al BAS para luego tomarlas como referencia en análisis posteriores

de conectividad. Por último, en el tercer estudio se utilizaron ambos estímulos con el objetivo de generalizar los resultados a diversos tipos de reforzadores.

Otra cuestión hace referencia a si las diferencias individuales en función del BAS se dan a nivel de conectividad entre regiones. De modelos psicobiológicos como la RST se deriva la idea generalizada de que todo proceso motivacional no puede localizarse exclusivamente en una sola región cerebral, sino que depende de la interacción de diversas estructuras. En contra de las ideas localizacioncitas del siglo XIX, en la actualidad se distingue entre los conceptos de especialización e integración funcional (Friston, 2002). Las investigaciones centradas en el estudio de la especialización funcional tratan de estudiar qué áreas concretas están implicadas en un determinado proceso. Por el contrario las investigaciones cuyo objeto de estudio es la integración funcional tratan de estudiar cómo se conectan entre si estas áreas. Ambos tipos de investigaciones son necesarias si se quiere tener una perspectiva completa del fenómeno de estudio. La mayoría de investigaciones dedicadas al estudio de las bases cerebrales del BAS lo han hecho desde una perspectiva de especialización funcional. En esta tesis se investigan las bases neurales del BAS desde ambas aproximaciones. Concretamente, en el primer estudio se utiliza un enfoque de especialización funcional mientras que en los otro dos se utilizan los dos enfoques.

Una última cuestión es si las diferencias individuales en función del BAS se representan en otros sistemas cerebrales que interaccionan con el sistema de recompensa, como el sistema atencional. Durante mucho tiempo, la emoción y la cognición han sido tratadas como entidades diferentes. Sin embargo, los nuevos avances en neurociencia muestran que esta visión es deficiente y que si se pretende explicar la conducta compleja a partir del funcionamiento cerebral es necesario atender a la interacción entre ambos procesos (Pessoa, 2008). En relación con la RST, se ha propuesto que el déficit de inhibición de la respuesta relacionada con la predicción de eventos negativos en los sujetos con un BAS hiperactivo está relacionado con una excesiva focalización de la atención hacia las señales de recompensa que restringe la recogida de información de otras señales y la consideración de respuestas alternativas (Patterson y Newman, 1993). En el tercer estudio de esta tesis, se estudió la implicación de las redes atencionales en el procesamiento de las señales de recompensa y su relación con el rasgo de personalidad sensibilidad a la recompensa.

Finalmente, en los estudios incluidos en esta tesis se han tomado diversas decisiones metodológicas:

1. El cuestionario para medir la reactividad del BAS: En los tres estudios incluidos en esta tesis se utilizó la escala SR del SPSRQ (Torrubia y cols., 2001) para evaluar las diferencias individuales en el rasgo de personalidad sensibilidad a la recompensa. Las escalas del SPSRQ muestran buena consistencia interna y fiabilidad test-retest (Torrubia y cols., 2001). El SPSRQ ha sido traducido a 15 idiomas y es ampliamente utilizado en investigación para medir diferencias individuales bajo el marco teórico del modelo de Gray, tanto en niños (Luman y cols., 2012) como en adultos (Torrubia y cols., 2008). La escala SR del SRSPQ muestra un mejor ajuste con la última versión de la RST ya que sus ítems consideran la respuesta tanto a estímulos condicionados como incondicionados (Smillie y cols., 2006). Además, ha demostrado tener una buena validez de contenido y correlaciona altamente con otras medidas relacionadas con la sensibilidad a la recompensa, como NS, RR, "drive", FS y escalas de impulsividad (Caseras y cols., 2003).
2. Las diferencias de género: Diversos estudios han mostrado la existencia de diferencias entre hombres y mujeres en los principales aspectos de estudio de esta tesis, como son el cerebro y la personalidad. Por ejemplo, se ha visto que los hombres muestran una mayor puntuación que las mujeres en escalas asociadas con el BAS como SR (Torrubia y cols., 2001) o "Sensation Seeking" (Cross y cols., 2011). Además, se han observado diferencias entre hombres y mujeres tanto anatómicas como funcionales en zonas cerebrales del sistema de recompensa (Good y cols., 2001; Andersen y cols., 2012). Debido a la variabilidad existente entre hombres y mujeres en estos factores, las muestras seleccionadas para los estudios incluidos en esta tesis estaban formadas exclusivamente por hombres.

En resumen, en esta tesis se ha utilizado la fMRI para estudiar la relación entre el rasgo de personalidad sensibilidad a la recompensa y las diferencias individuales en la actividad y en la conectividad de las áreas pertenecientes al sistema de recompensa. En el primer estudio, se utilizó un paradigma de condicionamiento clásico para estudiar la relación entre las puntuaciones en la escala SR y la actividad cerebral en respuesta a imágenes eróticas y a señales condicionadas a estas. En el segundo estudio se utilizó un

paradigma de aprendizaje instrumental con recompensas monetarias para estudiar la relación entre las puntuaciones en SR y las diferencias individuales en la actividad y la conectividad cerebral. Por último, en el tercer estudio se utilizaron dos paradigmas de aprendizaje instrumental, uno con recompensas monetarias y otro con estímulos sexuales, para estudiar cómo la modulación de las redes funcionales atencionales durante la anticipación a la recompensa se asocia con las puntuaciones en SR.

2.1.1 Objetivos e hipótesis de la investigación

En general, se busca estudiar diferencias individuales relacionadas con la dimensión de sensibilidad a la recompensa, en la actividad y la conectividad de áreas cerebrales involucradas en el procesamiento de la recompensa (especialmente en el mesencéfalo, estriado ventral, amígdala y OFC) durante procedimientos de condicionamiento clásico e instrumental apetitivo. Los objetivos específicos de la investigación son estudiar la relación entre:

1. las diferencias individuales en la sensibilidad a la recompensa y la activación cerebral durante la presentación de estímulos sexuales.
2. la sensibilidad a la recompensa y la actividad cerebral en respuesta a señales condicionadas de recompensa mediante paradigmas de condicionamiento clásico e instrumental.
3. la sensibilidad a la recompensa y la conectividad cerebral de áreas pertenecientes al sistema de recompensa durante el procesamiento de señales de recompensa en un paradigma de aprendizaje instrumental.
4. la sensibilidad a la recompensa y la modulación de redes atencionales como la red de activación por defecto (DMN, del inglés: default mode network), la red atencional dorsal (DAN, del inglés: dorsal attention network) o la red frontoparietal (FPN, del inglés: frontoparietal network) durante el procesamiento de señales de recompensa en paradigmas de aprendizaje instrumental.

En base a estos objetivos, formulamos las siguientes hipótesis:

1. Existirá una correlación positiva entre las puntuaciones de SR y la actividad cerebral en áreas de recompensa durante la presentación de estímulos sexuales.
2. Se encontrará una asociación entre las puntuaciones de SR y la actividad cerebral en áreas pertenecientes al sistema de recompensa durante la respuesta a

señales condicionadas de recompensa tanto en paradigmas de condicionamiento clásico como instrumental.

3. Existirán diferencias individuales relacionadas con la sensibilidad a la recompensa en la conectividad funcional entre áreas cerebrales pertenecientes al sistema de recompensa durante la anticipación de recompensas.
4. Mediante el análisis de redes atencionales, se observará una mayor modulación en redes cerebrales que incrementan la atención hacia estímulos externos en presencia de señales de recompensa en individuos con elevada sensibilidad a la recompensa.

Los estudios mediante los cuales se ponen a prueba estas hipótesis son investigaciones ya publicadas, en prensa o sometidas en revistas internacionales, por lo que están escritos en inglés. A continuación se incluyen estos estudios con su formato de publicación o tal y como se sometieron a esta.

2.2 Estudio 1

Reward sensitivity is associated with brain activity during erotic stimulus processing

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Reward Sensitivity Is Associated with Brain Activity during Erotic Stimulus Processing

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Abstract

The behavioral approach system (BAS) from Gray's reinforcement sensitivity theory is a neurobehavioral system involved in the processing of rewarding stimuli that has been related to dopaminergic brain areas. Gray's theory hypothesizes that the functioning of reward brain areas is modulated by BAS-related traits. To test this hypothesis, we performed an fMRI study where participants viewed erotic and neutral pictures, and cues that predicted their appearance. Forty-five heterosexual men completed the Sensitivity to Reward scale (from the Sensitivity to Punishment and Sensitivity to Reward Questionnaire) to measure BAS-related traits. Results showed that Sensitivity to Reward scores correlated positively with brain activity during reactivity to erotic pictures in the left orbitofrontal cortex, left insula, and right ventral striatum. These results demonstrated a relationship between the BAS and reward sensitivity during the processing of erotic stimuli, filling the gap of previous reports that identified the dopaminergic system as a neural substrate for the BAS during the processing of other rewarding stimuli such as money and food.

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Introduction

The reinforcement sensitivity theory (RST) proposes the existence of a neurobehavioral system involved in the processing of appetitive stimuli [1–3]. This system is called the behavioral approach system (BAS) and its primary function is to bring together the individual with biological rewards such as sex and food. The biological substrate of the BAS is thought to comprise brain areas belonging to the dopaminergic reward system [3], which mainly includes subcortical structures such as the ventral tegmental area, substantia nigra, basal ganglia or amygdala, and prefrontal areas such as the orbitofrontal cortex (OFC), medial prefrontal cortex (PFC), and anterior cingulate cortex (ACC) [4,5].

As claimed by the RST, BAS reactivity increases as a function of the appetitive value of a reward cue or reinforcer, and varies among individuals, resulting in a stable personality trait called reward sensitivity. Behavioral studies have consistently confirmed that individuals with higher scores on measures of reward sensitivity have stronger appetitive conditioning and prefer immediate reward more than low scorers [6,7]. Accordingly with the RST, previous fMRI studies have shown an association between individual differences in reward sensitivity and brain activity in different BAS-related areas when responding to rewards. For example, Beaver et al. (2006) showed that reward sensitivity was positively associated with activity in the midbrain, ventral striatum (VS), and OFC in response to pictures of appetizing foods [8]. In addition, studies using monetary rewards demonstrated a positive correlation between measures of reward sensitivity and activity in the nucleus accumbens (NAcc), ventral tegmental area, and OFC during processing of reward cues and reinforcers [9–11]. In sum, fMRI results have been consistent with the RST, showing that reward sensitivity increases the response of reward brain areas during processing of both reward cues and reinforcers such as money or appetizing foods, leaving an open gap for the processing of sex as a biological reward.

Neural differences in sexual behavior have been less explored in the framework of the RST. Behavioral data have shown that stronger reward sensitivity predisposes a person to be engaged in more sexual experiences, be more curious about sexual topics in the media, and be more sexually excitable [12–17]. Sexual behavior is one of the most important goal-directed behaviors essential for the survival of the animal species and is thought to engage brain mechanisms supporting reward processing [18]. A key component of sexual behavior is sexual arousal, defined as physical and psychological readiness to perform sexual behavior [19]. Sexual arousal may be initiated by external stimuli or may be produced by endogenous factors. Recent fMRI studies have used erotic stimuli to study brain areas involved in sexual arousal [19,20]. These studies showed involvement of BAS-related areas such as the OFC, medial PFC, ACC, VS, and amygdala in sexual arousal. In addition, studies have explored the brain areas involved in processing cues that predict sexual stimuli. For example, activity in the OFC has been demonstrated in response to cues associated with sexual images in participants aware of the contingency [21]. However, no previous studies have analyzed the relationship

between individual differences in reward sensitivity and brain activation during anticipation of and reactivity to erotic stimuli.

To study the association between reward sensitivity and the processing of sexual cues and stimuli in more detail, we adapted an event-related fMRI task [22] where erotic and neutral pictures were presented after cues that were 50% or 100% predictive of the erotic stimuli. In line with the RST, we hypothesized stronger activation in BAS-related areas during both the presentation and anticipation of sexual stimuli. In addition, we hypothesized that BAS-related areas involved in the processing of anticipatory cues would show greater activity for cues that were 100% predictive than 50% predictive due to greater contingency between the cue and erotic image. Finally, we expected to observe increased activity in BAS-related areas in participants with high reward sensitivity during the processing of cues and sexual stimuli.

Methods

Participants

Forty-five heterosexual men ($M_{age} = 24.08$, $SD = 3.71$, years of education = 13.27 ± 2.93) took part in this study. All participants completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [23] for a measure of individual differences in reward sensitivity. Three participants were excluded from the personality analyses (see Personality Analysis) because they left more than two items unanswered on the Sensitivity to Reward (SR) scale. The mean score on the SR scale was 12.04 ($SD = 4.48$, range: 2–24, $N = 42$) and scores followed a normal distribution (Kolmogorov-Smirnov test: $D = .12$, $p > .11$); thus, the scores of this sample were similar to those obtained in previous studies [23–26]. None of the participants included in the study had a history of head injury with loss of consciousness, currently used psychoactive medications, or were previously or currently diagnosed with DSM-IV Axis I or II disorders, or severe medical or neurological illnesses. Participants provided written informed consent prior to participating in this study and were paid for their participation. The study was approved by the Ethics Committee of the Universitat Jaume I of Castellon.

Experimental Design and Stimuli

The task used was an adaptation of an earlier study focused on the anticipation of and reactivity to emotionally aversive stimuli [22]. Each trial consisted of a warning cue (X, O, or ?) presented for 1 s and then a fixation point presented for a variable interval of 6, 7, 8, 9, or 10 s, which was then succeeded by a picture presented for 1 s. For appetitive trials, an X cue was always followed by an erotic picture ($Ep_{100\%}$). For neutral trials, an O cue was always followed by a neutral picture ($Np_{100\%}$). For ambiguous trials, a question mark cue was followed half of the time by an erotic picture ($Ep_{50\%}$) and the other half by a neutral picture ($Np_{50\%}$). Participants were informed that X and O cues were always followed by erotic pictures and neutral pictures respectively, whereas a question mark cue was followed by either erotic or neutral pictures. Before scanning, participants underwent an exemplary paradigm for 9 min 12 s using a set of erotic and neutral images different from the experimental set. All symbols were white and presented on a black background. Trial order was pseudorandomized with the stipulation that no trial type be presented more than twice in a row. The intertrial interval varied between 6, 7, 8, 9, and 10 s, and was pseudorandomized after both cue and picture presentation. This interval was based on the paradigm of reference in order to optimize jittering for estimation of the hemodynamic response in both the anticipation and response periods [22]. Trial length varied from 14 to 22 s with an average trial length of 18 s.

There were three functional runs, each consisting of eight erotic trials, eight neutral trials, and eight ambiguous trials (totals: 24 positive, 24 neutral, and 24 ambiguous). Each functional scan began with a 10 s black screen, resulting in scan lengths of 7 min, 7 min 15 s, and 7 min 30 s respectively. Runs were randomized among participants. Using a response box (NordicNeuroLab, Bergen, Norway) during the fMRI experiment, participants were instructed to push a single button with their index finger after each cue and each picture to ensure a constant level of attention during picture viewing [27]. Participants were also instructed to respond to 1 s presentations of a fixation cross in isolation during the experimental paradigm (six per run, total = 18) as null events. This stimulus served to maintain participants' attention to the cue and picture stimuli, and to control for the effects of stimulus response with absent contingencies during reward anticipation and reactivity [28].

During the fMRI experiment, participants viewed 72 pictures (36 erotic and 36 neutral) from the International Affective Picture Set [29] at a resolution of 800×600 pixels with no picture shown more than once. Based on published norms [30], erotic pictures with the highest pleasant valence ratings ($M = 7.55$, $SD = 1.54$) and highest arousal ratings ($M = 6.97$, $SD = 2.06$) comprised the erotic appetitive set, which primarily included photographs of couples and undressed adult women. The selected neutral pictures (e.g., household items) had neutral valence ratings ($M = 5.03$, $SD = 1.31$) and low arousal ratings ($M = 2.88$, $SD = 2.03$). In contrast with other studies involving erotic images [31,32], we did not use non-erotic pictures of humans for our neutral condition. These stimuli entail diverse variables, such as attractiveness [33], body shape [34], or social valuation [35], that can influence activity in brain areas within the dopaminergic system. Considering how the objective of this study was not to disentangle the specific brain areas responding to sexual arousal but to study the relationship between individual differences in personality and brain activity in response to erotic pictures and cues, we consider pictures of household items better for our neutral condition.

FMRI Acquisition

Imaging was performed using a 1.5 T Siemens Avanto (Erlangen, Germany) MRI scanner. Functional images were acquired using a gradient-echo T2*-weighted echo-planar MR sequence (TR = 2000 ms, TE = 30 ms, matrix = $64 \times 64 \times 30$, voxel size = 3.5 mm^3, flip angle = 90°, slice gap = .5 mm). We acquired 30 interleaved axial slices oriented parallel to the hippocampus. There were 213 functional volumes for the first run, 218 for the second run, and 214 for the third run. Prior to the functional MR sequences, a high-resolution T1-weighted structural sequence was acquired (TR = 11 ms, TE = 4.9 ms, flip angle = 90°, voxel size = $1 \times 1 \times 1$ mm).

FMRI Analysis

Image processing and statistical analysis were carried out using SPM8 (Wellcome Trust Center for Neuroimaging, London, UK). The first two scans were excluded to allow for equilibration effects. Preprocessing of the functional scans included noise filtering using the ArtRepair toolbox (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) to repair slice artifacts through interpolation (from before and after scans), slice time correction, realignment to correct for motion-related artifacts, spatial normalization after extracting normalization parameters from the segmentation of each participant's high-resolution

anatomical acquisition (see FMRI Acquisition), and smoothing with an 8-mm (FWHM) Gaussian kernel.

After preprocessing, a general linear model was used to calculate significant hemodynamic changes among the conditions [36]. For the first-level (within-subjects) analyses, each participant's preprocessed time series were modeled to each condition of interest using the hemodynamic response function and its temporal derivate. Eight regressors were defined for modeling the cues (X, O, and ?), outcomes ($Ep_{100\%}$, $Np_{100\%}$, $Ep_{50\%}$, and $Np_{50\%}$), and fixation cross. Furthermore, the six realignment parameters modeling residual motion were also included as regressors of noninterest. Intrinsic autocorrelations were removed via high-pass filter with a cut-off frequency of 1/128 Hz.

Second-level (random-effects) whole-brain voxel-wise analyses were performed to reveal brain activity of the group under the different conditions. For the anticipatory period, one-sample *t*-test analyses were conducted using estimates of BOLD contrasts from the first-level analyses (X>O and ?>O) to obtain BOLD signal differences in response to erotic and ambiguous cues relative to neutral ones. In addition, a paired *t* test was performed to compare differences in the BOLD signal between erotic and ambiguous cues. For the outcome period, a two-way (Condition [erotic, neutral] x Probability [100%, 50%]) repeated-measures ANOVA was performed to compare differences in brain activity regarding the presentation of erotic pictures versus neutral pictures. Additionally, we carried out an exploratory analysis in order to study brain areas that responded to the interaction between condition and probability. Statistical analyses were done at a threshold of $p<.05$ family-wise error (FWE) cluster corrected. The FWE correction was obtained applying a voxel-wise threshold of $p<.001$ uncorrected and a minimum extent threshold of 22 contiguous voxels. The threshold was selected based on Monte Carlo simulations using the Resting-State fMRI Data Analysis Toolkit (REST; http://www.restfmri.net).

Personality Analysis

Correlation analyses were performed in order to study the relationship between SR scores and brain activity during the anticipation and outcome conditions. Following previous studies of individual differences [11,37,38], we analyzed the association between reward sensitivity and brain activity by correlating an individual's SR scores and the mean value of activity in specific brain areas of interest. Our analysis was restricted to volumes of interest (VOIs) in areas belonging to the dopaminergic system, including the midbrain, striatum, amygdala, medial PFC, OFC, and insula [5,39]. The peak maximum coordinates of dopaminergic areas that showed significance in the whole-brain voxel-wise analyses were used to define the VOIs. Every VOI consisted in an 8-mm radius sphere centered on the peak voxel. For each participant, the mean BOLD contrast estimates of all active voxels within the VOI were calculated. Finally, these values were included in a partial correlation with SR scores, removing the effect of age. We included age as a covariate because previous evidence has shown that this variable is related to brain activity within the dopaminergic system [40,41]. The correlation analysis threshold was set to $p<.05$ Bonferroni FWE corrected. Based on this method, we divided the a priori selected threshold of $p<.05$ by the number of tests performed ($k=9$; see Results), which stabilized statistical levels as significant if less than.0055.

Behavioral Analysis

The median reaction times (RTs) of responses to anticipatory cues and responses to images were separately recorded for each participant to perform behavioral analyses. Paired *t* tests were carried out to study differences among anticipatory cues (X>?, X>O, and ?>O). To study differences during the outcome period, a two-way (Condition [erotic, neutral] x Probability [100%, 50%]) repeated-measures ANOVA was conducted. Finally, in order to study personality effects on RT, we performed partial correlations between SR scores and the RTs for erotic conditions (cues and images), controlling RTs for their respective neutral conditions.

Results

Behavioral Results

Behavioral analyses showed slower RTs for ambiguous cues ($M_?=458.4\pm116.2$ ms) than for both erotic cues ($M_X=445.22\pm126.64$ ms, $t=2.85$, $p=.007$) and neutral cues ($M_O=436.8\pm139.7$ ms, $t=3.67$, $p=.001$). No differences were found between RTs for erotic and neutral cues ($p>.05$). On the other hand, the analysis of RTs for images ($M_{Ep100\%}=388.5\pm128.9$, $M_{Np100\%}=360.2\pm99.1$, $M_{Ep50\%}=389.6\pm125$, $M_{Np50\%}=374.8\pm121.8$) showed a main effect of condition, $F(1, 44)=11.18$, $p=.001$, indicating slower RTs for erotic than neutral images. This result may signify that participants pay more attention to erotic than neutral images. However, these results should be cautiously interpreted given that participants were not instructed to respond as soon as possible but to answer as a measure of their attention, following the paradigm of reference [22]. Finally, no significant correlation was obtained between SR scores and RTs.

