UNIVERSITAT DE BARCELONA

Correlatos neurobiológicos de las alteraciones de regulación emocional en los trastornos de salud mental

Víctor de la Peña Arteaga

Correlatos neurobiológicos de las alteraciones de regulación emocional en los trastornos de salud mental

Memoria de tesis doctoral presentada por

Víctor de la Peña Arteaga

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Dirigida por:

Carles Soriano Mas[1,2,3]

Tutor: **José Manuel Menchón Magriñá**[1,2,4]

1. *Grupo de Psiquiatría y Salud Mental, Programa de Neurociencias, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat.*
2. *Centro de Investigación Biomédica en Red - Salud Mental (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid.*
3. *Departamento de Psicología Social y Psicología Cuantitativa, Facultad de Psicología, Universitat de Barcelona - UB, Barcelona.*
4. *Departamento de Ciencias Clínicas, Facultad de Medicina, Universitat de Barcelona - UB, L'Hospitalet de Llobregat.*

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El doctor **Carles Soriano Mas** como director de tesis,

CERTIFICA:

Que **Víctor de la Peña Arteaga** ha realizado la Tesis Doctoral que lleva por título *"**Correlatos neurobiológicos de las alteraciones de regulación emocional en los trastornos de salud mental"*** y que está en condiciones para ser defendida para la obtención del Grado de Doctor por la Universidad de Barcelona frente al correspondiente tribunal.

Para que así conste se firma la siguiente certificación,

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"Rather than being a luxury,
emotions are a very intelligent way
of driving an organism toward
certain outcomes."

António Damásio

Agradecimientos

Un doctorado, un pasaporte, cuatro pisos, casi cinco años y un montón de amigos después se termina esta gratificante etapa de mi vida. La suma de experiencias y los conocimientos adquiridos la convierten en una de las mejores hasta el momento. Es imposible agradecer a cada persona que ha formado parte de este proceso, pero intentaré resumirlo de la mejor manera.

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Índice

Abreviaturas

ACI	Análisis de componentes independientes
AMPreS	Área motora pre-suplementaria
CCA	Corteza cingulada anterior
COF	Corteza orbitofrontal
CPF	Corteza prefrontal
CPFdl	Corteza prefrontal dorsolateral
CPFdm	Corteza prefrontal dorsomedial
CPFvl	Corteza prefrontal ventrolateral
CPFvm	Corteza prefrontal ventromedial
CPP	Corteza parietal posterior
EMT	Estimulación magnética transcraneal
IRM	Imágenes por resonancia magnética
IRMf	Imágenes por resonancia magnética funcional
RFPI	Red frontoparietal izquierda
TAG	Trastorno de ansiedad generalizada
TAS	Trastorno de ansiedad social
TCC	Terapia cognitivo conductual
TDAH	Trastorno por déficit de atención e hiperactividad
TLP	Trastorno límite de la personalidad
TOC	Trastorno obsesivo compulsivo
TPOC	Trastorno de la personalidad obsesivo-compulsiva

Enumeración de los artículos

Tesis en formato de compendio de artículos.

La tesis consta de un objetivo general y 6 objetivos específicos, dentro de 3 artículos publicados.

A continuación, se citan los artículos, junto al orden en el cual serán referidos a lo largo de este documento:

Artículo 1: ***De la Peña-Arteaga V**, Berruga-Sánchez M, Steward T, Martínez-Zalacaín I, Goldberg X, Wainsztein A, Abulafia C, Cardoner N, Castro MN, Villarreal M, Menchón JM, Guinjoan SM, Soriano-Mas C. An fMRI study of cognitive reappraisal in major depressive disorder and borderline personality disorder. Eur Psychiatry. 2021; 64(1): e56.*
doi: 10.1192/j.eurpsy.2021.2231.
Factor de impacto: 7,156
Cuartil: C1
Área de conocimiento: Psiquiatría

Artículo 2: ***De la Peña-Arteaga V**, Morgado P, Couto B, Ferreira S, Castro I, Sousa N, Soriano-Mas C, Picó-Pérez M. An fMRI study of frontal networks in obsessive-compulsive disorder during cognitive reappraisal. Aceptado para su publicación en European Psychiatry: septiembre 2022.*
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Artículo 3: ***De la Peña-Arteaga V**, Fernández-Rodríguez M, Silva Moreira P, Abreu T, Portugal-Nunes C, Soriano-Mas C, Picó-Pérez M, Sousa N, Ferreira S, Morgado P. An fMRI study of cognitive regulation of reward processing in generalized anxiety disorder (GAD). Psychiatry Res Neuroimaging. 2022; 324: 111493.*
doi: 10.1016/j.pscychresns.2022.111493.
Factor de impacto: 2,493
Cuartil: C3
Área de conocimiento: Neuroimagen

Resumen

Introducción

El procesamiento de las emociones es esencial para la experiencia humana, y una correcta regulación cognitiva de este proceso es crucial para el bienestar y la salud mental. De ahí surge la necesidad de estudiar la relación entre la psicopatología y las alteraciones de regulación emocional. Esta necesidad ha tenido un interés creciente para parte de la comunidad científica en los últimos años, principalmente para tratar de entender en profundidad este proceso tan complejo, específicamente desde un punto de vista neurobiológico.

Hipótesis

Se presume que las dificultades, es decir la falta o falla, en los procesos de regulación emocional están presentes en una diversidad de patologías mentales y son parte integral de su fisiopatología.

Objetivo

El objetivo del presente trabajo es investigar los correlatos neurobiológicos de las alteraciones de regulación emocional, a través de técnicas de neuroimagen funcional, en distintas poblaciones clínicas.

Métodos

En distintos centros hospitalarios, se estudiaron mediante técnicas de neuroimagen algunos aspectos de la regulación emocional en las siguientes patologías mentales: trastorno depresivo mayor (TDM), trastorno límite de la personalidad (TLP), trastorno obsesivo compulsivo (TOC) y trastorno de ansiedad generalizada (TAG). En todos los casos las poblaciones clínicas se compararon con una muestra de controles sanos. Dichas técnicas se desarrollaron a través de dos paradigmas diseñados para el análisis de imágenes por resonancia magnética funcional (IRMf). Posteriormente, se estudiaron activaciones en todo el cerebro, conectividad funcional entre áreas de interés y el resto del cerebro y, finalmente, redes cerebrales mediante un análisis de componentes independientes (ACI).

Resultados principales

En todas las muestras de sujetos con alguna de las patologías estudiadas se encontraron alteraciones estadísticamente significativas en el proceso de la regulación emocional. En estos sujetos, se hallaron cambios en la activación de áreas regulatorias clave, dificultades en la conectividad funcional entre áreas regulatorias y otras áreas de relevancia específica y, también, alteraciones en redes neurales completas. Algunos de estos hallazgos tuvieron correlación con aspectos psicométricos específicos para cada patología.

Conclusiones

A través de los estudios mostrados se puede concluir que el déficit observado en el proceso de regulación de las emociones es un común denominador en las patologías de salud mental. Sin embargo, se pueden describir diferencias específicas en las deficiencias observadas entre los distintos trastornos estudiados. Dicho hallazgo mejora la caracterización funcional de estos trastornos. El estudio de estos correlatos neurobiológicos es de importancia, ya que permite generar estrategias terapéuticas inspiradas biológicamente orientadas a mejorar el proceso de la regulación emocional en pacientes con distintas patologías mentales.

Palabras clave

- Actividad cerebral
- Emoción
- Análisis experimental de la conducta
- Procesos mentales

1. Introducción

1.1 Marco conceptual de la regulación emocional

La emoción se entiende como un conjunto de estados complejos de interacción psicológica y fisiológica que, en mayor o menor grado, clasifican y otorgan valor a los eventos de la vida diaria. Dicha valoración se refiere a la facilidad que posee un organismo para sentir si los eventos en su entorno son más o menos deseables. La emoción es esencial para la experiencia humana, es un componente constante en las relaciones entre individuos y una fuerza motivadora de la conducta. La emoción ejerce un poderoso efecto sobre la razón y la cognición (1). Sin duda se trata de un proceso complejo y multifacético que involucra diferentes componentes evaluativos, que asignan el significado y la relevancia a eventos reales o imaginarios (2).

La regulación emocional ocurre cuando las valoraciones implicadas en este proceso se modulan conscientemente para regular las emociones, como durante la reevaluación de emociones negativas a términos neutrales o positivos. La capacidad de llevar a cabo este proceso de manera óptima, es un factor importante para determinar el bienestar o la presencia de psicopatología (3,4). El estudio de la regulación emocional es, por tanto, de mucho interés para las disciplinas de la salud mental. Una parte trascendental de lo anterior se refiere a la investigación de los correlatos neurobiológicos de la emoción humana y sus procesos asociados, que llevan años estudiándose desde la perspectiva de la neurociencia y la neuroimagen (1,5).

La emoción y su regulación no son procesos aislados. Al contrario, se encuentran altamente interrelacionados con otros procesos y estrategias mentales como la cognición y la conducta. El procesamiento emocional se ha visto relacionado con la percepción, la atención, la memoria, el aprendizaje y el proceso de toma de decisiones, entre otros (1). Resulta muy interesante la relación existente entre este último y la regulación emocional. Según la hipótesis del marcador somático, las emociones ejercen un efecto muy importante sobre el proceso de toma de decisiones y, de tal forma, cobran una importancia adicional sobre la vida y conducta humanas (6). Un importante

argumento que respalda lo anterior, es la evidencia de que ambos procesos tienen sustratos neurobiológicos en común (7).

Adicionalmente, dentro del proceso de toma de decisiones se pueden encontrar otros subprocesos como el control cognitivo de la recompensa, definido como el control cognitivo del deseo de estímulos hedónicos, que también comparte los mismos fundamentos neurobiológicos con la regulación emocional. Lo anterior es de particular interés, ya que demuestra la versatilidad de ciertas regiones cerebrales y la estrecha interrelación que existe entre cognición, emoción y conducta (8).

Los argumentos anteriores confirman que la emoción y su regulación intervienen en una gran diversidad de procesos conductuales, lo que las hace indispensables para la correcta honestasteis de la salud mental.

1.1.1 Modelo teórico de la regulación emocional

Para organizar de manera más efectiva toda la información existente con respecto a la regulación emocional, se ha popularizado la teoría/modelo del proceso de la regulación emocional (9). En esta teoría, se distinguen cinco familias de estrategias (ver **Tabla 1**) que se pueden utilizar durante el proceso de generación de emociones que, a su vez, contiene cuatro fases. Estas estrategias se incorporan dentro de un proceso regulatorio de otras cuatro etapas. Las interacciones se explican a continuación: en primer lugar, se identifica la necesidad de regular las emociones, para posteriormente seleccionar la estrategia adecuada y, finalmente, ser implementada. Durante todo este proceso existe un monitoreo del éxito de la estrategia seleccionada. Dicho proceso es cíclico y se repite hasta obtener los resultados conductuales apropiados para cada situación de la vida en particular (10,11). En la **Figura 1** se ejemplifican, mediante un esquema, las interacciones entre fases, estrategias y etapas del proceso emocional.

Cada una de las etapas del proceso de regulación emocional pasa por un sistema de valoración que consiste en tres elementos básicos: percepción, valoración y acción. La percepción se refiere a una representación, en la memoria de trabajo, del estado emocional actual y el deseo de regular el mismo. Posteriormente hay una ponderación (valoración) entre el estado emocional actual, el estado regulado deseado y su discrepancia; a la emoción se le asigna un valor positivo o negativo. Finalmente, se

genera una respuesta a la gran discrepancia emocional llamada la acción, que implica un cambio cognitivo a la valoración emocional (12,13).

La reevaluación cognitiva es la estrategia del modelo en la que más se han enfocado los estudios de investigación. Es una estrategia de modulación que permite reformular los estímulos o escenarios que inducen emociones en términos positivos, lo que conduce a una disminución de la actividad simpática y el afecto negativo, a un mejor funcionamiento interpersonal y a un aumento del bienestar tanto físico como emocional. Se considera que la reevaluación cognitiva es una estrategia generalmente adaptativa y efectiva (11,13–15). Los estudios presentados en esta tesis doctoral se basan principalmente en esta estrategia regulatoria.

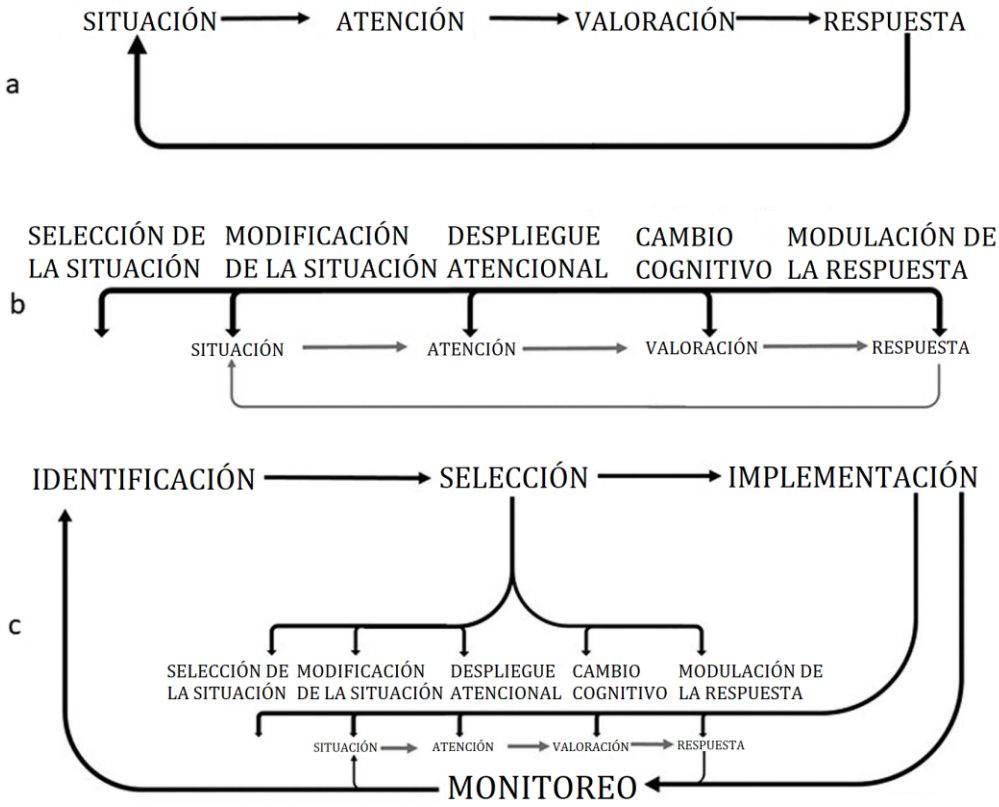

Figura 1. Modelo del proceso de la regulación emocional: a) fases del proceso de generación de emociones, b) las cinco familias de estrategias que se utilizan para regular emociones, organizadas según las fases de generación, c) descripción de las cuatro etapas del proceso de regulación y su interacción con las estrategias de regulación y las fases de generación de emociones. Las flechas hacen referencia a ciclos repetitivos. Adaptado de McRae & Gross, 2020 (11).

Familia de estrategias	**Estrategia**	**Definición**
Selección de la situación	Evitación	Disminución del compromiso inicial con situaciones emocionales.
Modificación de la situación	Petición directa	Tomar medidas para influir en una situación una vez dentro de la misma.
Despliegue atencional	Distracción	Dirigir la atención (interna o externa) lejos de la situación emocional, hacia aspectos no emocionales de la situación o situaciones no emocionales.
	Rumiación	Dirigir recurrentemente la atención hacia las causas y consecuencias de la emoción.
Cambio cognitivo	Reevaluación cognitiva	Reinterpretar o reevaluar la situación emocional y/o las metas.
	Aceptación	Acoger emociones con juicio no valorativo.
Modulación de la respuesta	Supresión expresiva	Prevenir la expresión externa del estado emocional interno.
	Intervención fisiológica	Alterar directamente la fisiología asociada a las emociones usando acciones o sustancias.

Tabla 1. Familias de estrategias de regulación emocional: Se muestran los tipos de estrategias y sus definiciones. Adaptado de McRae & Gross, 2020 (11).

1.2 Neurobiología de la regulación emocional

Desde una perspectiva neurobiológica, la regulación emocional depende de numerosas regiones, circuitos, redes e interacciones cerebrales. En estudios relativamente recientes se ha observado que los fundamentos biológicos principalmente parten de los circuitos que vinculan diferentes regiones de la corteza, en particular áreas

de la corteza prefrontal (CPF), con estructuras subcorticales, como la amígdala, relacionadas con la respuesta emocional (15–17).

Distintas áreas de la corteza prefrontal se han visto implicadas en el procesamiento de las emociones. A continuación, se enlistan las principales áreas asociadas y sus posibles funciones:

- Corteza prefrontal ventromedial (CPFvm): Evidencia reciente respalda a esta área cerebral como la vía de modulación principal de las áreas subcorticales (18). Se trata de una región integradora de valoraciones afectivas entre la corteza, el estriado ventral y la amígdala (19). De manera interesante, para el procesamiento de amenazas, también juega un papel integrador esencial para la adaptación del comportamiento tanto en contextos positivos como negativos (20). Se considera parte de un sistema neuronal que asigna el valor de las elecciones conductuales, durante el proceso de toma de decisiones (19). De esta manera, es fundamental para la representación de la recompensa y la toma de decisiones basadas en valores (21). Finalmente, existe evidencia de que la CPFvm está implicada en la generación de emociones negativas como la ansiedad y el miedo (21), por lo que sin duda se trata de un área de altísimo interés científico en el estudio de la psicopatología.

- Corteza prefrontal ventrolateral (CPFvl): Esta región desempeña un importante papel en la selección e inhibición de respuestas (22), particularmente en la inhibición de evaluaciones emocionales (23). Por lo anterior, se podría considerar un área de ejecución de la conducta dentro del sistema prefrontal. Esta región está implicada en la selección de respuestas apropiadas para las metas conductuales y en la recuperación de información de la memoria semántica, que luego puede usarse para desarrollar nuevas valoraciones (4,24).

- Corteza prefrontal dorsolateral (CPFdl): Esta región se asocia a distintas funciones ejecutivas (25). En el contexto de la regulación emocional parece estar más relacionada con la manipulación activa de la información para evaluar a los estímulos emocionales y es responsable de mantener los objetivos de elección conductual (19). Adicionalmente, se trata de una estructura importante para la

regulación cognitiva, ya que actúa en la modulación de la CPFvm durante este proceso (26–28).

- Corteza prefrontal dorsomedial (CPFdm) y área motora pre-suplementaria (AMPreS): La CPFdm tiene una participación en la atribución de estados mentales emocionales propios y ajenos (19), mientras que la AMPreS (junto con las regiones dorsomediales y frontoparietales) calcula los ajustes necesarios para lograr un comportamiento regulador de las emociones (18).

- Corteza orbitofrontal (COF): Con respecto a su función durante la regulación emocional, esta área se caracteriza por regular, particularmente a la baja, a las áreas subcorticales (18). Esta región se encuentra anatómicamente yuxtapuesta a la CPFvm (29) y ambas parecen estar asociadas con el proceso de toma de decisiones, que como se menciona anteriormente, es un proceso íntimamente relacionado con la regulación de las emociones. Ambas áreas, por lo tanto, integran información de los dos procesos (7).

Además de las estructuras corticales ya mencionadas, existen otros sistemas cerebrales cuya función es importante para el proceso de regulación emocional. En las siguientes tres estructuras se generan las experiencias emocionales a nivel primario:

- Amígdala: Está implicada en la percepción y codificación de estímulos relevantes para metas afectivas, ya sean recompensas o castigos. Le otorga un valor a los estímulos, ya que es sensible en detectar y desencadenar estímulos de excitación y de amenaza (19).

- Cuerpo estriado ventral: Está involucrado en el aprendizaje de las señales responsables de la predicción de recompensas y reforzamientos. Se podría decir que codifica el valor de recompensa de los estímulos (19).

- Ínsula: En esta estructura se generan representaciones o mapas de los estados internos corporales asociados con las emociones y, en particular, se asocia con la experiencia afectiva negativa (19).

Durante la reevaluación cognitiva, al parecer, se reclutan áreas prefrontales y parietales, particularmente la corteza parietal posterior (CPP) de la red de atención

dorsal, que están asociadas a procesos de control ejecutivo y que, a su vez, se utilizan durante el procesamiento emocional y del afecto. La corteza parietal resulta de especial interés en otras estrategias de regulación como el distanciamiento (30). Las interacciones entre estas áreas se pueden visualizar de mejor manera en la **Figura 2**.

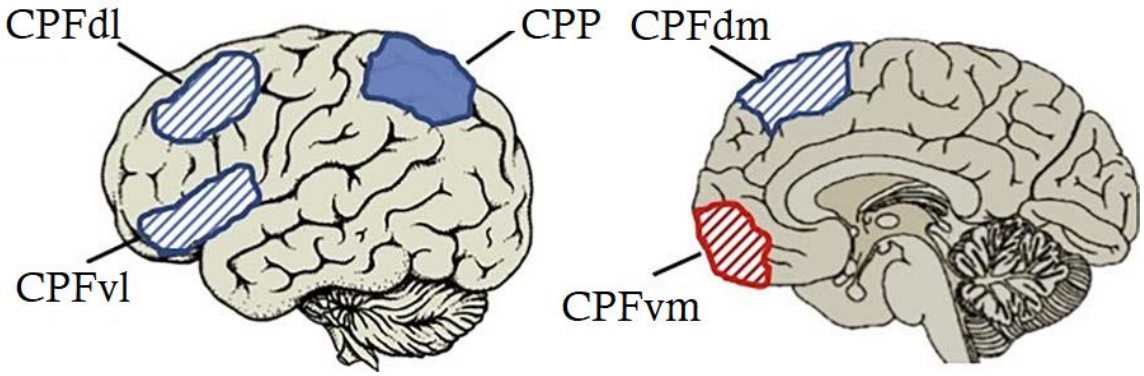

Figura 2. Regiones corticales asociadas con la reevaluación cognitiva: En azul se observan las áreas con capacidad de reinterpretación o reevaluación, mientras que en rojo (CPFvm) se indica la región que es capaz de reducir el afecto negativo al responder a estímulos aversivos. Las regiones con líneas representan áreas con rasgos de tendencia a la autorregulación. Adaptado de Silvers & Guassi Moreira, 2019 (30). *Abreviaturas: CPFdl, corteza prefrontal dorsolateral; CPFdm, corteza prefrontal dorsomedial; CPFvl, corteza prefrontal ventrolateral; CPFvm, corteza prefrontal ventromedial; CPP, corteza parietal posterior.*

1.2.1 Integración neurofisiológica de la cognición y la emoción

Como se ha mencionado anteriormente, diversas estructuras cerebrales se han estudiado de forma independiente en el contexto de la regulación emocional. Sin embargo, muchas de las interacciones entre las áreas corticales y las subcorticales permanecen en investigación constante para esclarecer dichas relaciones. Entender la forma en la que se integran estas regiones, así como sus circuitos y redes asociadas, es indispensable para profundizar en el entendimiento del procesamiento emocional. Una investigación reciente ha mostrado evidencia sobre la conectividad funcional entre las principales regiones corticales, particularmente prefrontales, y subcorticales en este proceso. Las regiones corticales implicadas son la CPFdl, la CPFvm, la CPFvl y el AMPreS. Sus hallazgos respaldan la función de la CPFvm como el nodo central a través

del cual estas regiones modulan directamente la actividad de la amígdala y la actividad límbica (18). Ver **Figura 3**.

