UNIVERSITAT DE BARCELONA

Multimodal Neuroimaging of Emotion Regulation Strategies in Clinical and Healthy Control Samples

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CERTIFY that they have guided and supervised this doctoral thesis entitled **"Multimodal Neuroimaging of Emotion Regulation Strategies in Clinical and Healthy Control Samples"**, which is presented in order to obtain the title of doctor by the candidate Maria Picó Pérez. They thereby assert that this thesis fulfills all the required criteria to be defended.

“Always look at the bright side of life,

(whistles)”

Monty Python's Life of Brian

“It’s a popular fact that 90 percent of the brain is not used and,

like most popular facts, it is wrong. ... It is used.

One of its functions is to make the miraculous seem ordinary,

to turn the unusual into the usual.

Otherwise, human beings, faced with the daily wondrousness of everything,

would go around wearing a stupid grin, saying “Wow,” a lot.

Part of the brain exists to stop this from happening.”

Terry Pratchett, Small Gods

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Foreword

This thesis has been developed within the framework of the Doctoral Program in Medicine and Translational Research at the University of Barcelona. All the research results included have been developed in the Laboratory of Neuroimaging and Mental Health within the Department of Psychiatry at Bellvitge University Hospital. This unit is linked to the Department of Clinical Sciences of the University of Barcelona and is part of the research group in Psychiatry and Mental Health of Bellvitge Biomedical Research Institute (IDIBELL, Catalan acronym). This group is a consolidated research group of the Government of Catalonia (2017 SGR 1247) and the Biomedical Research Networking Centre in Mental Health (CIBERSAM, Spanish acronym) of the Carlos III Health Institute. Part of the work was conducted in collaboration with the Department of Psychiatry and Mental Health of the Groote Schuur Hospital, Cape Town, South Africa, under the supervision of Prof. Dr. Dan J. Stein.

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The present thesis includes four accepted peer-reviewed journal articles, three of them already published and another one currently in press. It has been written in accordance with the procedures indicated by the University of Barcelona and it is presented in order to obtain the International Doctorate award, which is granted by this Institution. The supervisors of this thesis are Dr. Carles Soriano-Mas and Dr. M. del Pino Alonso.

With regards to the structure of the thesis, after a general introduction on emotion regulation, and a methodology section particularly focused on the different neuroimaging analyses techniques used, results of these four studies are reported in the following order:

1. **Picó-Pérez M**, Alonso P, Contreras-Rodríguez O, Martínez-Zalacaín I, López-Solà C, Jiménez-Murcia S, Verdejo-García A, Menchón JM, Soriano-Mas C (2017). Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity. Brain Imaging Behav, 12(4):1022-1031. doi: 10.1007/s11682-017-9762-3.

2. **Picó-Pérez M**, Ipser J, Taylor P, Alonso P, López-Solà C, Real E, Segalàs C, Roos A, Menchón JM, Stein DJ, Soriano-Mas C (2018). Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder. *In press.*
3. Steward T*, **Picó-Pérez M***, Mata F, Martínez-Zalacaín I, Cano M, Contreras-Rodríguez O, Fernández-Aranda F, Yucel M, Soriano-Mas C, Verdejo-García A (2016). Emotion regulation and excess weight: impaired affective processing characterized by dysfunctional insula activation and connectivity. PLoS One 11(3):e0152150. *Co-first Authorship.
4. **Picó-Pérez M**, Radua J, Steward T, Menchón JM, Soriano-Mas C (2017). Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. Prog Neuropsychopharmacol Biol Psychiatry, 79(Pt B): 96-104. doi: 10.1016/j.pnpbp.2017.06.001. Epub 2017 Jun 1. Review.

In the final part of the thesis, a general discussion is developed and a list of references is attached. An abstract in Catalan is also included with a similar structure to that disclosed. Finally, it should be mentioned that the present thesis' results have been presented in several international congresses as poster and abstract publications: 10th FENS Forum of Neuroscience, July 2016, Copenhagen; European College of Neuropsychopharmacology (ECNP) Workshop on Neuropsychopharmacology for Junior Scientists, March 2017, Nice; 30th European College of Neuropsychopharmacology (ECNP) Congress, September 2017, Paris; 73rd Annual Meeting of the Society of Biological Psychiatry (SOBP), May 2018, New York; 11th FENS Forum of Neuroscience, July 2018, Berlin. Moreover, these results have also been presented in the form of oral communications in national congresses: III Biomedical Research Congress (CIB), February 2015, Valencia; IX National Congress of Psychology Students (CNEP), March 2015, Valencia; 68th Conference of the Catalan Society of Neuropsychology, June 2016, Barcelona.

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aprenia apareixien 5 més que no entenia, tot pareguera més fàcil i interessant. Gràcies pel suport i la paciència. Trevor, compañero de papers. Aún me acuerdo de cuando Carles me dijo que ese año tendría que supervisar a un alumno de máster, y de decirte que no tenía mucho que enseñarte pero que lo iríamos descubriendo juntos. Podría decirse que no nos ha ido tan mal, ¿no? Gracias por complementar mis carencias, y por afrontar cada reto con optimismo. Parte de esta tesis es también tuya. Oren, per mi has sigut casi una directora de tesi més. Gràcies per tots els consells i les ensenyances, ets un exemple de com quan una s'esforça i li apassiona el que fa, abans o després arriba la recompensa. Continua inspirant a futures estudiants com m'has inspirat a mi. Inés i Maria, Maria i Inés. Gràcies per la vostra amistat, pel suport incondicional. Sé que no exagere al dir que aquest camí no hauria sigut el mateix sense vosaltres. Confío en que nos espera un largo recorrido por delante juntas, y tengo mucha curiosidad por ver en las pedazo de IPs en que os convertiréis.