FMRI Results

Whole-brain analyses showed the involvement of BAS-related areas in both the anticipation of and reactivity toward erotic stimuli. Analyses of the anticipatory period demonstrated enhanced activity in the left OFC (x, y, z: −45, 38, −14; $z=3.73$, $k=25$) during the presentation of erotic cues in comparison with neutral cues. Moreover, activity in the left anterior insula (x, y, z: −42, 20, 1; $z=4.11$, $k=25$) was related to the presentation of ambiguous cues but not neutral cues (Figure 1). By contrast, no significant differences were found when erotic and ambiguous cues were compared.

During the image presentation period, cortical and subcortical brain areas showed stronger activity when participants viewed erotic pictures in contrast with neutral pictures. These areas included the OFC, medial PFC, lateral PFC, ACC, inferior temporal cortex, parietal cortex, occipital cortex, VS, amygdala, thalamus, and midbrain (see Figure 2 and Table 1 for details). Most of these areas were part of two big clusters: an anterior cluster that included frontal and limbic areas, and a posterior cluster that included occipitotemporal and parietal areas. Furthermore, a significant interaction between condition and probability was observed for activity in the bilateral precuneus (left x, y, z: −6, −67, 37; $z=4.09$, $k=25$; right x, y, z: 15, −58, 34; $z=3.93$, $k=34$). More specifically, we observed that in the erotic condition, the bilateral precuneus displayed greater activity during pictures with lower probability of appearance ($Ep_{50\%}$) than higher probability ($Ep_{100\%}$).

Personality Results

To determine which dopaminergic brain areas were related to reward sensitivity during sexual stimuli processing, we calculated the correlations between SR scores and brain activity of active dopaminergic areas that yielded significant main effects during the different task conditions. For the anticipatory period, the correlations between SR scores and activity in the left insula and

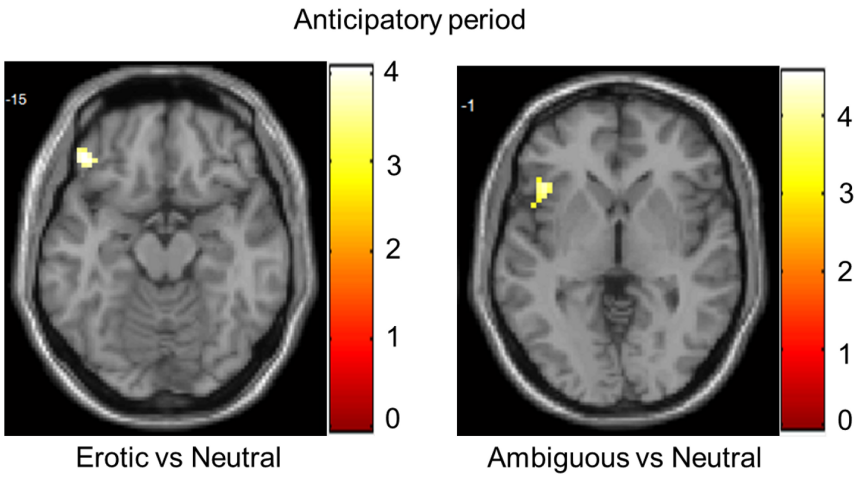

Figure 1. Brain activity during anticipatory cue processing. Images are presented in neurological convention (left is left) and with a threshold at $p<.05$ corrected. The color bars represent the *t* values applicable to the images and the numbers within the images correspond to z MNI coordinates.
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Table 1. Brain Regions Showing Increased Activity During Presentation of Erotic Images Compared With Neutral Images.

Region	Left (L) or Right (R) Side	Brodmann Area	Local Maxima Coordinates (x, y, z)	Z-Score	*k*
Posterior Cluster					
Fusiform Gyrus	R	20	42, −46, −17	>8	3381
Middle Temporal Gyrus	R	39	54, −64, 7	>8	
Parietal Superior	R	7	30, −52, 55	7.45	
Middle Occipital	R	19	36, −79, 22	6.03	
Parietal Superior	L	7	−21, −67, 49	5.69	
Parietal Inferior	L	40	−33, −49, 52	5.22	
Cuneus	R	18	9, −79, 16	5.20	
Posterior Cingulate	L	30	−6, −49, 19	5.06	
Anterior Cluster					
Inferior Frontal Cortex	R	45	54, 32, 7	6.94	3237
Lateral Prefrontal Cortex	R	6	45, 2, 52	6.18	
Orbitofrontal Cortex	R	47	36, 32, −17	5.81	
Medial Frontal Cortex	L	10	−3, 56, 1	5.79	
Insula	L	47	−24, 14, −20	5.70	
Orbitofrontal Cortex	L	47	−30, 29, −20	5.69	
Amygdala	L	–	−18, −4, −14	5.52	
Temporal Pole	L	38	−36, 20, −26	5.31	
Ventral Striatum	R	–	3, 8, −8	4.38	
Other Clusters					
Inferior Frontal Cortex	L	9	−42, 14, 25	4.31	175
Lateral Prefrontal Cortex	L	6	−42, −1, 55	3.75	
Fusiform Gyrus	L	20	−42, −37, −20	6.98	62
Midbrain	R	–	12, −28, −5	4.36	69
Supplementary Motor Area	–	8	0, 14, 55	4.29	87
Postcentral Gyrus	R	3	63, −19, 37	4.21	40

Note. $p<.05$ FWE corrected.
doi:10.1371/journal.pone.0066940.t001

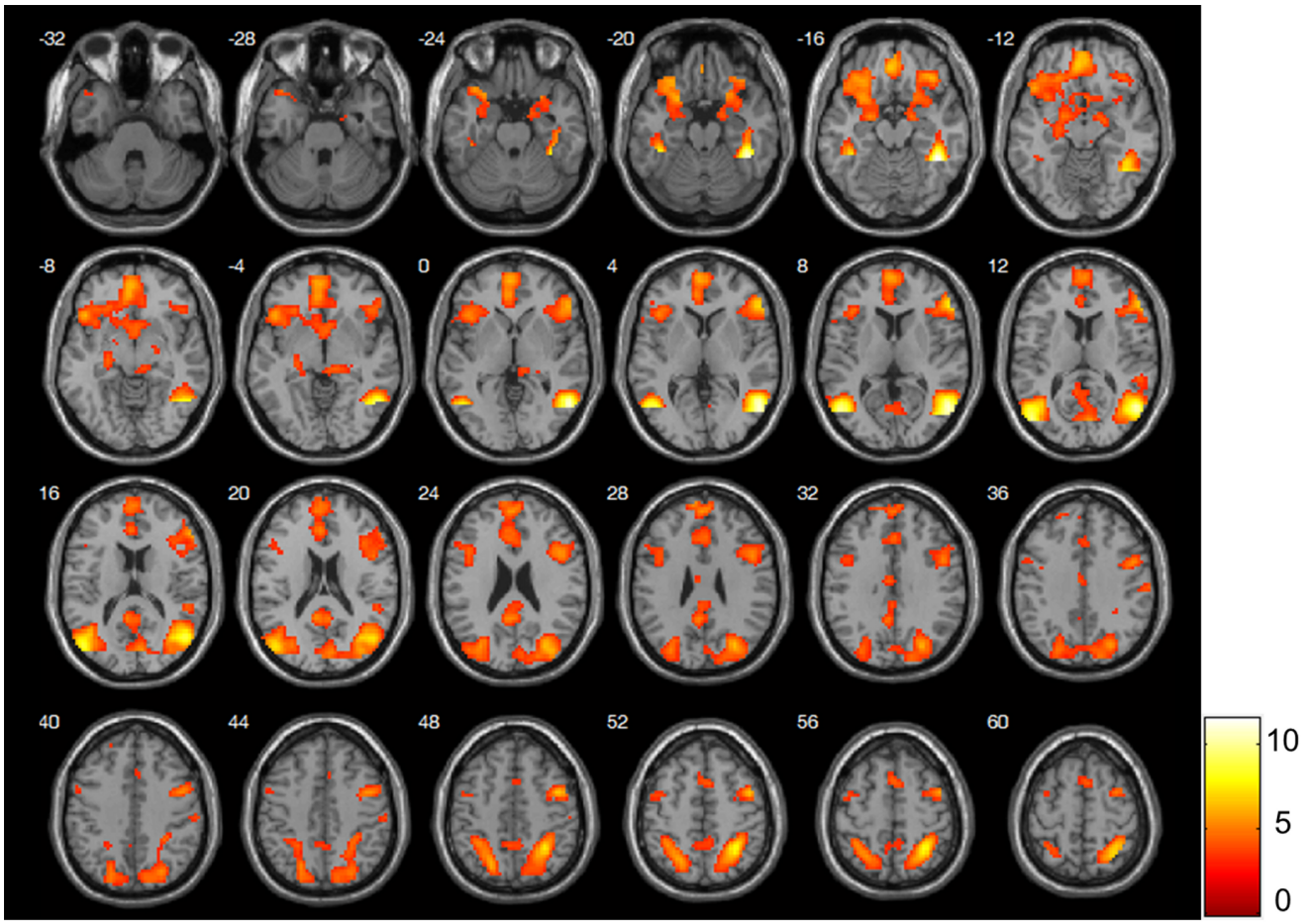

Figure 2. Brain activity during erotic picture processing. Images are presented in neurological convention (left is left) and with a threshold at $p<.05$ corrected. The color bar represents the *t* values applicable to the image and the numbers within the images correspond to z MNI coordinates.
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left OFC (i.e., the two active areas during anticipation) were not significant (Table 2).

For the image presentation period, we calculated the correlations between SR scores and brain activity during the processing of erotic pictures compared with neutral pictures in the bilateral OFC, left insula, medial PFC, right VS, left amygdala and midbrain. These analyses showed that SR scores positively correlated with brain activity in the left OFC ($r=.431$, $p<.05$ FWE corrected, $n=42$; see Figure 3a) and left insula ($r=.459$, $p<.05$ FWE corrected, $n=42$; see Figure 3b). In addition, we

Table 2. Partial Correlations Between SR Scores and Brain Activity, Removing the Effect of Age.

Contrast	Region	Left (L) or Right (R) Side	Brodmann Area	Sphere's Center Coordinate (x, y, z)	*r*
Erotic Cues vs. Neutral Cues	Orbitofrontal Cortex	L	47	−45, 38, −14	.09
Ambiguous Cues vs. Neutral Cues	Insula	L	47	−42, 20, 1	.15
Erotic Pictures vs. Neutral Pictures	Orbitofrontal Cortex	R	47	36, 32, −17	.31*
	Orbitofrontal Cortex	**L**	**47**	**−30, 29, −20**	**.43**
	Medial Frontal Cortex	L	10	−3, 56, 1	.03
	Insula	**L**	**47**	**−24, 14, −20**	**.45**
	Midbrain	R	–	12, −28, −5	.12
	Ventral Striatum	R	–	3, 8, −8	.31*
	Amygdala	L	–	−18, −4, −14	.23

Note. Brain areas in bold show a significant correlation with SR scores at $p<.05$ corrected.
*Brain areas correlated with SR scores at $p<.05$ uncorrected.
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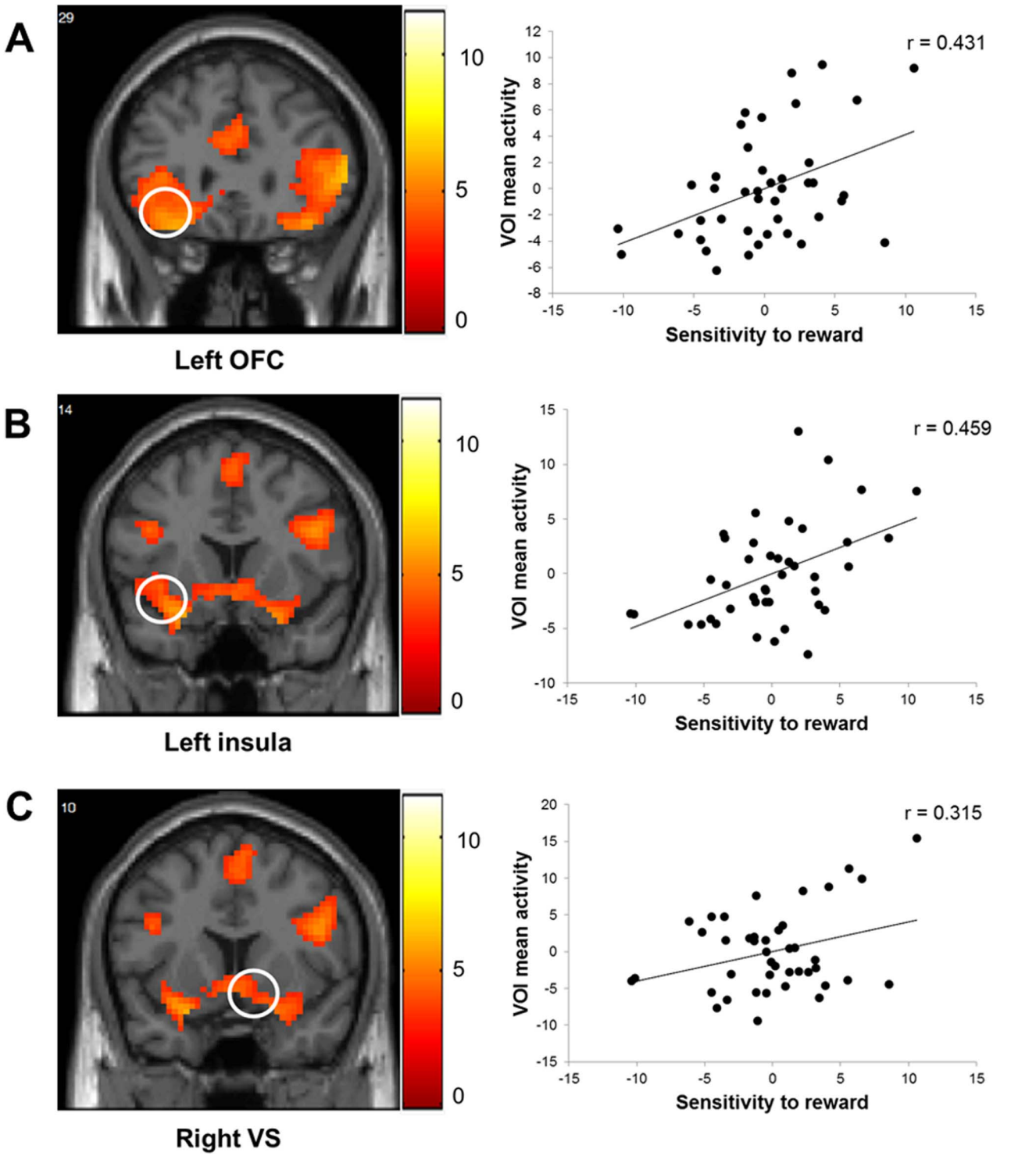

Figure 3. Brain areas showing positive correlation with SR scores. Left panel shows brain activity in the left orbitofrontal cortex (OFC) (a), left insula (b), and right ventral striatum (VS) (c) during erotic picture processing ($p<.05$ corrected). Images are presented in neurological convention (left is left). The color bar represents the *t* values applicable to the image and the numbers within images correspond to y MNI coordinates. Right panel shows scatterplots displaying the partial correlation between SR scores and mean VOI activity in the left OFC (a), left insula (b), and right VS (c) during erotic picture processing after removing the effects of age. The scatterplots' axes represent the residual values from linear regressions with age as the independent variable and the other variables of interest (i.e., SR scores or mean brain activity) as the dependent variable.
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observed a positive correlation between SR scores and brain activity in the right VS using a lower statistical threshold of $p<.05$ uncorrected ($r=.315$, $p<.05$ uncorrected, $n=42$; See Figure 3c). The correlations are summarized in Table 2.

Discussion

In this study, we adapted an event-related emotional task to investigate the relationship between individual differences in reward sensitivity and brain activity during the anticipation of and reactivity to appetitive (erotic) stimuli. As expected, brain areas of the BAS showed enhanced activity during both the anticipation and presentation of erotic stimuli. Crucially, we demonstrated that activity in some of these BAS-related brain areas in response to erotic pictures was greater in individuals with stronger reward sensitivity. Thus, the results of this study were partially in consonance with the predictions of Gray's RST since the SR scores were associated with activity in response to sexual pictures but not to cues predicting their appearance.

Brain Activity during the Emotional Task

In order to study the different stages of sexual stimuli processing, we analyzed the picture viewing period and anticipatory period separately. Analysis of the anticipatory period yielded results consistent with our first hypothesis. As expected, we showed the involvement of BAS-related areas in the processing of erotic-anticipatory cues. By contrast, we did not find higher activity for erotic cues in comparison with ambiguous cues in BAS-related areas; thus, our second hypothesis was not supported by our data. Specifically, we demonstrated that the left lateral OFC responded to reward cues, whereas the left anterior insula responded to ambiguous cues. Recent computational models of reward processing have proposed that the lateral OFC supports flexibility by maintaining an activation-based working memory of recent reward history [42]. Deco and Rolls (2005) proposed that the OFC encodes reward rules (expectations about stimulus-contingency associations) that can be quickly reversed if expected rewards are not obtained [43]. Previous fMRI studies showed an enhanced OFC response during anticipation of reward [44,45] and of erotic pictures in participants who were aware of contingencies between the cue and outcome [21]. On the other hand, activity in the anterior insula has been associated with anticipation of uncertain outcomes [46,47]. Furthermore, increased anterior insula response was observed during decisions involving ambiguity when compared with those only involving risk [48]. Overall, our findings showed that lateral frontal areas are involved in the processing of erotic-anticipatory cues, suggesting a possible dissociation between the more ventral areas (i.e., OFC) involved in processing unambiguous cues and more dorsal areas (i.e., insula) involved in processing ambiguous cues. Future research should confirm this possibility.

The analysis of brain areas involved in processing erotic pictures compared with neutral pictures showed enhanced activity in the occipitotemporal cortex, parietal cortex, VS, amygdala, thalamus, midbrain, ACC, insula, lateral PFC, OFC, and medial PFC. Activity in these areas during erotic stimulation has been explained by models of sexual arousal comprising four coordinate components: cognitive, motivational, emotional, and physiological [19,31,49]. According to these models, activity in the occipitotemporal, parietal, and orbitofrontal areas are related to the cognitive component of sexual arousal [19,31,49,50]: the evaluative process that categorizes stimuli as sexual and directs attention to them. Furthermore, activity in the insula, amygdala, rostral ACC, and medial PFC are linked to the emotional component [19,20,31,50]: the processing of the subjective experience of hedonic feelings associated with sexual arousal. In addition, the rostral ACC and anterior insula constitute the physiological component of sexual arousal [19,31]: the autonomic and endocrinological changes that lead the individual to readiness for sexual behavior. Finally, the VS, thalamus, caudal ACC, and lateral PFC embody the motivational component [19,20,31]: the processes that direct behavior to a sexual goal and the perceived urge to engage in sexual behavior. Although the functional interpretation of our results based on previous studies are rather speculative, we have replicated the results obtained in previous studies that associated erotic stimuli [20,31,49,50,51] with enhanced activity in brain areas involved in sexual arousal.

In addition to the study of brain areas active during erotic stimuli presentation, we performed an exploratory analysis to investigate a possible effect of interaction between condition and probability on brain activity. The result of this analysis showed that under the erotic condition, the bilateral precuneus displayed enhanced activity in response to erotic pictures with 50% probability of appearance but not those with 100% probability of appearance. A previous study found increased activity in this area during the receipt of rewards when no decision making was involved [52] while another study linked the parietal cortex to the assessment of probabilities during decision making [53]. Thus, this activity may represent evaluation of reward probability during ambiguous trials. Contrary to previous studies where reward probability was manipulated [54–56], we did not find activity in neither the VS nor the OFC associated with probability of erotic picture appearance. However, methodological differences may explain the discrepancy. For example, previous studies used different reward stimuli such as money or pleasant taste. Additionally, these studies employed probabilities lower than 50%, and showed a connection between higher activity in these brain areas and outcomes with lower probability of appearance [54,56]. Thus, the 50% probability of reward used in this study may be not sufficient to generate significant differences in the activity of these brain regions.

Correlational Effects between Personality Measure and Brain Activity

The crucial result of the present study is that reward sensitivity shows a relationship with brain activity in response to sexual stimuli presentation in brain areas related to the BAS. To be specific, participants with higher SR scores displayed enhanced activity in the left OFC, left insula, and VS while viewing erotic pictures. The association between reward sensitivity and left OFC activity may represent individual differences in the encoding of reward value. The OFC integrates sensory, affective, and motivational information to derive the value of potential reward outcomes [57]. This area has been implicated in coding the current value of stimuli [58–60], holding them in working memory to anticipate future consequences of behavior [42,57]. Enhanced activity in this area has been shown during erotic reward presentation [61], whereas decreased activity has been observed after reward devaluation [62]. Thus, the increased activity in the left OFC exhibited by participants with high reward sensitivity in this study may represent their attribution of higher reward value to erotic stimuli.

The relationship between left insula activity and reward sensitivity could be related to individual differences in emotion experience. The insula has been associated with several brain functions such as the processing of interoceptive information, emotional awareness, perception of body movement, and cognitive control [63]. Previous fMRI studies on erotic stimulation showed that insula activity increases during the presentation of erotic stimuli [20,49,50,51,61,32] under penis stimulation [64] and correlates with penis turgidity [20,32,65,66]. These findings suggest the implication of the insula in monitoring interoceptive responses and are consistent with the proposed role of the insula in

conscious feeling. Thus, higher insula activity in participants with high reward sensitivity may represent a stronger experience of sexual arousal in these participants. Hence, this result agrees with studies showing that participants with higher reward sensitivity display higher susceptibility to positive affect [67].

The VS is a key region of the dopaminergic reward system that is thought to be the neural substrate for individual differences in reward sensitivity [3,68,69]. These individual differences have been associated with the structural and functional variability of the NAcc. For example, the NAcc in individuals with high reward sensitivity shows diminished volume [24], more random resting-state neural dynamics [70], and increased response to reward-related stimuli [8–11]. NAcc activity in response to erotic stimuli has been related to the motivational component of sexual arousal [31]. Although of marginal statistical significance, the results of this study support increased incentive motivation attributed to participants with high reward sensitivity [3,68,69].

Taking these results together, we demonstrated that participants with high reward sensitivity display enhanced brain activity in areas associated with the different components of sexual arousal upon presentation of erotic pictures. These results are in line with previous research showing an association between reward sensitivity and stronger sexual arousability and excitability [12–17]. On the basis of these results, we may speculate that sexual arousal is at least partly mediated by BAS structures, and individual differences in reward sensitivity may modulate sexual arousal. Future research is necessary to confirm these hypotheses.