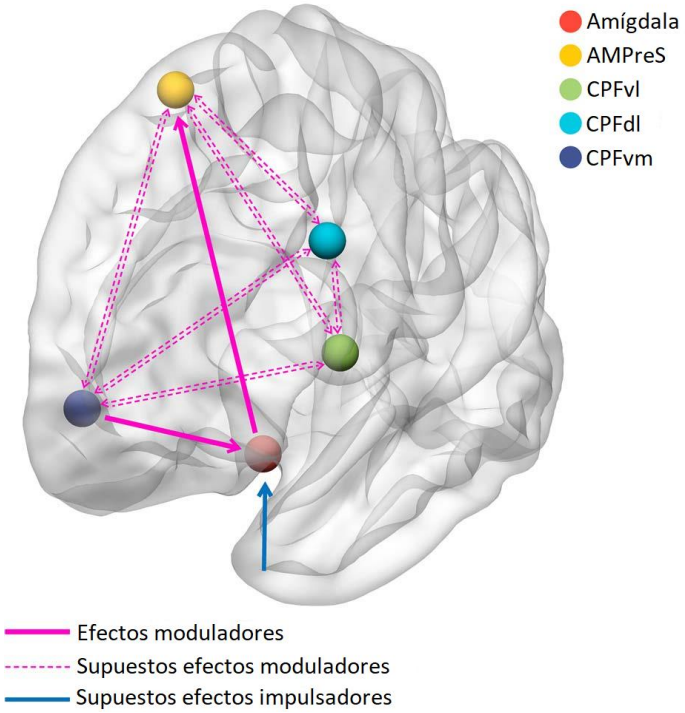

Figura 3. Modelo de interacción propuesto entre distintas áreas de la corteza y la amígdala: la línea azul marca la vía de entrada por la amígdala y las líneas rosas (no discontinuas) las vías principales de modulación con sus direcciones. Adaptada de Steward *et al.*, 2021 (18). *Abreviaturas: AMPreS, área motora pre-suplementaria; CPFdl, corteza prefrontal dorsolateral; CPFvl, corteza prefrontal ventrolateral; CPFvm, corteza prefrontal ventromedial.*

Además del efecto que ejerce directamente la corteza frontal sobre diversas estructuras subcorticales, también se han propuesto modelos que involucran interacciones entre la corteza frontal y otras cortezas como la parietal y la temporal. Más específicamente, investigaciones recientes han intentado explorar los efectos reguladores de las redes de control cognitivo frontoparietal, en las regiones de procesamiento emocional subcorticales, describiendo alteraciones en los principales trastornos neuropsiquiátricos (17,31).

El estudio de las redes cerebrales proporciona una descripción más completa de las alteraciones que implican la acción coordinada de diferentes regiones del cerebro, más allá de la mera descripción de disfunciones de activación específicas de regiones concretas. Existen trabajos recientes sobre regulación emocional con este enfoque (32).

Es interesante mencionar que estas redes de acción neural coordinada pueden compartir e integrar funciones como la toma de decisiones. Un ejemplo de esto es el control cognitivo de la recompensa, definido como el control cognitivo del deseo de estímulos placenteros. Este tipo de control y la regulación de los estados emocionales, como por ejemplo a través de la reevaluación cognitiva, son ejemplos de toma de decisiones basadas en modelos. Ambas estrategias parecen compartir fundamentos neurobiológicos comunes, lo que implica la activación de diversas regiones prefrontales mediales y laterales (8).

1.3 Fisiopatología de la regulación emocional

Se cree que la disfunción de las regiones, circuitos y redes anteriormente mencionados genera dificultades en la regulación de las emociones, lo que seguidamente puede constituir una parte importante de la conducta desadaptativa y, por ende, de la psicopatología (33). Existe un modelo teórico propuesto con respecto al mecanismo de la desregulación emocional. Éste se relaciona con las etapas de regulación emocional propuestas en el modelo del proceso de regulación emocional. Las dificultades en cada uno de los elementos básicos del sistema de valoración de cada etapa podrían estar representando diferentes tipos de fallas en el sistema. Es interesante este modelo, porque no se enfoca exclusivamente en el elemento básico de acción de la etapa de implementación (12). Algunas propuestas teóricas de posibles mecanismos en los que la regulación falla en distintos trastornos mentales se pueden consultar en la **Tabla 2**.

Desde el punto de vista neurobiológico, existe evidencia que respalda que las alteraciones en los circuitos entre regiones prefrontales y regiones subcorticales están asociadas con la desregulación emocional (18,34). Más adelante se expondrán a detalle otros fundamentos neurobiológicos específicos asociados con los trastornos mentales.

Etapas de regulación	**Elemento regulatorio**	**Aspectos clínicos y descripción**
Identificación	Percepción	**Ataques de pánico:** representación excesiva de signos sutiles de estados emocionales actuales. **Sesgo de desvinculación en la ansiedad:** representación excesiva de información amenazante por tiempo prolongado **Alexitimia:** representación disminuida de los estados emocionales
	Valoración	**Evitación experiencial:** sobrevaloración de los costes de los estados emocionales **Conducta de apego en el trastorno de personalidad dependiente:** infravaloración de los beneficios de la regulación intrínseca
	Acción	**Indefensión aprendida en la depresión:** falla en transformar una meta regulatoria en acción
Selección	Percepción	**Escape del yo en atracones y comportamiento suicida:** representación excesiva de opciones regulatorias desadaptativas.
	Valoración	**Autolesiones no suicidas y abuso de sustancias:** valoración positiva de categorías regulatorias desadaptativas.
	Acción	**Cambio cognitivo en el autismo:** deterioro de la habilidad para activar categorías regulatorias adaptativas.
Implementación	Percepción	**Tácticas a largo plazo en el TDAH:** representación disminuida de las tácticas regulatorias adaptativas.
	Valoración	**Preocupación en TAG:** valorando positivamente tácticas regulatorias desadaptativas.
	Acción	**Distracción positiva en la depresión mayor:** habilidad deteriorada de activar tácticas regulatorias adaptativas.
Monitoreo	Cesamiento	**Rumiación en la depresión:** detener demasiado tarde una táctica regulatoria desadaptativa. **Baja autoeficacia regulatoria en TAS:** detener demasiado pronto una táctica regulatoria adaptativa.
	Cambio	**Depresión, ansiedad y TPOC:** cambiar desde una táctica implementada ineficiente demasiado tarde. **Estados maníacos en el trastorno bipolar:** cambiar entre categorías regulatorias demasiado pronto.

Tabla 2. Alteraciones teóricas en etapas del proceso de regulación emocional: Se muestran ejemplos de aspectos clínicos asociados con las alteraciones. Nótese que un mismo trastorno puede tener alteraciones en diferentes aspectos clínicos. Adaptado de Sheppes, 2015 (12).
Abreviaturas: TAG, trastorno de ansiedad generalizada; TAS, trastorno de ansiedad social; TDAH, trastorno por déficit de atención e hiperactividad; TPOC, trastorno de la personalidad obsesivo-compulsiva.

1.4 Alteraciones de la regulación emocional en los trastornos de salud mental

La falta de equilibro en el procesamiento emocional se asocia con la infelicidad humana y es un común denominador de toda la gama de patologías mentales (1). Sin embargo, diferentes patologías pueden tener distintos tipos de problemas en la regulación emocional. Entender los mecanismos existentes de desregulación es de suma importancia para un mejor entendimiento de la fisiopatología de estas enfermedades mentales (12). Enfocándose en la reevaluación cognitiva, varios estudios han demostrado que los pacientes con trastornos psiquiátricos tienen dificultades para utilizar esta estrategia (35). Independientemente, un metaanálisis observó que, en general, las estrategias de regulación inadaptadas están mucho más relacionadas con las personas que presentan psicopatología, concluyendo que es peor la presencia de estrategias inadaptadas, que la ausencia de estrategias adaptativas (36). Por ende, los problemas de la regulación emocional se podrían clasificar como un proceso transdiagnóstico en las enfermedades mentales, donde el uso de la reevaluación cognitiva es reducido y el uso de estrategias inadaptadas como la rumiación negativa está aumentado, por poner un ejemplo (37). Por lo anteriormente expuesto, el estudio de la emoción y su regulación es elemental para la salud mental y sus disciplinas asociadas.

1.4.1 La regulación emocional en los trastornos del estado de ánimo

Las alteraciones en la regulación de las emociones son fundamentales en los trastornos del estado de ánimo. Esta tesis se enfocará principalmente en el trastorno depresivo mayor (TDM), una patología prevalente que se caracteriza por un abatimiento del ánimo con consecuencias psicológicas, biológicas y sociales (38). Los pacientes con TDM, poseen un perfil clínico distintivo y presentan alteraciones cognitivas

relacionadas con los elementos básicos del procesamiento emocional (39). Estas alteraciones se han asociado con una disminución del reclutamiento prefrontal durante el control voluntario explícito de las emociones (40).

En un metaanálisis reciente que explora las alteraciones de regulación emocional en poblaciones con trastornos del estado de ánimo y ansiedad, se localizó un patrón disfuncional de activación cerebral durante la reevaluación cognitiva (17). Se describe que los pacientes reclutaron en menor grado las redes frontoparietales en comparación con los controles sanos. Por otra parte, los participantes sanos presentaron mayor activación en áreas asociadas con la experiencia emocional como la ínsula, el cerebelo, el giro precentral y el giro occipital inferior, así como en áreas cuya activación podría ser consecuencia de mecanismos compensadores como el giro supramarginal y el lóbulo parietal superior. Por último, en este estudio también se identificó que la activación en la CPFvl y el giro temporal superior estaban asociados a estrategias como la reinterpretación emocional, mientras que la corteza medial frontal y parietal se asociaron con las estrategias de distanciamiento. De manera interesante, otro metaanálisis anterior encontró que los problemas de regulación emocional parecen estar más relacionados con los trastornos afectivos y de ansiedad que con otros trastornos externalizantes como los trastornos de la conducta alimentaria o los trastornos por uso de sustancias (36).

1.4.2 La regulación emocional en los trastornos de la ansiedad y trastorno obsesivo compulsivo

Dentro de los trastornos de ansiedad, el trastorno de ansiedad generalizada (TAG) es uno de los trastornos psiquiátricos más comunes, con hasta un 20% de adultos afectados cada año. Se caracteriza por una tendencia excesiva y persistente de preocuparse por los acontecimientos cotidianos de la vida, convirtiéndose en un estado permanente de preocupación (41).

Como se ha mencionado anteriormente, los pacientes con trastornos de ansiedad presentan dificultades en la regulación emocional y tienen un aumento del uso de estrategias inadaptadas, con un perfil neurobiológico específico y similar al de los trastornos afectivos (17,36). Sin embargo, dentro de los fundamentos neurobiológicos de la ansiedad, el procesamiento de amenazas posee una importancia clave para otros

aspectos reguladores. En este proceso, la CPFvm parece jugar un papel muy relevante como centro integrador esencial para la adaptación del comportamiento tanto en contextos positivos como negativos. Por lo anterior, se podría asumir que la CPFvm podría estar actuando como un conector entre la ansiedad, el procesamiento de recompensas, la regulación emocional y los sistemas de amenazas (20) y, de hecho, algunos estudios sugieren que las personas con niveles más altos de ansiedad rasgo o trastorno de ansiedad generalizada (TAG) parecen tener alteraciones en esta área del cerebro (20,42). Otra área cortical que se ha visto vinculada en esta patología sería la corteza cingulada anterior (CCA), cuya hipofunción en este trastorno se ha investigado en diversas revisiones anteriores (43,44).

Las estructuras cerebrales subcorticales relevantes para la ansiedad, la amenaza y el miedo son la amígdala, otras áreas límbicas y el tálamo (43). La amígdala representa una estructura de particular importancia en la neurobiología de la ansiedad, ya que se considera un centro crítico para los circuitos funcionales entre la CPF, particularmente la CPFvm, y otras estructuras subcorticales como el tálamo y el área ventral tegmental. Al parecer, la conectividad funcional de la amígdala se encuentra alterada en pacientes con TAG (44,45). Además de la amígdala, el tálamo tiene un papel en el control del comportamiento y el procesamiento emocional. Su papel como estructura reguladora en las conductas asociadas a la ansiedad parece ser muy notorio y se ha demostrado, en varios estudios, que activaciones en el núcleo paraventricular del tálamo generan ansiedad y estados aversivos (46,47).

Otra patología de relevancia para este trabajo es el trastorno obsesivo compulsivo (TOC) caracterizado por pensamientos y conductas intrusivos, con una tendencia a la severidad y discapacidad (48). Está demostrado que los pacientes con TOC se caracterizan por presentar dificultades en la regulación cognitiva y emocional (49–51). Algunos estudios sugieren que estos pacientes podrían tener dificultades para activar redes frontoparietales cuando se requiere control cognitivo (52), mostrando menor reclutamiento de la CPFdl, así como una conectividad fronto-límbica disminuida (53,54). Aunque el patrón de alteraciones observadas en pacientes con TOC puede diferir de lo que se observa en los trastornos de ansiedad en condiciones específicas, como en la regulación implícita de las emociones durante la respuesta activa, donde la conectividad prefronto-límbica puede aumentarse (55), tales diferencias son más

difíciles de apreciar, por ejemplo, durante la anticipación de estímulos emocionales inespecíficos al trastorno (56). Recientemente se han resumido las alteraciones neurobiológicas, principalmente en la conectividad frontoparietal, en la regulación cognitiva de las emociones en pacientes con TOC en el estudio de Ferreira *et al.*, 2020 (57).

1.4.3 La regulación emocional en los trastornos de la personalidad

Dentro de estos trastornos resulta de especial interés el enfoque en el trastorno límite de la personalidad (TPL) cuya principal característica es la inestabilidad emocional que puede conducir al paciente incluso al suicidio (58). Las personas con este trastorno muestran fluctuaciones importantes en el funcionamiento del sistema subcortical, lo que se traduce en falta de habituación e hipersensibilidad a las señales de amenaza (59,60). Se ha sugerido previamente que lo anterior es la base de varias de las manifestaciones clínicas de este trastorno, incluidas la inestabilidad afectiva, las relaciones intensas y tumultuosas, la dificultad para controlar la ira, la impulsividad, las tendencias suicidas y la autolesión deliberada (que se cree que tiene una función reguladora de las emociones) (61,62). Una revisión reciente resume las alteraciones neurobiológicas de este trastorno como una desregulación del control voluntario de las emociones, que junto con otros mecanismos, lleva a los pacientes a la disfunción interpersonal y al deterioro de la interocepción emocional (63).

1.4.4 Impacto clínico de la regulación emocional y ventajas de su abordaje terapéutico

La investigación acerca de los fundamentos biológicos y conductuales de la regulación emocional es de gran importancia por su capacidad traslacional al estudio de las ciencias clínicas. Por ejemplo, se ha estudiado que parte de la respuesta y los cambios neurales observados en la terapia cognitivo conductual (TCC), están mediados por cambios regulatorios de las respuestas emocionales (64). A mayor desarrollo científico sobre la regulación de las emociones, más aplicaciones en salud mental se podrían hallar. Sin duda, esta justificación le brinda una novedosa perspectiva a este campo de estudio de la conducta humana. La implementación de estos conocimientos sobre la terapéutica psicológica y psiquiátrica se podría llevar a cabo de distintas maneras y explorando métodos que regulen la actividad cerebral y la actividad de redes

neuronales. Entre estos métodos se encuentra la estimulación cerebral profunda y otros enfoques de neuromodulación, la neurorretroalimentación basada en IRMf, así como enfoques psicoterapéuticos alternativos, como terapias atencionales y conductuales, basados en la investigación sobre las emociones y su regulación (12,65–67).

2. Hipótesis

La hipótesis de esta tesis se centra en que la regulación emocional es un proceso complejo, altamente interrelacionado con otros procesos conductuales, que influye de manera contundente sobre la salud mental de los individuos. Se presume que las dificultades en este proceso, es decir la falta o falla de regulación, están presentes en una diversidad de patologías mentales.

Se anticipa encontrar diferencias a nivel neurofisiológico, estudiadas a través de distintas metodologías de análisis de neuroimagen, entre los individuos sanos y los pacientes con enfermedad mental, específicamente en trastornos del estado de ánimo y aquéllos de la personalidad. Adicionalmente, se anticipa que entre los distintos trastornos mentales haya diferencias en los patrones neurales de procesamiento emocional, demostrando que este proceso pueda estar alterado de diversas maneras según la patología estudiada. Finalmente, también se presume que estos cambios neurobiológicos estarán correlacionados con mediciones clínicas y conductuales.

De manera muy específica, se anticipa encontrar alteraciones en la regulación emocional de las poblaciones estudiadas a distintos niveles. Inicialmente, a nivel de actividad fisiológica en regiones concretas del cerebro, pero también a nivel de redes cerebrales y la conectividad funcional entre las mismas, principalmente involucrando a la corteza cerebral y a áreas subcorticales como las regiones límbicas.

3. Objetivos

Objetivo general

Investigar los correlatos neurobiológicos de las alteraciones de la regulación emocional, a través de técnicas de neuroimagen funcional en distintas poblaciones.

Objetivos específicos

1. Evaluar las diferencias de actividad neuronal, así como de conectividad interregional, que existen entre sujetos sanos y pacientes con trastornos psiquiátricos (TDM y TLP), durante el proceso de regulación emocional.

2. Evaluar las diferencias de actividad neuronal, así como de conectividad interregional, que existen entre grupos de pacientes con distintos trastornos psiquiátricos (TDM contra TLP), durante el proceso de regulación emocional.

3. Caracterizar las redes cerebrales implicadas y sus respectivas alteraciones durante el proceso de regulación emocional.

4. Explorar las diferencias en las distintas redes funcionales, que describen patrones coordinados de actividad cerebral entre las regiones de la corteza frontal y otras áreas del cerebro, entre individuos sanos y una población clínica (TOC).

5. Explorar las diferencias en el control cognitivo de las recompensas, proceso asociado con el procesamiento emocional, entre individuos sanos y pacientes con un trastorno de salud mental (TAG).

6. Examinar las activaciones cerebrales, así como la conectividad funcional entre regiones específicas de procesamiento cognitivo-emocional con otras áreas del cerebro, entre sujetos sanos y pacientes (TAG).

4. Material, métodos y resultados

4.1 Artículo publicado 1

Objetivo/s:

En el artículo se contrastan los objetivos específicos 1 y 2 de la tesis.

1. Evaluar las diferencias de actividad neuronal, así como de conectividad interregional, que existen entre sujetos sanos y pacientes con trastornos psiquiátricos (TDM y TLP), durante el proceso de regulación emocional.

2. Evaluar las diferencias de actividad neuronal, así como de conectividad interregional, que existen entre grupos de pacientes con distintos trastornos psiquiátricos (TDM contra TLP), durante el proceso de regulación emocional.

Título del artículo:

An fMRI study of cognitive reappraisal in major depressive disorder and borderline personality disorder

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Resumen:

Antecedentes: Un común denominador de los fenotipos clínicos del trastorno límite de la personalidad (TLP) y el trastorno depresivo mayor (TDM) es el deterioro de la regulación emocional. Aunque estas dos condiciones se han estudiado ampliamente por separado, no está claro si sus deficiencias en la regulación emocional se basan en alteraciones neurobiológicas compartidas o distintas.

Métodos: Contrastamos los correlatos neurales de la regulación de las emociones negativas en una muestra de pacientes adultos con TLP (n = 19), pacientes con TDM (n = 20) y controles sanos (n = 19). La regulación emocional se evaluó utilizando un paradigma, previamente establecido, de reevaluación cognitiva de imágenes de resonancia magnética funcional. Evaluamos tanto las activaciones relacionadas con la tarea como las modulaciones de la conectividad interregional.

Resultados: En comparación con los controles sanos, los pacientes con TLP y TDM mostraron una activación disminuida homóloga en la corteza prefrontal ventrolateral derecha (CPFvl) durante la reevaluación cognitiva. Además, el grupo TDM presentó activaciones disminuidas en otras áreas prefrontales (cortezas dorsolateral izquierda y orbitofrontal bilateral), mientras que el grupo TLP se caracterizó por un patrón más extenso de alteración en la conectividad entre la CPFvl y las cortezas de la corriente ventral visual. durante la reevaluación.

Conclusiones: Este estudio identificó, por primera vez, un contribuyente neurobiológico compartido a los déficits de regulación emocional en TDM y TLP caracterizado por una actividad reducida de la CPFvl, aunque también observamos alteraciones específicas de cada trastorno. En TDM, los resultados sugieren un déficit primario en la fuerza de las activaciones prefrontales, mientras que en TLP se define mejor por las interrupciones de conectividad entre las regiones temporales de procesamiento de emociones y la CPFvl. Estos hallazgos corroboran, en términos neurobiológicos, los diferentes perfiles de alteraciones de la regulación emocional observados en estos trastornos.

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An fMRI study of cognitive reappraisal in major depressive disorder and borderline personality disorder

Víctor De la Peña-Arteaga[1,2], Mercedes Berruga-Sánchez[1], Trevor Steward[3], Ignacio Martínez-Zalacaín[1,2], Ximena Goldberg[4,5], Agustina Wainsztein[6,7,8,9], Carolina Abulafia[6,7], Narcís Cardoner[4,5,10], Mariana N. Castro[6,7,11], Mirta Villarreal[6,7,8], José M. Menchón[1,2,5], Salvador M. Guinjoan[6,12,13] and Carles Soriano-Mas[1,5,14*]

[1]Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), L'Hospitalet de Llobregat, Spain; [2]Department of Clinical Sciences, School of Medicine, Universitat de Barcelona (UB), L'Hospitalet de Llobregat, Spain; [3]Melbourne School of Psychological Sciences, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Victoria, Australia; [4]Mental Health Department, Unitat de Neurociència Traslacional, Parc Tauli University Hospital, Institut d'Investigació i Innovació Sanitària Parc Taulí (I3PT), Sabadell, Spain; [5]Network Center for Biomedical Research on Mental Health (CIBERSAM), Carlos III Health Institute (ISCIII), Madrid, Spain; [6]Consejo Nacional de Investigación Científica y Tecnológica (CONICET), Buenos Aires, Argentina; [7]Grupo de Investigación en Neurociencias Aplicadas a las Alteraciones de la Conducta (Grupo INAAC), Instituto de Neurociencias FLENI-CONICET, Buenos Aires, Argentina; [8]Departamento de Salud Mental, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina; [9]Instituto de Investigaciones Biomédicas, Facultad de Medicina, Universidad Católica Argentina, Buenos Aires, Argentina; [10]Department of Psychiatry and Forensic Medicine, School of Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain; [11]Department of Physiology and Department of Mental Health, Medicine School, University of Buenos Aires, Buenos Aires, Argentina; [12]Neurofisiología I, Facultad de Psicología, Universidad de Buenos Aires, Buenos Aires, Argentina; [13]Laureate Institute for Brain Research, Tulsa, Oklahoma, USA and [14]Department of Psychobiology and Methodology in Health Sciences, Universitat Autònoma de Barcelona, Bellaterra, Spain

Abstract

Background. One common denominator to the clinical phenotypes of borderline personality disorder (BPD) and major depressive disorder (MDD) is emotion regulation impairment. Although these two conditions have been extensively studied separately, it remains unclear whether their emotion regulation impairments are underpinned by shared or distinct neurobiological alterations.