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Per suposat, moltes gràcies també a la meua família. Als meus pares, per inculcar-me la cultura de l'esforç, sense la qual seria impossible haver arribat fins ací, i per respectar sempre les meues decisions. Moltes gràcies *Hermanitos*. M'heu ajudat a prendre decisions rellevants, però a més, com a germana xicoteta, he après i m'he aprofitat de manera vicària de totes les vostres experiències, dels vostres èxits, dels vostres fracassos. És evident que heu influït i molt en el que he sigut, soc i seré, i també en el que aconseguit. Aquest "èxit" és també vostre.

Juanca, el company més proper a tota aquesta història. Has sigut comprensiu més enllà de l'imaginable amb l'estil de vida que he dut aquests anys, de pràcticament avisar-te hui que demà me'n vaig de congrés, d'estades per ací i estades per allà. Estic profundament agraïda a aquell agost de 2013, ja que aquest camí només l'hauria pogut compartir amb algú com tu. A més, Barcelona i la nostra relació sempre estaran profundament lligades. Per molt que m'haja agradat queixar-me del preu dels alquilers, les distàncies i les multituds, aquests anys han sigut infinitament millors per tindre't a tu al meus costat. Hem après junts, hem crescut junts, hem viatjat i viscut mil experiències, però el més important: ens hem divertit. I si una cosa és segura és que ens seguirem divertint (més encara amb l'arribada de Ralf!), visquem en Almoines o en Braga, i siga el que siga que ens depare aquest futur incert.

List of Abbreviations

5-HTT	Serotonin Transporter Gene
ACC	Anterior Cingulate Cortex
ACT	Acceptance and Commitment Therapy
AD	Axial Diffusivity
AES-SDM	Anisotropic Effect-Size Signed Differential Mapping
AI	Anterior Insula
APA	American Psychiatric Association
BD	Bipolar Disorder
BIS-11	Baratt Impulsiveness Scale-11
BLA	Basolateral Amygdala
BMI	Body Mass Index
BNST	Bed Nucleus of the Stria Terminalis
BOLD	Blood-Oxygen-Level Response
BPD	Borderline Personality Disorder
CERQ	Cognitive Emotion Regulation Questionnaire
CMA	Centromedial Amygdala
CO_2	Carbon Dioxide
COMT	Catechol-*O*-Methyltransferase Gene
DERS	Difficulties in Emotion Regulation Scale
dACC	Dorsal Anterior Cingulate Cortex
DBS	Deep Brain Stimulation
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
DWI	Diffusion-Weighted Imaging
EEG	Electroencephalography
EMG	Electromyography
EPM	Extended Process Model
ERI	Emotion Regulation Interview
ERQ	Emotion Regulation Questionnaire
FA	Fractional Anisotropy

FDR False Discovery Rate

fMRI Functional Magnetic Resonance Imaging

fNV Fractional Volume

FWE Family-Wise Error

GAD General Anxiety Disorder

GM Gray Matter

HARS Hamilton Anxiety Rating Scale

HC Healthy Controls

HDRS Hamilton Depression Rating Scale

IAPS International Affective Picture System

ICA Independent Component Analysis

IOG Inferior Occipital Gyrus

LA Left Amygdala

LPP Late Positive Potential

MD Mean Diffusivity

MDD Major Depressive Disorder

MNI Montreal Neurological Institute

MRI Magnetic Resonance Imaging

MTG Middle Temporal Gyrus

MTL Medial Temporal Lobe

NFB Neurofeedback

NIMH National Institute of Mental Health

OC Obsessive-Compulsive

OCD Obsessive-Compulsive Disorder

OFC Orbitofrontal Cortex

PAG Periaqueductal Gray

PANAS Positive and Negative Affect Schedule

PCA Principal Component Analysis

PCC Posterior Cingulate Cortex

PCG Post-Central Gyrus

PD Panic Disorder

PFC Prefrontal Cortex

PPI Psychophysiological Interaction

PTSD Posttraumatic Stress Disorder

PVA	Perception-Valuation-Action
RA	Right Amygdala
rACC	Rostral Anterior Cingulate Cortex
RD	Radial Diffusivity
RDoC	Research Domain Criteria
rmPFC	Rostromedial Prefrontal Cortex
ROI	Region of Interest
rTMS	Repetitive Transcranial Magnetic Stimulation
sgACC	Subgenual Anterior Cingulate Cortex
SMA	Supplementary Motor Area
SPL	Superior Parietal Lobule
SPM	Statistical Parametric Map
SPSS	Statistical Package for the Social Sciences
STG	Superior Temporal Gyrus
STS	Superior Temporal Sulcus
SUD	Substance Use Disorder
TAS-20	Toronto Alexithymia Scale-20
tDCS	Transcranial Direct Current Stimulation
TFCE	Threshold-Free Cluster Enhancement
TPJ	Temporoparietal Junction
vACC	Ventral Anterior Cingulate Cortex
VBM	Voxel-Based Morphometry
vlPFC	Ventrolateral Prefrontal Cortex
vmPFC	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area
WM	White Matter
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YFAS	Yale Food Addiction Scale

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INTRODUCTION

1. Introduction

1.1. Theoretical background of emotion and emotion regulation

Emotions are an essential part of our lives. They direct attention to key features of the environment, optimize sensory input, adjust decision making, prepare behavioral responses, facilitate social interactions, and enhance episodic memory (Gross, 2014). However, emotions can harm as well, particularly when their type, intensity, or duration is not appropriate for a given situation. At such moments, we draw upon an inherent human capacity: **emotion regulation**.