No association between reward sensitivity and brain activity regarding erotic cues was found in the analysis of the anticipatory period. Despite how the RST predicts that reward sensitivity modulates both classical and instrumental conditioning, the role of reward sensitivity in classical conditioning has been a matter of controversy [71]. Previous studies using instrumental tasks and monetary rewards have demonstrated the association between reward sensitivity and brain activity during the anticipation of reward cues [10,11]. By contrast, to our knowledge, no study has showed a relationship between reward sensitivity and brain activity during the anticipatory period in associative tasks. Thus, the results of this study do not support our hypothesis that reward sensitivity modulates the anticipation of reward in associative conditioning, at least when presenting erotic pictures as rewards. Nevertheless, several issues must be taken into account regarding this result. First, in relation to Corr's (2001) arguments regarding the implications of Pavlovian associations in the RST [72], the anticipatory cue of this study may be understood as a second-order association since the erotic pictures are not sexual behavior in and of themselves, which would be unconditioned stimuli. Second, it is important to note that the task procedure we used is not classical conditioning because participants were asked to make a response after each cue and after each picture in order to control their attention throughout the task. Since the objective of this study was to generalize the relationship between reward sensitivity and brain activity in response to erotic stimuli in an event-related paradigm, we adapted the task from previous studies that were not conceived to study Pavlovian conditioning. Thus, future research employing a more specific paradigm is necessary to disambiguate the role of reward sensitivity in brain activity during associative learning.

Limitations and Future Lines of Research

Several limitations must be considered before interpreting the results of this study. First, we did not employ a physiological measure of sexual arousal (i.e., penile turgidity or heart rate) to confirm the relationship between brain activity and sexual arousal. Nevertheless, previous findings confirmed the capacity of visual sexual stimuli to generate sexual arousal [20,32,65,66]. Second, the study sample is composed fully of heterosexual men. We did not include women in our study to control for sex differences in sexual processing [51] and the personality trait of reward sensitivity [23]. Thus, the results of the present study are only generalizable to men. Third, the anticipatory cues may have semantic connotations that can introduce variability depending on the individual's experiences (i.e., "?" as a symbol of uncertainty). These cues were selected based on the paradigm of reference [22]. However, a way to avoid this problem would be to randomize the cues among participants or to use cues without any semantic connotation (i.e. fractal images), which should be taken into account in future studies and the interpretation of our results. Finally, the erotic images used in this study differed from the neutral images in terms of valence and arousal. Hence, this study does not speak to which of the factors is driving the observed results. Thus, the relationship between valence, arousal, and individual differences in brain activity in response to erotic stimuli should be addressed in future research. Additionally, given the results of this study, it would be interesting to study the influence of reward sensitivity on sexual disorders and the possible influence of reward sensitivity on women's brain activity associated with sexual arousal.

Conclusions

In sum, in this study, we showed that brain areas related to the BAS are engaged in the expectation and processing of erotic stimuli. We further found that individual differences in the personality trait of reward sensitivity is associated with brain activity in these areas during the processing of sexual stimuli, filling in the gap regarding the relationship between reward sensitivity and brain activation during erotic stimulus processing.

Author Contributions

Conceived and designed the experiments: ABL JCB CA VC. Performed the experiments: VC JCB PF PR. Analyzed the data: VC NVC. Wrote the paper: VC ABL CA.

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2.3 Estudio 2

Reward sensitivity modulates connectivity among reward brain areas during processing of anticipatory reward cues

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Reward sensitivity modulates connectivity among reward brain areas during processing of anticipatory reward cues

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Keywords: dopamine, fMRI, nucleus accumbens, orbitofrontal cortex, personality

Abstract

Reward sensitivity, or the tendency to engage in motivated approach behavior in the presence of rewarding stimuli, may be a contributory factor for vulnerability to disinhibitory behaviors. Although evidence exists for a reward sensitivity-related increased response in reward brain areas (i.e. nucleus accumbens or midbrain) during the processing of reward cues, it is unknown how this trait modulates brain connectivity, specifically the crucial coupling between the nucleus accumbens, the midbrain, and other reward-related brain areas, including the medial orbitofrontal cortex and the amygdala. Here, we analysed the relationship between effective connectivity and personality in response to anticipatory reward cues. Forty-four males performed an adaptation of the Monetary Incentive Delay Task and completed the Sensitivity to Reward scale. The results showed the modulation of reward sensitivity on both activity and functional connectivity (psychophysiological interaction) during the processing of incentive cues. Sensitivity to reward scores related to stronger activation in the nucleus accumbens and midbrain during the processing of reward cues. Psychophysiological interaction analyses revealed that midbrain–medial orbitofrontal cortex connectivity was negatively correlated with sensitivity to reward scores for high as compared with low incentive cues. Also, nucleus accumbens–amygdala connectivity correlated negatively with sensitivity to reward scores during reward anticipation. Our results suggest that high reward sensitivity-related activation in reward brain areas may result from associated modulatory effects of other brain regions within the reward circuitry.

Introduction

Reward sensitivity is a trait that predisposes to a variety of disinhibition disorders, including attention deficit hyperactivity disorder, psychopathy, drug abuse and addiction, pathological gambling, and eating disorders (see Bijttebier *et al.*, 2009 for review). Behavioral studies have associated this trait with enhanced reward processing and learning, a preference for immediate reward, and lower inhibitory control in reward contexts (Corr, 2004; Ávila & Torrubia, 2008), as well as active avoidance under punishment contingencies (Gray, 1981, 1991; Smillie & Jackson, 2005).

The brain regions of the dopaminergic reward system are thought to constitute the neural substrate for individual differences in reward sensitivity (Gray, 1991; Depue & Collins, 1999; Pickering & Gray, 2001). The neural structure of the dopaminergic reward system forms a loop in which dopaminergic midbrain areas, such as the ventral tegmental area (VTA) and substantia nigra (SN) complex, send projections to limbic and prefrontal brain areas, and receive afferent fibers from most of these areas (Düzel *et al.*, 2009; Haber & Knutson, 2010). Substantial literature links this system to motivation and goal-directed behaviors, and the system is thought to modulate diverse cognitive processes that allow the attainment of reward and the relief from punishment [see Berridge & Robinson (1998) for a review].

Individual differences in reward sensitivity have been associated with the structural and functional variability of definite reward-related areas within the dopaminergic system. For example, individuals with high reward sensitivity show diminished striatum volume (Barrós-Loscertales *et al.*, 2006), increased white-matter tract strength between the nucleus accumbens (NAcc) and amygdala (Cohen *et al.*, 2009), more random resting-state neural dynamics (or irregular fluctuating time series) in the NAcc and orbitofrontal cortex (Hahn *et al.*, 2012), and increased NAcc and midbrain responses to reward anticipation (Beaver *et al.*, 2006; Carter *et al.*, 2009; Hahn *et al.*, 2009; Cámara *et al.*, 2010). Although these studies provide evidence that reward sensitivity modulates the structure and functioning of brain reward areas, the role of this trait in the connectivity between these regions remains unclear.

In this study, we investigated how individual differences in reward sensitivity modulate the activity and functional connectivity of reward brain areas during the processing of valence and incentive magnitude in a monetary incentive delay (MID) task. This paradigm involves approach and active avoidance processes that are supposedly

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mediated by individual differences in reward sensitivity according to Gray's model (Arnett & Newman, 2000; Ávila, 2001; Smillie & Jackson, 2005). Previous functional magnetic resonance imaging (fMRI) studies have been focused on the relationship between reward sensitivity and reward cues involving the NAcc, midbrain, orbitofrontal cortex, and amygdala (Beaver *et al.*, 2006; Carter *et al.*, 2009; Hahn *et al.*, 2009). However, no previous fMRI studies have considered the involvement of reward sensitivity in brain reactivity to both approach and active avoidance cues, as others have investigated behaviorally (Arnett & Newman, 2000; Smillie & Jackson, 2005). On the basis of previous reports, we hypothesized that there was an enhanced response of brain reward areas (e.g. NAcc and orbitofrontal cortex) during the processing of the motivational valence of cues by individuals with stronger reward sensitivity. Moreover, we explored the relationship between reward sensitivity and brain areas involved in processing the incentive magnitude of stimuli independently of their valence. Finally, we studied the regional brain connectivity among reward-related areas associated with individual differences in reward sensitivity.

Materials and methods

Participants

Forty-four male undergraduates (age, 23.4 ± 4.1 years; years of education, 13.8 ± 2.2) participated in this fMRI study. Participants were physically and psychologically healthy, with no history of mental disorders, head trauma, or drug abuse. All participants provided written informed consent prior to participation. The study was approved by the ethical committee of the University Jaume I. All study procedures conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki; printed in the *British Medical Journal*, 18 July 1964).

Measure of reward sensitivity

All participants completed the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (Torrubia *et al.*, 2001) as a measure of reward sensitivity. The mean sensitivity to reward (SR) score was 11.72 (standard deviation, 4.65; range, 2–24), and scores followed a normal distribution (Kolmogorov–Smirnov test: $D = 0.113$, $P > 0.10$). Thus, these scores were consistent with those obtained from other samples (Torrubia *et al.*, 2001; Barrós-Loscertales *et al.*, 2006, 2010). The Sensitivity to Punishment and Sensitivity to Reward Questionnaire has been translated into 15 languages, and is widely used to assess reward sensitivity in adults (Torrubia *et al.*, 2008) and children (Luman *et al.*, 2012). Previous studies have shown that the SR scale has good content validity and strongly correlates with other measures of reward sensitivity, such as reward responsiveness, drive, fun-seeking, novelty-seeking, and impulsivity scales [see Torrubia *et al.* (2008) for review].

Experimental design and stimuli

The goal of our experiment was to analyse the association between individual differences in reward sensitivity and the functional activity and effective connectivity of reward brain areas during the anticipation of monetary incentives. We used an adaptation of the MID task described by Knutson *et al.* (2001, 2003), including all high and low reward and punishment conditions (Fig. S1). Before entering the scanner, all participants were given instructions on the task and completed a practice session. The practice session was thought to minimize later learning effects, and provided an estimate of each individual's reaction time (RT), to standardize task difficulty within the scanner. For each participant, the median RT of correct trials during the practice session was implemented as a cut-off RT in the main experiment. All participants were initially paid €20 for their participation. At the end of the experiment, participants received an individually adjusted bonus, depending on their performance in the experimental task.

Inside the scanner, participants performed two 8-min runs of the MID task. Each run consisted of 60 trials, giving a total of 120 trials. There were four kinds of event, defined by a high reward cue, a low reward cue, a high punishment cue, and a low punishment cue. Each trial consisted of one of those cues presented for 500 ms, followed by a black screen that appeared for a variable duration (2000–2250 ms), and then by a white target square that appeared for 100 ms, to which participants had to respond by pressing a response button as quickly as possible. After the participant responded, a black screen appeared for a variable duration (2000–4000 ms), followed by a feedback screen (duration of 1500 ms) that notified participants of whether they had won or lost money during that trial and indicated their cumulative total at that point. As previously noted, each event was defined by the initial appearance of a different cue: a circle with two horizontal lines, indicating the possibility of winning €3 (high reward cue; $n = 24$); a circle with one horizontal line, indicating the possibility of winning €0.20 (low reward cue; $n = 24$); a square with two horizontal lines, indicating the chance to avoid losing €3 (high punishment cue; $n = 24$); and a square with one horizontal line, indicating the chance to avoid losing €0.20 (low punishment cue; $n = 24$). Therefore, the cues informed participants of the potential valence of the outcome (reward or punishment) and its incentive magnitude (high or low). A triangle ($n = 24$) was the cue for non-incentive trials in which participants neither won nor lost money. Participants had to respond after each incentive cue, but they did not respond to non-incentive cues, because these cues were not followed by a target stimulus (white square). We modified the original MID task in this way in order to perform comparisons without disentangling reward anticipation from action preparation. These comparisons may produce interesting results when the effects of modulation of brain processing by reward sensitivity are analysed, as the effects of individual differences on instrumental approach and active avoidance behavior may arise from the joint effects of valence (Hahn *et al.*, 2009) and motor responses in our regions of interest (ROIs), e.g. the striatum (Guitart-Masip *et al.*, 2011). On the other hand, it is probably mediating the differences showed in previous behavioral studies on reward sensitivity [see Pickering & Gray (2001) and Ávila & Torrubia (2008) for reviews]. Additionally, we could isolate the motivational effects in our study by means of a factorial design with two valence conditions (reward and punishment) and two incentive magnitude conditions (high and low), as motor effects are controlled for by the motivational conditions.

Trial types were pseudo-randomly ordered within each run. The intertrial interval was randomized between 2000 and 4000 ms. Participants were instructed to respond as quickly as possible to target stimuli to achieve the rewards or avoid the punishments. The task was programmed and presented with PRESENTATION software (Neurobehavioral Systems, Albany, CA, USA). Visual stimuli were displayed in the scanner with Visuastim goggles (Resonance Technology, Northridge, CA, USA). Stimulus presentation was synchronized with the scanner acquisition with a SyncBox (Nordic NeuroLab, Bergen, Norway), and behavioral task performance was recorded with a ResponseGrip (Nordic NeuroLab).

fMRI acquisition

Image acquisition was performed with a 1.5-T Siemens Avanto MRI scanner (Siemens, Erlangen, Germany). Functional images were acquired with a T2*-weighted echo-planar imaging sequence (TR/TE, 2000/30 ms; matrix, 64 × 64 × 30; voxel size, 3.5 mm^3; flip angle, 90°; number of volumes per run, 251). Thirty 3.5-mm-thick slices centered parallel to the hippocampi were axially acquired with a 0.5-mm interslice gap. Structural images were acquired with a T1-weighted sequence (TR/TE, 11/4.9 ms; flip angle, 90°; voxel size, 1 mm^3), which facilitated the localization and coregistration of functional data.

fMRI preprocessing and analysis

The analyses focused on changes in the blood oxygen level-dependent contrast during the anticipatory cue periods. Data were preprocessed and analysed with the Statistical Parametric Mapping (SPM) 5 software package (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/). The first two scans for each participant in each run were excluded from the analyses, to discount any artefacts related to the transient phase of magnetization. For preprocessing purposes, the time series of voxels were interpolated intravolume to a middle slice (in terms of acquisition time), to correct the acquisition of non-simultaneous slices (slice order: ascending interleaved). Later, motion correction was carried out by taking the first image of the first session as the reference image, obtaining a subsequent realignment average image, and using this average image as a reference for the other session's motion correction. This correction was made with a six-parameter rigid body transformation. An anatomical image for each participant was coregistered to his average functional image with a rigid body transformation. Then, the anatomical acquisition was segmented and normalized. This normalization was completed according to the Montreal Neurological Institute (MNI) template by applying an affine transformation followed by non-linear deformation with the basis functions defined in the SPM program (Ashburner & Friston, 1999). Computed transformation parameters from the anatomical image normalization after segmentation were applied to each participant's functional time series (voxels rescaled to a final voxel size of 3 mm^3). Finally, the images were spatially smoothed with a 6-mm isotropic Gaussian kernel.

Significant hemodynamic changes among the conditions were examined with the general linear model (Friston *et al.*, 1995). In the first-level (within-subjects) analysis, a statistical model was computed for each participant by applying a canonical hemodynamic response function combined with its time derivative. The fMRI time series data were high-pass-filtered to eliminate low-frequency components. The four conditions of interest (high reward cue, low reward cue, high punishment cue, and low punishment cue) were modeled as separate regressors in a general linear model. Furthermore, we modeled separate regressors for the eight outcomes (win or loss in each incentive trial) and the non-incentive cue. The six motion correction parameters from each participant were included in the model as 'nuisance' variables. Finally, statistical contrast images were generated to obtain the brain activation for anticipatory periods.

ROIs

Predefined ROIs included the NAcc, amygdala, medial orbitofrontal cortex (mOFC), and midbrain, based on previous studies of reward sensitivity (Beaver *et al.*, 2006; Hahn *et al.*, 2009). All of these structures were defined according to the AAL (Tzourio-Mazoyer *et al.*, 2002) or the Wake Forest University PickAtlas (Maldjian *et al.*, 2003) for self-defined ROIs. Discrete ROIs were defined for the amygdala and the mOFC, the latter including the bilateral rectus gyrus from the AAL toolbox (Tzourio-Mazoyer *et al.*, 2002). The NAcc was defined as a 6-mm-radius sphere at ±10, 8, −4 [*x*, *y*, *z*; MNI coordinates based on Cools *et al.* (2002) and Barrós-Loscertales *et al.* (2006)], whereas the midbrain was defined as a 6-mm-radius sphere at 0, −20, −12 [*x*, *y*, *z*; MNI coordinates based on Telzer *et al.* (2010)], which mainly includes the VTA–SN complex.

fMRI analysis: overall task activations

fMRI analyses were conducted to study brain areas responding to both the reward and incentive magnitude conditions, depending on reward sensitivity. Theoretical models of personality have proposed that reward sensitivity modulates both signals of reward and signals of relief from punishment (Gray, 1991; Pickering & Gray, 2001). In addition, previous studies have shown that some dopaminergic brain areas respond to the salience of stimuli independently of their valence (Knutson *et al.*, 2005; Jensen *et al.*, 2007). Thus, it is possible that reward sensitivity modulates brain areas responding to both reward and incentive magnitude. To study brain activity related to reward cues and high incentive cues, we performed a two-way [valence (reward, punishment) × incentive magnitude (high, low)] repeated-measures ANOVA, in a second-level random-effects analysis with the contrast images (high reward, low reward, high punishment, and low punishment) extracted from the first-level analysis.

Moreover, we implemented a conventional subtraction analysis between the reward cues (high and low) and non-incentive cue (neutral triangle). The objective of this contrast was to study the whole process of reward anticipation, including motivation and motor preparation components, given the interest in these in the analysis of individual differences in personality based on previous comments (see Experimental design and stimuli). We hypothesized that this comparison might change the effect of individual differences on brain activity during reward anticipation, allowing the study of modulation of the ROIs by reward sensitivity. We performed a comparison of reward cues and the non-incentive cue for each participant in the first-level analysis, and used the resulting contrast images in a one-sample *t*-test in the second-level analysis. Reported results were those that survived a small volume correction (SVC) with a statistical significance threshold of $P < 0.05$ [family-wise error (FWE) corrected].

Analysis of effects of reward sensitivity on task-related activations

To analyse the modulatory effect of personality on brain activation, three multiple regression analyses were performed between SR scores and the resulting contrast images obtained in the first-level analysis: (i) reward vs. punishment; (ii) high incentive vs. low incentive; and (iii) reward vs. neutral. The nuisance effects of age were regressed out. Analyses were carried out on each ROI with SVC, with a statistical significance threshold of $P < 0.05$ (FWE corrected).

Functional connectivity analysis: psychophysiological interaction (PPI)

Following previous studies on personality (Haas *et al.*, 2006; Cremers *et al.*, 2010), connectivity analyses were performed to study

the relationship between reward brain networks and reward sensitivity. Once we had identified the ROIs that showed effects of reward sensitivity on task-related activations, we performed PPI analyses (Friston *et al.*, 1997), using these ROIs as source (seed) regions to study whether connectivity among these areas and the other ROIs was also related to reward sensitivity. These connectivity analyses were performed for the same contrasts of interest (psychological variables: reward vs. punishment, high incentive vs. low incentive, and reward vs. neutral) used to study task-related activations associated with SR scores. This resulted in a total of six independent PPI analyses: two regions (right NAcc and midbrain; see Results), each with three psychological variables (each contrast of interest). For each participant, we extracted the time series from the first eigenvariate of all active voxels within the right NAcc and midbrain ROIs (seed regions). Then, the time series were deconvolved, and each PPI was calculated as the element-by-element product of the deconvolved time series and a vector representing the psychological variable (Gitelman *et al.*, 2003). These products were subsequently reconvolved with the hemodynamic response function and entered as regressors in a first-level analysis together with the physiological variable (the time series extracted from the seed region) and the vector of the psychological variable.

Then, we performed second-level analyses, including the PPI regression coefficients (changes in connectivity) in: (i) a one-sample *t*-test to assess positive or negative changes in connectivity at the group level in each described PPI; and (ii) multiple regression analyses with SR scores as a regressor of interest and age as a covariate, to investigate the relationship between each measure of connectivity change and SR scores. Once again, the analyses were restricted to the ROI (SVC, $P < 0.05$, FWE corrected).

Behavioral data analyses

The percentage of hits (successful responses) and mean of RTs were recorded for each participant. The hits and RTs for each incentive condition were used to perform two different 2 × 2 [valence (reward, punishment) × incentive magnitude (high, low)] repeated-measures within-subjects ANOVAs to study cue-related effects on behavioral performance. To investigate personality effects, we used correlations and partial correlations with performance variables (hits and RTs).

Results

Behavioral results

Mean RTs and percentages of hits are shown in Fig. 1 and Table 1. The repeated-measures ANOVA for RTs showed main effects of valence ($F_{1,43} = 5.69$, $P = 0.022$) and incentive magnitude ($F_{1,43} = 5.87$, $P = 0.02$), indicating faster RTs for reward than for punishment conditions, and for high than for low incentive conditions. These main effects were qualified by the significant valence × incentive magnitude interaction ($F_{1,43} = 12.27$, $P = 0.001$), indicating that participants responded faster after high reward cues than for the rest of the conditions.

TABLE 1. Behavioral results ($N = 44$)

	RT (ms)		Hits (%)	
Behavioral result	Mean	SD	Mean	SD
Overall task	189.1	28.2	82.9	10.18
High reward	184.87	24.27	86.83	10.51
Low reward	191.08	31.06	82.67	13.65
High punishment	191.06	31.37	82.19	9.98
Low punishment	189.39	27.96	79.92	13.03

Correlation with SR scores	RT (*r*)	Hits (*r*)
Overall task	0.172	0.074
Valence effect*	−0.119	0.060
Incentive effect†	**−0.331**	0.030

SD, standard deviation. The significant correlation at $P < 0.05$ (two-tailed) is presented in bold. *Partial correlation of reward cues' related variable controlled by punishment cues. †Partial correlation of high incentive cues' related variable controlled by low incentive cues. There were no significant associations for each independent condition without taking into account the effects of lower-level conditions.