Methods. We contrasted the neural correlates of negative emotion regulation across an adult sample of BPD patients ($n = 19$), MDD patients ($n = 20$), and healthy controls (HCs; $n = 19$). Emotion regulation was assessed using an established functional magnetic resonance imaging cognitive reappraisal paradigm. We assessed both task-related activations and modulations of interregional connectivity.

Results. When compared to HCs, patients with BPD and MDD displayed homologous decreased activation in the right ventrolateral prefrontal cortex (vlPFC) during cognitive reappraisal. In addition, the MDD group presented decreased activations in other prefrontal areas (i.e., left dorsolateral and bilateral orbitofrontal cortices), while the BPD group was characterized by a more extended pattern of alteration in the connectivity between the vlPFC and cortices of the visual ventral stream during reappraisal.

Conclusions. This study identified, for the first time, a shared neurobiological contributor to emotion regulation deficits in MDD and BPD characterized by decreased vlPFC activity, although we also observed disorder-specific alterations. In MDD, results suggest a primary deficit in the strength of prefrontal activations, while BPD is better defined by connectivity disruptions between the vlPFC and temporal emotion processing regions. These findings substantiate, in neurobiological terms, the different profiles of emotion regulation alterations observed in these disorders.

Research Article

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Address for correspondence:
*Carles Soriano-Mas
E-mail: csoriano@idibell.cat

Víctor De la Peña-Arteaga and Mercedes Berruga-Sánchez shared first authorship.

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Introduction

Emotion is a complex and multifaceted process that involves different evaluative components, including appraisal processes evaluating the meaning and relevance of actual or imagined events [1]. These appraisals may be consciously modulated to regulate emotions, such as during the reappraisal of negative emotions to neutral or positive terms. The ability to carry out this process

is an important factor for determining well-being and the presence of psychopathology [2,3]. One way to modulate such emotion appraisals is via cognitive reappraisal, an antecedent-focused cognitive control strategy that allows reframing emotion-inducing stimuli or scenarios in positive terms, which leads to decreased sympathetic activity and negative affect, better interpersonal functioning, and increased physical and psychological well-being [4].

In neurobiological terms, emotion regulation is characteristically implemented by the circuits linking different regions of the prefrontal cortex (PFC) with subcortical structures, such as the amygdala, related to emotional responding [5–7]. More specifically, regulatory input to subcortical structures is assumed to be mediated by activity in the dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortices (OFCs), with recent evidence supporting that disturbances in these circuits are associated with emotion regulation behavior [8,9]. Moreover, other PFC regions, such as the ventrolateral prefrontal cortex (vlPFC), have been shown to be implicated in selecting goal-appropriate responses and retrieving information from semantic memory, which can then be used to develop new appraisals [3,10].

Several studies have demonstrated that patients with psychiatric disorders have difficulties in using cognitive reappraisal [11], although the mechanisms of alteration may differ across conditions. Alterations in emotion regulation are central to both major depressive disorder (MDD) and borderline personality disorder (BPD); however, they may be underpinned by different pathological mechanisms. First, individuals with BPD show fluctuations in subcortical system functioning, which results in failure to habituate and hypersensitivity to threat cues [12,13]. Importantly, this has been suggested to underlie several of the pathological manifestations of this disorder, including affective instability, intense and tumultuous relationships, difficulty controlling anger, impulsivity, suicidal tendencies, and deliberate self-harm (thought to serve an emotion-regulating function) [14,15]. Patients with MDD, in contrast, present a distinctive clinical profile, and portray cognitive impairments related to basic elements of emotional processing [16]. These have been linked to decreased prefrontal recruitment during the explicit voluntary control of emotions [17]. Nevertheless, such putatively distinct neurobiological mechanisms of altered emotion regulation have not been directly compared. This comparison may be, however, of great interest not only to further understand the different mechanisms of psychological maladjustment in BPD and MDD, but also to develop disorder-specific approaches to improve emotion regulation capacity.

The present study is, to the best of our knowledge, the first to investigate the neurobiological underpinnings of disrupted emotion regulation in MDD and BPD using a cognitive reappraisal paradigm and the concurrent evaluation of regional brain activity with functional magnetic resonance imaging (fMRI). Moreover, given the central role of interregional connectivity alterations in neurobiological models of emotion regulation, we decided to not only assess task-related activations, but also task-modulations of interregional connectivity. We hypothesized that both MDD and BPD groups would differ from health controls (HCs) in measures of brain activity and connectivity during cognitive reappraisal. More specifically, we hypothesized that patients with BPD would show increased subcortical activations related to inefficient regulatory input from prefrontal areas, while patients with MDD would present reduced recruitment of prefrontal areas during cognitive reappraisal. Finally, we also anticipated that these neurobiological alterations would be correlated to core clinical measurements in both patient groups.

Methods

Sample

The study included three groups of participants: patients with BPD ($n = 19$), patients with MDD ($n = 20$), and HCs ($n = 19$), which were recruited at *Fundación Lucha contra las Enfermedades Neurológicas en la Infancia* (FLENI Foundation) in Buenos Aires, Argentina. The groups consisted of 19 males and 39 females, ranging from 21 to 63 years of age (mean = 41.26; SD = 13.11). Patients were consecutively recruited when attending the Department of Psychiatry at FLENI Foundation if they met DSM-5 diagnostic criteria for BPD or MDD. All participants were evaluated via a clinical interview in order to confirm their DSM-5 diagnosis (patients) or the absence of any present or past diagnosis of a psychiatric disorder (HCs). Table 1 summarizes the sociodemographic and clinical features of the study participants. As can be seen in this table, mean Hamilton Depression Rating Scale (HDRS) scores indicated that most patients with MDD were in remission at the time of study. Specifically, 65% of patients with MDD, and also 68% of patients with BPD, scored below the 7-point cutoff value for depression, and, therefore, results of this study should be considered as related to stable depression features more than to transient alterations related to fluctuations in mood state. Further information regarding the sample and exclusion criteria can be found in the Supplementary Material.

The present study was carried out in accordance with the latest version of the Declaration of Helsinki. The Ethics Committee in clinical research of FLENI Foundation approved the study. Signed informed consent was obtained from all participants.

Psychometric assessment

All participants completed the validated Spanish versions of the Cognitive Emotion Regulation Questionnaire (CERQ) and the Difficulties in Emotion Regulation Scale (DERS) to evaluate emotion dysregulation. Likewise, all subjects also completed the HDRS and the Hamilton Anxiety Rating Scale (HARS) to assess severity of depression and anxiety symptoms, respectively [18–24].

MRI acquisition

This information can be found in the Supplementary Material.

fMRI task, cognitive reappraisal paradigm

We used a well-validated paradigm to evaluate brain activations during emotion regulation with fMRI using negative images and in-scanner behavioral ratings [6,25]. Picture stimuli were obtained from the International Affective Picture System [26]. The task consisted of three conditions ("observe," "maintain," and "regulate") presented in an ABC design with four blocks per condition (i.e., a total of 12 blocks). An additional description of the task is detailed in the Supplementary Material. Like in most previous research, participants were instructed to use distancing or reinterpretation as reappraisal strategies. These are two antecedent-focused strategies acting before emotional responses have been completely generated. The former refers to rationalizing the content of a situation by adopting the perspective of an uninvolved observer, while the latter refers to changing the meaning of stimuli in order to view the outcome of a situation in a more positive light [27]. All blocks consisted of two consecutive images (each image was presented on screen for 10 s, with no interstimulus interval),

Table 1. Demographic and clinical characteristics of the study group.

Sample	HCs ($n = 19$)	BPD ($n = 19$)	MDD ($n = 20$)
Gender	*N*(%)	*N*(%)	*N*(%)
Female	15(79)	10(53)	14(70)
	(Mean ± SD)	(Mean ± SD)	(Mean ± SD)
Age	35.84 ± 10.38	37.68 ± 11.25^	49.80 ± 13.24°^
Psychometric evaluations			
CERQ reappraisal[a]	10.37 ± 4.57	8.32 ± 4.74	8.00 ± 3.65
CERQ rumination[a]	8.89 ± 3.16	9.74 ± 2.60	9.65 ± 3.11
DERS total	58.21 ± 15.10	96.95 ± 33.05*	89.15 ± 21.88°
HDRS total	0.16 ± 0.68	5.58 ± 5.80*	6.70 ± 6.35°
HARS total	0.68 ± 1.63	9.89 ± 9.27*	5.40 ± 4.10

Notes: Symbol references for significant pair-wise between-group differences: *HC–BPD; °HC–MDD; ^BPD–MDD.
Abbreviations: BPD, borderline personality disorder; CERQ, Cognitive Emotion Regulation Questionnaire; DERS, Difficulties in Emotion Regulation; HARS, Hamilton Anxiety Rating Scale; HCs, healthy controls; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder.
[a]Although no across-group differences were observed in these variables, in clinical groups, these values significantly differed (one-sample *t*-tests) from those obtained in a population of nondepressed older adults [18]: CERQ reappraisal (lower values in clinical groups), HCs: $p = 0.882$ (n.s.), BPD: $p = 0.098$ (trend-level), MDD: $p = 0.017$; CERQ rumination (higher values in all groups), HCs: $p = 0.019$, BPD: $p < 0.0005$, MDD: $p = 0.001$.

and each block was followed by 10s of baseline during which a cross fixation was presented on the screen to minimize carryover effects [28].

fMRI preprocessing and analysis

A thorough description of this section can be found in the Supplementary Material.

Results

The demographic and clinical characteristics of the sample are displayed in Table 1. Because patients were consecutively recruited, groups significantly differed in age (patients with MDD were older). For this reason, age was introduced as a nuisance covariate in all analyses.

Intrascanner ratings

Overall, in-scanner emotion ratings were the highest during the maintain blocks (mean = 3.08; SD = 0.89), followed by regulate (mean = 2.56; SD = 0.90) and observe (mean = 1.860; SD = 0.99) blocks ($F = 4.30$; $p = 0.02$). We did not observe, however, significant across-group differences or a group × condition interaction in these ratings.

fMRI task-related activations

In the regulate versus maintain contrast, a direct between-group comparison showed that when compared to HCs, individuals within the BPD and MDD groups presented overlapping decreased activations in the right vlPFC during cognitive reappraisal. In addition, patients with MDD, also in comparison to HCs, showed decreased activations in the left dlPFC and in the bilateral OFC (Figure 1A and Table 2). These results remained significant when controlling for sex in addition to age (Supplementary Table 1). Moreover, we observe no significant across-group differences during the Maintain > Observe contrast, although we observed a significant (at an uncorrected level) across-group activation in the right amygdala in this contrast, indicating successful emotion induction (Supplementary Table 2 and Supplementary Figure 1). Interestingly, in the Maintain > Observe contrast, we also observed that both patient groups tended to activate the vlPFC and the bilateral OFC more than HCs during the maintain condition, although at an uncorrected significance level (Supplementary Table 3).

gPPI analyses

Generalized psychophysiological interactions (gPPIs) revealed between-group differences when assessing right vlPFC connectivity. Specifically, in comparison to HCs, individuals from both the BPD and MDD groups showed a similar pattern of reduced connectivity with right posterior temporal areas (although peak coordinates of the different group comparisons were located in different gyri, all these clusters overlapped in the posterior temporal cortex). Nevertheless, the BPD group showed an additional cluster of decreased connectivity with the right vlPFC involving the left inferior temporal cortex. In addition, when directly comparing both clinical groups, patients with BPD showed decreased connectivity values in comparison to patients with MDD within these same clusters (Figure 2A and Table 3).

Correlations between clinical and imaging data

We observed a significant negative correlation between right vlPFC activation and CERQ rumination scores in the MDD group (Pearson's $r = -0.505$; $p = 0.023$; Figure 1B), which significantly differed ($z = -1.881$; $p = 0.03$) from the same correlation in the BPD group (Pearson's $r = 0.099$; $p = 0.686$). Nevertheless, the difference with the correlation in HCs (Pearson's $r = -0.22$; $p = 0.365$) did not reach statistical significance ($z = -0.954$; $p = 0.17$). Furthermore, we observed that patients with BPD showed a significant positive correlation between CERQ reappraisal scores and right vlPFC–left inferior temporal gyrus (ITG) connectivity (Pearson's $r = 0.644$; $p = 0.003$; Figure 2B). This correlation differed from what was observed in MDD (Pearson's $r = 0.004$; $p = 0.986$) and HC (Pearson's $r = -0.112$; $p = 0.648$) groups ($z = -2.208$; $p = 0.014$; and $z = -1.846$; $p = 0.032$, respectively). We found no further correlations between clinical and imaging data, including depression (HDRS) and anxiety (HARS) scores.

Discussion

Our results showed that both individuals with MDD and individuals with BPD display decreased activation in the vlPFC during cognitive reappraisal. Nevertheless, such hypoactivation was more extensive in the MDD group, who also showed a negative correlation between reappraisal-related vlPFC activity and rumination. Likewise, patients with MDD displayed other clusters of significant hypoactivation during cognitive reappraisal, including the left dlPFC and the bilateral OFC. Conversely, patients with BPD showed greater connectivity decreases between the vlPFC and left inferior and right posterior temporal regions during reappraisal. Furthermore, these connectivity alterations were significantly associated with psychometric measures of cognitive reappraisal. Overall, this pattern of results confirms our a priori hypotheses, since

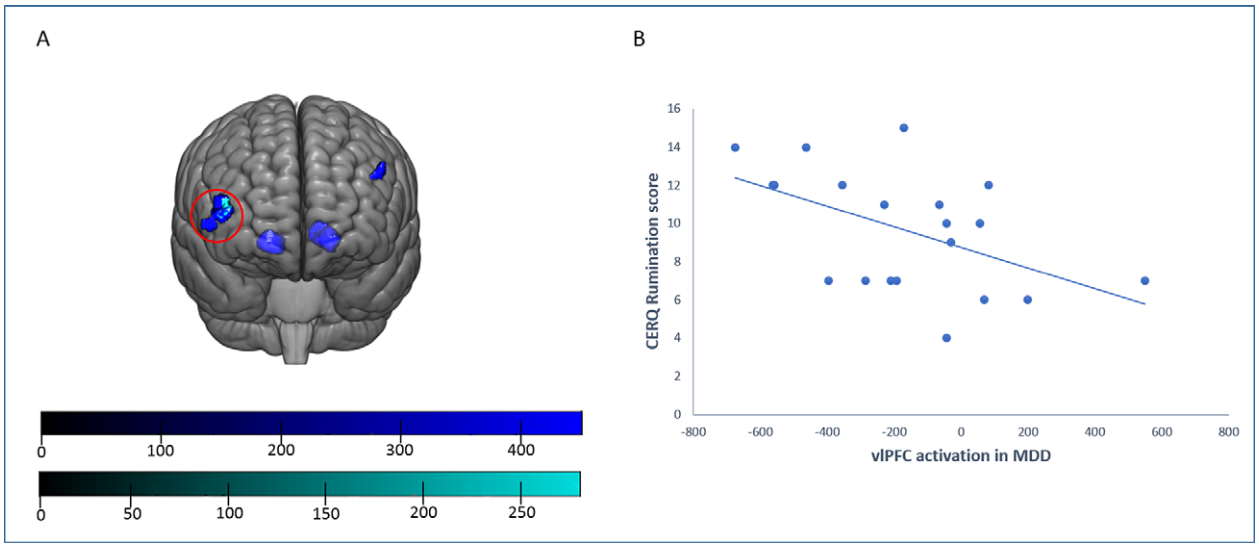

Figure 1. Between-group differences in task-related activations. (A) Patients with borderline personality disorder (BPD; cyan) and patients with major depressive disorder (MDD; blue) showed overlapping decreased activations in comparison to healthy controls (HCs) during emotion regulation in the right ventrolateral prefrontal cortex (vlPFC; red circle). Patients with MDD showed additional hypoactivation in the left dorsolateral prefrontal cortex and the orbitofrontal cortex (bilaterally). Top color bar: MDD versus HC TFCE (Threshold Free Cluster Enhancement) values; bottom color bar: BPD versus HC TFCE (Threshold Free Cluster Enhancement) values. (B) Correlation between Cognitive Emotion Regulation Questionnaire rumination scores and right vlPFC activation in patients with MDD.

Table 2. Regions showing significant activation differences during Regulate > Maintain.

Activations: Regulate > Maintain						
		MNI coordinates				
Contrast	Anatomical area	*x*	*y*	*z*	k_E	P_{FWE}
HCs > BPD	Right vlPFC	45	60	6	117	0.030
HCs > MDD	Right vlPFC	47	56	8	393	0.008
	Right OFC	18	38	−9	342	0.011
	Left OFC	−17	42	−9	443	0.011
	Left dlPFC	−47	45	33	65	0.018

Abbreviations: BPD, borderline personality disorder; dlPFC, dorsolateral prefrontal cortex; FWE, family-wise error; HCs, healthy controls; k_E, cluster extent; MDD, major depressive disorder; MNI, Montreal Neurological Institute; OFC, orbitofrontal cortex; vlPFC, ventrolateral prefrontal cortex.

patients with MDD seem to recruit prefrontal regions to a lesser extent during regulation of emotions, while the BPD group displayed inefficient regulatory input from prefrontal areas.

Our findings reporting decreased vlPFC activation during emotional processing in both patient groups are in agreement with previous research [29]. The vlPFC plays a crucial role in response selection and inhibition [30], and, in particular, in the inhibition of emotional appraisals [31]. Our present results are, therefore, indicative of cognitive reappraisal impairments in MDD and BPD that may be partly a consequence of ineffective management of inhibitory resources. Notably, the vlPFC has been related to the use of reinterpretation strategies during reappraisal, as opposed to the use of distancing strategies engaging parietal regions [7,32]. Consequently, MDD and BPD seem to share a diminished capacity to reinterpret negative emotions. Moreover, among MDDs, decreased vlPFC activation was inversely related to rumination scores, a core feature of the depression phenotype. This concurs with reports in HC samples [33] and other findings indicating that the lateral PFC plays a general inhibitory role limiting the impact, or carryover effects, of an emotional state onto emotional states evoked by subsequent events [34]. On the other hand, the lateralization of this finding to the right hemisphere is in agreement with previous reports in MDD [35] and BPD [36] samples, although not with recent meta-analytic evidence in anxiety and depression groups [7]. The recruitment of the right vlPFC has been associated with particular features of cognitive reappraisal, such as reiteratively implementing the same reappraisal strategies to counteract negative affect [37], or the implementation of operations needed to maintain strategies in working memory and to monitor its success during the late phases of emotional situations [38]. Therefore, the right hemisphere lateralization of findings observed here may stem as a consequence of the specific instructions given to participants in this study, whom may have probably implemented a limited choice of strategies, in interaction with a decreased capacity in the maintenance and monitoring of ongoing reappraisal efforts in patients.

Decreased activation of the dlPFC has been also previously reported in clinical samples, including not only depression and anxiety patients [11,39]. This region contributes to different executive functions [40], and, in the context of emotion regulation, its role seems to be related to the active manipulation of information to reappraise emotional stimuli [32]. This alteration concurs with the executive function alterations commonly described in depression samples [41]. In this case, however, findings were lateralized to the left hemisphere. This may be partially accounted for by the role of right dlPFC activation in negative emotion appraisal, which is related to depression severity and may, therefore, compensate for the executive function-related hypoactivations allegedly occurring during reappraisal [6,42].

Regarding the hypoactivations also observed in the medial OFC in patients with MDD, it should be noted that this region, like other medial prefrontal structures, has been shown to downregulate activity in subcortical structures [9], and, indeed, its functional connectivity with the amygdala is increased during threat-induced anxiety in HCs [43]. According to our findings, the medial OFC of patients with MDD is probably not properly exerting this downregulatory input into emotion-processing structures, including, but

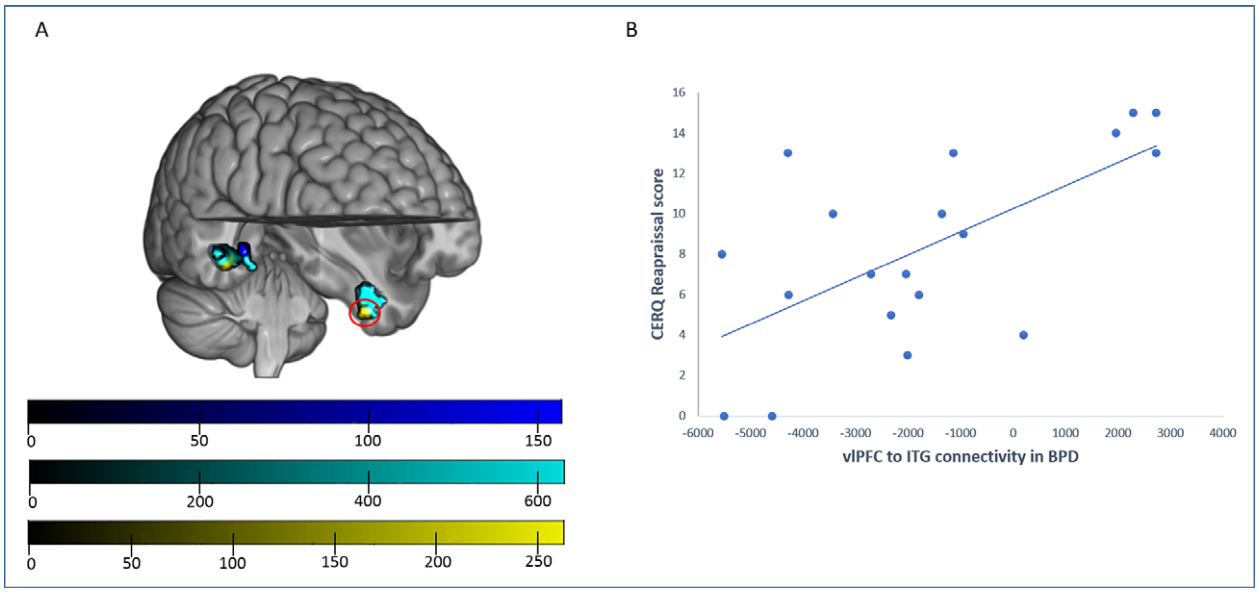

Figure 2. Between-group differences in generalized psychophysiological interaction (gPPI) analyses from the right vlPFC seed. (A) In comparison to healthy controls (HCs), patients with major depressive disorder (MDD; blue) showed a decreased connectivity with right posterior temporal areas, involving the medial temporal gyrus and the parahippocampal gyrus. Patients with borderline personality disorder (BPD; cyan) showed also decreased connectivity with posterior temporal areas (in this case, with peak differences in the fusiform gyrus) and, specific to these subjects, with the left inferior temporal gyrus (ITG). Moreover, patients with BPD showed, in comparison to the MDD group (yellow), decreased connectivity between the right vlPFC and the left ITG and the right fusiform gyrus. Top color bar: MDD versus HC TFCE (Threshold Free Cluster Enhancement) values; middle color bar; BPD versus HC TFCE (Threshold Free Cluster Enhancement) values; bottom color bar; BPD versus MDD TFCE (Threshold Free Cluster Enhancement) values. (B) The Cognitive Emotion Regulation Questionnaire reappraisal scores correlated positively with right vlPFC–left ITG connectivity (red circle) in the BPD group.