There are three major historical antecedents to the study of emotion regulation within the field of psychology. The first is the **psychodynamic study of defense**, initiated by Sigmund Freud a century ago. This line of work has examined the regulation of anxiety and other negative emotions using clinical descriptions and individual-difference studies of perceptual defenses against processing negatively arousing stimuli, and specific defenses such as repressive coping (Erdelyi, 1974; Paulhus, Fridhandler and Hayes, 1997). The second antecedent is the **stress and coping tradition** that grew out of the psychodynamic approach in the 1960s. This line of work focused on the management of situations that tax or exceed the resources of the person (Lazarus and Folkman, 1984). The best example of this approach is the now classic study of reappraisal showing that subjective and physiological responses decreased when a film of a potentially upsetting surgical procedure was viewed in analytical and detached terms (Lazarus and Alfert, 1964). The third antecedent is the **developmental study of self-regulation**, which had its roots in the study of socioemotional development. This work showed that children would be more likely to choose a preferred but delayed reward by thinking about available treats in abstract ways that decreased their immediate impulse to eat them (Mischel, Shoda and Rodriguez, 1989). Currently, contemporary research builds on the influence from all these different lines of research to describe when, how, and with what consequences individuals regulate their emotions, using both behavioral and neuroscience methods (Ochsner and Gross, 2005).

1.1.1. Models of emotion and emotion regulation

Several models of emotion regulation have been developed, with the field of emotion regulation having exponentially increased in the past decades (Fig. 1.1.). However, in order to fully understand these models, it is best to review first the processes that generate emotions.

Current models (Ochsner and Gross, 2005) posit that emotions are valenced responses to external stimuli and/or internal mental representations that: (1) involve changes across multiple response systems (e.g., experiential, behavioral, and physiological) (Larsen *et al.*, 2008); (2) are distinct from moods, in that they often have identifiable objects or triggers (Parkinson, 1996); (3) can be either unlearned responses to stimuli with intrinsic affective properties (e.g., an unconditioned response to an aversive shock) or learned responses to stimuli with acquired emotional value (e.g., a conditioned response or stimulus–reward association) (Mauss, Bunge and Gross, 2007); (4) can involve multiple types of appraisal processes that assess the significance of stimuli to current goals (Scherer, Schorr and Johnstone, 2001); and (5) depend upon different neural systems (Davidson, 2000; Ochsner and Barrett, 2001; Phillips *et al.*, 2003b).

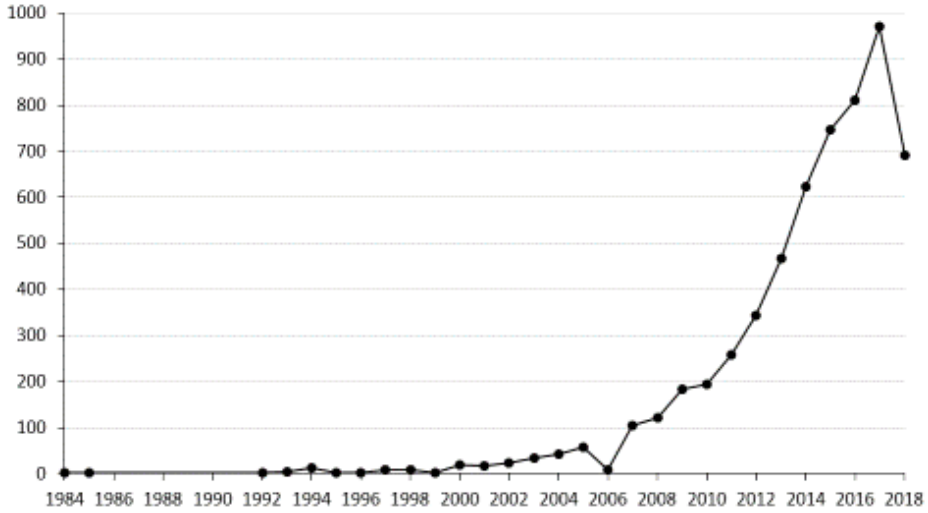

Figure 1.1. Increase in the number of publications on emotion regulation throughout the last decades.

In line with this definition, the **modal model of emotion** (Fig. 1.2.) describes emotions as involving person-situation transactions that compel attention, have meaning to an individual in light of currently active goals, and give rise to coordinated yet flexible multisystem responses that modify the ongoing person-situation transaction in crucial ways. The sequence begins with a psychologically relevant situation (either external or internal), which can be attended in various ways, and give rise to appraisals that constitute the individual's assessment of what the situation means in light of relevant goals (Ellsworth and Scherer, 2003). The emotional responses generated by these unfolding appraisals involve changes in experiential, behavioral, and neurobiological response systems. Finally, the emotional responses can often lead to

changes in the environment that alter the probability of subsequent instances of that and other emotions (Gross, 2014).