The repeated-measures ANOVA for hits also showed significant main effects of valence ($F_{1,43} = 15.65$, $P < 0.001$) and incentive magnitude ($F_{1,43} = 9.24$, $P = 0.004$), but the effect for the valence × incentive magnitude interaction did not reach significance ($P > 0.1$). *Post hoc* analyses indicated that the percentage of hits was higher for high than for low incentive cues and for reward than for punishment cues.

The results of Pearson correlations and partial correlations between SR scores and performance are shown in Table 1. Only the correlation between SR scores and RTs for high incentive cues reached significance when the effect of low incentive cues was controlled, confirming that individuals with higher SR scores responded faster in high incentive conditions.

fMRI results

The results from the overall task (Fig. 2) showed stronger NAcc activation for reward cues than punishment cues (right: 9, 12, 0; *Z*-

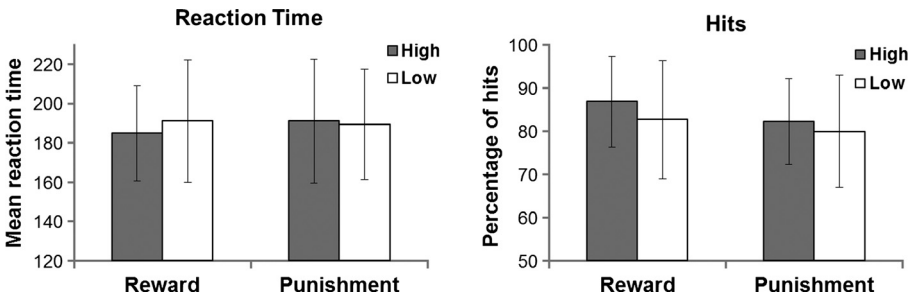

FIG. 1. Mean RTs and accuracies during MID task completion for each condition. Left: mean RTs for each incentive condition. Right: percentage of hits for each incentive condition. Dark bars represent high incentive conditions, and white bars represent low incentive conditions. *Post hoc* analyses showed that the high reward condition yielded a higher percentage of hits and lower RTs than the rest of the incentive conditions ($P < 0.05$).

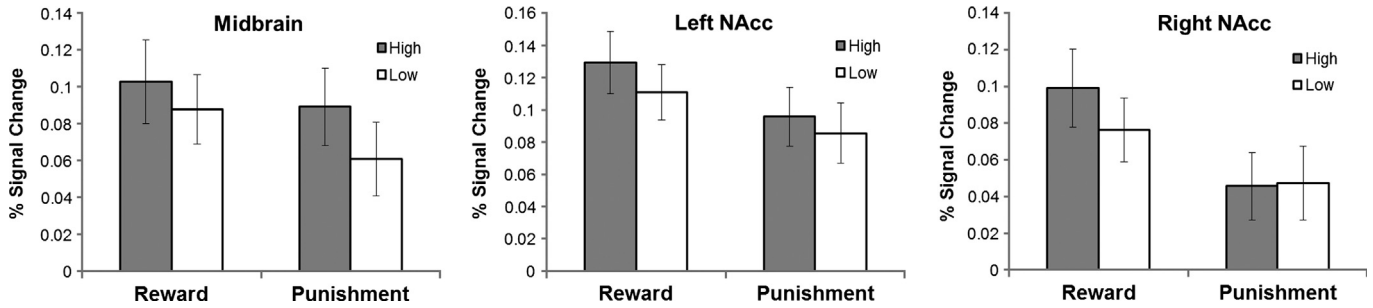

FIG. 2. Mean percentage signal change for each condition across all voxels within the midbrain and NAcc ROIs. Dark bars represent high incentive conditions, and white bars represent low incentive conditions.

score = 5.35; $P < 0.05$, FWE corrected; cluster size, 486 mm^3) (left: −9, 6, 0; *Z*-score = 3.97; $P < 0.05$, FWE corrected; cluster size, 405 mm^3), and for high incentive cues than low incentive cues (right: 15, 12, −6; *Z*-score = 4.07; $P < 0.05$, FWE corrected; cluster size, 270 mm^3). In addition, the midbrain was more activated in response to high incentive cues than in reponse to low incentive cues (−6, −21, −12; *Z*-score = 2.92; $P < 0.05$, FWE corrected; cluster size, 81 mm^3). These results are in agreement with those of previous studies that have shown midbrain response according to stimulus incentive magnitude (Knutson *et al.*, 2005). Finally, the comparison of reward cues and the non-incentive cue showed activation in the bilateral NAcc (right: 9, 12, 0; *Z*-score = 6.57; $P < 0.05$, FWE corrected; cluster size, 999 mm^3) (left: −9, 6, 0; *Z*-score = 6.21; $P < 0.05$, FWE corrected; cluster size, 1161 mm^3) and midbrain (−3, −24, −9; *Z*-score = 4.09; $P < 0.05$, FWE corrected; cluster size, 378 mm^3), in agreement with the greater response of these areas to high reward cues. Whole brain voxel-wise results from the overall task are summarized in the Supporting Information (Table S1 and Fig. S2, S3, S4).

Effects of reward sensitivity on task-related activations

Multiple regression analyses showed that SR scores correlated positively with right NAcc activation (12, 6, −6; *Z*-score = 3.20; $P < 0.05$, FWE corrected; cluster size, 108 mm^3) and left midbrain activation (−3, −18, −15; *Z*-score = 4.07; $P < 0.05$, FWE corrected; cluster size, 135 mm^3) for reward cues as compared with punishment cues (Fig. 3a). Furthermore, SR scores did not correlate with activation in the ROIs for the comparison either between high incentive cues and low incentive cues, or between reward and non-incentive cues. Thus, these findings showed modulation of the NAcc and midbrain activation by reward sensitivity during reward processing, as shown in previous studies (Carter *et al.*, 2009; Hahn *et al.*, 2009). Therefore, these ROIs were used for later PPI analysis, as previously described (see Materials and methods). No other positive or negative correlations were found.

PPI results

One-sample *t*-test analyses did not show any significant main effects (positive or negative) for any ROI. Nevertheless, we found that reward sensitivity modulated changes in connectivity among reward-related brain areas under incentive processing. More specifically, we found a negative association between midbrain–mOFC connectivity and SR scores for high vs. low incentive cues (0, 36, −15; *Z*-score = 3.73; $P < 0.05$, FWE corrected; cluster size, 297 mm^3; Fig. 3b). Thus, the connectivity between the midbrain and mOFC

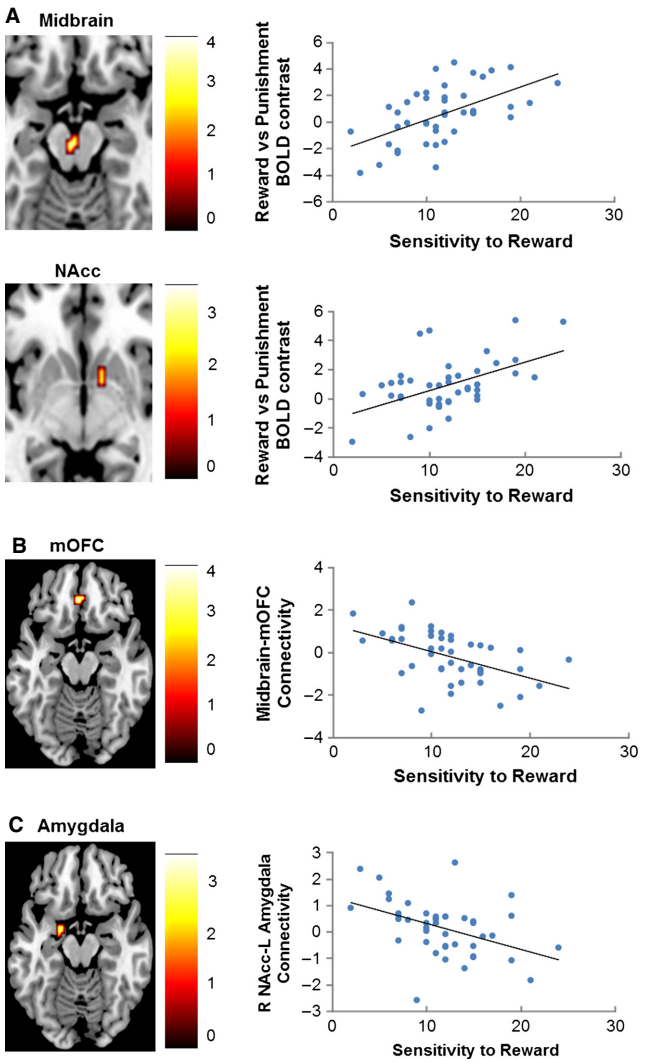

FIG. 3. fMRI results at $P < 0.05$ (FWE corrected). (A) Left: brain regions (midbrain and NAcc) showing positive correlation with SR scores during reward anticipation as compared with punishment anticipation. Right: scatterplots of mean cluster activity within the ROIs (midbrain and NAcc) and SR scores. (B) Left: resulting image of the PPI analyses for high as compared with low incentive cues, with the midbrain as a source region and SR scores as a regressor. Right: scatterplot of mean cluster weights for the interaction term in the mOFC and SR scores. (C) Left: resulting image of the PPI analyses for reward as compared with neutral conditions, with the right NAcc as a source region and SR scores as a regressor. Right: scatterplot of mean cluster weights for the interaction term in the amygdala and SR scores. Images are presented in neurological convention (left is left). The color bar represents the *t*-values applicable to the image.

during incentive processing is dependent on individual differences in reward sensitivity. In order to study whether this effect was driven by reward or punishment cues, we performed two PPI analyses with high vs. low reward cues and high vs. low punishment cues separately as psychological variables. We did not observe any significant effect of SR scores for these two contrasts at predefined statistical thresholds. Thus, we may conclude that the reported effects result from the high incentive condition rather than being driven by either of the valence conditions. Likewise, no positive or negative correlations with SR scores and brain connectivity were found regarding valence processing.

Additionally, analysis of connectivity when we compared reward cues and the non-incentive cue showed that connectivity between the NAcc and left amygdala was negatively associated with SR scores (-21, 0, -15; Z-score = 3.23; $P < 0.05$, FWE corrected; cluster size, 189 mm^3; Fig. 3c). This finding represents modulation of connectivity between the NAcc and left amygdala by reward sensitivity during the processing of reward cues as compared with neutral cues.

Discussion

In this study, we have shown that individual differences in reward sensitivity modulate neural connectivity between the midbrain and mOFC under high incentive conditions, independently of the anticipation of possible wins or losses. We also found that activity in the NAcc and midbrain is stronger for individuals with higher SR scores, which is consistent with previous reports (Carter *et al.*, 2009; Hahn *et al.*, 2009). Crucially, our results showed that the trait of reward sensitivity modulates brain activity but also connectivity among reward-related brain regions.

In our study, SR scores were linked to increased activity in the NAcc and midbrain during the processing of reward cues as compared with punishment cues. These results replicated those of a previous study using the MID task, in which reward and punishment conditions were included (Carter *et al.*, 2009). In contrast, in disagreement with our hypothesis, we did not find an association between NAcc response and SR scores for reward cues as compared with neutral cues, an extension of results reported by Hahn *et al.* (2009). One explanation for this negative result may be that the effects of individual differences in reward sensitivity on striatum activity were only driven by the motivation component of reward anticipation, and not by its motor preparation component. That is, the anticipation of a motor response when a reward cue was present did not modulate the association between reward sensitivity and the NAcc, or at least not in the same direction. Thus, this result implies an importance of motivational contingencies in earlier behavioral studies in which RTs under reward conditioning were modulated by reward sensitivity (see Ávila & Torrubia, 2008). Future studies targeting these interaction effects could better clarify the neural basis of modulation of motor or cognitive responses by reward sensitivity under reward cueing.

On the other hand, in a previous study, Hahn *et al.* (2009) used a modified version of the MID task in which only reward (not punishment) conditions were included, and their results may have involved different contextual effects for modulation of the previously described brain activation by reward sensitivity (Patterson & Newman, 1993; Ávila & Torrubia, 2008; Ávila *et al.*, 2008). Moreover, the difference in effects of reward sensitivity on NAcc activity between our research and the study of Hahn *et al.* (2009) may be related to previous findings with the MID task that demonstrated NAcc modulation by available alternative incentives, with the worst available alternative being an anchor for NAcc activation (Cooper *et al.*, 2009). Therefore, modulation of dopaminergic activity by reward sensitivity during reward anticipation may be dependent on the referenced worst available alternative, inducing different contextual effects in different event designs. On the other hand, the NAcc has been shown to be involved in both approach and active avoidance behaviors (Salomone *et al.*, 1997). Our results could be interpreted as primary modulation of the NAcc by reward sensitivity during approach anticipation as compared with active avoidance, or as opposite modulation of the NAcc by reward sensitivity during approach and active avoidance behaviors. In future studies, it will be important to consider both contextual and condition effects to analyse how the reward sensitivity specifically modulates the response of the NAcc and midbrain to reward cues.

The crucial result of our study is that reward sensitivity modulates neural dynamics among reward brain areas. Higher SR scores were associated with relatively less connectivity between the midbrain and mOFC during processing of high incentive cues. That is, the activity of the midbrain during the processing of high incentive cues seems to be more dependent on the mOFC in individuals with lower reward sensitivity. The mOFC is involved in processing reward outcomes (Haber & Knutson, 2010), and lesions to it cause increased reward sensitivity (Bechara *et al.*, 2000). Previous results with the MID task related the midbrain to the cue's incentive magnitude independently of its valence (Knutson *et al.*, 2005). Overall, the caudal VTA might contribute to enhance learning in the novelty-processing and/or reward-processing contexts (Krebs *et al.*, 2011). Animal studies have shown that the mOFC is implicated in the regulation of dopaminergic neuron activity (Overton *et al.*, 1996; Tong *et al.*, 1996, 1998; Aston-Jones *et al.*, 2009), in that electrical stimulation of the orbitofrontal cortex induces both inhibitory and excitatory responses in dopaminergic neurons (Lodge, 2011). Specifically, Sesack *et al.* (2003) reported that glutamatergic neurons from the prefrontal cortex selectively target dopaminergic mesocortical neurons and GABAergic mesoaccumbens neurons, suggesting that prefrontal cortex glutamatergic firing leads to inhibition of mesoaccumbens dopaminergic neurons, whereas prefrontal cortex hypofunction may promote subcortical dopaminergic transmission. Therefore, the effect of the mOFC on midbrain activity may reflect individual differences in reward sensitivity during the processing of high incentive stimuli. Moreover, we should note that cues involve reward and active avoidance anticipation, two processes that were suggested to be subserved by reward sensitivity and the behavioral activation system from the reinforcement sensitivity theory. Further studies may contribute to clarifying the role of this coupling in the relevancy effect of salient stimuli and the maintenance of reward-seeking and active avoidance behavior in individuals with strong reward sensitivity (Takahashi *et al.*, 2009).

The connectivity between the right NAcc and left amygdala during anticipation of reward cues was modulated by individual differences in reward sensitivity, involving motor preparation for response that correlated negatively with SR scores. This indicates that participants with high reward sensitivity had relatively less connectivity between the NAcc and amygdala when processing reward cues. The amygdala is a brain area composed of a group of nuclei involved in emotional learning and expression (Cardinal *et al.*, 2002). Despite this area being classically linked to fear and anxiety processing, it is actually thought to play a more general role in encoding and updating the motivational and affective value of stimuli (Cardinal *et al.*, 2002; Gottfried *et al.*, 2003; Morrison & Salzman, 2010; Seymour & Dolan, 2008). The amygdala may

contribute to goal-directed behavior though direct projections to the NAcc and other regions of the striatum (Friedman *et al.*, 2002; Fudge *et al.*, 2002; Haber & Knutson, 2010), and through projections to dopaminergic areas in the midbrain (Cardinal *et al.*, 2002; Pauli *et al.*, 2012). This network is thought to be important for learning stimulus–reward associations (Everitt *et al.*, 1989; Murray, 2007; Pauli *et al.*, 2012) and maintaining a representation of affective or rewarding properties of conditioned cues (Cardinal *et al.*, 2002). Thus, lower connectivity between the NAcc and amygdala in individuals with greater reward sensitivity may represent lower flexibility in updating reward value. Consistent with this result, previous findings showed that amygdala lesions promote the selection of immediate rather than larger delayed rewards (Winstanley *et al.*, 2004), reduce aversion to monetary loss (De Martino *et al.*, 2010), increase risk choices when considering potential gains (Weller *et al.*, 2007), and increase the selection of high reward but ultimately high punishment decks in the Iowa Gambling Task (Bechara *et al.*, 1999). Thus, the amygdala seems to be crucial for appropriate decision-making, and its impairment may cause impulsive choices. Finally, the lack of modulation of NAcc–amygdala connectivity by reward sensitivity when reward cues are compared with punishment cues may be explained by the supposed role of the amygdala in processing both reward and punishment stimuli.

Limitations

A limitation of this study is inherent to the interpretation of PPI analyses. The PPI in itself is insufficient to assess the direction of effects. This is an important limitation, considering, for example, the argued roles of the mOFC and amygdala in regulating the activity of the midbrain and NAcc, respectively. Nonetheless, other studies, applying different methodologies, have provided more direct evidence for a top-down regulatory role in these networks (Overton *et al.*, 1996; Tong *et al.*, 1996, 1998; Aston-Jones *et al.*, 2009; Stuber *et al.*, 2011). On the other hand, the ROI definition of the midbrain (6-mm sphere) may include non-dopaminergic neurons in the region. We used this approach to study the midbrain because of the impossibility of uniquely selecting dopaminergic neurons of the VTA–SN complex in fMRI analyses. Likewise, it is important to note that the midbrain effects may not be exclusively mediated by dopaminergic neurons. Finally, we must be cautious in interpreting results obtained with the neutral condition as the control condition (i.e. NAcc–amygdala connectivity). These results may be driven by anticipation of incentive, preparation of motor responses for the attainment of objectives, or both. However, the neutral condition in this design did not involve a motor response, for two reasons: first, preparation of motor responses was better controlled by the other incentive conditions; and second, the study had the secondary objective of analysing modulation of reward response anticipation by reward sensitivity. This was of particular interest, given the focus of our research group (see Ávila & Parcet, 1997, 2001, 2002; Ávila, 2001; Ávila *et al.*, 2003), in that both processes involve the striatum (Guitart-Masip *et al.*, 2011).

To summarize, in this study we have replicated previous findings showing that reward sensitivity modulates brain activity in the NAcc and midbrain. In addition, we have demonstrated that reward sensitivity also modulates connectivity of the midbrain and NAcc with the mOFC and amygdala respectively. Our results suggest that high reward sensitivity-related activation in reward brain areas may partially result from associated diminished modulatory effects of other brain regions within the reward circuitry.

Supporting Information

Additional supporting information can be found in the online version of this article:

Fig. S1. Task structure.

Fig. S2. Brain areas showing significant activity for anticipation of reward vs. punishment.

Fig. S3. Brain areas showing significant activity for anticipation of high incentive vs. low incentive.

Fig. S4. Brain areas showing significant activity for anticipation of reward vs. the non-incentive condition.

Table S1. (a) Brain areas showing significant activity for anticipation of reward vs. punishment. (b) Brain areas showing significant activity for anticipation of high incentive vs. low incentive. (c) Brain areas showing significant activity for anticipation of reward vs. the non-incentive condition.

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Abbreviations

fMRI, functional magnetic resonance imaging; FEW, family-wise error; MID, monetary incentive delay; MNI, Montreal Neurological Institute; mOFC, medial orbitofrontal cortex; NAcc, nucleus accumbens; PPI, psychophysiological interaction; ROI, region of interest; RT, reaction time; SN, substantia nigra; SR, sensitivity to reward; SVC, small volume correction; VTA, ventral tegmental area.

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Supplementary Material

Table S1a: Brain Areas Showing Significant Activity for Anticipation of Reward Vs. Punishment

Areas	MNI peak coordinates (x, y, z)	Z-score	Size (mm^3)
- Middle cingulate cortex	12, -39, 36	5.62	2457
- Caudate left	-12, 6, 6	5.49	4752
- NAcc right	9, 12, 0	5.35	
- Caudate right	9, 6, 9	3.55	
- Inferior parietal cortex left	-30, -66, 42	5.05	2727
- Middle occipital cortex left	-21, -60, 22	4.47	
- Middle occipital cortex right	33, -72, 36	4.90	2403
- Superior parietal cortex right	39, -45, 57	4.89	1782
- Middle frontal cortex right	42, 42, 24	4.69	3969
- Insula left	-36, 15, -6	4.4	2052
- Thalamus	-6, -18, 12	4.31	1269
- Precentral cortex left	-42, 6, 33	4.31	1512
- Superior frontal cortex right	18, 12, 51	4.10	1944
- Posterior cingulate cortex	0, -33, 27	4.09	594
- Middle frontal cortex left	-36, 45, 15	4.09	810
- Superior temporal cortex left	-39, -36, 9	4.01	540
- Middle temporal cortex left	-54, -18, 0	3.96	999
- Middle frontal cortex left	-27, 9, 51	3.90	756

$p < .001$, uncorrected with a minimum cluster of 540 mm^3.

Table S1b: Brain Areas Showing Significant Activity for Anticipation of High Incentive Vs. Low Incentive

Areas	MNI peak coordinates (x, y, z)	Z-score	Size (mm^3)
- Superior frontal cortex left	-15, 3, 66	4.70	837
- NAcc right	15, 12, -6	4.07	648

$p < .001$, uncorrected with a minimum cluster of 540 mm^3.

Table S1c: Brain Areas Showing Significant Activity for Anticipation of Reward Vs. the Non-incentive Condition

Areas	MNI peak coordinates (x, y, z)	Z-score	Size (mm^3)
- Precentral cortex left	-39, -18, 51	>8	154197
- Superior motor area left	-3, -3, 57	>8	
- Superior motor area right	3, 15, 45	>8	
- NAcc left	-9, 6, 3	>8	
- Putamen left	-21, 9, 3	7.59	
- NAcc right	9, 9, 3	7.55	
- Middle cingulate cortex	-6, 12, 36	7.46	
- Postcentral cortex left	-48, -33, 48	7.16	
Thalamus	-12, -15, 6	7.14	
- Inferior parietal cortex left	-30, -57, 45	6.65	
- Middle occipital cortex right	33, -72, 24	5.88	10611
- Superior occipital cortex right	27, -67, 30	5.42	
- Inferior parietal cortex right	26, -48, 51	4.67	
- Middle frontal cortex right	39, 45, 27	5.40	3699
- Middle frontal cortex left	-36, 48, 18	5.33	4860
- Precuneus	12, -66, 15	4.59	918

$p < .001$, uncorrected with a minimum cluster of 540 mm^3.