Table 3. Regions showing significant connectivity differences during Regulate > Maintain.

Connectivity (gPPI) → vlPFC: Regulate > Maintain						
		MNI coordinates				
Contrast	Anatomical area	*x*	*y*	*z*	k_E	P_{FWE}
HC > BPD	Right posterior temporal cortex (peak at FG)	48	−36	−14	475	0.001
	Left ITG	−39	−9	−33	364	0.002
HC > MDD	Right posterior temporal cortex (peak at PG)	33	−36	−6	58	0.007
	Right posterior temporal cortex (peak at MTG)	53	−35	−11	42	0.033
MDD > BPD	Right posterior temporal cortex (peak at FG)	45	−45	−8	161	0.009
	Left ITG	−35	−9	−39	54	0.024

Abbreviations: BPD, borderline personality disorder; FG, fusiform gyrus; FWE, family-wise error; gPPI, generalized psychophysiological interaction; HCs, healthy controls; ITG, inferior temporal gyrus; k_E, cluster extent; MDD, major depressive disorder; MNI, Montreal Neurological Institute; MTG, medial temporal gyrus; PG, parahippocampal gyrus; vlPFC, ventrolateral prefrontal cortex.

not limited to, the amygdala [7,9]. In addition, it is important to note that both the OFC and the vlPFC showed a trend to increase activation in patient groups during the Maintain condition (as compared to the control Observe condition). This result suggests that patients engage in a regulation effort during the Maintain condition, which may also contribute to the decreased activation levels in these same regions (especially in the MDD group) observed when contrasting Regulate and Maintain conditions.

Patients with BPD did, however, not show such extended prefrontal hypoactivation, but rather decreased functional connectivity between the vlPFC and visual association cortices of the ventral stream, implicated in complex visual feature detection and recognition of facial expression [44]. Different studies have consistently described hyperresponsiveness of the visual system in BPD patients when processing emotional information, especially, emotional faces, extending from primary cortices to association cortices of the temporal lobe [29,45–48]. Although we here have not observed such increased activation in the visual system, the regulatory input from the vlPFC cortex was diminished in patients with BPD, which seems to be a plausible mechanism to account for the visual hyperresponse described with other emotional tasks in the above studies. Likewise, although patients with MDD also showed some degree of decreased connectivity from the vlPFC to early visual perception areas, their clusters were less extended, and, at least for some of these clusters (i.e., right posterior fusiform gyrus), we also observed a significant difference between the clinical groups, with MDD patients showing significant connectivity increases in comparison to the BPD group.

According to these results, it can be concluded that alterations in cognitive reappraisal in patients with BPD (and to a lesser extent, in patients with MDD) could start at perceptive stages, before information reaches emotion-processing structures. Nevertheless, since

information is conveyed from these visual association to limbic cortices [49,50], it is expected that such (lack of) modulation of perceptive input will indirectly weaken the regulatory input from prefrontal structures to emotion-processing regions. In this sense, it is worth mentioning that only patients with BPD, but not patients with MDD, showed decreased connectivity between the vlPFC and more rostral parts of the ITG. It can, therefore, be suggested that as information progresses through the ventral stream, alterations in prefrontal modulation of visuo-emotional processing are exclusively observed in patients with BPD. Interestingly, alterations in the white matter tracts linking anterior brain areas with visual association cortices (i.e., the inferior fronto-occipital and the inferior longitudinal fasciculi) have been described in patients with BPD [51].

Overall, the above notions concur with recent reports suggesting that, in comparison to patients with MDD, patients with BPD show an exaggerated response during emotional induction paradigms [52]. It is also noteworthy that correlations between interregional connectivity alterations and emotion regulation scores were only observed in patients with BPD. Specifically, we observed a positive association between reappraisal scores and vlPFC–rostral ITG connectivity, indicating that prefrontal input at this particular stage of visuo-emotional processing within the ventral stream may critically determine emotion regulation success in this clinical group. In sum, these prefrontovisual association connectivity alterations observed in BPD are likely to account for the increased sensitivity to emotional aspects of the environment [53] and the general higher sensitivity to emotional stimuli and slow return of emotional arousal to baseline that characterize patients with BPD [54].

Importantly, the correlations between imaging and psychometric data observed in the clinical groups should be interpreted with caution, because CERQ scores did not differ across the study groups (although they significantly differed from those of a reference population; see Table 1). Nevertheless, our findings suggest that the extent of alterations in vlPFC activation (patients with MDD) and vlPFC–rostral ITG connectivity (patients with BPD) seems to be preferentially accounting for, among all the emotion regulation facets, interpatient variability in rumination and reappraisal, respectively. Anyhow, these do not exclude that these same neurobiological changes may be also related, to a lesser extent, to other emotion regulation facets, and this is probably the reason why these imaging alterations are significant at the group level.

The results of this study have to be interpreted in the context of the following limitations. First, our overall sample was small ($n = 58$, with 19/20 subjects per group), which may have limited the power of our analyses to detect additional significant findings. Nonetheless, we would like to stress that our subjects were carefully recruited according to strict inclusion criteria, and we have obtained several significant differences between the study groups at a strict family-wise error threshold. Likewise, the sample size of our study is similar to sample sizes in most neuroimaging emotion regulation studies in MDD or BPD samples (see, e.g., the studies included in the reviews and meta-analyses by Sicorello and Schmahl [13], Rive et al. [17], or Picó-Pérez et al. [7]). We acknowledge, however, that there are some notable exceptions to this trend, such as the studies by van Zutphen et al. ($n = 55$ BPD patients) [55] and Silvers et al. ($n = 60$ BPD patients) [56]. Second, patients with MDD were older than the other two groups, although this is reflective of the clinical setting in which this study took place and adds external validity to our study. Moreover, we controlled for age in all our analyses. Anyhow, future studies should try to provide a more accurate matching across study groups. This is especially important when comparing clinical groups overlapping in clinically relevant variables such as depression or anxiety. Although our clinical groups did not differ in these variables, an accurate matching of nuisance factors is expected to provide clearer results and, consequently, allow drawing straightforward conclusions. Third, we observed no significant across-group differences in intrascanner ratings, although this is commonly observed in emotion regulation studies and should not be interpreted as evidence of similar cognitive reappraisal implementation [7]. Indeed, our groups differed from HCs in psychometric measurements of emotion regulation (i.e., DERS scores). Moreover, intrascanner ratings showed that negative emotion reactivity was successfully induced in all groups. There are, nevertheless, different reasons for this lack of between-group differences in intrascanner ratings, such as the inherent limitations of subjective behavioral assessments, social desirability effects, or impaired self-awareness of emotional experience, as suggested by Zilverstand, Parvaz, and Goldstein [57]. Finally, we did not collect any measure of BPD severity [58], and we assessed dispositional use of emotion regulation strategies with a retrospective self-report measure. Although previous research has shown that such measurements may significantly predict real-life outcomes, such as well-being and depressive symptomatology [4], future research can benefit from real-time and real-life approaches, such as ecological momentary assessments.

Taken together, our findings indicate that MDD and BPD share an altered neural response during cognitive reappraisal involving the right vlPFC, indicating that this region is implicated in the emotion regulation shortcomings that characterize both disorders. Nevertheless, MDD patients showed a more widespread pattern of reduced prefrontal activation, which may be interpreted in the context of a pervasive alteration in executive functioning probably stemming from a primary deficit in the strength of prefrontal activations. On the other hand, BPD patients showed a more extended pattern of dysfunctional connectivity between prefrontal areas and visual association cortices that may lead to the higher sensitivity to emotional stimuli typically observed in these patients. These findings substantiate in neurobiological terms the existence of dissimilar profiles of emotion regulation alteration between these disorders, and may ultimately be of relevance for the development or optimization of clinical interventions aimed at restoring emotion regulation capacities.

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Data Availability Statement. The data that support the findings of this study and the brain maps of all analyses are available from the corresponding author upon reasonable request.

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Conflict of Interest. The authors declare none.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplementary material

An fMRI study of cognitive reappraisal in major depressive disorder and borderline personality disorder

De la Peña-Arteaga et al.

Methods

Sample

Exclusion criteria for patients included current or past presence of other psychiatric diagnoses (including psychotic symptoms but excluding nicotine addiction), or current or past presence of major neurological or medical conditions (including episodes of loss of consciousness>30 min). Controls were recruited form the same sociodemographic setting and were excluded if they reported the current or past presence of any psychiatric, neurological or major medical condition or if they reported current of past treatment with psychotropic medication. Participants from all groups were also excluded if they were not able to undergo the MRI exam or if anatomical abnormalities were detected in the MRI scan.

MRI acquisition

Functional magnetic resonance imaging (fMRI) data was acquired on a 3T General Electric HDx scanner with an 8-channel head coil. Change in blood-oxygenation-level-dependent (BOLD) T2* signal was measured using a gradient echo-planar imaging (EPI) sequence. Thirty-three contiguous slices were obtained in the AC-PC plane (TR=2s, TE=30ms, flip angle=90°, FOV=24cm, 64x64 matrix, voxel size=3.75 x 3.75 x 4, 247 volumes). A structural MRI was also acquired (for image pre-processing and detection of gross anatomical abnormalities) with the T1-weighted 3D fast SPGR-IR sequence (166 slides, 1.2mm thick slices, TR=6.988ms, TE=2.848ms, flip angle=8°, FOV=26cm, 256 x 256 matrix).

fMRI task, cognitive reappraisal paradigm

At the beginning of each block of the task, a word appeared in the middle of the screen for four seconds to provide instructions to participants for the upcoming block. If the instruction was to "observe", the images that followed were neutral in content and participants were required passively observe them without trying to alter their emotional response. If the instruction was to "maintain", the presented images that followed were negative and participants were instructed to actively sustain the negative emotions elicited by the images. Finally, if the instruction was to "regulate," the images were always negative in content and participants had to reappraise and reduce the intensity of negative emotions by means of previously trained cognitive reappraisal techniques.

The paradigm was executed using Presentation software (Neurobehavioral Systems, Inc.) and images were presented to subjects by means of a projector and a screen placed at the feet of participants, who were able to see the images trough a mirror system mounted on the head coil.

After the presentation of the second picture of each block, the intensity of the negative emotion experienced by was self-rated by participants on a 1–5 number scale (1 being 'neutral' and 5 being 'extremely negative'). Subjects provided these responses through an fMRI-compatible response pad (Lumina 3G Controller, Cedrus Corporation) placed near their right hand.

fMRI pre-processing and analysis

All fMRI images were initially preprocessed using the Wavelet Despike procedure within the BrainWavelet Toolbox to remove high and low frequency artefacts induced by abrupt physical movements (1). Remaining image processing was performed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm) running on MATLAB R2017a. Functional images were realigned to the mean position of all scans and co-registered to their respective T1 images, which were used for normalization to MNI space. Subsequently, normalization parameters were applied to the functional time-series, which were finally smoothed with an 8-mm full width at half maximum (FWHM) kernel.

Regulate vs. maintain was defined as the contrast of interest for first-level (single-subject) analysis. This contrast allows for the delineation of brain activations associated with cognitive reappraisal (2). Conditions were modelled for the 20 seconds that the images

were displayed and did not include instruction, rating and rest periods. The BOLD response at each voxel was convolved with the SPM12 canonical hemodynamic response function (HRF) using a 128-s high-pass filter.

Contrast images from first-level comparisons were carried forward to second-level analyses. Between-group comparisons in task activations were conducted with a one-way ANOVA model including the three groups (HCs, MDD and BPD patients) as the main factor. Age was introduced as a nuisance covariate in these analyses.

To investigate between-group differences in task-induced connectivity between the brain regions activated during the cognitive reappraisal task, we also performed a generalized form of psychophysiological interactions (gPPI) analyses in SPM12. Specifically, the impact of the contrast of interest (the 'psychological' factor) on the strength of time-course correlations of our empirically obtained region of interests (ROI, the 'physiological' factor) was explored. First-level design matrices (subject-wise level) included the regressors of the different task blocks (i.e., observe, maintain and regulate), and functional connectivity maps were estimated for the selected seeds by including the signal of interest in interaction with the task blocks, while controlling for the raw signal of the seed and the task blocks. Resulting images were then included in a one-way ANOVA model (second-level) to assess between-group effects.

Our whole-brain analyses were corrected for multiple comparisons using a voxel-wise nonparametric permutation testing with the threshold-free cluster enhancement (TFCE) method (3) as implemented in the SPM-TFCE toolbox v174 (http://dbm.neuro.uni-jena.de/tfce/). Significance threshold was set at $p<0.05$, family-wise error (FWE) whole-brain corrected.

Analysis of psychometric data were carried out with SPSS v. 25 (IBM Corp; Armonk, NY). Specifically, we first extracted with SPM the first eigenvariate from peak voxels of above analyses, and these values were compared between-groups with independent sample t-tests, while linear associations with psychometric data were estimated using Pearson's correlations. In these last analyses, associations were considered significant if significance p values were below 0.05 and effect sizes were moderate to large ($|r|>0.24$) (4).

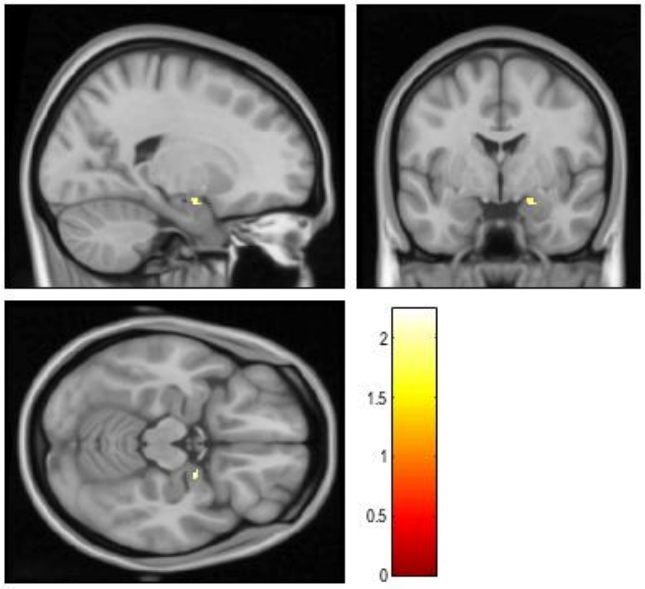
Results

Activations: Regulate>Maintain						
Contrast	Anatomical Area	MNI Coordinates			k_E	P_{FWE}
		x	y	z		
HCs>BPD	Right vlPFC	45	60	6	28	0.042
HCs>MDD	Right vlPFC	47	56	8	210	0.017
	Right OFC	18	38	-9	172	0.031
	Left OFC	-17	42	-9	234	0.025
	Left dlPFC	-47	45	33	11	0.040

Supplementary Table 1. *Regions showing significant activation differences during Regulate>Maintain (controlling for age and sex).* Abbreviations: BPD = Borderline Personality Disorder; dlPFC = Dorsolateral Prefrontal Cortex; FWE = Family-Wise Error; HCs= Healthy Controls; k_E = Cluster extent; MDD = Major Depressive Disorder; MNI = Montreal Neurological Institute; OFC = Orbitofrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex.

Activations: Maintain>Observe						
Contrast	Anatomical Area	MNI Coordinates			T	P uncorrected
		x	y	z		
Maintain>Observe	Right Amygdala	21	-5	-18	2.25	0.014

Supplementary Table 2. *Regions showing across-group activation in the in Maintain>Observe contrast*.



Supplementary Figure 1. *Across-group activation in right amygdala in the Maintain>Observe contrast. Colour bar indicates t-value.*

Activations: Maintain>Observe						
Contrast	Anatomical Area	MNI Coordinates			k_E	P uncorrected
		x	y	z		
MDD>HCs	Right vlPFC	50	54	5	62	0.005
	Right OFC	12	39	-15	190	0.016
	Left OFC	-3	35	-14	336	0.007
BPD>HCs	Right vlPFC	45	59	11	237	<0.001
	Right OFC	14	36	-12	183	0.012
	Left OFC	-17	42	-9	471	0.002

Supplementary Table 3. *Regions showing significant activation differences during Maintain>Observe within the vlPFC cluster.* Abbreviations: BPD = Borderline Personality Disorder; HCs= Healthy Controls; k_E = Cluster extent; MDD = Major Depressive Disorder; MNI = Montreal Neurological Institute; OFC = Orbitofrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex.

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4.2 Artículo publicado 2

Objetivo/s:

En el artículo se contrastan los objetivos específicos 3 y 4 de la tesis.

3. Caracterizar las redes cerebrales implicadas y sus respectivas alteraciones durante el proceso de regulación emocional.

4. Explorar las diferencias en las distintas redes funcionales, que describen patrones coordinados de actividad cerebral entre las regiones de la corteza frontal y otras áreas del cerebro, entre individuos sanos y una población clínica (TOC).

Título del artículo:

An fMRI study of frontal networks in obsessive-compulsive disorder during cognitive reappraisal

Disponible a través de la URL:

Pendiente.

Resumen:

Antecedentes: Los pacientes con trastorno obsesivo compulsivo (TOC) presentan dificultades en la regulación cognitiva de las emociones, posiblemente por el reclutamiento ineficiente de patrones distribuidos de regiones de la corteza frontal. El objetivo del presente estudio es caracterizar las redes cerebrales y sus disfunciones relacionadas con las alteraciones de la regulación emocional observadas durante la reevaluación cognitiva en el TOC.

Métodos: Se compararon pacientes adultos con TOC (n=31) y controles sanos (n=30) durante la realización de un protocolo de reevaluación cognitiva con imágenes por resonancia magnética funcional (IMRf). Se utilizó un análisis de componentes independientes (ACI) libre para analizar las alteraciones a nivel de red durante la experiencia y la regulación emocionales. También se exploraron las correlaciones con los instrumentos psicométricos.

Resultados: Los análisis se centraron en 6 redes que incluyen a la corteza frontal. Los pacientes con TOC mostraron una menor activación de la red frontotemporal en comparación con los controles sanos ($F(1,58) = 7.81$, $p = 0.007$) durante la reevaluación cognitiva. Se observó una tendencia similar en la red frontoparietal izquierda (RFPI).

Conclusiones: El presente estudio demuestra que los pacientes con TOC muestran una menor activación de redes específicas que involucran a la corteza frontal durante la reevaluación cognitiva. Estos resultados deberían ayudar a caracterizar mejor los procesos psicológicos que modulan el miedo, la ansiedad y otros síntomas centrales de los pacientes con TOC, así como las alteraciones neurobiológicas asociadas, desde una perspectiva a nivel de sistema.

An fMRI study of frontal networks in obsessive-compulsive disorder during cognitive reappraisal

Víctor De la Peña-Arteaga[1,2,3], Pedro Morgado[3,4,5], Beatriz Couto[3,4], Sónia Ferreira[3,4,5], Inês Castro[3,4], Nuno Sousa[3,4,5], Carles Soriano-Mas[1,6,7], Maria Picó-Pérez[3,4,5,8].

1. Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Spain.
2. Department of Clinical Sciences, School of Medicine, Universitat de Barcelona - UB, L'Hospitalet de Llobregat, Spain.
3. Life and Health Sciences Research Institute (ICVS), School of Medicine, Universidade do Minho, Braga, Portugal.
4. ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal.
5. 2CA-Clinical Academic Center, Braga, Portugal.
6. Network Center for Biomedical Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
7. Department of Social Psychology and Quantitative Psychology, Universitat de Barcelona - UB, Barcelona, Spain.
8. Departamento de Psicología Básica, Clínica y Psicobiología, Universitat Jaume I, Castelló de la Plana, Spain.

Corresponding author: Carles Soriano-Mas, Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Spain.
E-Mail: csoriano@idibell.cat

Running title: Frontal networks of cognitive reappraisal in OCD.

Abstract

Background: Patients with Obsessive-Compulsive Disorder (OCD) present difficulties in the cognitive regulation of emotions, possibly because of inefficient recruitment of distributed patterns of frontal cortex regions. The aim of the present study is to characterize the brain networks, and their dysfunctions, related with emotion regulation alterations observed during cognitive reappraisal in OCD.

Methods: Adult patients with OCD (n=31) and healthy controls (HC; n=30) were compared during performance of a functional magnetic resonance imaging (fMRI) cognitive reappraisal protocol. We used a free Independent Component Analysis (ICA) approach to analyze network-level alterations during emotional experience and regulation. Correlations with behavioral scores were also explored.

Results: Analyses were focused on 6 networks encompassing the frontal cortex. OCD patients showed decreased activation of the frontotemporal network in comparison with HC ($F(1,58) = 7.81$, $p = 0.007$) during cognitive reappraisal. A similar trend was observed in the left frontoparietal network (LFPN).

Conclusions: The present study demonstrates that patients with OCD show decreased activation of specific networks implicating the frontal cortex during cognitive reappraisal. These outcomes should help to better characterize the psychological processes modulating fear, anxiety, and other core symptoms of patients with OCD, as well as the associated neurobiological alterations, from a system-level perspective.

Key words: Frontal networks, fMRI, OCD, cognitive reappraisal, emotion regulation.

Introduction

The neurobiological underpinnings of human emotion have been long studied from a neuroscience and neuroimaging perspective (1,2). More specifically, in recent years, considerable research efforts have been directed to explore the regulatory effects of frontoparietal cognitive control networks on subcortical emotional processing regions, describing alterations across major neuropsychiatric disorders (3,4). However, such alterations have been comparatively less studied in obsessive-compulsive disorder (OCD).