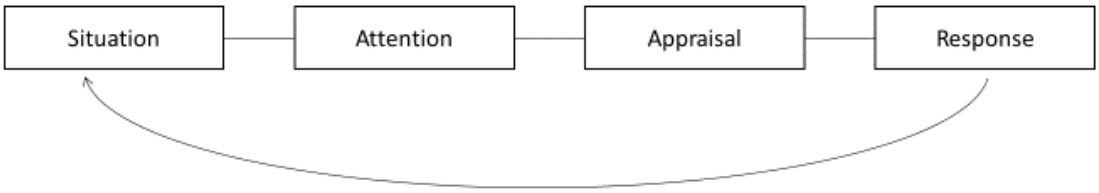

Figure 1.2. Modal model of emotion. Adapted from Gross, 2014.

Emotion regulation involves the initiation of new, or the alteration of ongoing, emotional responses through the action of regulatory processes. This includes the processes that individuals use to influence which emotions they have, when they have them, and how they experience and express these emotions (Gross, 1998b). These are very relevant processes that can be found across all of our daily lives. Defending a PhD dissertation is an example of situation that tests our ability to regulate our emotions and puts them under the predominance of our long-term goal: becoming a Doctor. There are several ways by which we can try to do this, yielding an enormous variety of emotion-regulation strategies, since any activity that impacts people's emotions may be recruited in the service of emotion regulation. Finding an underlying order in people's ways of regulating emotions therefore represents an important scientific challenge.

One of the most typical **categories for classifying emotion-regulation strategies** are those involving **targets and functions of emotion regulation**. The emotion-generating systems that are targeted in emotion regulation include attention, knowledge (i.e., cognitions), and bodily responses. On the other hand, the functions of emotion regulation include satisfying hedonic needs, supporting specific goal pursuits, and facilitating the global personality system. Different emotion-regulation strategies can then be classified in terms of their targets and functions (Koole, 2009). Another framework that has become very popular for the study of emotion regulation is the **process model of emotion regulation** (Gross, 1998b). This information-processing model takes the modal model of emotion as its starting point, and treats each step in the emotion-generative process as a potential target for regulation (Fig. 1.3.). It considers similar relevant targets of regulation as the targets and functions model, but with the difference that in the process model the temporal aspect of emotion generation and regulation is also relevant. There are five points at which individuals can regulate their emotions, representing five families of emotion regulation processes: situation selection,

situation modification, attentional deployment, cognitive change, and response modulation. As previously mentioned, these families are distinguished by the point in the emotion-generative process at which they have their primary impact, and will be further described in the following section. A broad distinction between them can be made by differentiating **antecedent-focused strategies**, those occurring early in the emotion-generative process (situation selection, situation modification, attentional deployment and cognitive change), and **response-focused strategies**, those occurring late in the emotion-generative process (response modulation).

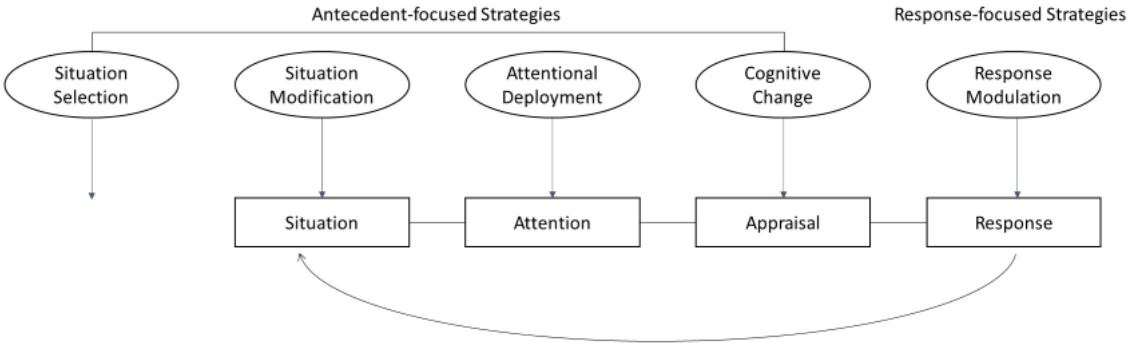

Figure 1.3. Process model of emotion regulation. Adapted from Gross, 2014.

More recently, the process model has been reviewed with the aim to integrate emotion regulation within a broader framework, resulting into the **extended process model** (EPM) of emotion regulation (Etkin, Büchel and Gross, 2015; Gross, 2015). The impetus for this framework came from the observation that neural systems implicated in emotion generation and regulation overlapped in important ways with neural systems implicated in other literatures that typically are not jointly considered. The EPM holds that emotions, like other types of affect, result from the **operations of valuation systems**. Valuation can be schematized as a three-stage processing cycle starting with a perception stage which takes various kinds of stimuli as inputs; a valuation stage which dynamically appraises the value of these stimuli given current goals, context, and prior experience with similar stimuli; and an action stage which comprises valuation-appropriate responses ranging from covert adjustments of low-level sensory or higher-level cognitive processes to overt adjustments of a wide range of response systems. This perception-valuation-action (PVA) sequence repeats itself as the aftermath becomes the input for the next PVA sequence, thus setting in motion a new PVA cycle (Fig. 1.4.). Multiple valuations are computed for a given stimulus, and these vary along a continuum of representational complexity, with more complex valuations typically taking longer to compute than less complex valuations. At the lowest level of this continuum, core valuations are made, which represent relatively direct associations between percepts and basic

physiological and behavioral responses at the action stage (e.g., snake → fear response). At an intermediate level, contextual valuations evaluate inputs that represent combinations of stimulus-response links and at least three types of contextual information: the historical as well as current social and motivational contexts of the person. Contextual valuations indicate whether an object is positive or negative in the present context, and therefore whether it should be sought or avoided at the present time. Finally, at the highest level of this continuum, conceptual valuations represent appraisals of stimuli that are abstract and often verbalizable (Ochsner and Gross, 2014). In the context of emotion regulation, these three stages correspond to identification (concerned with whether to regulate emotion), selection (concerned with what strategy to use to regulate emotion), and implementation (concerned with implementing a particular tactic suited to the present situation) stages (Gross, 2015).