Figure S1: Task structure.

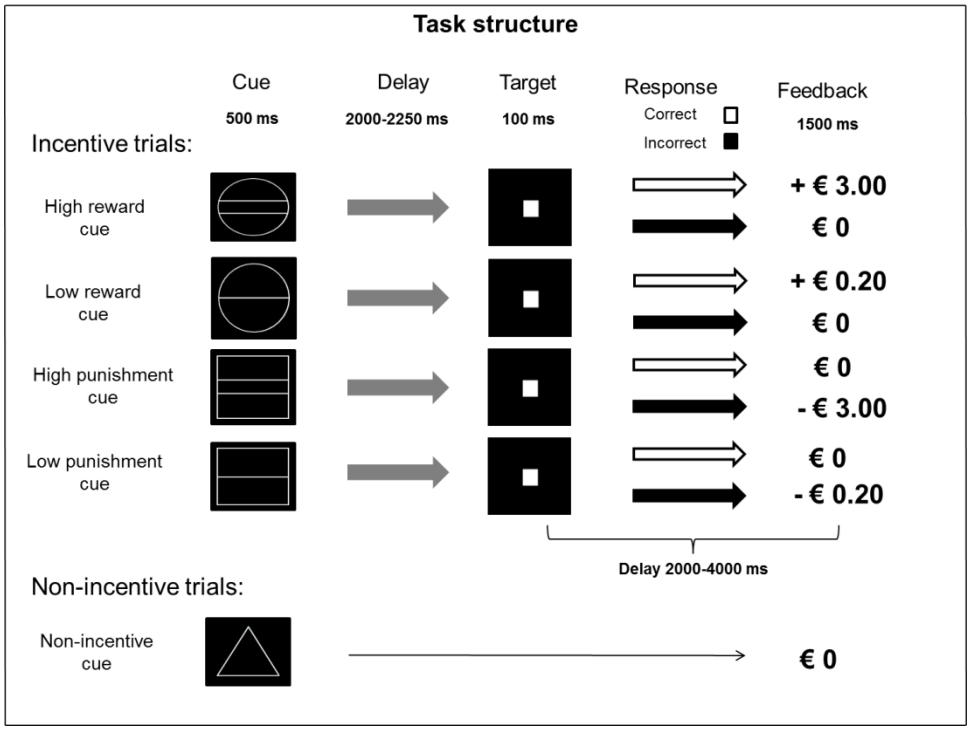
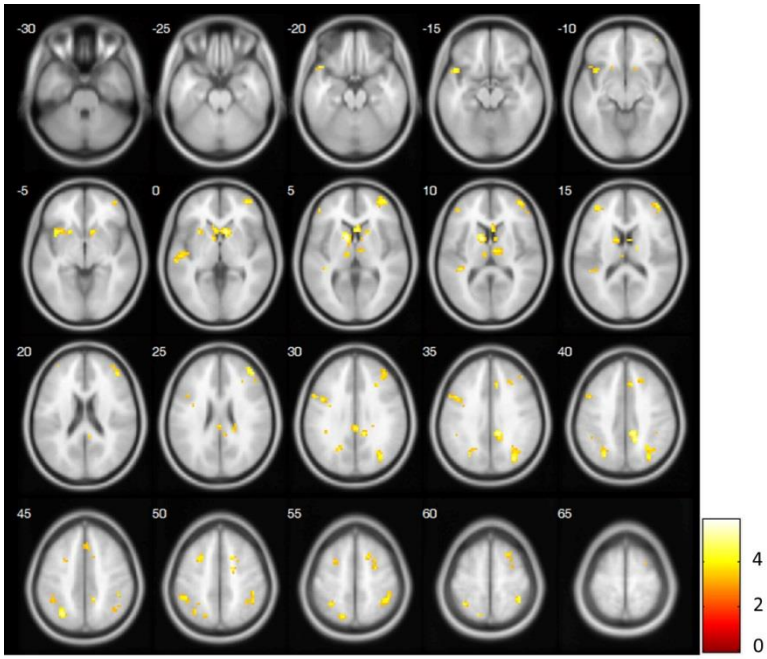
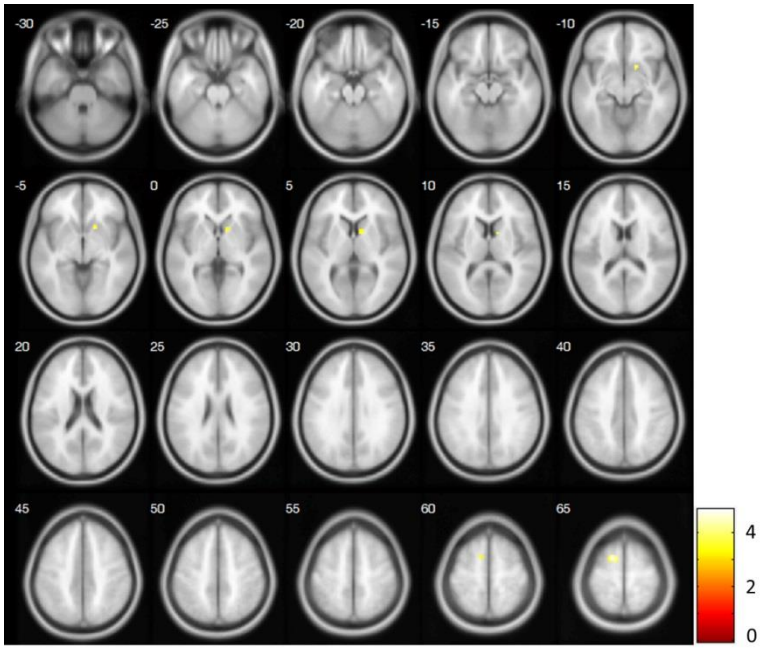


Figure S2: Brain areas showing significant activity for the anticipation of reward vs. punishment.



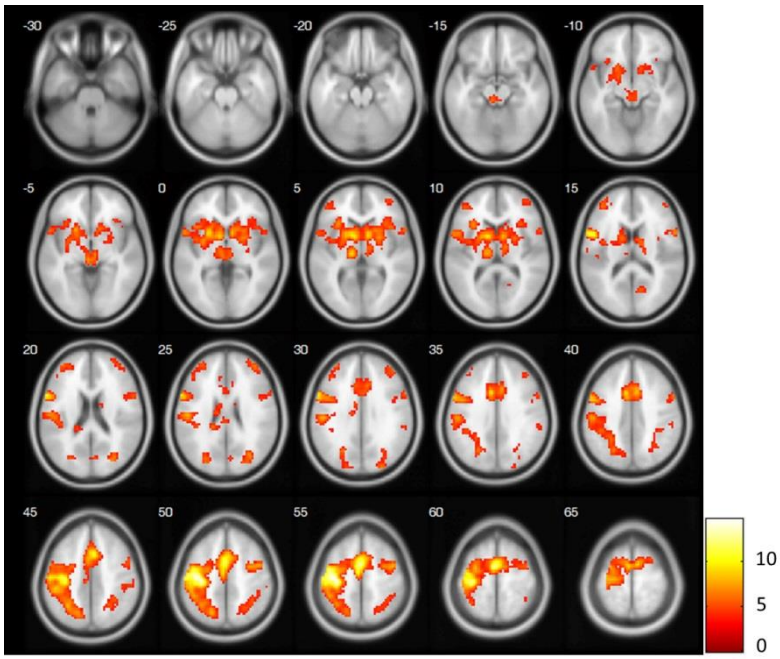
Images are presented in neurological convention (left is left) with a threshold of $p < .001$, uncorrected with a minimum cluster of 540 mm^3. The color bar represents the *t* values applicable to the image and the numbers within the images correspond to z MNI coordinates.

Figure S3: Brain areas showing significant activity for anticipation of high incentive vs. low incentive.



Images are presented in neurological convention (left is left) with a threshold of $p < .001$, uncorrected with a minimum cluster of 540 mm^3. The color bar represents the *t* values applicable to the image and the numbers within the images correspond to z MNI coordinates.

Figure S4: Brain areas showing significant activity for anticipation of reward vs. the non-incentive condition.



Images are presented in neurological convention (left is left) with a threshold of $p < .001$, uncorrected with a minimum cluster of 540 mm^3. The color bar represents the *t* values applicable to the image and the numbers within the images correspond to z MNI coordinates.

2.4 Estudio 3

A New Window to Understanding Individual Differences in Reward Sensitivity from Attentional Networks

Costumero V, Barrós-Loscertales A, Bustamante JC, Fuentes P, Rosell-Negre P, Ventura-Campos N and Ávila C.

Sometido a revisión

Abstract:

Existing evidence suggests that the presence of reward cues modifies the activity in attentional networks; however, the nature of these influences remains poorly understood. Here, we adopted an independent component analysis (ICA) in two fMRI datasets corresponding to two incentive delay tasks, which compared the response to reward (money and erotic pictures) and neutral cues, and yielded activations in the nucleus accumbens using a General Linear Model approach. Across both experiments, ICA revealed that both the right frontoparietal network and default mode network time series were positively and negatively modulated by reward cues, respectively. Moreover, this dual neural response pattern was enhanced in individuals with strong reward sensitivity. Therefore, ICA may be a complementary tool to investigate the relevant role of attentional networks on reward processing, and to investigate reward sensitivity in normal and pathological populations.

Introduction:

Emotion and attention represent fundamental psychological processes that influence perception, action and conscious experience. Humans use to confront with a myriad of simultaneous competing stimuli but have a limited processing capacity. The brain must meet the challenge of selecting only those stimuli most relevant for ongoing behavior and survival. In this sense, presence of reward cues is widely thought to modulate the salience of behavioral goals and to influence attention and behavioral control in relation to goal pursuit and completion (Shah et al. 2002; Ivanov et al. 2011). While our understanding of the interaction between motivation and cognitive control has grown (Small et al. 2005; Locke and Braver 2008; Mohanty et al. 2008; Engelmann et al. 2009; Pessoa 2009; Beck et al. 2010; Daniel and Pollmann 2010; Padmala and Pessoa 2011), the neurobiological mechanisms by which appetitive motivation affects the ability to control attention to task demands and to influence task performance remain poorly characterized.

The mesocorticolimbic dopamine (DA) system has been implicated in a number of neurological and psychiatric disorders, including Parkinson's disease, ADHD, obsessive-compulsive disorder, depression and drug addiction, and also in individual differences in reward sensitivity. Although the specific role of DA is a controversial matter (Salamone and Correa 2012), the most widely accepted function of DA is to mediate reward and stimulus salience processes. The key structures to help to understand DA action on the brain while processing reward-related cues are the striatum, the amygdala and the orbitofrontal cortex (OFC). Previous studies have shown that these areas frequently respond to the presence of reward cues and to reward, and are proposed to mediate individual differences to reward sensitivity in normal and pathological populations (Beaver et al. 2006; Carter et al., 2009; Hahn et al., 2009; Camara et al., 2010; Costumero et al., in press).

Contrasting with the wide literature about the role of the striatum and the OFC in reward anticipation, very little is known about how reward-related increases in phasic DA delivery modulate cognitive control. Animal studies suggest that the frontoparietal structures involved in attention are also modulated by DA (Crofts et al., 2001), and that process information is related to reward contingencies (Platt and Glimcher, 1999; Sugrue et al., 2004) and may be involved in the integration of attentional control and motivation (Bendiksby and Platt, 2006). Accordingly, recent neuroimaging studies have

begun to probe the neural correlates of the interaction between motivation and cognitive control in humans (Small et al. 2005; Mohanty et al. 2008; Padmala and Pessoa 2011). Almost all the fMRI previous research done on reward processing relies on the general linear model (GLM), which is an excellent tool for finding regions that are engaged during a particular task assignment. However, the conventional GLM cannot identify the brain regions that are functionally connected to one another. The substantial basis of the neuroimaging literature that deals with reward sensitivity and its related disorders suggests that the emotional response to a reward cue is not localized in a single brain region, but should be studied in a more widespread network. The studies cited above showing changes in specific areas of fronto-parietal networks (Small et al. 2005; Locke and Braver 2008; Mohanty et al. 2008; Engelmann et al. 2009; Pessoa 2009; Beck et al. 2010; Daniel and Pollmann 2010; Padmala and Pessoa 2011), the alterations in P300 as a function of reward magnitude (Goldstein et al., 2008) as well as the existence of alterations in parietal and frontal areas in disinhibitory disorders (Dickstein et al 2006) suggest that the characterization of individual differences in reward processing could benefit from a functional connectivity (FC) approach that is not limited to functional segregated regions.

The study of temporal coherence in the activity of spatially remote brain areas, defined as FC, has acquired growing interest for the neuroimaging research in the last few years. One of the most promising analyses in fMRI that allow the investigation of functional networks is independent component analysis (ICA). ICA may serve to reveal the hidden factors underlying sets of random variables, measurements or signals. ICA assume that fMRI data are linear mixtures of independent source signals and attempt to extract maximally independent signals and their mixing coefficients. The driving principle behind ICA is that these independent source signals represent coherent groupings off MRI activations, often referred to as component maps, which imply a representation of a functionally connected network. As ICA is a data-driven approach, functional networks are generated without making any assumptions about the shape of the fMRI time courses. Thus they can capture coherent activity that is not strongly tracked with a task. However, functional networks are widely replicated across studies (Allen et al., 2011; Toro et al., 2008; Biswal et al., 2010; Segall et al., 2012), in different contexts like rest (Lee et al., in press), when subjects are engaged in an explicit task (Fox et al., 2006; Calhoun et al., 2008; Smith et al., 2009) or during different states of consciousness, such as sleep or sedation (Heine et al., 2012), and they develop during

one's lifespan (Thomason et al. 2011, 2013; Ferreira and Busatto, 2013). The study of functional networks has provided new insights into different pathologies (Rosazza and Minati, 2011). Nevertheless, it is imperative to understand the normal properties of large-scale networks for the proper study of the implications of network functioning changes under pathological conditions (Sepulcre et al., 2012). Thus, further evidence for the functioning of these networks in healthy populations under different conditions and their possible variations in gender, age or personality terms is necessary.

Previous studies have shown an association between DA and attentional networks such as the default mode network (DMN; Raichle et al., 2001), the dorsal attentional network (DAN; Corbetta and Shulman 2002) and the fronto-parietal network (FPN; Corbetta and Shulman 2002; Vincent et al., 2008). The general strategy to investigate these networks has involved the use of cognitive tasks (without motivational components) and the study of DA availability through PET techniques, pharmachological manipulations or genetically determined groups. These studies have demonstrated that increases in the levels of DA leads to a greater deactivation of the DMN (Tomasi et al., 2011; Minzenberg et al., 2011; Nagano-Saito et al., 2009; Nagano-Saito et al., 2008) and increased activity in the DAN and the FPN (Tomasi et al., 2011; Tan et al., 2007; Williams-Gray et al., 2007) during the task.

Yet as far as we know, no experiment has directly studied the changes in attentional networks due to the presence of reward cues. Reward cues are proposed to generate some phasic dopamine-dependent cognitive processes such as an increase in the effects of reward prediction error signals, the enhancement of neuronal response to reward-predicting stimuli or the reduction of reward discrimination (Schultz, 2011), which cannot be explained only from the striatum and the OFC response. The objective of the present study was to investigate how reward cues processing modifies activity in attentional networks, and how this process is modulated by individual differences in reward sensitivity. For this end, we performed two fMRI experiments corresponding to different incentive delay tasks in order to identify the functional networks responding to anticipation to reward correlating with reward sensitivity by means of ICA. We hypothesized an association between individual differences in reward sensitivity and the modulation of attentional networks by anticipation to reward.

Experimental Procedures:

Experiment 1

Participants

Forty-one male undergraduates (mean age = 23.3, SD = 4.1; mean years of education = 13.7, SD=2.2) participated in this fMRI study. Participants were physically and psychologically healthy with no history of mental disorders, head trauma, or drug abuse. Participants were informed of the nature of the research and signed written informed consent prior to participation. The study was approved by the Ethical Committee of the Universitat Jaume I (Spain).

Personality assessment

The Sensitivity to Reward (SR) Scale from the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001) was used as a measure of the reward sensitivity trait. Participants' SR mean score (11.6, SD=4.41, range: 3-21) was similar to those obtained in previous studies (Caseras et al., 2003; Barros-Loscertales et al., 2006, 2010). The SPSRQ has been translated into 15 languages and is widely used to assess reward sensitivity in adults (Torrubia et al., 2001) and children (Luman et al., 2012). The SR scale has good content validity and strongly correlates with other measures of reward sensitivity, such as reward responsiveness, drive, fun seeking, novelty seeking, and impulsivity scales (see Torrubia et al., 2008 for a review).

Experimental Design and Stimuli

This experiment was designed to study the relationship between individual differences in the reward sensitivity personality trait and brain activity during anticipation to possible rewards and punishments. The task was an adaptation of the monetary incentive delay task described by Knutson et al. (2001, 2003) and included all the high and low reward and punishment conditions (see Fig. S1). Before entering the scanner, all the participants were given instructions on the task and completed a practice session. The practice session was thought to minimize later learning effects and provided an estimate of each individual's reaction time (RT) to standardize task difficulty in the scanner. For each participant, the median RT of correct trials during the practice session was implemented as a cut-off RT in the main experiment. All the participants were initially paid 20 euros for their participation. At the end of the

experiment, participants received an individually adjusted bonus depending on their performance in the experimental task.

Inside the scanner, participants performed two 8-minute runs of the monetary incentive delay task. Each run consisted of 60 trials for 120 trials in all. There were four kinds of events defined by a high reward, low reward, high punishment and low punishment cue. Each trial consisted of one of those cues, which was presented for 500 ms. It was followed by a black screen of variable duration (2000–2250 ms) and then by a white target square that appeared for 100 ms to which participants had to respond by pressing a response button as quickly as possible. After the participant responded, a black screen with a variable duration of 2000–4000 ms appeared, followed by a feedback screen (1500 ms duration) that notified the participants whether they had won or lost money during that trial and indicated their cumulative total at that point. As previously noted, each event was defined by the initial appearance of a different cue: a circle with two horizontal lines indicating the possibility of winning 3 euros (a high reward cue; n=24); a circle with one horizontal line indicating the possibility of winning 0.20 euros (a low reward cue; n=24); a square with two horizontal lines indicating the chance of avoiding losing 3 euros (a high punishment cue; n=24); a square with one horizontal line indicating the chance of avoiding losing 0.20 euros (a low punishment cue; n=24). A triangle (n=24) was the cue for non-incentive trials in which the participants neither won nor lost money. The participants had to respond after each incentive signal, but they did not respond to non-incentive signals since they were not followed by a target stimulus (a white square).

Trial types were pseudo-randomly ordered within each run. The intertrial interval was randomized between 2000 ms and 4000 ms. Participants were instructed to respond as quickly as possible to target stimuli in order to achieve rewards or to avoid punishments. The task was programmed and presented using the Presentation software (Neurobehavioral Systems, Inc., Albany, USA). Visual stimuli were displayed in the scanner using Visuastim goggles (Resonance Technology, Inc., Northridge, USA). Stimulus presentation was synchronized with scanner acquisition using SyncBox (Nordic NeuroLab, Bergen, Norway) and behavioral task performance was recorded with a ResponseGrip (Nordic NeuroLab, Bergen, Norway). Reaction times (RT) and the percentage of hits (successful responses to obtain rewards or to avoid punishments) were recorded as behavioral data.

fMRI acquisition

Image acquisition was performed using a 1.5T Siemens Avanto MRI scanner (Siemens, Erlangen, Germany). Functional images were acquired using a T2*-weighted echo-planar imaging sequence (TR/TE = 2000/30 ms, matrix = 64 x 64 x 30, flip angle = 90°, number of volumes = 502). Thirty 3.5-mm-thick slices centered parallel to the hippocampi were axially acquired with a 0.5-mm interslice gap.

Image Preprocessing

Image processing was carried out using SPM8 (Statistical Parametric Mapping 8; The Wellcome Department of Cognitive Neurology, London, UK). Preprocessing of the functional scans included noise filtering using an Art Repair toolbox (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) to repair slice artifacts through interpolation, slice-timing correction, realignment to correct for motion-related artifacts, spatial normalization into the standard Montreal Neurological Institute space using SPM8's EPI template (voxel size $3mm^3$) and smoothing with full-width at a half maximum (FWHM) of the Gaussian kernel (8 mm).

General linear model analysis:

The GLM analysis (Friston et al., 1995) was performed with SPM8 to study brain activity in response to anticipatory cues. In the first-level analyses, a statistical model was computed for each participant. The GLM design matrix included separate regressors for each anticipatory cue, feedbacks and targets by applying a canonical hemodynamic response function and its time derivative. In addition, the six motion correction parameters from each participant were included in the model as 'nuisance' variables. The fMRI time series data were high pass-filtered with a cut-off frequency of 1/128 Hz to eliminate low-frequency components. Finally, statistical contrast images were generated by comparing reward (high and low) and non-incentive cues, as well as punishment (high and low) and non-incentive cues, to obtain brain activation for anticipatory periods.

The second-level analyses consisted in two one-sample t-tests using the contrast images from the first-level analyses. Region of interest (ROI) analyses were carried out to study brain activity for each contrast in the bilateral ventral striatum (VS), an area that has been highly related with reward anticipation (Knutson et al., 2001, 2005). The

VS ROIs were defined as a 6-mm-radius sphere at the [±10, 8, -4] MNI coordinates (based on Cools et al., 2002 and Barros-Loscertales et al., 2006). The statistical threshold was defined using small volume correction at $p<0.05$, FWE-corrected at the voxel level.

Independent Component Analysis

Group ICA was performed to obtain the functional brain networks underlying the fMRI data. ICA is a statistical method used to discover hidden factors from a set of measurements or observed data so that sources are maximally independent (see Calhoun et al., 2009 for a review). When applied to fMRI data, spatial ICA identifies temporally coherent networks which are spatially maximally independent. The main advantage of ICA is that it does not require *a priori* models of brain activity or connectivity to generate functional networks because it is a data-driven approach.