OCD patients are characterized for presenting difficulties in cognitive and emotional regulation (5–7). Previous studies suggest that these patients might have difficulties activating frontoparietal networks when cognitive control is required (8), showing less recruitment of the dorsolateral prefrontal cortex (dlPFC) as well as diminished frontal-limbic connectivity (9,10). Although the pattern of alterations observed in patients with OCD may differ from what is observed in anxiety disorders in specific conditions, such as the implicit regulation of emotions during active responding, where limbic-prefrontal connectivity may be increased (11), such differences are more difficult to appreciate, for instance, during the anticipation of disorder unspecific emotional stimuli (12). Alterations in the cognitive regulation of emotions in patients with OCD have been recently summarized in Ferreira et al., 2020 (13).

Network-based analyses are an interesting alternative to explore neurofunctional abnormalities in emotion regulation circuits in patients with OCD. These analyses provide a comprehensive description of alterations involving the coordinated action of different brain regions, beyond the mere description of regional-specific activation dysfunctions and have been recently applied to characterize disruptions in emotion regulation circuits in addictive disorders (14). More specifically, in view of the above reviewed literature, the examination of frontoparietal, frontotemporal and frontolimbic networks seems to be of special interest to characterize alterations of emotion regulation networks in OCD. In this sense, one possible methodological approach able to capture alterations in cognitive control networks is Independent Component Analysis (ICA), which has been used in the past to identify and evaluate networks mainly involving frontal regions (15). ICA is a data-driven approach that assumes that source signals of functional magnetic resonance imaging (fMRI) data represent coherent groupings of MRI activations, which implies the

representation of a functionally connected network. In task-fMRI studies, ICA allows to identify intrinsic functional connectivity networks and how the time courses associated with these networks are modulated by the task. This provides new insights into functional activity hidden from conventional voxel-wise general linear model analyses (16,17).

The aim of the present study is therefore to characterize the brain networks, and their dysfunctions, related to the (altered) emotion regulation phenotype observed in patients with OCD. For this, we explored OCD patients and healthy controls with functional magnetic resonance imaging (fMRI) while performing a cognitive reappraisal protocol. Brain activity during this task was characterized at the network level by using an ICA approach, and we explored for potential between-group differences in the different functional networks (e.g., components) describing coordinated patterns of brain activity between frontal cortex regions and other brain areas. We hypothesized that patients with OCD will exhibit alterations in networks involving frontotemporal, frontoparietal, and frontolimbic regions during the cognitive regulation of emotion. We believe these outcomes can contribute to a better understanding of emotional processing difficulties in OCD.

Methods

Sample

A total of 67 adult (≥18 years) individuals (35 OCD patients and 32 healthy controls) participated in the study. Six participants, however, were excluded due to MRI artifacts or suboptimal task performance. The final sample consisted therefore of 31 patients with OCD (17 females; mean age = 30.00, SD = 11.12 years) and 30 healthy controls (HCs, 16 females; mean age = 29.00, SD = 12.07 years). Patients were recruited at the Department of Psychiatry of *Hospital de Braga* (Braga, Portugal) and were diagnosed following DSM-5 criteria by an experienced psychiatrist. Additionally, the Mini-International Neuropsychiatric Interview (MINI) (18) was administered to explore other potential psychopathological alterations. Exclusion criteria for patients included current presence of other psychiatric diagnoses (Axis I or Axis II disorders), or current or past presence of major neurological or medical conditions. Most patients (80.64%) were medicated at the time of recruitment, although treatments were kept constant throughout

the study. Controls were recruited from the same sociodemographic setting and were excluded if they reported current or past presence of any psychiatric, neurological, or major medical condition, or if they reported current or past treatment with psychotropic medication. Participants from both groups were also excluded if they were not able to undergo the MRI exam, or if anatomical abnormalities were detected in the MRI scan. **Table 1** summarizes clinical and sociodemographic information of study groups.

All participants provided written informed consent before starting the study procedures, which was conducted according to the Declaration of Helsinki and received the approval of the institutional Ethics Committee of the University of Minho (Braga, Portugal) and *Hospital de Braga*. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Psychometric assessment

All participants completed the validated Portuguese versions of the Obsessive-Compulsive Inventory (OCI), an 18 items inventory measuring 6 groups of symptoms (washing, checking, ordering, hoarding, obsessing and neutralizing) (19,20), and the Emotion Regulation Questionnaire (ERQ), a tool assessing habitual use of two emotion regulation strategies: reappraisal and suppression (21,22). Additionally, OCD patients completed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) to measure symptom severity (23,24).

Imaging data acquisition

Data was acquired on a 3.0 Tesla clinical magnetic resonance imaging (MRI) scanner (Siemens Verio, Erlangen, Germany), equipped with a 32-channel head coil. All participants performed a cognitive reappraisal task inside the scanner (see below), during which we acquired a multi-band Echo-Planar Imaging (EPI) sequence, CMRR EPI 2D (R2016A, Center for Magnetic Resonance Research, University of Minnesota, Minnesota, USA) sensitive to fluctuations in the Blood Oxygenation Dependent Level (BOLD) contrast, with the following parameters: TR = 1000 ms, TE = 27 ms, FA = 62°, 2 mm^3 isometric voxel size, 64 axial slices over a matrix of 200 x 200 mm^2. This acquisition lasted for 7.8 minutes. The scanning session also included an anatomical gradient echo Magnetization-Prepared rapid acquisition in the sagittal plane [MPRAGE,

repetition time (TR) = 2420 ms, echo time (TE) = 4.12 ms, flip angle (FA) = 9°, field of view (FOV) = 176x256x256 mm^3, 1 mm^3 isometric voxel size].

fMRI cognitive reappraisal task

We used a well-validated cognitive reappraisal task (25,26), consisting in the presentation of series of blocks showing neutral or negative picture stimuli that participants must: (1) Observe (to passively observe neutral pictures); (2) Maintain (to actively focus on the emotions elicited by negative emotional pictures, sustaining them over time); or (3) Regulate (to reappraise the emotions induced by the negative emotional pictures by virtue of cognitive reappraisal techniques previously trained). Before scanning, participants were trained in distancing and reinterpretation strategies. For instance, in front of pictures depicting disturbing scenarios, they were told to reappraise their emotions by elaborating thoughts such as: (1) the scene is not real (e.g., the people on the screen are actors); (2) the situation will likely get better with time; (3) the situation is not as grave as it first appears (e.g., seeing the situation in a more positive light); and (4) the situation concerns unknown people and will not affect oneself. Participants were specifically instructed that they were not to use non-cognitive strategies (i.e., as looking away) during stimulus presentation. Picture stimuli were obtained from the International Affective Picture System (27) and were presented through an MRI-compatible angled mirror system (Lumina–Cedrus Corporation).

The task consisted of 12 blocks: 4 blocks for each condition. Conditions were pseudorandomized across the task to avoid the induction of sustained mood states. At the beginning of each block, a word (i.e., observe, maintain, or regulate) appeared in the middle of the screen for 4s to provide instructions to participants for the upcoming block. After the prompt, participants viewed two different pictures of equal valence for 10s each. After the presentation of the second picture, the intensity of the negative emotion experienced was self-rated by participants on a 1–5 number scale that appeared for 5s (1 being ‘neutral’ and 5 being ‘extremely negative’). Subjects provided these responses through an MRI-compatible response pad (Lumina–Cedrus Corporation). Each block was followed by 10s of baseline during which a cross fixation was presented to minimize carryover effects.

fMRI pre-processing and independent component analysis

The functional images were preprocessed using fMRIPrep 1.4.1 (28) (RRID:SCR_016216), which is based on Nipype 1.2.0 (29,30) (RRID:SCR_002502). A thorough description of the preprocessing pipeline can be found in the **Supplementary Material**. Regarding in-scanner movements, our exclusion criterion was a framewise displacement (FD) >0.5. Nevertheless, none of the participants surpassed this threshold, and therefore, no participants were excluded because of this reason. Additionally, a visual inspection of fMRIPrep output reports was performed to identify movement outliers and assess the accuracy of the coregistration.

Group ICA (31) was performed with the Gift toolbox (v3.0c) using the Infomax algorithm (32). Before ICA, voxel intensity was normalized, and data from all participants were pooled into a single dataset through a two-step data reduction approach using principal component analysis to enable the analysis of large data sets. Twenty-nine independent components were obtained after a free ICA analysis. Fifty ICA iterations were performed by ICASSO (33) to ensure stability of the estimated components. Finally, individual component maps and time courses were estimated using a group ICA 3 back-reconstruction approach. Because the ICA approach may identify noisy components corresponding to non-biological signal, such as movement artifacts, independent components of interest were selected after visual inspection of their spatial distribution (34). Specifically, components that were mainly present in regions that do not generate BOLD signal (white matter, ventricles, or outside the brain) were excluded from the analysis. In addition, to further refine component selection, a correlation with the component templates distributed by the Functional Imaging in Neuropsychiatric Disorders Lab (https://findlab.stanford.edu/functional_ROIs.html) was performed, using the Gift toolbox.

Statistical analyses

Behavioral data analyses

These analyses were conducted using SPSS v. 27 (IBM Corp; Armonk, NY). P values under 0.05 were considered statistically significant. Groups were compared on continuous variables using independent-sample t-tests or Mann-Whitney tests depending on the normality of the data. Sex/gender distribution between groups was analyzed using a chi-squared test. A 2x3 repeated-measures ANOVA was used to compare the intra-scanner

ratings of each condition (Observe, Maintain and Regulate) between both groups. Moreover, participants' self-reported success in lowering their intra-scanner negative emotion intensity was calculated by subtracting Regulate ratings from Maintain ratings (Success = Maintain - Regulate), while participants' reactivity during emotional processing was computed as Reactivity = Maintain - Observe.

Statistical analysis of the component spatial maps

To determine brain areas significantly related at the whole-sample level to each component time course, second-level one-sample t-tests were performed with Statistical Parametric Mapping (SPM12). Significance threshold was set at $p<0.05$, family-wise error (FWE) corrected for multiple testing. As per our hypotheses, analyses were focused on networks of interest encompassing the frontal cortex, which were visually identified in the results from the one-sample t-tests: the frontoparietal networks (dorsal, right and left), the default mode network, the salience network, and the frontotemporal network.

Statistical analysis of component time courses

To study how functional networks of interest were modulated by cognitive reappraisal, General Linear Model (GLM) was applied on each subject's component time courses using a design matrix representing the task. This yielded a set of beta-weights representing the modulation of component time courses by the GLM regressors. The GLM design matrix used in these analyses included separate regressors to model each of the conditions (observe, maintain, and regulate), which were convolved with the hemodynamic response function. Time derivatives and parameters that modeled residual motion were also included. Then, we performed separate second-level group analyses for the contrasts Maintain>Observe and Regulate>Maintain using the estimated beta-weights.

These group comparisons were performed in SPSS by means of a general linear model including group (OCD patient or control) as a fixed factor. Normality (Kolmogorov-Smirnov, or K-S) tests were performed to assure that components were normally distributed. Age was modelled as a nuisance covariate due to its known modulatory effects on emotion regulation networks (35,36). A false discovery rate (FDR) approach was used to correct for the number of networks.

Brain-behavior correlations

Linear associations between network activations and all behavioral scales scores (6 OCI, 2 ERQ and 3 Y-BOCS subscales) were assessed using Pearson correlations in SPSS. We also explored the associations between imaging and intra-scanner Success ratings. These correlations were performed both for the full sample and for each group separately at an exploratory, uncorrected, threshold.

Results

Sociodemographic and clinical characterization

Both groups were comparable in terms of age, years of education and sex/gender **(Table 1)**. The clinical information for the OCD group (age of onset, symptom severity, and medication status) is also shown in **Table 1**.

Behavioral results

Outside-scanner behavioral measures

There were no significant between-group differences on ERQ scores. Conversely, patients with OCD scored significantly higher in global and all symptom-specific OCI scores, except for the Hoarding score **(Table 1)**.

Intra-scanner ratings

We used a 2x3 repeated-measures ANOVA to compare the intra-scanner ratings of each condition (Observe, Maintain and Regulate) between groups; since the assumption of sphericity was violated, the Huynh-Feldt correction was used. We observed a significant main effect of condition ($F(1.711, 97.542) = 102.239$, $p < 0.001$), with post-hoc tests showing that Maintain ratings differed from Observe ratings, which indicated successful negative emotion induction during this condition for the whole sample ($t = -13.815$, $p_{holm} < .001$). Regulate scores also differed from Maintain scores, indicating successful emotion regulation ($t = 3.709$, $p_{holm} < .001$). There was no main effect of group ($F(1, 57) = 0.043$, $p = 0.836$), nor any interactions between group and condition ($F(1.711, 97.542) = 2.299$, $p = 0.114$). Nevertheless, the Success variable significantly differed between the study

groups ($t(57) = 2.34$, $p = 0.023$), with HC showing more successful regulation, while there were no significant between-group differences in the Reactivity variable.

ICA results

Out of the 29 components obtained, we excluded 18 of them due to a lack of correlation with any recognizable network. The remaining 11 networks were identified as: primary visual, language, secondary visual, cerebellum, salience, auditory, default mode, left frontoparietal, dorsal frontoparietal or dorsal attention network (DAN), right frontoparietal, and frontotemporal network. As per our hypotheses, from these networks we selected those encompassing frontal cortex regions (**Figure 1**).

Brain regions characterizing each network can be seen in **Figure 1**. Most of these networks are those usually identified during the resting state (37). Nevertheless, we also identified a less common frontotemporal network, which included medial temporal lobe structures (including the amygdala), and cortical areas such as the bilateral fusiform gyri (FG), the middle and inferior frontal gyri (MFG, IFG), the angular gyrus (AG), the claustrum, the middle and superior temporal gyri (MTG, STG), the precuneus, the anterior cingulate cortex (ACC), and the precentral gyrus (PG) **(Figure 1)**.

Analysis of components time courses

We obtained two different results in the Regulate>Maintain contrast. All the components were normally distributed (all p values of the K-S test >0.05). We observed a between-group difference within the frontotemporal network, with patients with OCD showing a decreased activation of this network during cognitive reappraisal (corrected model: $F(2,58) = 5.84$, $p = 0.005$, $p_{FDR\text{-}corr} = 0.030$; group effect: $F(1,58) = 7.81$, $p = 0.007$) **(Figure 2)**. Moreover, within the left frontoparietal network (LFPN) we observed a trend-level decreased activation in patients with OCD during reappraisal (corrected model: $F(2,58) = 3.99$, $p = 0.024$, $p_{FDR\text{-}corr} = 0.072$; group effect: $F(1,58) = 3.60$, $p = 0.063$). These results are displayed in **Figure 3A**.

No significant results were observed in the Maintain>Observe contrast.

Brain-behavior correlations

We assessed Pearson's correlations between clinical variables and brain activity within

the frontotemporal and left frontoparietal networks. Within the OCD group, LFPN (Regulate>Maintain) activity correlated negatively with the OCI obsessing subscale score (Pearson's r = -0.407, $p = 0.029$) (**Figure 3B**). No further correlations were observed with psychometric scores or intra-scanner Success ratings.

Discussion

Alterations in emotion regulation capacities contribute, to a varying extent, to the symptom profile of most neuropsychiatric disorders (3,38). Recent research using dynamic casual modeling (DCM) has found that dynamic interactions between frontal regions and the amygdala form a recursive feedback loop, which determines the effectiveness of emotion-regulatory actions (39). OCD is no exception to this rule, and it has been indeed considered to be a disorder of self-regulation and behavioral inhibition, which may be accounted for by alterations in the recurrent projections linking the frontal cortex with subcortical structures (40). Beyond cortico-striatal circuits, such fronto-subcortical projections also involve fronto-amygdalar connections, implicated in the modulation of fear and anxiety symptoms in patients with OCD (41). In this study, we focused our analyses in networks encompassing the frontal cortex, since it has been shown that neurobiological underpinnings of emotion regulation alterations typically involve blunted responses in frontal areas during cognitive reappraisal (4). Herein, we show that the network displaying larger alterations in OCD was that linking prefrontal regions such as the ventrolateral and dorsolateral prefrontal cortices, typically showing decreased activations in clinical populations during cognitive reappraisal in activation-based studies (3), with medial temporal lobe structures (i.e., the amygdala) and other temporal and parietal cortical areas. Our results therefore align with the previous literature highlighting the importance of prefrontal-limbic disruptions for OCD.

The decreased values observed in the frontotemporal network in the OCD sample should be carefully interpreted. These values refer to the average signal across the different regions of the network, which involve cortical (frontal, temporal and parietal) and subcortical structures (i.e., amygdala). At first sight, our findings may seem in apparent contradiction with studies describing heightened limbic activation and increased connectivity between fusiform and dorsolateral prefrontal cortices and the amygdala

during emotional processing in OCD (11). Those results were nevertheless obtained during an emotional face processing paradigm, and not during voluntary emotion regulation. Indeed, it has been reported that the regions of the frontotemporal network may display differential patterns of activation across different phases of emotional processing in patients with OCD (10). Specifically, this study showed increased amygdala reactivity to negative stimuli and decreased dorsolateral prefrontal cortex engagement together with a diminished frontal-amygdala connectivity during emotion regulation. Although our network approach does not allow for assessing such differential activations across the different regions of the frontotemporal network, the overall decreased network activity reported here may be interpreted as related to a decreased engagement during cognitive reappraisal of the wide area of cortical regulatory regions. This, in turn, could trigger dysregulated activity in the amygdala. Furthermore, our results in the frontotemporal network can be related to the structural white matter alterations, in terms of decreased fractional anisotropy in clusters within the uncinate fasciculus, observed in OCD patients with a diffusion tensor imaging (DTI) approach (42).

Obsessive-compulsive symptoms have been traditionally linked to alterations in cortico-striatal circuits (43). It may therefore be questioned to what extent the frontolimbic alterations may contribute to core disorder's symptoms or merely have an impact on unspecific fear and anxiety symptoms. In this sense, it has been shown that disrupted emotion regulation may lead to obsessive-compulsive symptoms through indirect pathways involving alterations in positive affect and decreased cognitive flexibility (44). Likewise, the inability to downregulate emotions may lead to the deployment of suppression strategies, which have been linked to the occurrence of obsessive thoughts (45). Moreover, at the neural level, dysregulated amygdala input to the prefrontal cortex has been shown to disrupt cognitive processes depending on cortical-striatal circuitry in patients with OCD (46).

The trend-level decrease in left FPN activity also described in our OCD sample can be interpreted in similar terms. This network comprises cortical frontoparietal regions, which have been shown to participate in the downregulation of emotions (4,47) and partially overlap with those included in the frontotemporal network, as well as some subcortical clusters mainly located in ventral striatal areas. Interestingly, this left FPN activity decrease correlated with obsessing symptoms. In previous studies from our group, we have shown that these symptoms correlate with increased amygdala reactivity to negative

stimuli (48), as well as with a reduced connectivity between the ventral striatum and limbic regions (49). Present results seem to support these previous findings suggesting that increased amygdala reactivity observed in individuals with obsessing symptoms stem from an inefficient control from cortical frontoparietal and striatal regions.

This study is not without limitations. First, although the network approach allows characterizing brain activity during cognitive reappraisal in terms of patterns of regions of coordinated activity, and, therefore, in terms of functional brain units, it lacks specificity regarding putative activation differences across the regions of the network. Second, emotion regulation success was exclusively assessed with subjective intra-scanner ratings, which have shown lower reliability and validity in previous studies (3). Future studies should consider including other approaches, such as psychophysiological measurements, to overcome this issue. Finally, most of the patients were medicated, creating a potential effect that cannot be isolated and could bias results.

In sum, this study indicates that patients with OCD show decreased activation of frontotemporal and frontoparietal networks during cognitive reappraisal, which can eventually lead to limbic hyperreactivity in front of aversive stimuli. Such emotion regulation difficulties can not only increase unspecific fear and anxiety symptoms, but also interact with the expression of core OCD symptoms. Our results should help to better characterize the psychological processes modulating the clinical profile of patients with OCD, as well as the associated neurobiological alterations. Moreover, the network approach used in this study allows the description of brain alterations from a system-level perspective, which is aligned with recent accounts on the effects and mechanisms of action of different treatment strategies for OCD (50–52). Further research on the predictive value of network-level activity on treatment response -including pharmacological, psychological and neuromodulation treatments- is therefore warranted. Likewise, it will also be important to develop treatment approaches aimed at modulating network activity. In this sense, the system-level effects of regulating neural activity within discrete regions, such as in deep brain stimulation and other neuromodulation approaches, should be assessed, while incipient neuromodulation techniques, such as fMRI-based neurofeedback, may be probably developed with the aim of regulating network-level activity.

Figures

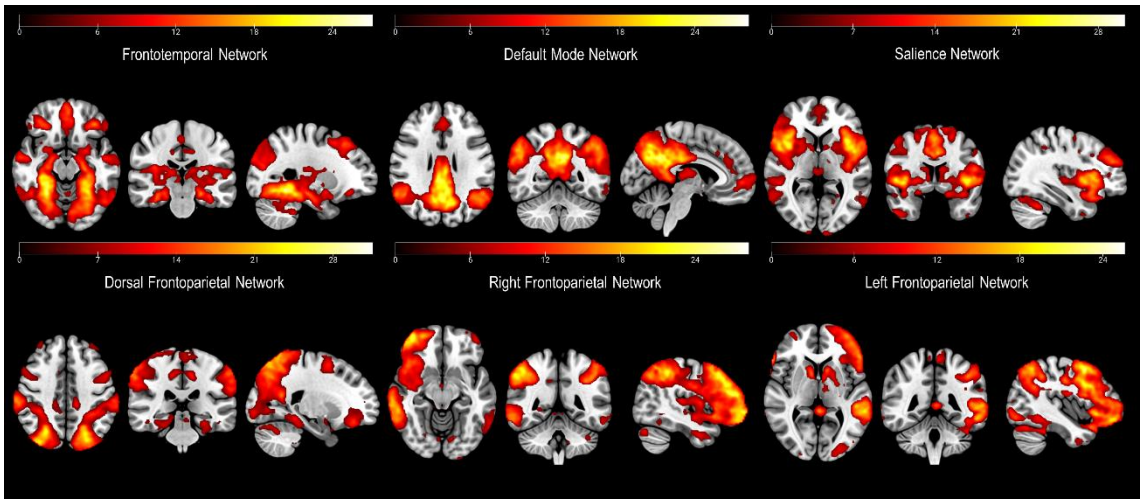

Figure 1. Depiction of the networks of interest (i.e., including parts of the frontal cortex) derived from the Independent Component Analysis (ICA).