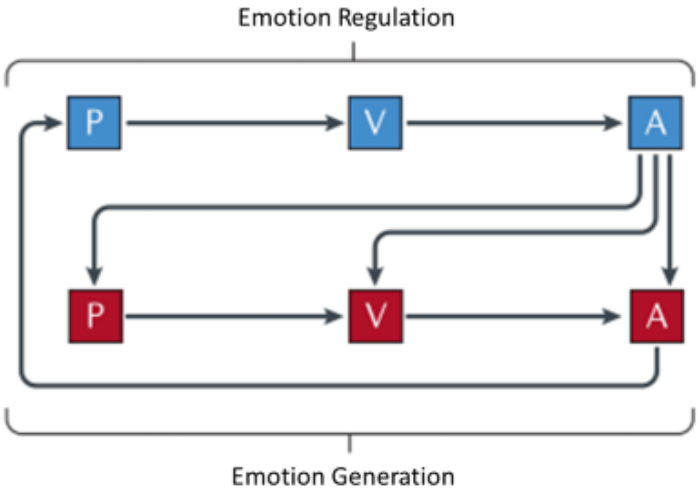

Figure 1.4. A valuation perspective on emotion generation and regulation. Emotion generation is a PVA sequence (red boxes), with the valuation stage reflecting a "good for me–bad for me" judgment about a stimulus, which triggers a multi-componential set of actions (for example, physiological, cognitive, motoric and subjective actions). Emotion regulation also involves a PVA sequence (blue boxes), with its action being regulation of the emotional response, affecting any component of the emotion generation PVA sequence. Adapted from Etkin, Büchel and Gross (2015).

Finally, another potentially useful classification of emotion regulation strategies distinguishes between **automatic (or implicit) versus controlled (or explicit) emotion-regulation** processes. An attractive aspect of this distinction is that it cuts across the complete range of emotion-regulation strategies (Mauss, Bunge and Gross, 2007). In this line, Etkin, Büchel and Gross (2015) used a computational approach to distinguish between model-free (or implicit) emotion regulation, which functions entirely on prediction error feedback (e.g., extinction learning),

and model-based (or explicit) emotion regulation, which consists of the implementation of an internal model to guide behavior (e.g., reappraisal, which will be described in the following section). They conceptualize model-based regulation as being particularly helpful in situations in which model-free regulation would not be selected, despite its lower implementation cost, because doing so would take too long to effectively regulate emotion or because prediction error-based adjustments alone could not achieve the desired regulation outcome.

1.1.2. Emotion regulation goals, strategies and outcomes

Regardless of the model that we use to frame emotion regulation, we can identify three core features: (1) emotion regulation has a goal – what people are trying to accomplish; (2) which is achieved through specific emotion regulation strategies – the particular processes that are engaged in order to achieve that goal; and (3) it provokes an outcome – the consequences of trying to achieve that particular emotion regulation goal using that particular strategy.

Emotion regulation goals can include efforts to decrease or increase either the magnitude or duration of negative or positive emotions. Although it might seem counterintuitive to down-regulate positive emotions or up-regulate negative emotions, this is explained by the fact that people are not always motivated by hedonic considerations (the wish to increase short-term pleasure and decrease short-term pain); instead, quite often people are also motivated by instrumental considerations, which might make us sacrifice our short-term pleasure in the service of a long-term goal (Gross, 2014). Whether our goal is to decrease or increase a particular emotion, there are several strategies that we can implement to try to achieve this goal.

Our description of different emotion regulation strategies is based on the process model of emotion regulation, the most popular and used model in the emotion regulation literature up to date. Despite this, the same strategies that will be described can also be characterized within the criteria of the targets and functions model, in terms of the PVA sequence, and can be also located on the implicit-explicit continuum. As mentioned in the previous section, the process model distinguishes five families of regulatory processes (see Fig. 1.3.):

- Situation selection. This type of emotion regulation involves taking actions that make it more or less likely that one will end up in a situation that one expects will give rise to desirable or undesirable emotions.
- Situation modification. It refers to directly modifying a situation (understood as modifying external, physical environments) so as to alter its emotional impact. Efforts

to modify a situation may effectively call a new situation into being, making it sometimes difficult to distinguish between situation selection and situation modification.