Group ICA was done using Gift toolbox (v1.3i, http://icatb.sourceforge.net). The optimal number of independent components (ICs) was 20, which were calculated using the minimum description length (MDL) criteria (Li et al, 2007). A principal component analysis (PCA) was used to reduce data dimensionality following a two-step data reduction approach (Calhoun et al., 2001). Then, ICA decomposition was performed with an Infomax algorithm (Bell and Sejnowski, 1995) to reach the final number of 20 ICs found with the MDL criteria. Twenty ICA iterations were performed by ICASSO (Himberg et al., 2004) to ensure the stability of the estimated ICs (see Fig. S2). Then, individual IC maps and time courses were computed using back-reconstruction based on the aggregate components of the ICA and the results from the data reduction step (Erhardt et al., 2011). Finally, individual ICs were scaled to z-scores.

The spatial maps generated by ICA were averaged across runs and one-sample t-tests at the second-level analyses were performed with SPM8 (at $p<1x10^{-12}$ FDR-corrected; k=30) to determine the brain regions that significantly relate with each IC time series for the whole group. This analysis provides a map of functionally connected brain regions belonging to each IC.

Following previous studies (Kim et al., 2009a; Kim et al., 2009b; Ye et al., 2012; Juárez et al., 2012), we performed GLM analyses on the IC time courses to

analyze the engagement of functional networks under tasks conditions. Thus, the regression analysis was performed in each IC time course using the estimated GLM design matrix. This analysis yields a set of beta-weights representing the modulation of the ICs time courses by the GLM regressors in relation to the baseline. The beta-weights for each condition were averaged across runs. Furthermore, the beta-weights for reward (high and low) and punishment (high and low) conditions were also averaged in order to acquire a whole measure of reward and punishment anticipation as this facilities comparability with Experiment 2. These beta-weights were then used to perform the second-level analyses.

As ICA constitute a data-driven approach and since some ICs may represent artifacts or brain networks that do not relate to the experimental conditions, we used 3-step IC selection criteria based on previous studies (Kim et al., 2009a; Kim et al., 2009b; Sambataro et al., 2010; Stevens et al., 2007; Ye et al., 2012; Zhang and Li 2012). Thus, the ICs of interest were selected in three consecutive stages: 1) those ICs whose ICASSO-calculated coefficient of stability was lower than 0.9 were considered unstable and were removed for further analyses; 2) the ICs were correlated with prior probabilistic maps of gray matter, white matter and cerebral spinal fluid (CSF), provided by the MNI templates of SPM8, so that those ICs with a spatial correlation higher than r^2=0.02 with white matter, greater than r^2=0.05 with CSF or a lower correlation with gray matter than the correlation with white matter or CFS, was not considered to be primarily located within grey matter and removed; 3) a one-way repeated measures ANOVA was performed with the beta-weights for each anticipatory condition to determine which IC showed differential involvement during the anticipatory period for the whole group, and the ICs that did not show significant differences at the $p<.05$ FDR-corrected level were considered to not be task-related and were removed for subsequent analyses.

After identifying the ICs of interests relating with the task using ANOVA, *post hoc* analyses were performed with these ICs to study how time courses are modulated by the different task conditions ($p<0.05$, corrected). Furthermore, correlation analyses were done to study the relationship between reward sensitivity and the engagement of

functional connected brain networks under task conditions. Thus, the beta-weights for each anticipatory cue of those ICs of interest were correlated with the SR scores.

Experiment 2

Participants

Thirty heterosexual men (mean age = 23.7, SD=3; mean years of education = 13.9, SD=2.4) took part in this study. None of the participants included in the study reported a history of DSM-IV Axis I or II disorders, severe medical illnesses or neurological illnesses, history of head injury with loss of consciousness, or current use of psychoactive medications. Participants were informed of the nature of the research, provided written informed consent prior to participating in this study and were paid €30 for their participation. The study was approved by the Human Subjects Committee of the Universitat Jaume I of Castellón (Spain).

Personality assessment

As in Experiment 1, we used the SR scale from the SPSRQ. The participants' mean SR score was 11.5 (SD=5.3 range: 3-20), similar to Experiment 1 and the previous studies cited above.

Experimental design and stimuli

In order to study the role of the reward sensitivity personality trait in anticipation to non-monetary rewarding stimuli we performed an incentive delay task including erotic and neutral pictures as an outcome (See Fig. S1). The instrumental task began with a discriminative cue presented for 500 ms which signalled the trial type. A white square (target) appeared after the cue and remained for 100 ms in a random interval lasting between 2 and 2.25 seconds. Whenever the participants responded, a picture was presented for 1 second after a randomizing interval (6-10 seconds). The participants were asked to make a response when they saw the target stimuli. When the participants did not respond within a 2-second temporal interval (response window) after the target stimuli presentation, a "#" symbol appeared for 1 second, indicating that this trial had not been properly performed. Four experimental trial types were included in this experiment in order to manipulate the motivational value of the anticipatory cue and the

motor response anticipation effects. In the continuous reward trials (n=32), "X" indicated that whenever the participants responded to the target stimulus, an erotic picture would be presented. In the partial reward trials (n=32), "?" indicated that the participants had to respond quickly to view an erotic picture, otherwise a neutral picture would be presented. Thus as in the continuous reward trial, this condition involved anticipatory responses to reward stimuli, but in this case, the outcome depended on the participants' RT. The task difficulty for these trials was individualized for each subject based on RT, and was updated during the task depending of on-going execution, thus ensuring at least about 60% of accuracy. In the neutral trials, a "triangle" (n=32) indicated that participants would be presented with a neutral picture after their response. Hence, this condition involves action preparation to respond to target stimuli correctly, but without emotional contingences. Finally in the control trials, the participants passively saw a "circle" (n=32) followed by a neutral picture without the target stimuli being presented. Therefore, this last condition did not involve motivational effects neither motor preparation, allowing us study the modulation of attentional networks by action preparation without motivational contingences, since previous studies have shown a main effect of motor preparation on the activity of key regions within the reward system (Guitart-Massip et al., 2011). The task was divided into four runs. Each run consisted of 32 trials with 128 trials in all. Trial types were pseudo-randomly ordered within each run. The inter-trial interval was randomized between 6 and 10 seconds. The erotic pictures set included photographs of couples and undressed adult women, whereas the neutral pictures set included house-hold items and scenes of daily life. The resolution image was 800x600 pixels and no picture was shown more than once. Before entering the scanner, all the participants were given instructions about the task and completed a practice session to minimize later learning effects. After the scan session, the subjects valued all the pictures on both the valence and arousal dimensions (on a scale of 1-9). The task programming software and stimulus presentation tools were the same as in Experiment 1. RT and the percentage of hits (successful responses in partial reward trials) were recorded as behavioral data.

FMRI Acquisition

Image acquisition was performed using a 1.5 T Siemens Avanto MRI scanner (Siemens, Erlangen, Germany). Functional images were acquired using a T2*-weighted gradient-echo echo-planar imaging sequence (Slices per volume = 30, TR/TE = 2500/48

ms, matrix = 64 x 64 x 30, flip angle = 90°, number of volumes = 840). Thirty 3.5-mm-thick slices centered to AC-PC were axially acquired with a 0.3-mm interslice gap.

Image Preprocessing

The preprocessing implemented in the fMRI images for this experiment was the same as in Experiment 1 (see Experiment 1, image preprocessing).

General linear model analysis:

The GLM analyses for this experiment were similar to Experiment 1. After performing the GLM design matrix, statistical contrast images were generated by separately comparing the continuous and partial trials with neutral and control trials. One-sample t-test was done in the second-level analysis for each generated contrast. ROI analyses were carried out for each contrast in the VS using small volume correction at $p<0.05$, FWE-corrected at the voxel level.

Independent Component Analysis

The ICA performed for this experiment was similar to those implemented in Experiment 1, the only difference being that the optimal number of ICs determined by the MDL criteria for this experiment was 28.

Results:

Experiment 1

Behavioral results:

The means and standard deviations for RT and hits are presented in Supplementary Table 1. Paired t-tests were performed to study the differences in RT and hits between conditions. The results reveal that participants responded faster (t_{40}=-2.4; p=0.02) and more successfully (t_{40}=3.9; $p<0.001$) for reward cues than for punishment cues.

GLM results

As expected, ROI analyses (See Figure 1) showed increased bilateral VS activity while reward cues were presented as compared to the non-incentive cues (right: MNI

peak maximum = 6, 8, 1, Z-score = 3.65, k= 9; left: MNI peak maximum = -6, 8, 1, Z-score = 3.07, k= 4). Furthermore, increased right VS activity was noted during the presentation of the punishment cues in comparison to the non-incentive cues (MNI peak maximum = 6, 8, 1, Z-score = 3.13, k= 4). These results are in consonance with previous reports showing increased VS activity while processing both the reward and punishment anticipatory cues (Carter et al., 2009). The whole brain voxel-wise results for each contrast are summarized in Supplementary Table 2.

ICA results

Four ICs (C4, C5, C9 and C10) passed the selection criteria and were, therefore, selected as ICs of interest. Each IC was defined based on the similarities between the ICs spatial maps and the networks shown in previous resting state studies using bigger samples (Allen et al., 2011; Segall et al., 2012). Thus, the four ICs of interest were identified as the DMN (C4), the left FPN (C5), the right FPN (C9) and the frontal network (C10). No component resembling the DAN was obtained in this experiment. Table 1 summarizes the brain areas belonging to the spatial map of each IC of interest.

The one-way repeated measures ANOVA showed how each IC of interest was modulated by anticipatory conditions (see Figure 2 and Figure 3). The DMN exhibited greater negative modulation for the reward and punishment cues than the non-incentive cues. Furthermore, the left FPN displayed higher negative modulation for the reward cues than for the non-incentive cues, while the right FPN showed larger positive modulation for the reward cues than for both punishment and the non-incentive cues. No differences between punishment and the non-incentive cues were found for both the right and left FPN, suggesting specific FPN engagement during reward anticipation. Finally, the frontal network displayed lower negative modulation for both the reward and punishment cues than for the non-incentive cues.

Reward sensitivity relationship with task-related modulation of the ICs:

Correlation analyses between the SR scores and beta-weights for each anticipatory condition were done to study the relationship between reward sensitivity and functional networks (Table 2). This analysis showed that the SR scores correlated negatively with the DMN during the anticipation of both monetary rewards and

punishments. In addition, the SR scores correlated positively with the right FPN during the anticipation of both monetary rewards and punishments.

Experiment 2

Behavioral results:

The means and standard deviations for RT, hits and subjective ratings are presented in Supplementary Table 1. A one-way repeated measure ANOVA was performed using the RTs for each incentive condition to study differences in performance. Significant differences were obtained between the RTs' incentive cues ($F_{(1.5,45)}$=9.7; p=0.001) showing that the participants were faster for partial reward than for continuous reward and neutral cues.

Two paired t-tests were run according to the participants' image ratings to study the subjective reward stimuli value. The analyses revealed that the erotic picture set was significantly rated as more pleasant (t_{29}=9.2; p<0.001) and arousing (t_{29}=11.1; p<0.001) than the neutral picture set, thus confirming that erotic pictures were subjectively positive for participants.

GLM results

The ROI analyses in this experiment (See Figure 1) showed higher bilateral VS activity during the presentation of partial reward as compared to the neutral cues (right: MNI peak maximum = 15, 8, -5, Z-score = 4.31, k= 38; left: MNI peak maximum = -9, 5, -2, Z-score = 4.22, k= 33) and to the control cues (right: MNI peak maximum = 9, 11, -2, Z-score = 3.76, k= 12; left: MNI peak maximum = -9, 5, -5, Z-score = 3.65, k= 22). Furthermore, increased activity in the left VS was seen during continuous reward cues as compared to both the neutral (MNI peak maximum = -9, 8, 1, Z-score = 3.4, k= 17) and control (MNI peak maximum = -9, 8, -5, Z-score = 3.16, k= 12) cues. These results generalize to sexual rewards the findings showing VS involvement in anticipation to monetary rewards (Knutson et al., 2001). The whole brain voxel-wise results for each contrast are summarized in Supplementary Table 2.

ICA results

For this experiment, four ICs (C3, C7, C19 and C26) passed the selection criteria and were, therefore, selected as ICs of interest. Similarly to Experiment 1, each IC was

defined based on its similarities with the networks shown in previous studies (Allen et al., 2011; Segall et al., 2012). Thus, the four ICs of interest shown in this experiment were identified as the left sensory motor network (C3), the right FPN (C7), the DMN (C19) and the cerebellum (C26). In this experiment, the DAN (C23) did not pass the selection criteria given a greater spatial correlation than r^2=0.02 with white matter. The brain areas belonging to the spatial map of each IC of interest are summarized in Table 1.

The ANOVA results for this experiment (Figure 2 and Figure 3) showed that the left sensory motor network displayed a higher positive modulation for all the instrumental conditions (continuous reward, partial reward and neutral) than the control condition, suggesting the involvement of this network in anticipation to movement. Additionally, the partial reward cues showed larger positive modulation than both the continuous and neutral cues, indicating that the requirement of fast responses had an effect on this network. The right FPN displayed greater positive modulation for both reward conditions than the control cues. The partial reward cues also showed higher positive modulation than the neutral cues. Overall, the effects of the right FPN were modulated mainly by the requirement of response and the presence of reward cues requiring a faster response. The DMN exhibited a larger negative modulation for the instrumental conditions when compared to the control condition, which suggests its involvement in movement anticipation. Additionally, the fact that the partial reward cues presented higher negative modulation than both the continuous reward and neutral cues once again hinted that the requirement of fast responses to obtain rewards modulates this network. Finally, the cerebellum showed an effect of movement anticipation which was due to larger positive modulation for the instrumental cues than for the control cues. Despite the DAN not passing the selection criteria, its possible involvement in the task using ANOVA was checked. Nevertheless this component did not show task-related differences.

Reward sensitivity relationship with task-related modulation of the ICs:

The Pearson's correlations between the SR scores and IC task-related modulation appear in Table 2, and reveal that the SR scores correlated negatively with DMN modulation upon the onset of the continuous and partial reward cues, but not while processing the neutral and control cues.

Furthermore, the SR scores correlated positively with the right FPN modulation while processing all the conditions. We ran additional partial correlations to ascertain if the reward or requirements of the motor response modulate the magnitude of the correlations. When regressed out for activity during the neutral condition, the correlation found between the SR scores and activity upon the onset of the continuous reward cues remained significant ($r=0.47$, $p = 0.009$). The same correlation during partial reward showed a significant tendency ($r=0.36$, $p = 0.055$). When controlling for network modulations under the control condition, the SR scores correlated positively with the network modulation during partial ($r=0.52$, $p = 0.003$) and continuous ($r=0.53$, $p = 0.003$) reward. Thus, the presence of the reward cues seemed to contribute to modulate the activity in the right FPN.

Discussion:

Across two different experiments, we used ICA to identify the anatomical components of the putative brain networks involved in processing reward cues based on their synchronous activation by filtering out the noise/artifactual components of the fMRI signal. We were also able to examine individual differences in the functioning of these networks in accordance with the reward sensitivity scores. Our results confirm our hypotheses about the involvement of two attentional networks in reward processing: the right FPN and the DMN. As expected, the presence of reward cues positively and negatively modulated the right FPN and the DMN, respectively. It is noteworthy that both effects were enhanced in individuals who obtained higher scores in reward sensitivity. These results reveal that a response to reward cues is not merely circumscribed to the "classical" reward brain areas, but to attentional networks that are also regulated by dopamine. The relevance of these data may also prove important for brain disorders associated with deficits in reward processing.

As far as we know, the present experiments are the first to investigate the relationship between attentional networks and the processing of reward cues using ICA. The results of both experiments consistently show that processing reward cues positively modulates right FPN activity and negatively modulates DMN activity, while there is no task effect for the DAN. Consistently with the DMN pattern of deactivation shown in other studies (Raichle and Snyder, 2007), we demonstrate that the DMN time series were more negative for reward cues than for neutral ones. In Experiment 1, the

DMN displayed greater negative modulation for both reward and punishment cues than non-incentive cues. In Experiment 2, the results indicate that the DMN time series were more negative while processing reward cues, especially when delivery of reward depends on a subject's performance. The DMN has been associated with internal cognitive processes and it deactivates when attention is paid to external stimuli (Raichle et al., 2001; Greicius et al., 2003). Previous research has repeatedly shown that, during cognitive tasks, the higher the task demands, the stronger DMN deactivation is (Harrison et al., 2011). It is important to note that this deactivation has been suggested to depend on dopamine (Argylean et al., 2008; Engelmann et al., 2009; Tomasi et al., 2011; Dang et al., 2012). The present study also shows that the motivational stimulus value also modulates DMN deactivation independently of task demands since reward conditions are not cognitively harder than neutral ones. This result is consistent with a previous report which did ROI analyses to show that reward cues and cues anticipating high task demands deactivate specific DMN areas when compared to non-reward and low task demand cues (Krebs et al., 2012). Overall, the pattern of the DMN results is consistent with the proposal that the suppression of this network is important for goal-directed externally-oriented cognition (Anticevic et al., 2012; Spreng 2012).

The DAN is hypothesized to modulate externally directed attention by amplifying the saliency of the relevant cues of the environment in accordance with current action goals (Corbetta and Shulman, 2002; Ptak and Schnider, 2010). As our tasks involved fewer spatial orienting, eye movement or visuospatial integration requirements, especially when comparing reward and neutral cues, the DAN did not prove relevant in these tasks. In Experiment 1, we were unable to identify the DAN in any component. In Experiment 2, we obtained the DAN in the ICA (C23), but this network did not showed differential involvement in task conditions. In other words, the presence of reward cues does not modulate DAN activity if compared with neutral cues. It is feasible that this network focuses on controlling purely cognitive operations to guide spatial orienting in accordance with relevant stimuli and personal goals.

Finally, the right FPN time series increased in the presence of reward cues if compared with non-reward cues. In Experiment 1, we found that this network was more engaged in situations involving reward and punishment, whereas in Experiment 2, the presence of reward cues and the requirement of fast responses to obtain reward seemed to increase the activity of this network. It has proposed that the right FPN is specialized in the detection of behaviorally relevant stimuli, particularly when they are salient or

unexpected (Corbetta and Shulman, 2002). In this sense, the results of the present study indicate that the activity of the network is not only related to the need to select between different stimuli in conflict monitoring, planning and reasoning (Kroger et al., 2002; van den Heuvel et al., 2003; Wager et al., 2004), but it also seems to exert an arousing effect when processing reward stimuli, and it probably participates in preparing the motor response.

The specific role of the right FPN has been recently depicted by considering the interaction of attentional networks, the characteristics of the task and the role of dopamine (Spreng et al., 2010, 2013). Vincent and colleagues (2008) noticed that the FPN is physically interposed between the DAN and the DMN, and these authors suggested that the FPN may flexibly couple to the DMN or the DAN, depending on the attentional demand of the task. Spreng and colleagues (2010) gave evidence about how both the DMN and DAN appear to compete for positive coupling with FPN. They reported increased DAN and FPN activity, but diminished DMN activity, when performing a visuospatial planning task, but found increased DMN and FPN activity and reduced DAN activity when an autobiographical planning task. These results led to the proposal that the FPN is coupled to not only the DMN during internal cognition, but also to the DAN during external cognition. The data obtained in the present study indicate that the DAN is not relevant in those tasks which require the processing of a single reward cue (i.e., not requiring selective attention), and only the right FPN and the DMN are positively and negatively involved, respectively. These results are, therefore, in line with the idea that the FPN endogenously focus the attention to relevant stimuli and, when necessary, it probably couples its activity with the relevant networks involved in the task.

This action of the attentional networks has been proposed to be mediated by dopamine because, on the one hand, reward cues phasically increase dopamine in the brain (Wightman and Robinson, 2002) and, on the other hand, activity in the right FPN is modulated by dopamine (Tan et al., 2007; Williams-Gray et al., 2007). The presence of reward cues phasically increases the firing of dopamine neurons in basal ganglia and the frontal cortex (Schultz et al., 1998; Stalnaker et al., 2012). Mesocorticolimbic DA has also been proposed to mediate not only increased activity in the FPN (Tan et al., 2007; Gordon et al., 2012; Nagano-Saito et al., 2008), but also the relationship of this network with other attentional networks (Dang et al., 2012). Likewise, dopamine was

related to decreases in DMN (Nagano-Saito et al., 2009; Tomasi et al., 2011). Hence we may tentatively propose that the presence of reward cues leads to increases in right FPN activity and to decreases in DMN throughout DA.

This link between dopamine and activity in attention networks is indeed more relevant if we focus on the fact that the main effects obtained in this study are mainly driven by individual differences in reward sensitivity. In both experiments, we accomplished a modulation in the right FPN and the DMN, while processing reward cues related positively and negatively to the SR scores, respectively. Individual differences in reward sensitivity have been previously associated with structural abnormalities in the striatum (Barros-Loscertales et al., 2006) and with dopamine levels (Pickering and Gray, 2001). Previous studies have also shown that reward sensitivity is associated with stronger activity in the striatum and/or with the OFC when processing reward cues (Hahn et al., 2009; Carter et al., 2009). For the first time, our ICA reveals that reward sensitivity is also linked to a distinct activity in attentional networks.

Previous studies have reported results that are consistent with our data. First, one interesting result as regards the right FPN was that reward sensitivity is associated with the modulation of this network under the non-rewarded conditions in Experiment 2, but not in Experiment 1. This result agrees with recent results that relate reward sensitivity to a stronger probability of adopting a proactive control mode in contexts with intermittent rewards (Jimura et al. 2010). Proactive control has been related with sustained and anticipatory activity in the right dorsolateral PFC, an area belonging to the right FPN. Thus, intermittent reward contexts with mixed reward and neutral trials can be associated with the adoption of a proactive mode by high reward sensitive subjects, which led them to the sustained and anticipatory maintenance of goal-relevant information throughout the task (Braver, 2012). Based on the results of Experiment 1, we may tentatively propose that this effect should not be observed in mixed rewards and punishments contexts.