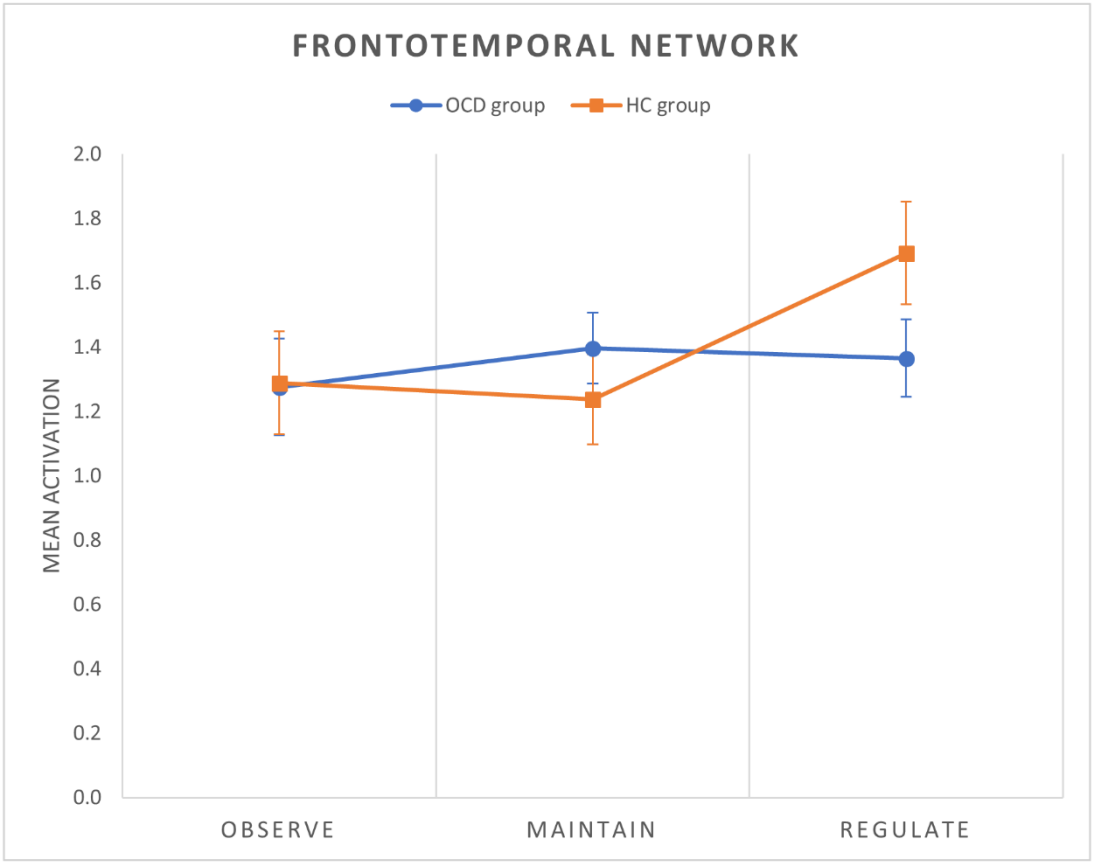

Figure 2. Mean group activations during each condition of the cognitive reappraisal task

in the frontotemporal network. Error bars indicate standard error of the mean.

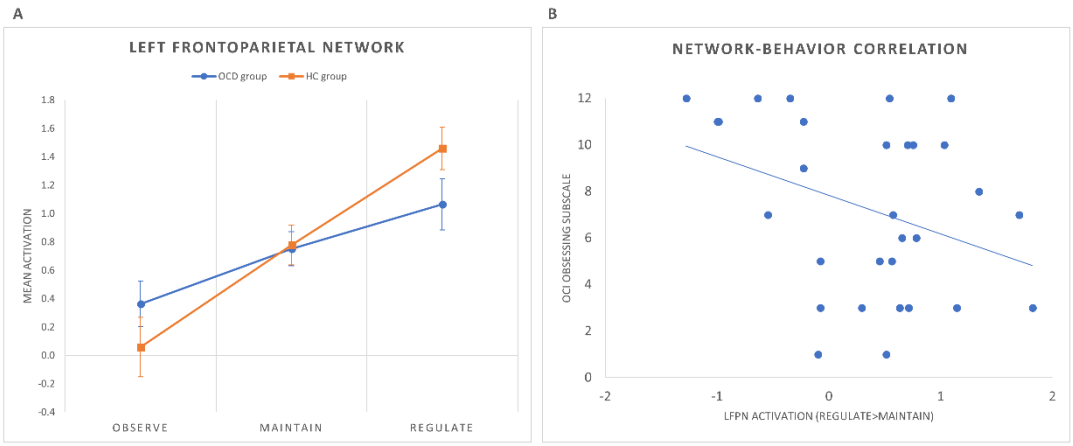

Figure 3. A) Mean group activations during each condition of the cognitive reappraisal task in the Left Frontoparietal Network (LFPN). Error bars indicate standard error of the mean. **B)** Scatter plot (and linear trend) depicting the correlation between OCI obsessing subscale scores and LFPN activation (Regulate>Maintain contrast) in patients with OCD.

Table 1. Demographic and clinical characteristics of the sample.

	OCD (N = 31)	*HC (N = 30)*	*Statistic (p-value)*
Age, Mean (SD)	30 (11.12)	29 (12.07)	*U* = 410.5 (0.435)
Sex/gender, N females (%)	17 (54.83)	16 (53.33)	$\chi^2(1) = 0.01$ (0.906)
Years of education, Mean (SD)	13.03 (3.81)	13.80 (3.83)	*U* = 525 (0.385)
Age of onset, Mean (SD)	17.38 (7.74)	-	-
Medication, N (%)			
SSRI	17 (54.83)	-	-
Tricyclic	2 (6.45)	-	-
SSRI + Tricyclic	5 (16.12)	-	-
SSRI + AP	1 (3.22)	-	-
Unmedicated	2 (6.45)	-	-
Naïve	4 (12.90)	-	-
Y-BOCS Compulsions	13.74 (2.30)	-	-
Y-BOCS Obsessions	11.96 (3.11)	-	-
Y-BOCS Total	25.71 (4.93)	-	-
OCI Washing	4.23 (3.45)	1.63 (1.99)	*U* = 237.5 (**0.001***)
OCI Checking	6.03 (3.78)	2.23 (2.09)	*U* = 178.5 (**< 0.001***)
OCI Ordering	5.93 (3.70)	3.76 (2.48)	*t*(58) = -2.66 (**0.010***)
OCI Hoarding	3.46 (3.24)	3.33 (2.82)	*U* = 449.5 (1.0)
OCI Obsessing	7.26 (3.68)	2.43 (2.62)	*U* = 131.5 (**< 0.001***)
OCI Neutralizing	4.23 (3.80)	1.90 (1.93)	*U* = 309.5 (**0.035***)
OCI Total	30.93 (15.76)	15.43 (10.24)	*t*(58) = -4.51 (**< 0.001***)
ERQ Reappraisal	26.19 (8.15)	29.36 (7.73)	*t*(59) = 1.55 (0.124)
ERQ Suppression	14.74 (5.19)	14.70 (5.77)	*t*(59) = -0.03 (0.976)
Reactivity	1.92 (1.64)	2.52 (0.92)	*U* = 546 (0.157)
Success	0.31 (0.95)	0.87 (0.87)	*t*(57) = 2.34 (**0.023***)

Total *N* = 60 for the OCI subscales, *N* = 60 for the ratings' Reactivity variable and *N* = 59 for the Success variable. Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitors; AP, antipsychotics; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; OCI, Obsessive-Compulsive Inventory; ERQ, Emotion Regulation Questionnaire.

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Conflict of interest

P Morgado has received in the past 3 years grants, CME-related honoraria, or consulting fees from Angelini, AstraZeneca, Bial Foundation, Biogen, DGS-Portugal, FCT, FLAD, Janssen-Cilag, Gulbenkian Foundation, Lundbeck, Springer Healthcare, Tecnimede and 2CA-Braga.

Data availability

The data that support the findings of this study and the brain maps of all analyses are available from the corresponding author upon reasonable request.

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Supplementary material

Methods

Image preprocessing

Results included in this manuscript come from preprocessing performed using fMRIPrep 1.4.1 (Esteban et al., 2018, 2020; RRID:SCR_016216), which is based on Nipype 1.2.0 (Gorgolewski et al., 2011; RRID:SCR_002502).

Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), distributed with ANTs 2.2.0 (Avants et al., 2008; RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9; Zhang et al., 2001; RRID:SCR_002823). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1; Dale et al., 1999; RRID:SCR_001847), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (Klein et al., 2017; RRID:SCR_002438). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al., 2009; RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym), FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model (Evans et al., 2012; RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym).

Functional data preprocessing

First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. A deformation field to correct for susceptibility distortions was estimated based on a field map that was co-registered to the BOLD reference, using a custom workflow of fMRIPrep derived from D. Greve's epidewarp.fsl script and further improvements of HCP Pipelines (Glasser et al., 2013). Based on the estimated susceptibility distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve & Fischl, 2009). Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9; Jenkinson et al., 2002). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 (Cox & Hyde, 1997; RRID:SCR_005927). The BOLD time-series, were resampled to surfaces on the following spaces: fsaverage5. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD time-series were resampled into several standard spaces, correspondingly generating the following spatially-normalized, preprocessed

BOLD runs: MNI152NLin2009cAsym, MNI152NLin6Asym. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA; Pruim et al., 2015) was performed on the preprocessed BOLD on MNI space time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggresively" denoised runs were produced after such smoothing. Additionally, the "aggressive" noise-regressors were collected and placed in the corresponding confounds file. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (CompCor; Behzadi et al., 2007). Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer). Finally, *fslmaths* was used to spatially smooth (with a FWHM kernel of 8mm) the resulting time-series.

Many internal operations of fMRIPrep use Nilearn 0.5.2 (Abraham et al., 2014; RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation.

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4.3 Artículo publicado 3

Objetivo/s:

En el artículo se contrastan los objetivos específicos 5 y 6 de la tesis.

5. Explorar las diferencias en el control cognitivo de las recompensas, proceso asociado con el procesamiento emocional, entre individuos sanos y pacientes con un trastorno de salud mental (TAG).

6. Examinar las activaciones cerebrales, así como la conectividad funcional entre regiones específicas de procesamiento cognitivo-emocional con otras áreas del cerebro, entre sujetos sanos y pacientes (TAG).

Título del artículo:

An fMRI study of cognitive regulation of reward processing in generalized anxiety disorder (GAD)

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Resumen:

Antecedentes: La regulación cognitiva puede afectar el proceso de toma de decisiones. Los pacientes con trastorno de ansiedad generalizada (TAG) parecen tener un deterioro en la regulación cognitiva del procesamiento de recompensas en relación con los estímulos alimentarios. Este estudio tiene como objetivo explorar el impacto del TAG en la regulación cognitiva de las recompensas relacionadas con los alimentos.

Métodos: Pacientes con TAG (n = 11) y controles sanos (n = 15) realizaron una tarea de regulación cognitiva del anhelo con imágenes de alimentos, mientras se sometían a una adquisición de imágenes de resonancia magnética funcional (IRMf). Las diferencias entre grupos en la conectividad funcional se midieron utilizando regiones semilla de la corteza prefrontal dorsolateral (CPFdl) y la corteza prefrontal ventromedial (CPFvm) durante la regulación cognitiva.

Resultados: Durante la regulación cognitiva, hubo una interacción significativa para la conectividad funcional entre la CPFdl derecha y las CPFvm bilaterales con el tálamo. Los pacientes con TAG tenían una conectividad funcional más baja para las condiciones de regulación cognitiva (distancia e indulgencia) que para la condición no regulada en estos grupos, mientras que los controles sanos presentaban el patrón opuesto. El grupo TAG presentó puntajes fijos de valoración de alimentos después de la regulación cognitiva.

Conclusiones: Los participantes con TAG mostraron inflexibilidad en la valoración de las imágenes de los alimentos, lo que podría estar producido por déficits de regulación cognitiva sustentados por alteraciones de la conectividad funcional entre las regiones prefrontales y el tálamo. Estos resultados en pacientes con TAG, muestran la presencia de rigidez cognitiva y dificultad en la modulación de las respuestas cognitivas durante la toma de decisiones.

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An fMRI study of cognitive regulation of reward processing in generalized anxiety disorder (GAD)

Víctor De la Peña-Arteaga [a,b,c], Marcos Fernández-Rodríguez [c,d], Pedro Silva Moreira [c,d,e], Tânia Abreu [c,d], Carlos Portugal-Nunes [c,d], Carles Soriano-Mas [a,f,g], Maria Picó-Pérez [c,d,h], Nuno Sousa [c,d,h], Sónia Ferreira [c,d,h], Pedro Morgado [c,d,h,*]

[a] Psychiatry and Mental Health Group, Neuroscience Program, Institut d'Investigació Biomèdica de Bellvitge - IDIBELL, L'Hospitalet de Llobregat, Spain.
[b] Department of Clinical Sciences, School of Medicine, Universitat de Barcelona - UB, L'Hospitalet de Llobregat, Spain.
[c] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal.
[d] ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal.
[e] Psychological Neuroscience Lab, CIPsi, School of Psychology, University of Minho, Braga, Portugal.
[f] Network Center for Biomedical Research on Mental Health (CIBERSAM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
[g] Department of Social Psychology and Quantitative Psychology, Universitat de Barcelona UB, Barcelona, Spain.
[h] 2CA-Clinical Academic Center, Braga, Portugal.

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ABSTRACT

Background: Cognitive regulation can affect the process of decision making. Generalized anxiety disorder (GAD) patients seem to have an impairment in cognitive regulation of reward processing concerning food stimuli. This study aims to explore the impact of GAD in cognitive regulation of food-related rewards.
Methods: GAD patients (n=11) and healthy controls (n=15) performed a cognitive regulation craving task with food images while undergoing a functional magnetic resonance imaging (fMRI) acquisition. Between-group differences in functional connectivity were measured using dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) seeds during cognitive regulation.
Results: During cognitive regulation, there was a significant interaction for functional connectivity between the right dlPFC and bilateral vmPFC with the thalamus. GAD patients had lower functional connectivity for cognitive regulation conditions (distance and indulge) than for the non-regulated condition in these clusters, while control participants presented the opposite pattern. GAD group presented fixed food valuation scores after cognitive regulation.
Conclusions: GAD participants showed inflexibility while valuating food images, that could be produced by cognitive regulation deficits underpinned by functional connectivity alterations between prefrontal regions and the thalamus. These results show cognitive inflexibility and difficulty in the modulation of cognitive responses during decision making in GAD patients.

1. Introduction

Cognitive reward control, defined as the cognitive control of craving for hedonic stimuli, and the cognitive regulation of emotional states are examples of model-based decision making. These strategies seem to share common neurobiological underpinnings, implying the activation of the dorsolateral prefrontal cortex (dlPFC) among other prefrontal regions (Brandl et al., 2019). Moreover, previous functional magnetic resonance imaging (fMRI) studies demonstrated that participants could modulate decision making in various scenarios, such as food selection and craving, through valuation regulation and behavioral control (Ferreira et al., 2019; Hutcherson et al., 2012). The results of these studies suggested that the main areas involved in cognitive regulation are the ventromedial prefrontal cortex (vmPFC) and the dlPFC. The vmPFC is critical for the representation of reward and value-based decision making (Hiser and Koenigs, 2018), while the dlPFC acts in the regulation of the vmPFC during cognitive regulation (Hare et al., 2009; Hutcherson et al., 2012; Kober et al., 2010). The dlPFC is responsible for preserving

* Corresponding author. Phone: 351 253 604928
E-mail address: pedromorgado@med.uminho.pt (P. Morgado).

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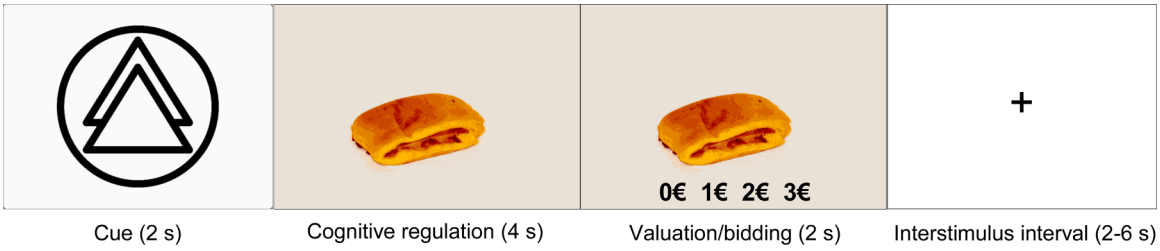

Fig. 1. Representation of the functional magnetic resonance task. The instruction was presented with a cue. After, a food item was displayed, and participants had to cognitively regulate their craving accordingly to the cue (distance - downregulation; natural - no regulation; indulge - upregulation). Participants were asked to give a monetary value to the food item in accordance to their craving (from 0 to 3 €) after cognitive regulation.

Table 1
Results for statistical tests on demographic information and psychometric scales

	GAD	Control	Statistical effect	Test value	*P* value	*E*ffect size
Age	29.0 (17.0)	26.0 (21.5)	Group	$U = 84.0$	$p = 0.958$	
Sex	6 female | 5 male	8 female | 7 male	Group	$\chi^2(1) = 4.0 \times 10^{-3}$	$p = 0.951$	
Education	12.0 (5.0)	17.0 (2.0)	Group	$U = 129.0$	$p = 0.015$	$rc = 0.6$*
Anxiety (BAI)	26.8 ± 17.6	6.0 ± 3.2	Group	$F_{(1, 23)} = 10.0$	$p = 0.004$	$\eta^2 = 0.3$*
			Education	$F_{(1, 23)} = 5.6$	$p = 0.027$	$\eta^2 = 0.1$*
			Group	$F_{(1, 23)} = 7.8$	$p = 0.010$	$\eta^2 = 0.2$*
Depression (BDI)	16.4 ± 12.8	3.3 ± 2.5	Education	$F_{(1, 23)} = 2.1$	$p = 0.159$	
Stress (PSS)	22.8 ± 7.9	10.6 ± 5.8	Group	$F_{(1, 23)} = 10.7$	$p = 0.003$	$\eta^2 = 0.3$*
			Education	$F_{(1, 23)} = 4.0$	$p = 0.056$	

Values represent median (interquartile range) and mean ± standard deviation. *Statistical significance; GAD – general anxiety disorder; BAI - Beck Anxiety Inventory; BDI - Beck Depression Inventory; PSS - 10 items Perceived Stress Scale: rc - rank-biserial correlation.

choice goals while the vmPFC represents the decisions' value relative to the goals (Ochsner et al., 2012). Furthermore, there is evidence that the vmPFC is involved in the generation of negative emotion, such as anxiety and fear (Hiser and Koenigs, 2018). Regarding threat processing, the vmPFC seems to play a very important role as an integrative center essential to behavioral adaptation in both positive and negative contexts. Therefore, the vmPFC might be acting as a connector between anxiety, reward processing and threat systems (Hu, 2018), and, indeed, some studies suggest that individuals with higher levels of trait anxiety or generalized anxiety disorder (GAD) seem to have alterations in this brain area (Hu, 2018; Greenberg et al., 2013).

On this matter, GAD is one of the most common psychiatric disorders, with up to 20% of adults affected each year. It is characterized by a persistent overexpressed worry about everyday life ordinary events, becoming a permanent state of worry (Munir and Takov, 2021). GAD patients tend to overestimate the advantages (Ladouceur et al., 1997) and underestimate the disadvantages of worrying (Brown et al., 1993). They use worry as an ineffective cognitive attempt to problem solving. Anxiety levels seem to interfere with the responses associated with food consumption (Santa Cecília Silva et al., 2017). Regarding the relationship between anxiety and food perception, studies have shown that anxiety can both increase (Hakkarainen et al., 2004; Suzuki et al., 2016; Yannakoulia et al., 2008) or decrease (Deboer and Smits, 2013; Herman et al., 1987) food intake, appetite, and the enjoyment of food. Therefore, it is coherent to examine decision making and cognitive reward regulation in populations with anxiety through a food valuation assessment, as done in previous work with an obsessive-compulsive disorder population (Ferreira et al., 2021). Furthermore, the study of the neural substrates of approach and avoidance processes is relevant for understanding dysfunctions associated with anxiety disorders. Accordingly, value-based decision making tasks, like food valuation, have been previously used to investigate these substrates (Aupperle and Paulus, 2010). Besides the vmPFC, some other relevant brain structures for anxiety, threat and fear are the amygdala, other limbic areas, and the thalamus (Goossen et al., 2019). In particular, the thalamus has a role in behavioral control and emotional processing. Its role in anxiety-like behavior as a regulator structure seems to be highly notorious and it has been shown that activations in some thalamic regions generate anxiety and aversive states (Barson et al., 2020; Kirouac, 2015). Hence, both vmPFC and the thalamus seem to play a crucial role in the regulation of emotional processing in anxious individuals.

On top of that, a recent publication has shown evidence regarding functional connectivity between cortical and subcortical regions in cognitive emotional regulation. The proposed cortical regions implicated are the dlPFC, vmPFC, ventrolateral prefrontal cortex (vlPFC) and the presupplementary motor area (preSMA). Their findings support the vmPFC as the primary conduit through which these regions directly modulate amygdala activity (Steward et al., 2021).

Besides theoretical knowledge, the neurobiological basis of GAD has not been substantially studied yet and there is still a need to go further to bridge the gap between fundamental research and clinical practice (Goossen et al., 2019; Mochcovitch et al., 2014). The aim of this study is to explore cognitive reward control differences between GAD patients and healthy controls (HC) in a food reward-processing task in terms of behavior and brain function and functional connectivity. We used an adaptation of Hutcherson's et al., 2012 task described in Ferreira's et al., 2019 study, which involves cognitive regulation of craving before valuating food pictures. We examined whole-brain activation as well as functional connectivity with the vmPFC and dlPFC, as both areas are relevant for cognitive reward control and model-based decision making processes. We expected to find differences in the behavior between groups, observing them both in self-reported measurements and task activations. In addition, in the GAD group we anticipated to notice less functional connectivity between cortical regions — related to reward processing, decision making and cognitive regulation (vmPFC and dlPFC) — and limbic regions, because of emotional arousal and cognitive regulation impairments related to this population of patients.

2. Methods

2.1. Participants

The study included Portuguese, Caucasian, mostly right-handed (1 left-handed GAD patient) participants. They were eligible if they were at least 18 years old and reported no history of traumatic brain lesion or substance abuse and MRI contraindications.

The GAD group included 11 participants (6 females) with median (interquartile range) age of 29.0 (17.0) years (21 to 44 years) and 12.0

Table 2
Results for statistical tests of behavioral variables associated with the functional magnetic resonance imaging task. Parameters correspond to the valuation before (pre) and after (post) cognitive regulation.