- Attentional deployment. It refers to directing attention within a given situation in order to influence one's emotions. One of the most common forms of attentional deployment is distraction, which focuses attention on other aspects of the situation or moves attention away from the situation altogether.
- Cognitive change. This occurs early in the emotion-generative process, before the emotional response has fully developed, and refers to modifying how one appraises a situation so as to alter its emotional significance, either by changing how one thinks about the situation or about one's capacity to manage the demands it poses. One particularly well-studied form of cognitive change is reappraisal, which includes two types of sub-strategies: **reinterpretation**, which refers to changing the meaning of stimuli in order to view the outcome of a situation in a more positive light (e.g., deciding that an image of weeping people outside a church is actually of a wedding instead of a funeral); and **distancing**, which refers to rationalizing the content of a situation by adopting the perspective of an uninvolved observer (e.g., when viewing a scene depicting a wounded person, presuming that the person is actually an actor). Also, we can distinguish between negative reappraisal (i.e., reframing a negative event as less negative) and positive reappraisal (i.e., reframing a negative event as more positive). Other strategies included in this family are for example **acceptance**, which refers to thoughts of resigning yourself to what has happened, and **rumination**, which refers to thinking about the feelings and thoughts associated with the negative event.
- Response modulation. It occurs late in the emotion-generative process, after response tendencies have already been initiated, and refers to directly influencing experiential, behavioral, or physiological components of the emotional response. A common form of response modulation involves regulating emotion-expressive behavior, and one well-researched example of this is expressive suppression, in which a person tries to inhibit ongoing negative or positive emotion-expressive behavior.

Finally, these different ways of regulating emotions may have different **consequences**, both immediately and over the long term. The two strategies that have been compared more often in terms of their outcomes are **reappraisal** and **expressive suppression**. This is an interesting contrast because although both strategies are commonly employed to down-regulate emotion, suppression is behaviorally oriented while reappraisal is cognitively oriented, and

they take place at different times during the emotion-generative process. We can consider the outcomes of regulating emotions by means of these strategies at different levels (Gross, 2014):

- Affectively, suppression has been shown to lead to decreased positive but not negative emotion experience (Gross and Levenson, 1993, 1997; Gross, 1998a), increased sympathetic nervous system responses (Gross and Levenson, 1993, 1997; Gross, 1998a; Harris, 2001; Demaree *et al.*, 2006), and greater activation in emotion-generative brain regions such as the amygdala (Goldin, McRae, *et al.*, 2009). Moreover, people who report using suppression strategies more often experience less positive emotion and more negative emotion, including painful feelings of inauthenticity as well as depressive symptoms (Gross and John, 2003; Moore, Zoellner and Mollenholt, 2008; Nezlek and Kuppens, 2008). On the other hand, reappraisal has been shown to lead to decreased levels of negative emotion experience and increased positive emotion experience (Gross, 1998; Ray *et al.*, 2010; Lieberman *et al.*, 2011; Szasz, Szentagotai and Hofmann, 2011; Wolgast, Lundh and Viborg, 2011; Feinberg *et al.*, 2012), has no impact on or even decreases sympathetic nervous system responses (Gross, 1998; Wolgast, Lundh and Viborg, 2011; Kim and Hamann, 2012; Shiota and Levenson, 2012), and leads to lesser activation in emotion-generative brain regions such as the amygdala (Ochsner and Gross, 2008; Ochsner *et al.*, 2004; Goldin *et al.*, 2009; Kanske *et al.*, 2011) and ventral striatum (Staudinger *et al.*, 2009). Also, people who use reappraisal strategies experience and express more positive emotions and less negative emotions, including fewer depressive symptoms (Gross and John, 2003; Nezlek and Kuppens, 2008).
- Cognitively, suppression has been shown to have a negative effect on memory (Richards and Gross, 2000, 2006; Johns, Inzlicht and Schmader, 2008). By contrast, reappraisal either has no impact on subsequent memory or actually improves it (Richards and Gross, 2000; Hayes *et al.*, 2010), and can enhance performance on standard explorations (Jamieson *et al.*, 2010).
- Socially, suppression leads to less appreciation from social interaction partners, and to an increase in partners' blood pressure levels (Butler *et al.*, 2003). Moreover, individuals who typically use suppression report avoiding close relationships and having less positive relations with others (Gross and John, 2003; Srivastava *et al.*, 2009; English, John and Gross, 2013). On the other hand, reappraisal has no detectable adverse consequences for social affiliation (Butler *et al.*, 2003), and individuals who

typically use reappraisal are more likely to share their emotions and report having closer relationships with friends (Gross and John, 2003; Mauss *et al.*, 2011).

By contrast, instead of comparing these two strategies, in their meta-analysis, Webb, Miles and Sheeran (2012) compared the effectiveness of the three broad emotion regulation processes described by Gross' process model (i.e., attentional deployment, cognitive change, and response modulation) over experiential, physiological, and behavioral measures of emotional outcomes. They observed that cognitive change processes (strategies involving reappraisal) had a small-to-medium sized effect on emotional responses and proved to be more effective than strategies involving attentional deployment (distraction or concentration) or response modulation, which had no or small-sized effects on emotional responses. The differential effectiveness of these three broad families of emotion regulation processes supports the conceptual distinctions made by the process model. It is worth mentioning that besides this general idea, within each broad category (e.g., attention-focused strategies) variability in its effectiveness can be found depending on the specific strategy implemented. For example, distraction has been shown to have benefits over concentration (Webb, Miles and Sheeran, 2012). Moreover, suppressing the expression of emotion has proven to be effective, while suppressing the experience of emotion or thoughts of the emotion-eliciting event has not. On the other hand, within cognitive change strategies, similar effectiveness has been observed between reinterpreting the emotional stimulus and using perspective taking (i.e., distancing), consistent with empirical work that directly compared these two types of reappraisal strategies (Ochsner *et al.*, 2004).