The second related issue stems from diverse behavioral studies which show that individuals with stronger reward sensitivity possess an attentional system which is directed at seeking and effectively detecting relevant environmental stimuli by means of the conscious focalization of attention on locations or stimuli associated with reward (Derryberry and Reed, 1994; Ávila, 2001; Avila and Parcet, 2002). Consequently, these individuals pay more attention to reward cues at the expense of ignoring punishment

cues (Patterson et al., 1987; Ávila, 2001). The results of the present study indicate stronger activity in right FPN and more deactivation in the DMN when processing reward cues given the possible neural architecture of these behavioral data. In other words, individuals with stronger reward sensitivity focus more on reward cues, which reduces the probability of changing the reward-directed behavior by internal cues (see the model depicted by Patterson and Newman, 1993 for a behavioral description of this process). Third, psychophysiological research supports the present data. Parvaz and colleagues (2012) measured reward sensitivity from the amplitude of P300 to the expectation of different magnitudes of reward. Expectation of a high reward yielded a stronger P300 response than expectation of a non-reward, and this difference correlates with the gray matter volume of several prefrontal cortex areas. Consistently with the results of the present study, the above authors highlighted the importance of prefrontal integrity to modulate attentional responses to reward cues. Fourth, several neurocognitive models on individual differences applied to diverse fields such as psychopathology (Volkow et al., 2011), adolescence (Ernst et al., 2006) or personality (Pickering and Gray, 2001; Depue and Collins, 1999), establish that attention modulates reward processing to a certain degree. The results of the present study offer a new procedure to investigate these effects and to test these models. In general terms, all these models propose that some frontoparietal areas modulate the action of the reward brain areas and that they help determine reward sensitivity and probability of approach. However, the specific effect of the DMN on these models is still not well-established.

Another point of interest in the present study is the comparison of the ICA and GLM results. Using the traditional GLM analyses, both the datasets employed in the present study have shown a consistent activation of the ventral striatum. However, traditional GLM analyses proved less specific to find consistent differences across studies in the areas included in the right FPN or the DMN networks. Besides, ICA showed the reverse pattern of results, with differences in attentional networks, but not in those networks involving classical "reward areas" such as the striatum. With these results, we can consider ICA to be a new, alternative way to investigate individual differences in reward sensitivity, which offer promising applications to psychiatric disorders (depression, psychopathy, ADHD, substance abuse, etc.) characterized by deficits in reward processing.

Conclusions:

Using ICA, we have shown that attentional networks are modulated by motivational cues across two reward-related tasks. Specifically, we demonstrate that reward cues positively modulate the right FPN and negatively modulate the DMN time series. We also show that the modulation in the right FPN and the DMN while processing reward cues relates positively and negatively to the SR scores, respectively. As processing reward cues entails no visuospatial requirements, the DAN network does not participate in the tasks. The ICA procedure applied to reward processing opens a new window to investigate reward processing and individual differences in reward sensitivity.

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Table 1 Brain regions belonging the ICs of interest

Component	Region	Brodmann areas	Maximum peak coordinates (MNI)	k	Maximum peak t value
Experiment 1					
Default Mode Network (DMN, C04)					
	Precuneus	7, 30, 29, 31	-9 -55 28	1754	34.43
	Medial PFC	10, 32, 9, 11	-6 53 7	693	23.75
	Talamus	-	-6 -13 7	62	14.91
	Angular gyrus left	39	-42 -70 34	73	14.28
	Angular gyrus right	39	42 -67 37	32	13.53
Left Frontoparietal Network (FPN, C05)					
	Inferior parietal left	40, 39, 21, 22, 31, 7, 19	-51 -52 43	2432	25.83
	Superior frontal cortex	8, 6	-12 35 52	767	19.46
	Inferior frontal cortex left	47, 45	-51 29 -5	256	16.40
	Inferior parietal right	40	54 -61 40	133	15.41
	Postcentralgyrus left	4	-21 -37 58	49	13.08
Right Frontoparietal Network (FPN, C09)					
	Inferior parietal right	40, 7, 39	54 -58 43	1064	24.62
	Inferior parietal left	40, 7	-39 -58 46	453	19.73
	Middle frontal gyrus right	8, 9, 10, 6, 46	45 14 49	878	19.18
	Middle Temporal right	21	63 -34 -8	143	16.69
	Medial PFC	8	0 32 46	152	16.07
	Posterior cingulate	31	3 -31 28	95	15.85
	Precuneus	7	3 -76 46	40	12.68
Frontal network (C10)					
	Medial and lateral PFC	10, 8, 9, 32, 6, 24, 11	-3 50 4	4862	28.1
	Inferior frontal cortex left	47, 45	-45 14 -5	252	19.81
Experiment 2					
Sensory motor network (C03)					
	Poscentralgyrus left	3, 40, 2, 4, 6	-42 -31 55	595	24.8
Right Frontoparietal Network (FPN C07)					
	Middle frontal gyrus right	10, 8, 9	36 53 -2	822	26.49
	Inferior parietal right	40, 7	39 -58 43	576	26.17
	Inferior parietal left	40	-45 -52 49	159	24.01
	Posterior cingulate	31	3 -28 37	64	17.79
Default Mode Network (DMN, C19)					
	Angular gyrus left	19,39	-42 -82 31	170	28.43
	Precuneus	29, 30	9 -55 16	323	21.48
	Medial PFC	10, 11	0 44 -14	146	19.33
	Angular gyrus right	39	42 -82 34	146	18.67
Cerebellum network (C26)					
	Cerebellum	-	-30 -46 -35	1635	34.84

Table 2 Pearson correlation between the SR scores and IC task-related modulation

Experiment 1

Condition	DMN (C04)	Left FPN (C05)	Right FPN (C09)	Frontal network (C10)
Reward	-0.41**	0.01	0.32*	0.01
Punishment	-0.45**	-0.04	0.35*	-0.01
Neutral	-0.16	-0.16	-0.04	0.03

Experiment 2

Condition	Sensory motor network (C03)	Right FPN (C07)	DMN (C19)	Cerebellum network (C26)
Continuous reward	0.17	0.63**	-0.48**	-0.03
Partial reward	0.11	0.52**	-0.45*	-0.02
Neutral	0.11	0.49**	-0.07	-0.21
Control	0.05	0.42*	-0.19	-0.10

*p<0.05 uncorrected (two tailed)

**p<0.01uncorrected (two tailed)

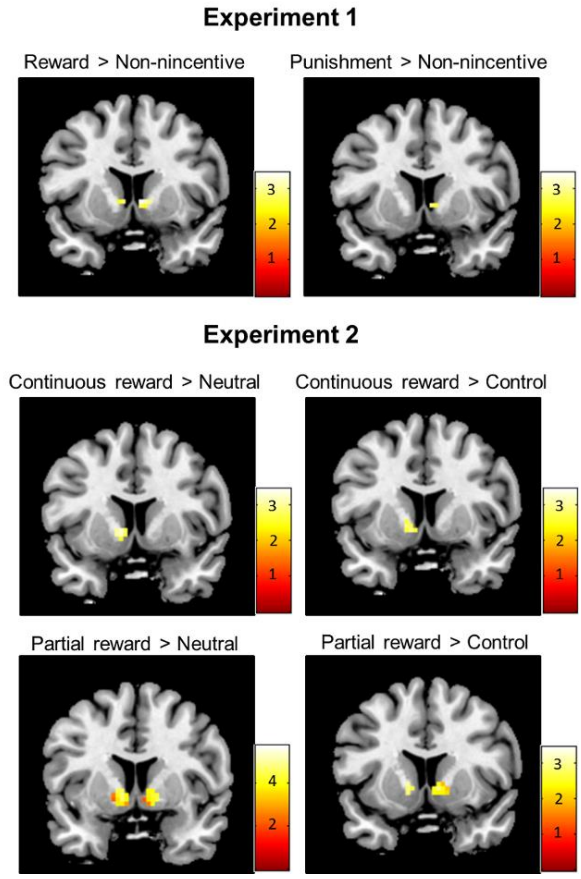


Figure 1 Activity in VS ROIs obtained from GLM analyses. Images are presented in neurological convention (left is left) and with a threshold at p <0.05 FWE corrected. The color bar represents the t values applicable to the image.

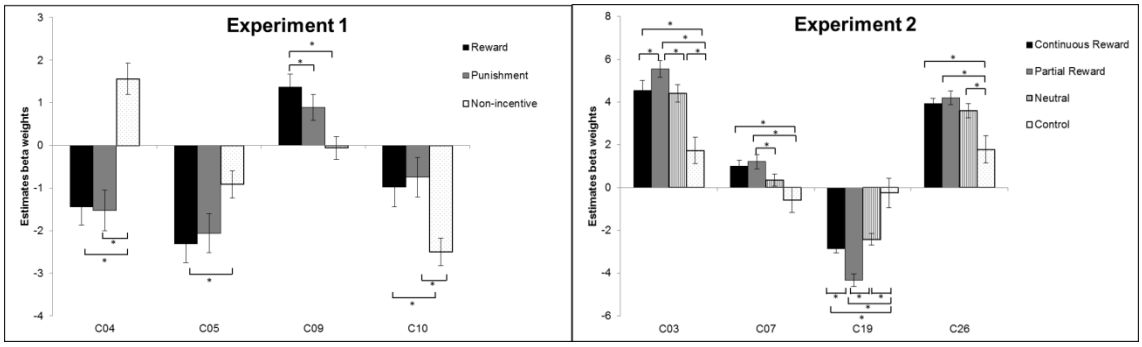


Figure 2 Mean and standard error bars for the anticipatory cues beta-weights in each IC of interest.

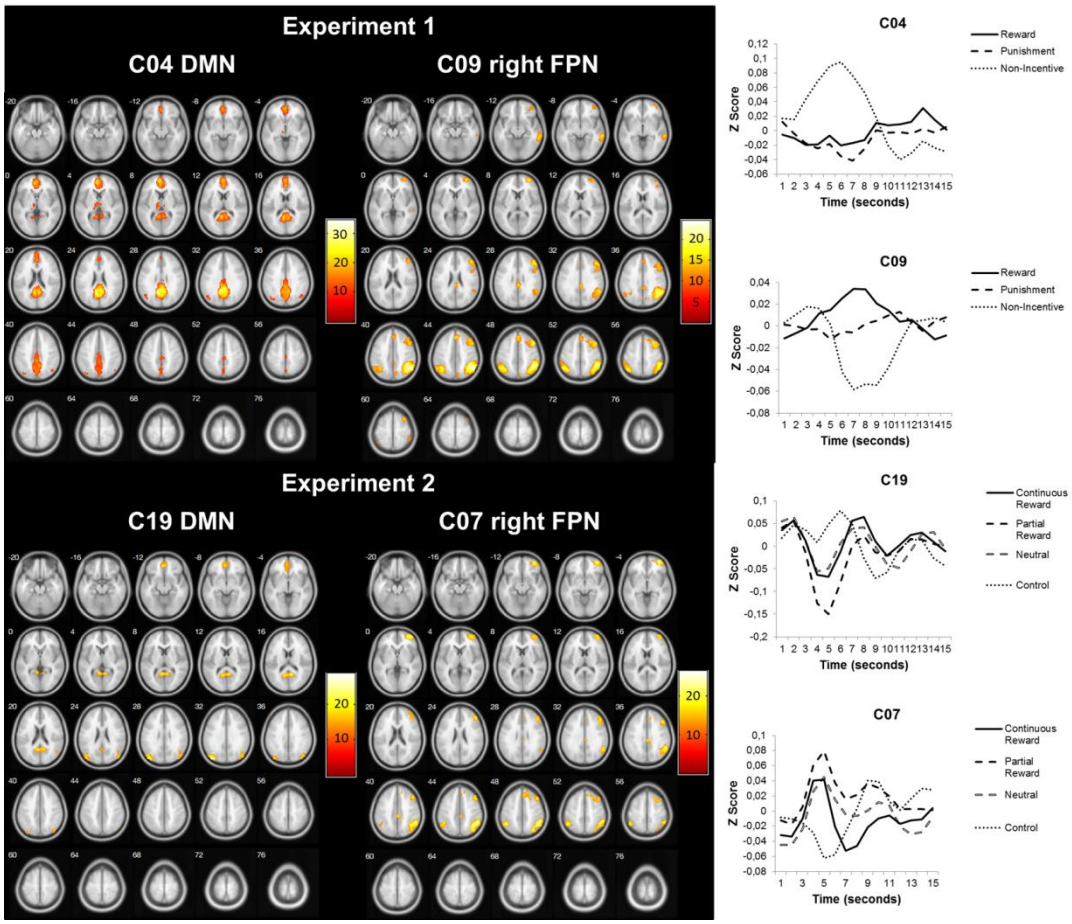
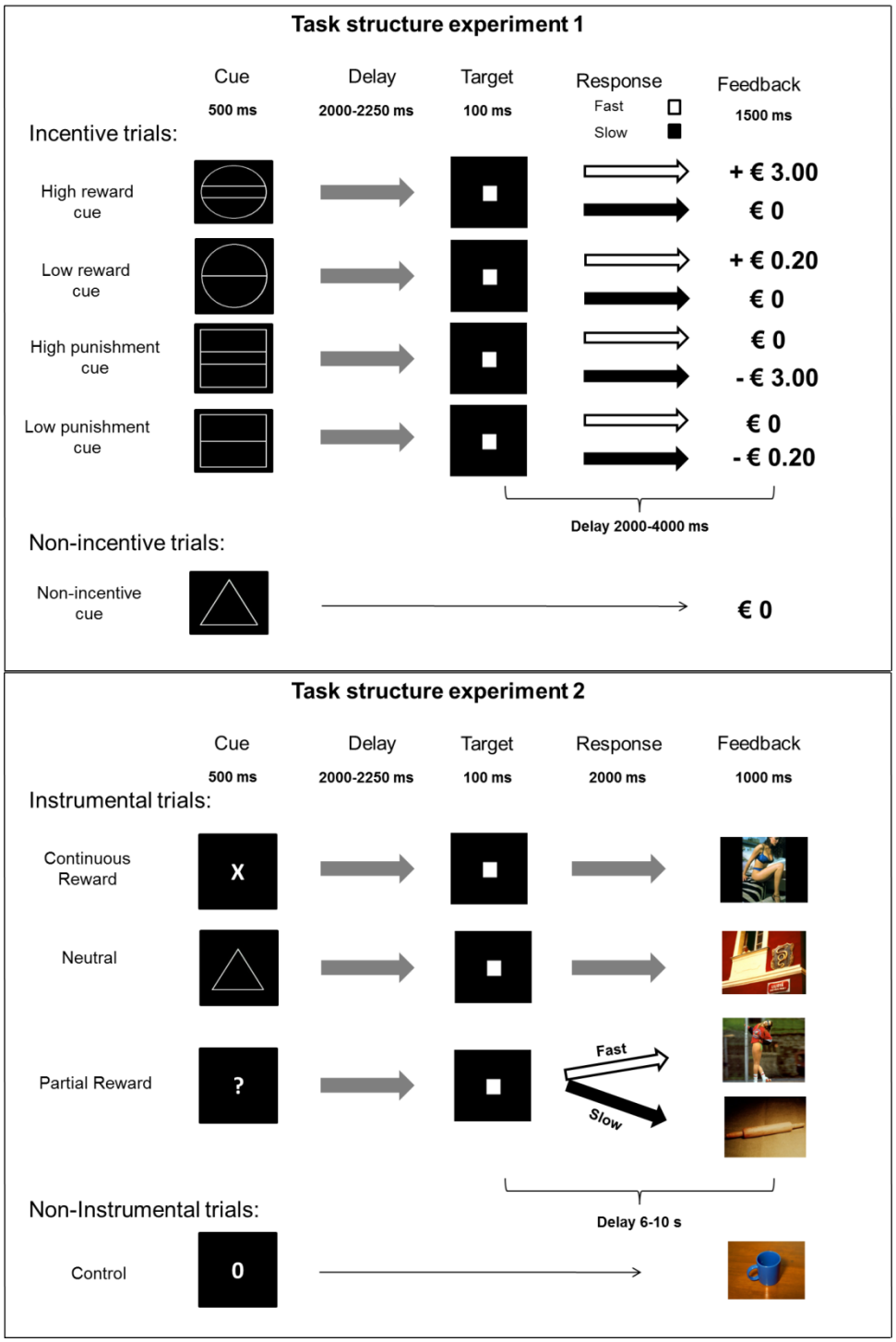


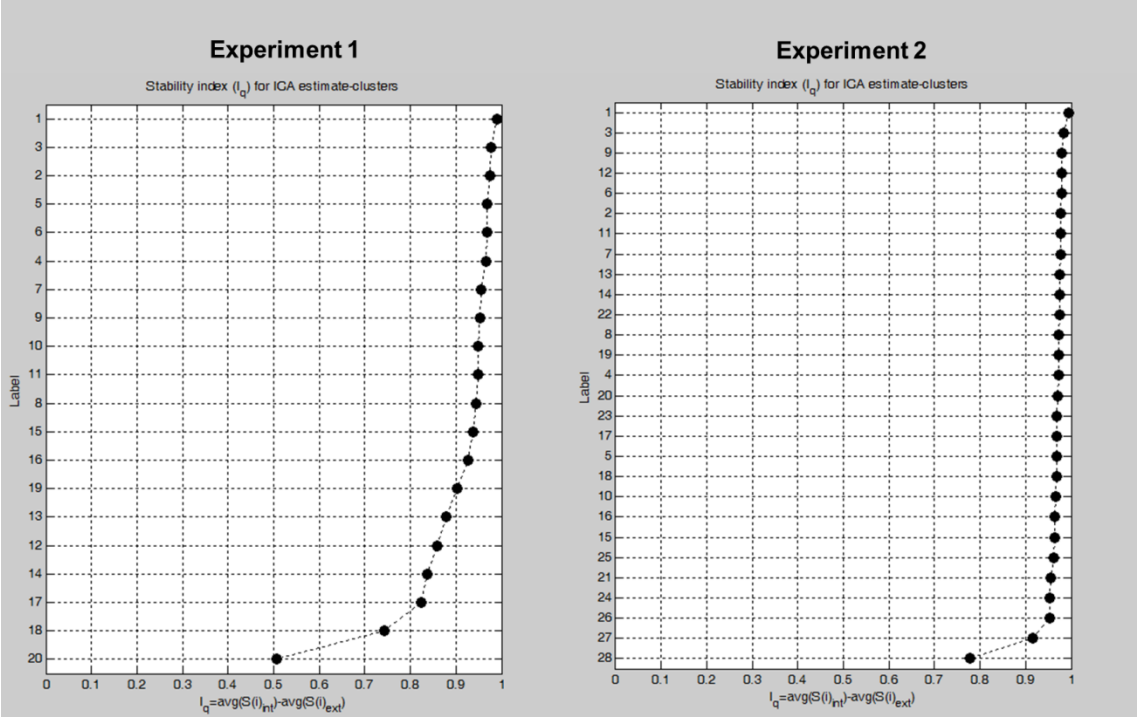
Figure 3 Networks showing task-related modulation in both experiments. Images are presented in neurological convention (left is left). The statistical threshold is $p<1x10^{-12}$ FDR-corrected with a minimum extent threshold of 30 contiguous voxels. The color bar represents the t values applicable to the image, while the numbers in the images correspond to the z MNI coordinates.

Supplementary Material

Supplementary figure 1: Tasks structure.



Supplementary Figure 2: Stability index measured with ICASSO.



This Figure depicts the stability index measured with ICASSO (20 iterations) for each component in Experiment 1 (left) and Experiment 2 (right). The components (y-axes) are ordered by their stability index (x-axes). All the components associated with reward sensitivity show a stability index above 0.95 (Experiment 1: C4=0.96, C9=0.95; Experiment 2: C7=0.97, C19=0.97).

Supplementary Table 1: Behavioral results

Experiment 1				
Behavioral	Reaction Time (ms)		Hits (%)	
	M	*SD*	*M*	*SD*
Reward	187.7	28.3	84.2	10.8
Punishment	190.1	30.5	80.3	10.2
Experiment 2				
Behavioral	Reaction Time (ms)		Hits (%)	
	M	*SD*	*M*	*SD*
CR	235.9	57.7	-	-
PR	217.8	58.2	59.7	7.4
N	245.6	65.7	-	-
Image ratings	Valence		Arousal	
	M	*SD*	*M*	*SD*
Appetitive set	6.8	1.1	6.4	1.3
Neutral set	4.7	1	3.4	1.2

M=mean; SD=standard deviation; ms=milliseconds; CR=Continuous reward; PR=Partial reward; N=Neutral

Supplementary Table 2: GLM whole brain results

Contrast	Region	Brodmann areas	Maximum peak coordinates (MNI)	k	Maximum peak z-score
Experiment 1					
Reward < non incentive					
	Postcentral left	6, 4, 7, 3, 40, 2, 5, 32, 24	-30 -34 64	4067	7.62
	Middle Frontal Gyrus right	10	33 53 25	116	4.85
	Middle frontal left	9	-33 44 37	40	4.07
Non incetive < reward					
	Middle Temporal Gyrus right	21	63 -7 -14	94	4.84
	Hippocampus Left	-	-24 -7 -26	42	4.29
	Middle Temporal Gyrus left	39	-57 -55 22	85	4.34
Punishment < non incentive					
	Caudate left	-	-3 5 13	290	5.35
	Middle Frontal Gyrus Right	10	33 53 25	40	4.44
	Postcentral left	6, 4, 3, 2, 5, 33, 40, 7	-30 -34 64	2644	7.35
Non incetive < punishment					
	Fusiform Gyrus right	20	42 -13 -32	63	4.05
	HippocampusLeft	-	-24 -7 -23	72	4.32
	Middle Temporal Gyrus right	21	63 -10 -14	31	4.65
	Precuneus right	7	15 -49 13	34	4.19
Experiment 2					
CR < N					
	Thalamus right	-	6 -19 4	66	4.07
	Calcarine left	18	-18 -100 -5	148	4.90
	Cuneus right	18	24 -97 -5	126	4.84
	Insula right	47	36 23 13	37	4.10
	Frontal Inferior operculum right	9	36 5 28	36	3.70
	Precuneus right	7	15 -61 37	68	4.44
N < CR					
	Fusiform Gyrus right	37	24 -37 -14	33	4.35
	Superior Occipital Gyrus right	19	21 -94 31	143	4.47
CR < C					
	Cerebelum right	-	24 -46 -29	60	4.30
	Cerebelum right	-	18 -61 -20	51	4.51
	Middle Occipital Gyrus right	18	30 -91 1	86	4.88
	Thalamus left	-	-6 -16 4	42	4.18
	Insula left	13	-33 11 7	73	4.87
	Precuneus right	40, 7	27 -52 43	160	4.75
	Cingulate Gyrus	6	-6 5 40	94	4.35
	Parietal Inferior left	40	-30 -49 43	275	4.36
C < CR					
	Middle Temporal Gyrus left	39	-45 -76 22	49	4.60
	Cuneus right	19	9 -88 40	40	3.59
PR < N					
	Cerebellum left	-	-6 -55 -26	107	4.47
	Middle Frontal Gyrus right	6, 32, 9, 24, 47, 8, 10, 13	33 41 28	2832	5.91
	Insula left	13	-42 14 4	232	5.17
	Cuneus left	18	-21 -100 -5	50	4.02
	Cuneus right	18	27 -100 -8	77	4.59
	Inferior Parietal right	40	57 -37 40	460	4.97
	Postcentral Gyrus left	40	-30 -46 61	337	4.35
	Middle Frontal Gyrus left	10	-33 41 25	34	3.78
	Precuneus right	7	12 -67 55	56	4.25
N < PR					
	Fusiform Gyrus right	37	21 -40 -14	126	4.64
	Cuneus right	19	21 -94 31	267	5.33

$p < 0.001$, uncorrected with a minimum cluster of 30 contiguous voxels

CR=Continuous reward; PR=Partial reward; N=Neutral; C = Control

Capítulo 3

Discusión General

Las investigaciones incluidas en esta tesis pretenden contribuir al desarrollo del modelo de Gray aportando datos empíricos sobre el funcionamiento de las áreas cerebrales asociadas al BAS. Para ello se estudió cómo se relacionan la respuesta y la conectividad funcional de las áreas cerebrales involucradas en el procesamiento de la recompensa con el rasgo de personalidad sensibilidad a la recompensa, durante diferentes paradigmas y utilizando diferentes reforzadores.