	GAD pre			GAD post			Control pre			Control post			Statistical effect	Test value	*P* value	Effect size
	Distance	Natural	Indulge	Distance	Natural	Indulge	Distance	Natural	Indulge	Distance	Natural	Indulge	Condition (distance, natural, and indulge)	$F_{(2, 46)} = 2.3$	$p = 0.116$	
Reaction time (ms)		-		768.5 ± 189.5	703.3 ± 149.2	774.0 ± 215.4		-		758.8 ± 160.9	699.2 ± 155.3	733.5 ± 170.1	Group × Condition	$F_{(2, 46)} = 0.3$	$p = 0.720$	
													Group	$F_{(1, 23)} = 0.6$	$p = 0.461$	
													Education	$F_{(1, 23)} = 1.1$	$p = 0.303$	
Valuation score (normalized)	0.45 ± 0.12	0.44 ± 0.13	0.47 ± 0.12	0.46 ± 0.10	0.48 ± 0.10	0.50 ± 0.07	0.53 ± 0.13	0.51 ± 0.14	0.54 ± 0.14	0.46 ± 0.08	0.55 ± 0.12	0.62 ± 0.12	Time (before and after cognitive regulation)	$F_{(1, 23)} = 0.1$	$p = 0.801$	
													Group × time	$F_{(1, 23)} = 0.3$	$p = 0.617$	
													Condition	$F_{(2, 46)} = 2.0$	$p = 0.146$	
													Group × condition	$F_{(2, 46)} = 3.0$	$p = 0.061$	
													Time × condition	$F_{(1.3, 30.0)} = 1.1$	$p = 0.324$[a]	
													Group × time × condition	$F_{(1.3, 30.0)} = 6.4$	$p = 0.011$	$\eta^2 = 1.1 \times 10^{-2}$*[a]
													Group	$F_{(1, 23)} = 2.4$	$p = 0.135$	
													Education	$F_{(1, 23)} = 2.4 \times 10^{-2}$	$p = 0.879$	

Values represent mean ± standard deviation.
[*] Statistical significance
[a] Greenhouse-Geisser correction for non-sphericity; GAD – general anxiety disorder

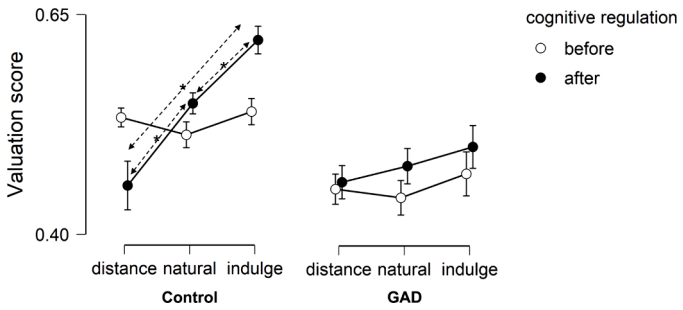

Fig. 2. Representation of the valuation score before (pre-task) and after (during the task) cognitive regulation. The scores were normalized by dividing by the maximum value. The control group modulated the valuation scores accordingly to the regulation condition (*statistically significant differences) while the generalized anxiety disorder (GAD) group presented fixed valuation scores after cognitive regulation. The graphs represent the mean and standard error values.

Table 3
Regions with different functional connectivity during cognitive regulation between the control and generalized anxiety disorder groups using the ventromedial and dorsolateral prefrontal cortical seeds ($p < 0.001$, minimum cluster size of 88 voxels).

Brain regions	Cluster size (voxels)	Peak voxel intensity	MNI peak voxel coordinates (mm)
R dlPFC seed			
L thalamus (pulvinar, ventral posterior lateral nucleus, lateral posterior nucleus); L lentiform nucleus (putamen).	108	17.1	-22 -22 8
R vmPFC seed			
R thalamus (medial dorsal nucleus, ventral lateral nucleus); brainstem, subthalamic nucleus; mammillary body.	96	14.3	10 -14 0
L vmPFC seed			
R thalamus (medial dorsal nucleus, ventral lateral nucleus, and ventral anterior nucleus).	106	14.6	10 -14 4

MNI - Montreal Neurologic Institute; L - left; R - right; dlPFC - dorsolateral prefrontal cortex; vmPFC - ventromedial prefrontal cortex.

(5.0) years of education (5 to 17 years). GAD participants were recruited at *Hospital de Braga* and diagnosed by experienced psychiatrists, using a semi-structured interview based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This clinical assessment allowed to exclude the presence of other psychiatric diagnoses, particularly depression, eating disorders and other anxiety disorders. All patients were medicated with a selective serotonin reuptake inhibitor (SSRI) antidepressant and had no comorbidities. No other medications were allowed.

The healthy control (HC) group included 15 participants (8 females) with no history of psychiatric or neurological conditions, not taking any psychiatric medication, with age of 26.0 (21.5) years (21 to 58 years) and 17.0 (2.0) years of education (11 to 20 years).

The groups were matched for sex (chi-squared test $\chi^2(1) = 4.0 \times 10^{-3}$, $p = 0.951$) and age (Mann-Whitney test $U = 84.0$, $p = 0.958$), but not for education ($U = 129.0$, $p = 0.015$, rank-biserial correlation 0.6), with GAD patients having lower education than controls. Thus, education was used as a covariate in further statistical analyses comparing the groups.

2.2. Sociodemographic and psychological scales

Information on sex, age, educational level and handedness was collected. Weight and height were also measured to prevent the inclusion of participants with an out of normal range body mass index.

Participants also filled the 10 items Perceived Stress Scale (PSS) (Cohen et al., 1983; Morgado et al., 2013), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and the Beck Depression Inventory (BDI) (Beck et al., 1996). The PSS measures last month's perception of unpredictable, uncontrollable, and overloaded life. The higher the score, the greater the intensity of perceived stress. The BAI measures last week severity of an individual's anxiety. Scores lower than 7 indicate minimal anxiety. Scores higher than 7, 15, and 25 indicate mild, moderate, and severe anxiety, respectively. The BDI measures the severity of depression and can be used as a screening tool. Scores lower than 14 indicate minimal depression. Higher scores indicate more severe depressive symptoms. The psychometric differences between-groups were analyzed with ANCOVA using education as a covariate.

2.3. fMRI task

The task was adapted from Hutcherson et al., 2012 and a full description can be found in previous work (Ferreira et al., 2019). It consisted in the valuation of 150 food pictures in two phases: pre-scan valuation task and in-scan regulation task.

The pre-scan valuation task provided a measure of the subjective baseline for food value (from 1, "Don't want it at all" to 4, "Want it a lot"). The in-scan regulation task measured food value (0, 1, 2 or 3€) after the cognitive regulation of craving (4s) for the same pictures randomly separated in three blocks: indulge, distance and natural; where participants tried to increment their craving, decrease it, or just allow spontaneous thoughts, respectively (**Fig. 1**). To increase craving and ensure truthful valuation during the task, participants were instructed to fast for at least 4h before the experiment and were informed that they would be rewarded with the food they obtained using an adapted version of Becker-DeGroot-Marschak auction (Becker et al., 1964; Plassmann et al., 2007).

2.4. Behavioral task fMRI data analysis

Differences in the reaction time during the task while participants bid for food were studied. A mixed-design ANCOVA was used with condition (distance, natural, and indulge) as within-subject factor, group as between-subject factor, and education as covariate.

Additionally, the variation of the food valuation scores after cognitive regulation was analyzed. A mixed-design ANCOVA was used with two within-subject factors (time [before and after cognitive regulation] and condition [distance, natural, and indulge]), group as between-subject factor, and education as covariate. The pre-regulation scores corresponded to the ratings of the food pictures before entering the scanner. The post-regulation scores were the participants' bids after cognitive regulation. Before the statistical analysis, the valuation scores were normalized by dividing them by the maximum value (pre-regulation scores 4, and post-regulation scores 3€).

Post-hoc repeated measures ANOVAs and paired *t*-tests were performed to explore statistically significant effects for interaction and within-subject effects, respectively, using Bonferroni correction for multiple comparisons (p_{bonf}).

2.5. MRI data acquisition

Scans were acquired on a clinical approved 1.5 T Siemens Magnetom Avanto system (Siemens Medical Solutions, Germany) using a 12-channel receive-only head array coil. For the functional acquisition, we used a T2* weighted echo-planar imaging acquisition: 38 interleaved axial slices, repetition time 2750 ms, echo time 30 ms, field of view 224 mm

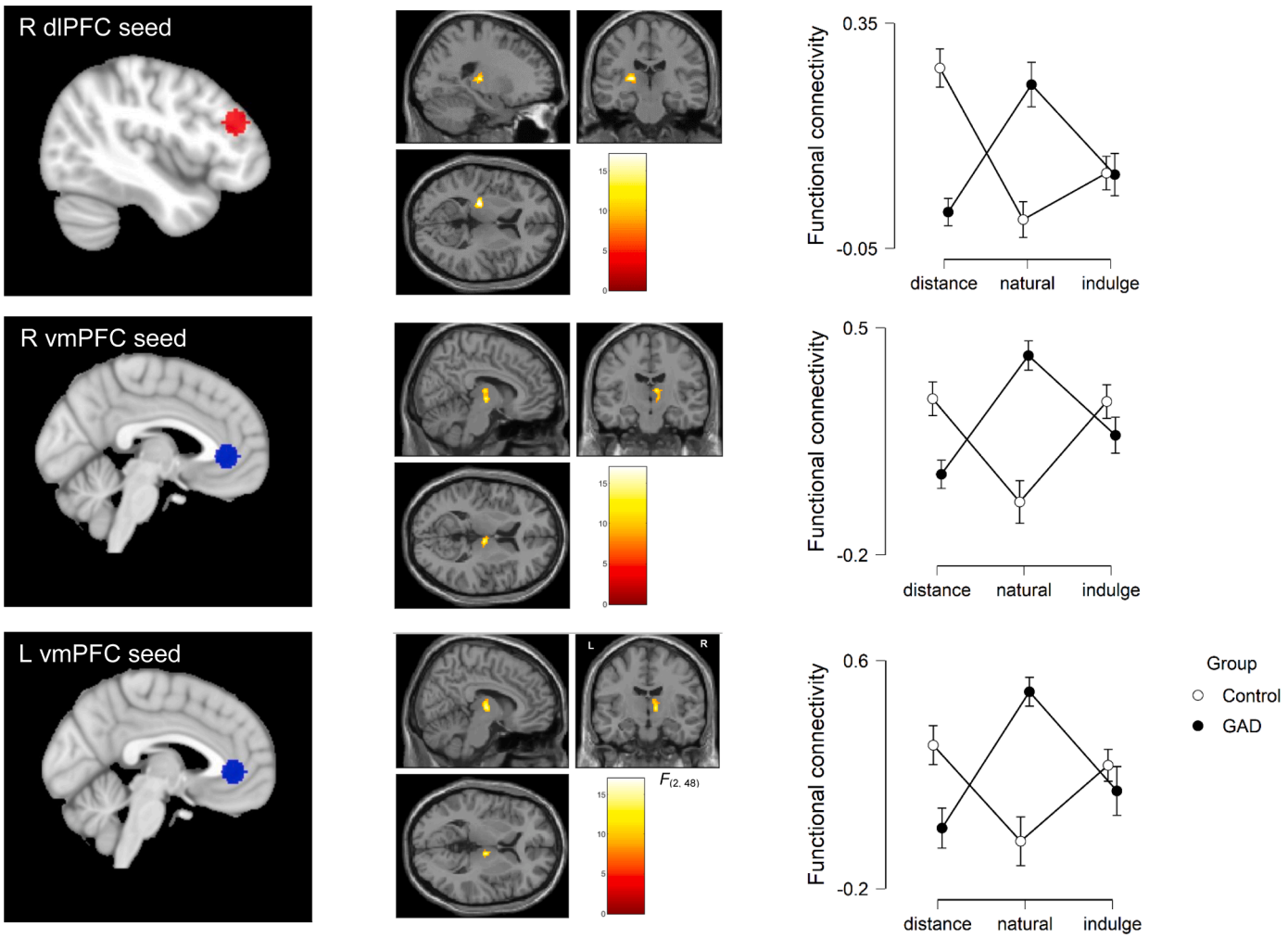

Fig. 3. Representation of statistically significant clusters of functional connectivity resulting from cognitive regulation during the task. We observed an interaction between group and condition (distance, natural and indulge) in all clusters. Post-hoc tests demonstrated that the functional connectivity during the regulated conditions was lower than the non-regulated condition in the generalized anxiety disorder group (GAD) while the opposite was observed for the control group (more information on Table 3 and 4).The graphs represent the mean and standard error values. L - left; R - right; dlPFC - dorsolateral prefrontal cortex; vmPFC - ventromedial prefrontal cortex.

× 224 mm, flip angle 90°, in-plane resolution 3.5 mm × 3.5 mm, slice thickness 3.5 mm, and between-slice gap 0.5 mm. To optimize the sensitivity in the orbitofrontal cortex, a tilted acquisition in an oblique orientation of 30° relative to the anterior-posterior commissure line was used. A total of 650 volumes were acquired during the task. The task stimulus was presented using the fully integrated fMRI system IFIS-SA (Invivo Corporation, United States) and the same system was used to record participants' key-press responses. One high-resolution T1-weighted Magnetization-Prepared Rapid Acquisition with Gradient Echo sequence, with 1 mm × 1 mm × 1 mm voxel size, repetition time 2.73 s, echo time 3.48 ms, flip angle 7°, field of view 234 mm × 234 mm, and 176 slices was acquired. This anatomical sequence was used to project the functional maps.

2.6. fMRI data analysis

The functional scans were preprocessed with the Statistical Parametric Mapping (SPM) version 12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, United Kingdom) using MATLAB version R2018a (The MathWorks Inc., United States). Preprocessing included: slice-timing correction using the first slice as reference; realignment to the mean volume of the acquisition; nonlinear spatial normalization to Montreal Neurological Institute (MNI) standard space and resampling to 2 mm × 2 mm × 2 mm voxel size; spatial smoothing with an 8 mm full-width at half-maximum Gaussian kernel; high pass temporal filtering at 128 s.

For the first-level analysis, one general linear model (GLM) was computed per participant. For this GLM, the regressors of interest included: the type of cognitive regulation trial (1 – distance, 2 – natural, and 3 – indulge) and the corresponding bid (4 – bids after distance trials, 5 – bids after natural trials, and 6 – bids after indulge trials). The bid regressors were parametrically modulated by the bid value (0, 1, 2, and 3€), the pre-rating score before the task (1 to 4), and the reaction time. Additional regressors included: 7 – the cue; 8 – the interstimulus interval; 9 – the omission bids; 10 – 16 the motion parameters estimated during the realignment step. The onset and duration of the regressors were defined according to the stimulus represented in **Fig. 1** with a boxcar function and the regressors were convolved with the canonical hemodynamic response function.

At the group level (second-level analysis), a random-effects analysis was performed using a mixed-design ANCOVA model for cognitive regulation during the task (enabled comparisons in average activation for each regulation trial between and within groups). The group (GAD vs. control) was introduced as the between-subject factor and each trial during cognitive regulation (distance vs. natural vs. indulge) as the within-subject factor. Education was used as a covariate. The model was

Table 4
Results for post-hoc tests on the statistically significant clusters found for cognitive regulation during the task for the interaction Group × condition (p-values with Bonferroni correction).

Statistical effect	Test value	*P* value	*Effect size*
R dlPFC seed			
GAD - Condition main effect	$\boldsymbol{F_{(2,\ 20)} = 11.4}$	$\boldsymbol{p = 9.876 \times 10^{-4}}$	$\boldsymbol{\eta^2 = 0.3}$*
Distance vs. Indulge	t = -1.6	$p = 0.392$	
Distance vs. Natural	t = -5.2	$p = 0.001$	d = -1.6*
Indulge vs. Natural	t = -2.7	$p = 0.070$	
Control - Condition main effect	$\boldsymbol{F_{(2,\ 28)} = 18.7}$	$\boldsymbol{p = 1.369 \times 10^{-5}}$	$\boldsymbol{\eta^2 = 0.4}$*
Distance vs. Indulge	t = 4.1	$p = 0.003$	d = 1.1*
Distance vs. Natural	t = 5.6	$p = 1.905 \times 10^{-4}$	d = 1.4*
Indulge vs. Natural	t = 2.0	$p = 0.205$	
R vmPFC seed			
GAD - Condition main effect	$\boldsymbol{F_{(2,\ 20)} = 14.9}$	$\boldsymbol{p = 2.182 \times 10^{-4}}$	$\boldsymbol{\eta^2 = 0.3}$*
Distance vs. Indulge	t = -1.7	$p = 0.384$	
Distance vs. Natural	t = -6.4	$p = 2.192 \times 10^{-4}$	d = -1.9*
Indulge vs. Natural	t = -3.3	$p = 0.024$	d = -1.0*
Control - Condition main effect	$\boldsymbol{F_{(2,\ 28)} = 10.1}$	$\boldsymbol{p = 9.688 \times 10^{-4}}$	$\boldsymbol{\eta^2 = 0.1}$*
Distance vs. Indulge	t = 0.1	$p = 1.000$	
Distance vs. Natural	t = 3.6	$p = 0.008$	d = 0.9*
Indulge vs. Natural	t = 3.6	$p = 0.009$	d = 0.9*
L vmPFC seed			
GAD - Condition main effect	$\boldsymbol{F_{(2,\ 20)} = 12.4}$	$\boldsymbol{p = 6.248 \times 10^{-4}}$	$\boldsymbol{\eta^2 = 0.4}$*
Distance vs. Indulge	t = -1.1	$p = 0.918$	
Distance vs. Natural	t = -6.7	$p = 1.573 \times 10^{-4}$	d = -2.0*
Indulge vs. Natural	t = -3.5	$p = 0.017$	d = -1.1*
Control - Condition main effect	$\boldsymbol{F_{(2,\ 28)} = 6.3}$	$\boldsymbol{p = 0.012}$	$\boldsymbol{\eta^2 = 0.1}$*
Distance vs. Indulge	t = 0.9	$p = 1.000$	
Distance vs. Natural	t = 2.9	$p = 0.038$	d = 0.7*
Indulge vs. Natural	t = 2.6	$p = 0.066$	

* Statistical significance. L - left; R - right; dlPFC - dorsolateral prefrontal cortex; vmPFC - ventromedial prefrontal cortex; GAD - generalized anxiety disorder.

implemented with the GLMFlex toolbox which uses partitioned error terms for within-group and between-group comparisons, enabling the estimation of all the effects of interest with a single model. Results were considered statistically significant after correcting for multiple comparisons using cluster correction (minimum cluster size of 88 voxels). The minimum cluster size was determined with 3DClustSim (AFNI version 17.0.13; National Institute of Mental Health). This program determines a minimum cluster size with Monte Carlo Simulation to achieve a corrected significance of $p < 0.05$ with an initial voxel-wise threshold of $p < 0.001$. The Automated Anatomical Labeling plugin for SPM was used to classify the brain regions.

2.7. Functional connectivity (FC) analysis

The FC of the dlPFC and vmPFC during the task was also studied by performing generalized psychophysiological (gPPI) analyses (McLaren et al., 2012). Four seed regions with 10 mm radius based on the results from Hutcherson et al., 2012 were defined: right (MNI 6, 39, 0) and left (MNI -6, 39, 0) dlPFC and right (MNI 48, 36, 24) and left (MNI -48, 36, 24) vmPFC. The gPPI beta maps were estimated for the task conditions (distance, natural, and indulge) during cognitive regulation. The GLMFlex toolbox was used to calculate differences between groups in FC using the ANCOVA described above (minimum cluster size of 88 voxels to correct for multiple comparisons) (Do and Telzer, 2019; Humbert and McLaren, 2014; Olivé et al., 2015).

2.8. Statistical analysis

The statistical analysis of psychometric, demographic, and behavioral data was performed with JASP (version 0.11.1.0; JASP Team [2018], The Netherlands). Differences were considered statistically significant if $p < 0.05$.

3. Results

3.1. Psychological and behavioral analysis

The GAD group presented higher values in all psychometric scales, namely, PSS, BAI, and BDI (Table 1).

We did not find statistically significant differences between and within groups nor interaction effects for the reaction time during food valuation (Table 2).

Concerning the valuation score, we found a significant group × time × condition interaction ($F_{(1.3,\ 30.0)} = 6.4$, $p = 0.011$, $\eta^2 = 1.1 \times 10^{-2}$, Greenhouse-Geisser correction for non-sphericity). Post-hoc repeated measures ANOVA (time and condition as within-subjects factors) demonstrated no statistically significant differences in the interaction time × condition for the GAD group ($F_{(2,\ 20)} = 1.5$, $p_{bonf} = 0.508$). For the control group this interaction effect was statistically significant ($F_{(1.2,\ 16.5)} = 18.7$, $p_{bonf} = 5.932 \times 10^{-4}$, $\eta^2 = 0.1$; Greenhouse-Geisser correction for non-sphericity). Further post-hoc repeated measures ANOVA (condition as within-subject factor) yielded statistically significant results after cognitive regulation ($F_{(1.3,\ 18.1)} = 19.1$, $p_{bonf} = 3.104 \times 10^{-4}$, $\eta^2 = 0.3$; Greenhouse-Geisser correction for non-sphericity) but not before cognitive regulation ($F_{(2,\ 28)} = 1.8$, $p_{bonf} = 0.378$) in the control group. Post-hoc paired *t*-test revealed differences among all conditions after cognitive regulation in the control group (distance vs. indulge t = -5.0, $p_{bonf} = 5.895 \times 10^{-4}$, d = -1.3; distance vs. natural t = -3.2, $p_{bonf} = 0.019$, d = -0.8; indulge vs. natural t = 5.0, $p_{bonf} = 6.000 \times 10^{-4}$, d = 1.3). Thus, the control participants modulated their bids for food according to the regulation condition while the GAD group presented fixed food valuation scores after cognitive regulation (Table 2 and Fig. 2).

3.2. Neuroimaging results

We did not find statistically significant differences in activation within and between subjects in whole-brain responses for cognitive regulation during the task. However, we observed statistically significant differences in functional connectivity with the seed regions. There was a statistically significant group × condition interaction for functional connectivity between the right dlPFC with the left thalamus, and between the left and the right vmPFC with the right thalamus (Table 3 and Fig. 3). Post-hoc tests with repeated measure ANOVA (condition as within-subject factor) and paired *t*-tests between conditions for each group demonstrated that GAD patients had lower functional connectivity for regulated conditions (distance and indulge) than for the natural condition in these clusters, while the control participants presented the opposite pattern (Table 4).

4. Discussion

To explore the neurobiological correlates of cognitive reward control of model-based decision making between GAD patients and healthy controls, we performed a food valuation task focused on cognitive regulation.