As a general conclusion from the outcomes described above, one could state that reappraisal is preferable to suppression. However, caution is required here, because the effects of emotion regulation may vary as a function of the context. Thus, the adverse social consequences of suppression are not evident in individuals with Asian values (Butler, Lee and Gross, 2007; Soto *et al.*, 2011; Hu *et al.*, 2014). Similarly, some of the benefits of reappraisal are moderated by particular situational aspects. For example, if emotional intensity is already high when reappraisal is engaged, it no longer has the experiential or physiological benefits seen in other contexts (Sheppes, Catran and Meiran, 2009). For this reason, engagement of reappraisal is preferred in lower intensity situations, whereas disengagement/distraction is preferred in higher intensity situations (Sheppes *et al.*, 2011). Thus, there is no such thing as one superior strategy that should be applied in all situations, instead, the most adaptive strategy to use will depend on the specific situation, the intensity of the emotion to regulate, and our own cultural values, among other factors.

1.1.3. Emotion regulation and related constructs

One final consideration of this section is that many different terms are used to refer to emotion-related processes, including affect, stress, and mood (Davidson, 1994). Sometimes, these terms are used in different ways by different researchers, raising some confusion. In order to better organize this terminology, one possibility is to consider **affect** as an umbrella term for states that involve relatively quick good-bad discriminations (Scherer, 1984; Gross, 2014). These affective states include (1) **emotions** such as anger and sadness, (2) **stress** responses to circumstances that exceed an individual's ability to cope, and (3) **moods** such as depression and euphoria. Although both emotion and stress involve whole-body responses to significant events, stress typically refers to negative affective responses, whereas emotion refers to both negative and positive affective states (Lazarus, 1993). Emotions may also be distinguished from moods, with moods typically lasting longer than emotions, and emotions being elicited by specific objects while moods are normally more diffuse (Parkinson, 1996).

In parallel with this, emotion regulation can be seen as subordinate to the broader construct of **affect regulation**. Under this broad heading, it may fall all types of efforts to influence our valenced responses (Westen, 1994), including (1) emotion regulation, (2) coping, and (3) mood regulation. **Coping** is different from **emotion regulation** both because of its predominant focus on decreasing negative affect and its emphasis on much larger periods of time. Likewise, in comparison with emotion regulation, **mood regulation** and mood repair are more concerned with altering emotion experience than emotion behavior, in part due to the less well-defined behavioral response tendencies of moods (Larsen, 2000). Still, to date, the commonalities and differences between the regulation of emotions, stress responses, and moods have not been clearly identified, although they are typically seen as related constructs that share psychological processes and part of their underlying neurobiology.

1.2. The neural bases of emotion and emotion regulation

1.2.1. Neural bases of emotion generation

In recent years, great efforts have been made to use neuroscience techniques to understand the mechanisms underlying emotion generation and regulation. Reviews and meta-analyses of functional magnetic resonance imaging (fMRI) studies indicate that a number of cortical and subcortical brain systems may play a key role in the appraisal and/or response stages of emotion generation (Kober, 2008; Wager *et al.*, 2008). Ochsner and Gross (2014) recently

framed these different brain systems within the context of the PVA model, distinguishing different networks of regions for each of the levels of valuation complexity (Fig. 1.5.):

- Core valuation. The network underlying this type of valuations involves primarily subcortical and brainstem systems implicated in affective learning and responding. Many of these systems, such as the ventral striatum, the amygdala, and the periaqueductal gray (PAG), receive signals from a variety of sensory inputs (Keay and Bandler, 2001; Packard, 2009), and can be involved in the valuation of a variety of stimuli. Core valuations for pain sensations, instead, involve dedicated pathways from the thalamus to nociceptive regions of the midcingulate cortex and anterior insula (AI) (Willis and Westlund, 1997). In addition, while the ventral striatum and the amygdala are typically linked with positive/appetitive and negative/aversive valuations, respectively, both human and animal studies suggest that sub-regions of each structure may play roles in both types of valuations (Holland and Gallagher, 2004; Wager *et al.*, 2008; Delgado *et al.*, 2009).
- Contextual valuation. This type of valuation involves at least three regions. The first comprises the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) (Price, 1999; Öngür, Ferry and Price, 2003), whose inputs include the output of both the core valuation level and the medial temporal lobe (MTL) and the cortical associative memory systems, which provide temporal and spatial context (Davachi, 2006; Murray, O'Doherty and Schoenbaum, 2007). The second is the superior temporal sulcus/temporoparietal junction (STS/TPJ), a multisensory zone that integrates expectations with feedback, and reorients attention accordingly, including instances when expectations must be adjusted according to the beliefs, actions, and intentions of others (Saxe, 2006; Young *et al.*, 2010). The third is the AI, which integrates and makes available to awareness information about current body states, especially those referring to one's current affective state (Craig, 2003; Harrison *et al.*, 2010; Kurth *et al.*, 2010; Zaki, Davis and Ochsner, 2012).
- Conceptual valuation. This final level involves at least four regions. The first two, the rostromedial (rmPFC) and dorsomedial (dmPFC) prefrontal regions implicated in attending to and explicitly judging the value of stimuli to elaborate semantically the affective value of a wide range of stimuli, from simple objects to the self (Zysset *et al.*, 2002; Cato *et al.*, 2004; Lindquist and Barrett, 2008; Mitchell, 2009; Lindquist *et al.*, 2012). A third region involved is the ventrolateral prefrontal cortex (vlPFC), which helps select desired and inhibit undesired value representations (Thompson-Schill,

Bedny and Goldberg, 2005; Lindquist and Barrett, 2008; Mitchell, 2009; Aron, Robbins and Poldrack, 2014). Finally, regions of the AI that support introspective awareness of body states may also be integral to the use of conceptual knowledge about body states to make judgments about one's current affective states (Craig, 2009; Harrison *et al.*, 2010; Zaki, Davis and Ochsner, 2012).