En la primera investigación presentada en esta tesis se estudió la relación entre las diferencias individuales en la sensibilidad a la recompensa y las variaciones en la actividad cerebral en respuesta a imágenes eróticas y a señales condicionadas a estas mediante un paradigma de condicionamiento clásico. Los resultados mostraron que los sujetos con alta sensibilidad a la recompensa mostraban mayor actividad en el OFC, la ínsula y el estriado ventral durante la presentación de imágenes eróticas. Estudios previos de fMRI han relacionado la actividad de estas mismas áreas con diferentes componentes del arousal sexual (Redouté y cols., 2000; Stoléru y cols., 1999, 2012). Por otro lado, otros estudios han mostrado que los sujetos con una alta reactividad del BAS se involucran en un mayor número de experiencias sexuales, tienen más curiosidad por temas relacionados con el sexo y muestran una mayor excitabilidad sexual (Aluja y Torrubia, 2004; Aluja y García, 2005; Carpenter y cols., 2008; Kantorowitz, 1978; Voigt y cols., 2009; Zuckerman y Litle, 1986). Todos estos hallazgos junto con los resultados de nuestra investigación sugieren que el arousal sexual está en parte localizado en áreas cerebrales asociadas al BAS, lo cual podría explicar la relación observada entre la sensibilidad a la recompensa y las diferencias individuales en la conducta sexual.

Los resultados de este estudio apoyan parcialmente el modelo de Gray al relacionar las diferencias individuales en la sensibilidad a la recompensa con la respuesta cerebral en zonas de recompensa ante estímulos sexuales, pero no ante las señales que los predicen. Un estudio previo de nuestro grupo de investigación ya había encontrado diferencias individuales en la actividad cerebral durante la presentación de

imágenes eróticas relacionadas con la sensibilidad a la recompensa (Barrós-Loscertales y cols., 2010). Concretamente, este estudio mostró que la sensibilidad a la recompensa se relacionaba con la actividad del córtex prefrontal medial, el córtex frontal inferior izquierdo y el córtex occipital durante la presentación de imágenes eróticas. Como se puede observar, estas áreas no coinciden con las encontradas en el primer estudio de esta tesis, lo cual puede estar explicado por diferencias en la tarea y el diseño experimental utilizado. En el estudio presentado en esta tesis se utilizó un diseño de eventos en el cual se estudia la respuesta cerebral ante estímulos presentados en un corto periodo de tiempo. Por otra parte, en el estudio de Barrós-Loscertales y cols. se utilizó un diseño de bloques donde las diferentes condiciones de la tarea se mantienen durante periodos largos de tiempo. La presentación de estímulos emocionales de carácter sexual durante periodos largos de tiempo puede producir que se observen respuestas relacionadas con procesos cognitivos como la atención sostenida o la inhibición del arousal sexual (Bühler y cols., 2008). Este efecto podría explicar los resultados del estudio de Barrós-Loscertales y cols. ya que como se discute en su artículo, la actividad en el córtex prefrontal medial puede asociarse con el post-procesado de la imágenes eróticas, mientras que la actividad en el córtex occipital y el córtex frontal inferior izquierdo pueden relacionarse con procesos atencionales y de control emocional, respectivamente (Barrós-Loscertales y cols., 2010). Por otro lado, el OFC, la ínsula y el estriado ventral son áreas relacionadas con el procesamiento motivacional/emocional de los estímulos. Por lo tanto, los resultados del primer estudio de esta tesis y los obtenidos por Barrós-Loscertales y cols. podrían ser complementarios ya que el primero mostraría que la sensibilidad a la recompensa se relaciona con el procesamiento motivacional/emocional de las imágenes eróticas, mientras que el segundo mostraría que la sensibilidad a la recompensa se relaciona con otros procesos asociados a la presentación prolongada de estas imágenes. Tomando en conjunto ambos estudios podemos concluir que existen diferencias individuales relacionadas con la sensibilidad a la recompensa en el procesamiento de las imágenes eróticas, del mismo modo que ocurre con otros reforzadores como el dinero (Carter y cols., 2009; Hahn y cols., 2009; Camara y cols., 2010b; Simon y cols., 2010; Cservenka y cols., 2012) o la comida (Beaver y cols., 2006).

El modelo de Gray propone que los sujetos con una alta sensibilidad a la recompensa tendrán un mayor aprendizaje pavloviano de estímulos apetitivos (Gray,

1975). Sin embargo, no hay muchas investigaciones que estudien el papel del BAS en este tipo de paradigma. En un estudio conductual que abordó esta cuestión se encontraron resultados tanto consistentes como inconsistentes con la teoría, aunque los autores concluyeron finalmente que sí parecía haber un efecto de condicionamiento clásico tal y como predecía el modelo de Gray (Corr y cols., 1995). En el primer estudio de esta tesis no se encontraron diferencias individuales relacionadas con la sensibilidad a la recompensa en la actividad cerebral producida por las señales condicionadas, por lo que este resultado estaría en contra el supuesto rol del BAS en el aprendizaje pavloviano. Sin embargo, hay que tener en cuenta diversos aspectos de este estudio a la hora de interpretar este resultado. Por un lado, aunque se ha observado que las imágenes eróticas activan zonas cerebrales implicadas en la conducta sexual (Stoléru y cols., 2012; Walter y cols., 2008; Bühler y cols., 2008) y producen efectos de condicionamiento (Klucken y cols., 2009), este tipo de estímulos no son en sí un reforzador primario, por lo que las asociaciones realizadas en este estudio pueden entenderse como un condicionamiento de segundo orden (Corr, 2001). Por otro lado, existen determinados aspectos del diseño experimental que por motivos de su adaptación al entorno de MRI difieren de los diseños comúnmente utilizados para estudiar el condicionamiento clásico, como por ejemplo el uso de intervalos inter-estimulares largos o la inclusión de respuestas no contingentes para el control atencional. Por lo tanto, aunque esta primera aproximación al estudio del condicionamiento clásico mediante fMRI en el contexto de la RST haya mostrado resultados negativos, se necesita un mayor número de investigaciones que clarifiquen el papel del BAS en este tipo de aprendizaje.

En la segunda investigación presentada en esta tesis se estudió cómo se relacionaba la sensibilidad a la recompensa con la actividad y la conectividad de las áreas cerebrales implicadas en el procesamiento de la recompensa durante un paradigma de aprendizaje instrumental con recompensas monetarias. Los resultados de este estudio replicaron los hallazgos de investigaciones anteriores (Carter y cols., 2009; Hahn y cols., 2009) mostrando que la sensibilidad a la recompensa se relaciona con la actividad del estriado ventral y el mesencéfalo durante la anticipación de recompensas monetarias. Además, en esta investigación se estudió la posibilidad de que las diferencias individuales en la actividad de estas áreas pudieran potenciarse por la interacción de efectos motores y motivacionales, ya que ambos procesos subyacen a las

estructuras del sistema dopaminérgico mesocorticolímbico (Guitart-Masip y cols., 2011). Sin embargo, se observó que al no eliminar el efecto motor del análisis la variabilidad se perdía, por lo este resultado sugiere que las diferencias individuales se dan por un efecto motivacional.

Los resultados de este segundo estudio mostraron diferencias individuales relacionadas con la sensibilidad a la recompensa tanto en la conectividad entre el mesencéfalo y el OFC medial como en la conectividad entre el estriado ventral y la amígdala. Concretamente se observó que los sujetos con una alta reactividad del BAS mostraban una menor conectividad entre mesencéfalo y el OFC durante la presentación de señales de alto incentivo así como una menor conectividad entre el estriado ventral y la amígdala durante la anticipación de recompensas. Se ha observado que lesiones tanto en OFC como en la amígdala producen conductas desinhibitorias e impulsividad (Bechara y cols., 1994, 1999; Mobini y cols., 2002; Winstanley y cols., 2004; De Martino y cols., 2010; Weller y cols., 2007), por lo que es posible que estas áreas sean importantes para la regulación de la respuesta motivacional producida por la actividad de las vías dopaminérgicas del mesencéfalo y del estriado ventral (Berridge y Robinson, 1998; Berridge, 2007). Tomando en conjunto los resultados de este estudio podemos plantear la hipótesis de que el patrón conductual observado en los sujetos con una alta reactividad del BAS está relacionado con una mayor respuesta motivacional producida por una menor regulación desde áreas de control emocional.

Por último, en la tercera investigación presentada en esta tesis se estudió cómo se relacionaba la sensibilidad a la recompensa con la modulación de las redes cerebrales de conectividad funcional mediante dos experimentos. En uno de ellos se utilizó un paradigma de aprendizaje instrumental usando recompensas monetarias como reforzador, mientras que en el otro se utilizó también un paradigma de aprendizaje instrumental, usando en este caso estímulos sexuales como recompensa. Los resultados de ambos estudios mostraron un patrón semejante. Por un lado, se observó que la DMN se modulaba negativamente durante la anticipación de recompensas mientras que por otro lado, la FPN derecha se modulaba positivamente. Estos resultados son similares a los observados en estudios previos donde se muestra una desactivación de la DMN (Raichle y cols., 2001; Greicius y cols., 2003) y una activación de la FPN (Corbetta y Shulman, 2002; Spreng y cols., 2010) durante la realización de tareas orientadas hacia estímulos externos. Se ha propuesto la hipótesis de que la DMN, la DAN y la FPN

forman un sistema atencional según el cual la DAN y la DMN se activarían en función de si la atención se centra hacia estímulos externos o internos respectivamente, mientras que la FPN se asociaría con ambas redes en función de las demandas atencionales de la tarea (Spreng, 2012; Spreng y cols., 2013). En relación a este modelo, los resultados de nuestro estudio mostrarían que en tareas donde la atención se centra ante un único estímulo la DAN no sería relevante, requiriéndose solamente la activación de la FPN. La activación de la FPN y no de la DAN en nuestro estudio apoya la propuesta de que la DAN se relaciona con la atención selectiva mientras que la FPN se relaciona con la detección de estímulos relevantes para la tarea (Corbetta y Shulman, 2002).

El principal resultado del tercer estudio en relación con la RST es que a través de los dos experimentos observamos diferencias individuales relacionadas con la sensibilidad a la recompensa tanto en la modulación negativa de la DMN como en la modulación positiva de la FPN. Específicamente observamos que cuanto mayor eran las puntuaciones en SR mayor era la modulación negativa de la DMN y positiva de la FPN respectivamente. Este resultado podría contribuir a la comprensión del mecanismo subyacente sugerido por modelos como el de Patterson y Newman (1993) según el cual los sujetos con una alta sensibilidad a la recompensa mostrarían una mayor focalización de la atención sobre los estímulos de recompensa disminuyendo así la probabilidad de cambiar la conducta dirigida hacia estos por la presencia de otros estímulos. Diversos estudios han mostrado que existe una asociación entre la dopamina y la actividad de las redes atencionales en el mismo sentido que se encuentran en este estudio en relación a la sensibilidad a la recompensa. Concretamente se ha visto que mayores niveles de dopamina, ya sean medidos mediante PET, inducidos por manipulación farmacológica o inferidos por la presencia de determinados genes, se asocian con una mayor activación de la FPN y con una mayor desactivación de la DMN (Tomasi y cols., 2011; Minzenberg y cols., 2011; Nagano-Saito y cols., 2009; Nagano-Saito y cols., 2008; Tan y cols., 2007; Williams-Gray y cols., 2007). Por lo tanto, teniendo en cuenta estas investigaciones podemos plantear la hipótesis de que las diferencias individuales observadas en la modulación de las redes atencionales estén relacionadas con la actividad de los circuitos dopaminérgicos relacionados con la recompensa.

En resumen, los resultados presentados en esta tesis muestran la existencia de diferencias individuales relacionadas con la sensibilidad a la recompensa tanto en la actividad como en la conectividad de áreas cerebrales implicadas en el procesamiento

de la recompensa, tal y como se predice a partir de los supuestos de la RST. En general los resultados presentados en esta tesis pueden ser relevantes para la comprensión de los mecanismos neurales que subyacen al sistema de recompensa y de cómo las diferencias individuales en el funcionamiento de este sistema se relacionan con los patrones de conducta asociados al rasgo de personalidad de sensibilidad a la recompensa.

3.1 Conclusiones

Las investigaciones presentadas en esta tesis nos permiten concluir que:

1- La presentación de imágenes eróticas en un diseño de eventos produce la activación de zonas pertenecientes al sistema de recompensa como el OFC, el estriado ventral, la amígdala, la ínsula, el córtex prefrontal medial o el mesencéfalo, mientras que la presentación de sus señales condicionadas produce actividad en el OFC lateral y la ínsula.

2- Las diferencias individuales en la actividad del OFC, la ínsula y el estriado ventral durante la presentación de imágenes eróticas se relacionan positivamente con las puntuaciones en SR.

3- Las diferencias individuales en la actividad del estriado ventral y el mesencéfalo durante la anticipación de recompensas monetarias se relacionan positivamente con las puntuaciones en SR.

4- Las puntuaciones en SR se relacionan negativamente con las diferencias individuales en la conectividad entre el OFC medial y el mesencéfalo durante la presentación de señales de alto incentivo, así como con las diferencias individuales en la conectividad entre la amígdala y el estriado ventral durante la anticipación de recompensas monetarias.

5- La anticipación tanto de recompensas monetarias como de estímulos sexuales modulan positivamente la actividad de la FPN derecha y negativamente la actividad de la DMN.

6- La modulación positiva de la FPN derecha durante la anticipación tanto de recompensas monetarias como de estímulos sexuales se relaciona positivamente con las puntuaciones de SR.

7- La modulación negativa de la DMN durante la anticipación tanto de recompensas monetarias como de estímulos sexuales se relaciona negativamente con las puntuaciones de SR.

Capítulo 4

Líneas futuras de investigación

Ya han pasado más de diez años desde la última revisión de la RST (Gray y McNaughton, 2000), a pesar de esto, el modelo de Gray sigue suponiendo hoy en día un excelente marco de referencia para el estudio biológico de la personalidad. Sin embargo, para que la RST siga contribuyendo en el futuro a la ciencia, debe continuar su desarrollo mediante la incorporación de nuevos datos empíricos que le permitan ser un modelo útil sobre el cual poder basar hipótesis que ayuden a explicar la conducta humana. En este sentido es necesario proponer nuevas líneas de investigación que den lugar a nuevos proyectos.

En primer lugar, se debe profundizar en el estudio de la conectividad cerebral. Hoy en día, la conectividad funcional es un campo nuevo y poco explorado, no solo en el ámbito de recompensa y la conducta motivada sino también en el resto de áreas de la neuropsicología. Los resultados obtenidos en los estudios de esta tesis presentan un punto de partida para el estudio de las diferencias individuales en la conectividad cerebral en relación a la sensibilidad a la recompensa, sin embargo todavía se requiere de mayor investigación empírica que ayude comprender de una forma más precisa cómo interaccionan las diferentes áreas cerebrales del sistema de recompensa y cómo las diferencias individuales en estas interacciones se relacionan con patrones de conducta a largo plazo.

En segundo lugar es importante atender a las interacciones cognitivo-motivacionales. El tercer estudio presentado en esta tesis muestra cómo las diferencias individuales en la sensibilidad a la recompensa no solo pueden encontrarse mediante el estudio de las áreas cerebrales "típicamente" asociadas al sistema de recompensa. De acuerdo con los modelos neuropsicológicos que destacan la relación entre los fenómenos emocionales y cognitivos (Damasio, 1994, 1996; Pessoa, 2008; Braver, 2012) las diferencias individuales en la sensibilidad a la recompensa deberían estar representadas en aquellos procesos cognitivos con los que el sistema de recompensa pudiera tener algún tipo de relación. Por lo tanto, futuras investigaciones deberán estudiar el papel que juegan las diferencias individuales en la sensibilidad a la

recompensa en las interacciones cognitivo-motivacionales atendiendo a diferentes procesos como atención, memoria o toma de decisiones.

En tercer lugar, otro campo que requiere mayor atención dentro del marco de la RST son las relaciones entre la genética, la actividad cerebral y la personalidad. Diversos estudios han encontrado diferencias en la actividad cerebral dentro del sistema de recompensa en función del polimorfismo de genes asociados con la dopamina (Camara y cols., 2010a; Yacubian y cols., 2007). Por otro lado se ha encontrado una relación de las diferentes variedades de estos genes y las puntuaciones de escalas asociadas al BAS como la NS o las escalas del BIS/BAS (Montag y cols., 2010; Lee y cols., 2007; Reuter y cols., 2006). Por lo tanto, futuras investigaciones podrían estudiar si el polimorfismo genético de genes relacionados con la dopamina tiene alguna influencia en las relaciones entre la actividad cerebral y el rasgo de personalidad sensibilidad a la recompensa.

Por último, otro aspecto importante es la aplicación de los conocimientos obtenidos desde el estudio de las diferencias individuales a la práctica clínica. El BAS se ha asociado con diferentes psicopatologías como el trastorno por déficit de atención con hiperactividad (Nigg, 2001; Mitchell y cols., 2006), la psicopatía (Hundt y cols., 2008; Kimbrel y cols., 2007; Ross y cols., 2007; 2009; Uzieblo y cols., 2007), la bulimia (Kane y cols., 2004; Beck y cols., 2009), el trastorno bipolar (Salavert y cols., 2007; Alloy y cols., 2006; Alloy y Abramson, 2010) el consumo de sustancias, (Franken y Muris, 2006; Franken y cols., 2006; Hundt y cols., 2008; Loxton y Dawe, 2006, 2007; Loxton y cols., 2008; O'Connor y cols., 2009; Pardo y cols., 2007; Simons y cols., 2008) o la depresión (Kimbrel y cols., 2007; Hundt y cols., 2007), por lo que estudiar si las diferencias individuales encontradas a nivel cerebral en población normal se encuentran también al comparar pacientes con estas patologías y sujetos control, podría contribuir al desarrollo de modelos neuropsicológicos que expliquen estas enfermedades. En este sentido los resultados obtenidos en esta tesis podrían utilizarse para el estudio de algunos trastornos. Por ejemplo, en relación con el primer estudio se ha visto que la dopamina es un neurotransmisor muy importante para la conducta sexual (Maclaran y Panay, 2011), por lo que es posible que las áreas dopaminérgicas motivacionales como el estriado ventral estén implicadas en alteraciones del deseo sexual ya sea por exceso o por defecto. Por otra parte, los modelos actuales sobre la adicción relacionan este trastorno con un patrón de actividad y conectividad similar al

observado en el segundo estudio, que consiste en una hiperactividad de las estructuras dopaminérgicas subcorticales junto con un menor control inhibitorio de las áreas frontales sobre estas (Volkow y cols., 2011). Por último, aproximaciones metodológicas como la utilizada en el tercer estudio podrían contribuir al estudio del trastorno por déficit de atención con hiperactividad ya que se han encontrado alteraciones en las redes atencionales en pacientes con esta patología (Castellanos y Proal, 2012).

El grupo de investigación en el que encuentro está llevando a cabo diferentes proyectos que pretenden abordar algunos de los temas que se acaban de mencionar. Por ejemplo, uno de estos estudios se ha centrado en investigar cómo se relaciona la sensibilidad a la recompensa con la respuesta funcional y la conectividad cerebral ante la recepción de recompensas monetarias y además, cómo se relaciona este rasgo de personalidad con el cambio conductual en función de la contingencia. Por otro lado, se está estudiando el papel que juega la sensibilidad a la recompensa en tareas donde se dan interacciones cognitivo-motivacionales, como tareas de "switch" o de "stop signal" con contingencias de recompensa. Además, se están aplicando estas tareas y las presentadas en esta tesis al estudio de la adicción a la cocaína, comparado muestras de sujetos controles con pacientes adictos y relacionando los resultados obtenidos con patrones de consumo. Por último, se están recogiendo muestras genéticas que nos permitirán en un futuro analizar cómo se relaciona la variabilidad genética con la actividad cerebral y la personalidad. Todas estas líneas de investigación nos permitirán en el futuro ampliar nuestros conocimientos no solo sobre la personalidad, sino también sobre el funcionamiento normal y patológico del sistema de recompensa, con lo que esperamos de esta forma aportar nuestra contribución al desarrollo científico en general y a de la neurociencia en particular.

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*** Las referencias específicas de los estudios presentados en esta tesis están incluidas en su sección correspondiente.**