As expected according to GAD symptomatic manifestations, we found that the GAD group presented more anxiety, stress, and depressive symptoms than the HC group. Patients with GAD usually have comorbidities with other mental disorders, and its connectedness with depression seems to be notable (Price et al., 2019). Nonetheless, our study sample did not have comorbidities and these symptoms might be

explained by the GAD diagnosis itself.

The results obtained during the food valuation task showed a tendency that the GAD group might have not performed an effective cognitive regulation, based on the lack of differences in valuation scores before and after applying the regulation. This may suggest inflexibility and that these individuals cannot recruit the brain areas required for the process of regulation, which is in line with previous fMRI studies (Görgen et al., 2014). Furthermore, some systematic reviews have suggested that emotional dysregulation as a cognitive dysfunction in GAD patients is related to prefrontal and anterior cingulate cortices hypofunction, as well as deficient cortex-amygdala functional connectivity (Goossen et al., 2019; Mochcovitch et al., 2014). Therefore, it would be interesting to further explore if cognitive reward control and emotional regulation are indeed interconnected processes. In this case, the cortex-amygdala-thalamus system might be impaired in GAD patients, who are also characterized by autonomic dysregulation as a main clinical manifestation (Makovac et al., 2016).

The subjective value given to food would be modified by personal perception or emotional value given to it. Coupled with the fact that anxiety levels seem to interfere with food associated responses (Santa Cecília Silva et al., 2017), GAD patients are characterized by having emotional dysregulations which make harder for them to solve some problematic situations (Behar et al., 2009). The above may be affecting the valuation part of the decision making process, making them unable to achieve differences even when they try to regulate their cognition. Consequently, value-based decision making tasks have been used to investigate the neural dysfunctions found in people with anxiety, as in the present study. In particular, prefrontal cortex dysfunction has been repeatedly implicated across anxiety disorders (Aupperle and Paulus, 2010).

The flexibility of dlPFC attribute representations may be especially important for compensating when regulation of the vmPFC fails, a finding also observed in other studies of cognitive regulation. Previous exploratory connectivity results suggested that this may derive, at least in part, from functional interactions with the vmPFC area that represented all choice-relevant attributes, with the strength of connectivity between dlPFC and vmPFC correlating with regulatory success (Tusche and Hutcherson, 2018). Moreover, it has been described that people with anxiety and related disorders show cognitive inflexibility and related impairments, which is directly related with the prefrontal cortex (Park and Moghaddam, 2017).

We sought for differences in FC using the dlPFC as seed. The dlPFC is key in cognitive regulation, modulating vmPFC activity which is important for reward valuation, linked to emotional value encoding and valuation process (Hare et al., 2009; Hutcherson et al., 2012; Kober et al., 2010). Our results demonstrated a contrasting pattern of FC between groups during regulation and no-regulation conditions. While GAD patients had more FC between the dlPFC/vmPFC and thalamus during the natural condition, the HC group had lower FC, and, when the regulation (up- or down-regulation) started, the FC increased in the HC group and decreased in GAD group. The fact that GAD patients had stronger dlPFC/vmPFC-thalamic connections during the natural condition may be linked to the concept of GAD patients maintaining a permanent state of worry as a strategy for constant emotional regulation (Saviola et al., 2020). It is worth mentioning that another explanation for these changes in FC might involve the thalamus directly. Studies have shown that hyperactivation of the thalamus might be associated with an increase in emotional distress and dysregulation (Geng et al., 2018; Mizuno-Matsumoto et al., 2013). Our results suggest that thalamus is recruiting dlPFC and vmPFC for regulation, as it is known to happen in other studies (Hutcherson et al., 2012). As recently described, it seems that a network involving different prefrontal regions, including the dlPFC and the vmPFC, is modulating subcortical structures, as the amygdala (Steward et al., 2021). Hence, the role of the thalamus in these complex networks should be furtherly studied to fully understand cortical/subcortical interactions. In this sense, the decreased connectivity that our GAD patients are showing could be implying a potential mechanism of their cognitive dysregulation.

Importantly, even though our sample did not have comorbidities, we cannot ensure that these differences are exclusively due to GAD trait because of the existent symptomatic manifestations of stress and depression. It would be interesting to compare these results with other types of anxiety disorders and stress, depression, or obsessive-compulsive disorder (OCD) groups, looking for differences or similarities. Interestingly, in one of our previous works with the same fMRI task in OCD participants, we observed similar valuation score results after regulation (Ferreira et al., 2021).

The main limitation of this study is the reduced number of participants, and that sample size assessment was not performed. We are aware that similar paradigms that study cognitive regulation and reward processes with a greater number of participants should be performed to have more robust results. In this line, during cognitive regulation it is expected, as documented before, to detect differences like decreasing dlPFC and increasing vmPFC activations (Hutcherson et al., 2012). We did not find such differences in our study, and this could be due to a lack of statistical power because of our small sample size. Nevertheless, we believe that our findings regarding connectivity among key areas of the prefrontal cortex and thalamus are a relevant addition to the existing literature, due to the reasons discussed earlier. Moreover, the selected task is specific to cognitive regulation of food craving. Therefore, our outcomes cannot be generalized to other forms of cognitive regulation or to other disorders. Another important limitation was the 1.5T MRI scan used, as we are aware that stronger magnetic fields are currently recommended for this type of behavioral studies. Lastly, our sample had a significant difference among groups regarding level of education. We used this variable as a covariate in analyses, but we are aware it might have not been enough.

Our results showed that GAD patients might experience difficulties in the cortical regulation of subcortical structures, specifically the thalamus, which might be causing them additional emotional distress and dysregulation; which could explain their behavioral inflexibility observed during the food valuation task. As cognitive reward control and emotional regulation systems seem to be highly interrelated, further studies trying to identify their differences and commonalities in specific clinical populations are needed to better understand the decision making process.

Data availability

The data that support the findings of this study and the brain maps of all analyses are available from the corresponding author upon reasonable request.

Ethics statement

This study was carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent. The protocol was approved by the Ethics Subcommittee for the Life and Health Sciences of University of Minho, Portugal, and by the Ethics Committee of the *Hospital de Braga*, Portugal.

Declaration of Competing Interest

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5. Discusión

5.1 Discusión global

Cada uno de los artículos que forman parte de la presente tesis doctoral cuenta con su propia discusión, incluida en cada publicación. A continuación, se presenta una discusión global que hace referencia al conjunto de resultados de los tres artículos.

A pesar de las diferencias en los enfoques metodológicos, las características de los grupos clínicos estudiados, y los centros de recolección de datos, los tres artículos se caracterizan por encontrar resultados en la misma dirección: los grupos de pacientes presentan algún tipo de alteración neurobiológica al ser comparados con los participantes sanos. Sin embargo, dichas alteraciones se observaron tanto a nivel regional como a nivel sistémico, así como en la conectividad entre distintas regiones de interés. Estos resultados se encuentran en sintonía con diversas investigaciones anteriores (43,68–70).

Tomando como punto de partida el modelo de regulación emocional propuesto por Steward *et al*., 2021 (18)(ver **Figura 1**), es particularmente interesante apreciar que los resultados de los artículos se enfocan en esas mismas áreas, cuando se toman como conjunto. El patrón de alteraciones prefrontales observado en los pacientes con TLP y TDM en la CPFvl, la CPFdl y la COF del artículo 1, sumado con las dificultades en la conectividad entre la CPFdl y la CPFvm con el tálamo durante el control cognitivo de las recompensas de pacientes con TAG del artículo 3, respaldan el modelo de interacciones entre todas estas áreas necesario para la adecuada regulación de las emociones. A pesar de que estos artículos estudiaron procesos distintos, se ha planteado que la regulación cognitiva de las recompensas y la regulación emocional comparten vías neurobiológicas comunes asociadas a la toma de decisiones (8). Por lo tanto, los resultados de esta tesis, al ser interpretados en conjunto, recalcan la importancia del modelo donde distintas áreas de la corteza prefrontal interactúan de forma coordinada con las estructuras subcorticales para generar un procesamiento emocional óptimo que lleve al bienestar mental. Por el contrario, alteraciones en este sistema se encuentran asociadas a la psicopatología (12,17,18,31). Serán necesarios, por tanto, estudios

adicionales de esta temática, explorando las interacciones y alteraciones en múltiples trastornos mentales, así como el desarrollo de terapéuticas fundamentadas en las interrelaciones propuestas por este modelo.

Pese a que el enfoque del artículo 2 es metodológicamente distinto y se caracteriza por alteraciones en redes completas, el resultado principal del mismo sobre la red frontotemporal está alineado también con el mismo modelo regulatorio anteriormente mencionado. Dicha red está compuesta por áreas relevantes que incluyen a la corteza prefrontal, la corteza temporal, el giro fusiforme, la precuña en la corteza parietal y algunas áreas subcorticales, siendo de particular interés zonas de la CPFvm y el AMPreS. De esta manera, esa red estaría vinculada a los resultados del artículo 1 y 3. Desafortunadamente, el enfoque utilizado por redes no permite evaluar las interacciones entre las diferentes áreas de la misma red, pero sin duda marca ciertas deficiencias en conectividad que presentaron los pacientes con TOC. No obstante, el artículo 3 brinda resultados desde un punto de vista más sistémico que resulta más novedoso en la patología estudiada (54,71). Investigaciones que analicen las interacciones entre áreas dentro de una misma red, como a través del modelado casual dinámico, deberían ser más exploradas en trastornos específicos para tener un mejor entendimiento de la conectividad funcional en esas patologías.

Tomando en cuenta los argumentos anteriores, se refleja la complementariedad que existe entre los artículos compilados. Por una parte, como se ha mencionado, agrupan resultados en áreas regulatorias de interés, pero también ligan dichas áreas con regiones de modulación perceptual o cognitiva (8,72,73). Al ser tomados como un conjunto, los distintos trastornos muestran diferencias en las alteraciones neurobiológicas de regulación emocional. En el TLP se observa una alteración característica en la modulación perceptual y en el TDM una alteración propiamente de la regulación emocional, mientras que en el TOC y el TAG se presentan dificultades entre las áreas frontales y las subcorticales como la amígdala y el tálamo, respectivamente. Se puede consultar la **Figura 4** a modo de resumen.

Haciendo referencia a las estrategias de regulación estudiadas, los artículos 1 y 2 utilizan exactamente la misma tarea de reevaluación cognitiva, por lo que los resultados pueden ser interpretados bajo una misma línea. Las dificultades observadas con respecto a esta estrategia adaptativa en tres diferentes poblaciones clínicas (TDM, TLP y TOC)

va de la mano con investigaciones anteriores (17,19,31,60). Este argumento refuerza la idea de una relación existente entre la psicopatología y el uso de estrategias desadaptativas (12). En este mismo sentido, el artículo 3 denota que los pacientes con TAG presentan cierto grado de inflexibilidad cognitiva que los podría estar llevando a la selección de estrategias de regulación emocional menos adaptativas (74).

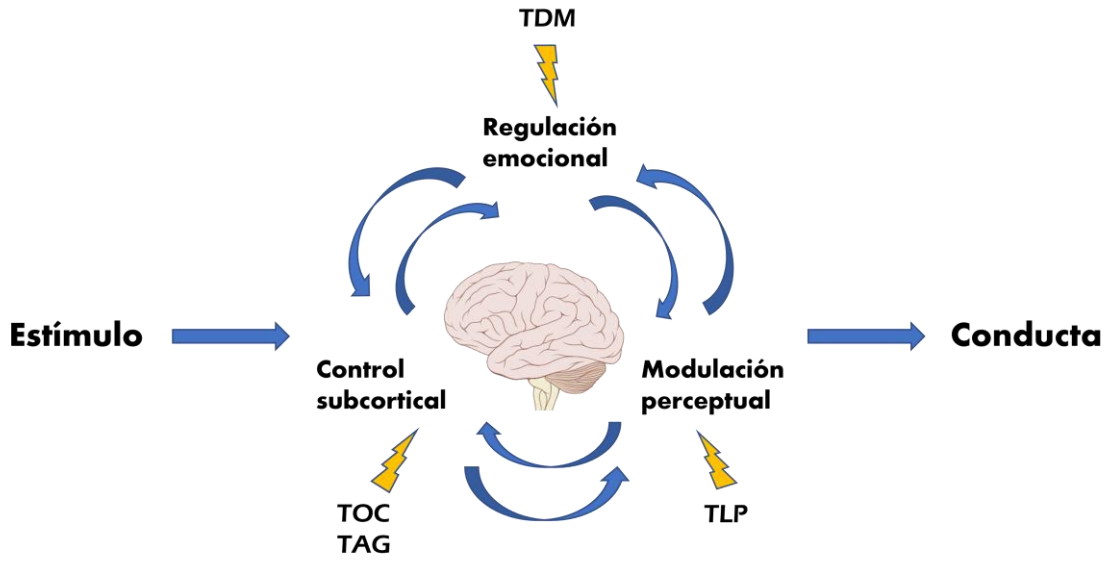

Figura 4. Resumen de interacciones entre los trastornos estudiados y los procesos neurobiológicos: los resultados de los artículos muestran diferencias en las alteraciones neurobiológicas en cada uno de los trastornos estudiados mostradas con los rayos. *Abreviaturas: TAG, trastorno de ansiedad generalizada; TDM, trastorno depresivo mayor; TLP, trastorno límite de la personalidad; TOC, trastorno obsesivo compulsivo.*

De manera interesante y en acuerdo con la bibliografía (75–77), en los artículos 1 y 2, los resultados neurobiológicos correlacionaron con mediciones sintomáticas específicas para los trastornos, asociando a los pacientes con TDM con rumiación y a los pacientes con TOC con obsesiones. En relación con lo anterior, los pacientes con TLP no presentaron ninguna asociación, pero existía la limitación de no haber incluido escalas de medición específicas para sintomatología de TLP. Por su parte, el artículo 3 tampoco cuenta con este tipo de correlaciones, pero representa la muestra más pequeña y menos significativa del conjunto. Sin embargo, la presencia de inflexibilidad cognitiva aunada a los problemas de conectividad en los pacientes con TAG podría estar haciendo referencia a defectos conductuales que comparten fundamentos neurobiológicos en esta población. El hecho de hallar estas correlaciones es relevante, porque crea un marco de referencia en el cual existe un enlace entre las manifestaciones clínicas y las

alteraciones cerebrales de los trastornos mentales. Esos hallazgos apoyan la necesidad de encontrar terapias basadas en resultados de estudios de investigación con neuroimagen.

Las disciplinas asociadas a la salud mental como la psicología, la psiquiatría y las neurociencias de ninguna manera se encuentran desconectadas entre sí. Estudios y exploraciones como la presente tesis doctoral, manifiestan sus vínculos y buscan conexiones entre las ciencias clínicas y la investigación neurocientífica como la neuroimagen.

5.2 Limitaciones

La presente tesis cuenta con algunas limitaciones que deben ser consideradas. Con excepción del artículo 2, las muestras utilizadas en los otros dos artículos son relativamente pequeñas y podrían representar un problema de poder estadístico o ser poco representativas. Estudios con un mayor número de pacientes, especialmente en patologías menos investigadas como el TLP, deben llevarse a cabo para ampliar el entendimiento de los fundamentos neurobiológicos de las mismas.

Por otro lado, los datos del artículo 3 se adquirieron con un escáner de IRM de 1,5 Teslas, cuyo poder de resolución no es óptimo para investigaciones recientes y, ahora, se prefieren estudios con escáneres de 3 Teslas como mínimo.

Una limitación importante con respecto a obtener conclusiones sobre la reevaluación cognitiva es que no se ha utilizado la misma tarea o paradigma de IRMf en los tres artículos; la tarea específica de reevaluación cognitiva solamente fue utilizada en los primeros dos artículos, por lo que no se puede concluir acerca de este proceso en todos los trastornos estudiados en esta tesis doctoral. Sin embargo, lo anterior no quiere decir que no se puedan discutir los resultados desde un punto de vista más general, enfocado en la regulación emocional y no únicamente en la reevaluación.

Finalmente, cabe destacar que los criterios de inclusión para los pacientes con relación al estadio de la enfermedad y al uso de fármacos para su tratamiento tampoco están unificados al haberse recolectado en distintos centros hospitalarios y países. Lo anterior implica la presencia de un sesgo por efecto de la medicación o por la gravedad

o etapa clínica de cada una de las patologías estudiadas. Dicho sesgo debe ser tomado en cuenta, para tener cautela en las interpretaciones de ciertos resultados.

5.3 Fortalezas

Las fortalezas de esta tesis doctoral se centran en su particular enfoque metodológico y en la diversidad de patologías estudiadas. Los estudios de neuroimagen funcional son costosos y las muestras generalmente pequeñas, por lo que recopilar muestras de distintos trastornos que estudien un proceso como eje central es una ventaja para la interpretación de resultados y la evaluación de hipótesis. En esta compilación se estudiaron alteraciones en la regulación emocional de cuatro trastornos distintos y prevalentes, comparándolos siempre con muestras de sujetos sanos como grupo control.

Por otra parte, la combinación de diferentes metodologías de neuroimagen aporta una gran fortaleza a la tesis porque, de esta manera, es capaz de abordar los correlatos neurobiológicos desde varios puntos de vista: activación cerebral de regiones de interés, activación de redes neuronales y conectividad funcional. Se han logrado examinar dos distintos paradigmas de neuroimagen, así como vincular a los procesos que estudiaban. Obtener resultados en una misma línea con distintos métodos les brinda robustez a las conclusiones del presente trabajo.

Por último, el desarrollo de los proyectos de investigación presentados ha sido multicéntrico, lo que les aporta mayor validez externa a los resultados. En este mismo sentido, dichos proyectos se sustentaron por importantes financiaciones y se realizaron por potentes grupos de investigación especializados en técnicas de neuroimagen con equipos multidisciplinarios. Lo anterior respalda una adecuada recolección de datos, así como calidad en el análisis e interpretación de éstos.

5.4 Implicaciones

La importancia de la investigación en medicina traslacional recae en el hecho de poder obtener resultados en entornos que quedan fuera de la investigación clínica y poderlos traspasar a contextos clínicos en donde finalmente resulten provechosos para la población general. El tema de la presente tesis se centra en una problemática relativa a la salud mental. Se presupone, a nivel general, que los resultados obtenidos pueden tener un efecto positivo sobre el diagnóstico y tratamiento de ciertos trastornos. El

conjunto de resultados de los artículos que compila esta tesis enmarca ciertos fundamentos neurobiológicos de aspectos regulatorios de las emociones en cuatro patologías comunes en la población general. Esta información es relevante ya que denota un común denominador tanto conductual como neuronal de la patología mental. La regulación emocional y sus fundamentos neurobiológicos deben ser tomados en cuenta a la hora del diagnóstico clínico y, sobre todo, durante el tratamiento.

Los tratamientos enfocados en mejorar los sistemas cerebrales y conductuales asociados a la regulación emocional, así como las terapias encaminadas al aprendizaje y utilización de estrategias regulatorias más adaptativas, podrían representar una gran ventaja sobre el curso clínico de estos trastornos. Intervenciones novedosas orientadas a la mejoría de estos procesos emocionales a través de enfoques neurobiológicos como la estimulación magnética transcraneal (EMT), la estimulación cerebral profunda, y la neurorretroalimentación entre otras, requieren mayor investigación y desarrollo. Dicho lo anterior, los resultados compilados en el presente trabajo cuentan con implicaciones clínicas y terapéuticas relevantes.

6. Conclusions

- We observed alteration in emotional regulation alterations when comparing healthy controls with clinical populations of the following disorders: major depressive disorder (MDD), borderline personality disorder (BPD), obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD).

- We identified a shared neurobiological pattern of emotion regulation deficits between MDD and BPD. Nevertheless, in MDD outcomes suggest a primary deficit in prefrontal activation, while BPD could be better defined by connectivity disruptions between prefrontal and temporal regions.

- In patients with OCD, we observed a decreased activation of specific brain networks, involving frontal regions, during cognitive reappraisal.

- Cognitive inflexibility and difficulties in the modulation of cognitive responses during decision making in GAD patients could be associated with a wider cognitive emotional alteration in this population.

- Differences found in each disorder help to better characterize a distinctive pathophysiological profile of emotional processing, as well as the psychological processes accounting for disorder-specific symptomatology.

- Neuroimaging, specifically functional magnetic resonance imaging (fMRI), seems to be a useful tool to study emotion regulation alterations, and, particularly, cognitive reappraisal, in clinical populations. Our knowledge will increase, however, with the continued use of novel and more precise neurobiological recording tools.

- The results of the present thesis are relevant in the sense that they provide information of utility for the design of therapeutic strategies aimed to enhance emotional regulation processes in patients with a variety of mental health pathologies.

7. English abstract

Introduction

The processing of emotions is essential for the human experience and a proper cognitive regulation of this process is crucial for well-being and mental health. Hence the need to study the relationship between psychopathology and emotional regulation alterations arises. This need has had a growing interest inside the scientific community in recent years. It prevails to try to fully understand this complex process, specifically from a neurobiological point of view.

Hypothesis

Difficulties (i.e., lack or failure) in emotional regulation are presumed to be present in several mental pathologies and are an integral part of their pathophysiology.

Aim

The aim of this work is to investigate the neurobiological underpinnings of emotional regulation alterations, through functional neuroimaging techniques in different clinical populations.

Methods

Different emotional regulation traits were studied using neuroimaging techniques in several research units, focusing on the following mental disorders: major depressive disorder (MDD), borderline personality disorder (BPD), obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD). In all cases the clinical populations were compared with a sample of healthy controls. These techniques were performed by two tasks designed for the analysis of functional magnetic resonance imaging (fMRI). Subsequently, whole-brain activations, functional connectivity between regions of interest and the rest of the brain, and brain networks were examined using independent component analysis (ICA).

Main results

In all the samples of subjects with the studied disorders, statistically significant alterations were found during emotional regulation. Among these subjects, outcomes were found regarding activation problems of key regulatory areas, difficulties in functional connectivity between regulatory areas and other regions of specific relevance, and network-level alterations. Some of these findings were correlated with specific behavioral scales for each pathology.

Conclusions

It can be concluded that the deficit observed in the process of regulating emotions is a common denominator in mental health pathologies. However, disorder-wise specific differences in the deficiencies of the process can be found. This finding improves the functional characterization of these disorders. The study of these neurobiological underpinnings is relevant, since it allows the design of therapeutic strategies aimed to enhance the process of emotional regulation in patients with different mental health pathologies.

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Declaración de código ético y buenas prácticas

EL DOCTORANDO

Don **Víctor de la Peña Arteaga,** con DNI **60023193R** declara que la tesis que presenta no contiene plagio, manifiesta conocer y consiente en que la tesis podrá ser sometida a procedimiento para comprobar su originalidad.

Firma Doctorando

EL DIRECTOR

El Doctor **Carles Soriano Mas,** declara que se han cumplidos los códigos éticos y de buenas prácticas, y que no tiene conocimiento de que se haya producido ningún plagio.

Firma Director