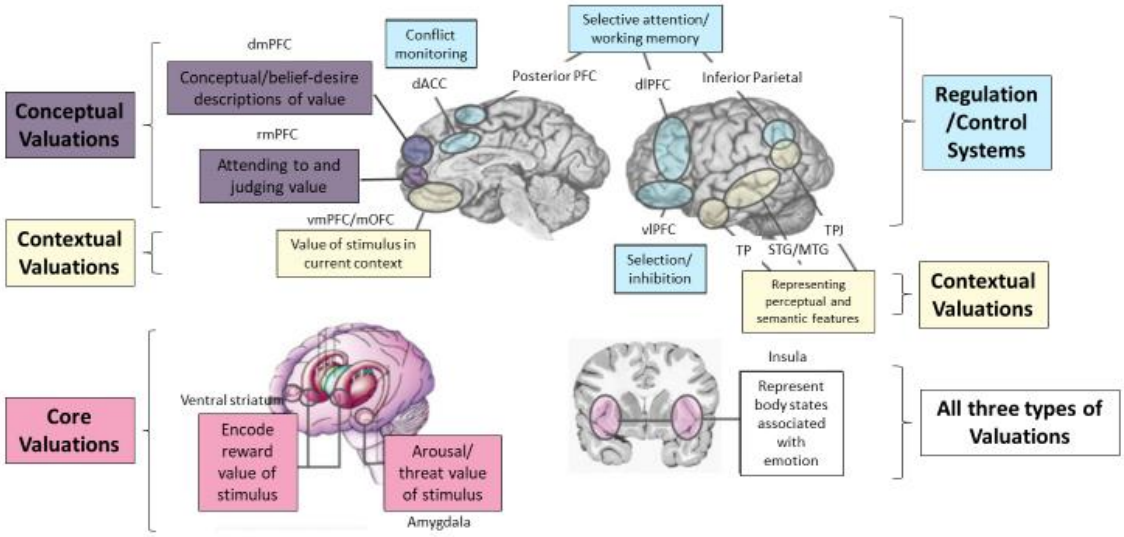

Figure 1.5. Neural systems supporting all three types of valuation (core valuation in pink, contextual valuation in yellow, and conceptual valuation in purple), and neural systems supporting regulation (light blue). Adapted from Ochsner, Silvers and Buhle (2012) and from Ochsner and Gross (2014).

1.2.2. Neural bases of emotion regulation

Cognitive reappraisal

Neuroscience techniques have also been used to unravel the neural bases of the different emotion regulation strategies, being reappraisal the one most commonly studied. The majority of studies to date have focused on reappraisal because it can be easily studied in an imaging environment. In contrast to other areas of emotion regulation research, reappraisal studies tend to be methodologically and conceptually more similar between them, and therefore provide a stronger basis for mechanistic inferences. Likewise, since reappraisal is among the most cognitively complex strategies, a model of emotion regulation derived from reappraisal should be generally applicable to cognitively simpler strategies and phenomena. With these considerations in mind, we first describe the brain mechanisms supporting emotion regulation that have been derived from studies of reappraisal (Ochsner, Silvers and Buhle, 2012; Ochsner and Gross, 2014).

Three types of neural systems have been described to be primarily involved in generating and applying reappraisals (Ochsner and Gross, 2005). Firstly, the dorsolateral and posterior prefrontal cortex (PFC), along with inferior parietal regions generally implicated in selective attention and working memory, may be used to direct attention to reappraisal-relevant stimulus features and hold in mind reappraisal goals as well as the content of one's reappraisal (Miller, 2000; Wager and Smith, 2003; Wager, Jonides and Reading, 2004). Secondly, the dorsal regions of the anterior cingulate cortex (ACC) implicated in performance monitoring may help track the extent to which one's current reappraisals are changing emotional responses in the intended way (Botvinick, Cohen and Carter, 2004). Thirdly, the regions of the vlPFC implicated in selecting goal-appropriate and inhibiting goal-inappropriate responses and information from semantic memory may be used to deliberately select a new stimulus-appropriate reappraisal according to one's initial pre-potent appraisal of that stimulus (Thompson-Schill, Bedny and Goldberg, 2005; Badre and Wagner, 2007). Finally, to the extent that one's reappraisal involves focusing on and interpreting or reinterpreting one's own emotional states or those of others, the dmPFC regions implicated in attributing mental states may also be active during cognitive reappraisal (Olsson and Ochsner, 2008; Mitchell, 2009) (Fig. 1.5.).

With respect to the emotion-related regions that are modulated by reappraisal, these include all regions described earlier as underlying core valuations, and, to a lesser extent, regions implicated in contextual valuations. The most commonly modulated region is the amygdala, followed by the ventral striatum, with the insula and the vmPFC being less commonly reported (Ochsner and Gross, 2005, 2008). In conclusion, this pattern of activations involves a fronto-parietal network of top-down control and has been consistently found across different fMRI meta-analyses (Kalisch, 2009; Diekhof *et al.*, 2011; Buhle *et al.*, 2013; Kohn *et al.*, 2014; Morawetz *et al.*, 2017) (Fig. 1.6.). Indeed, in functional connectivity studies, the abovementioned frontal regions have been found to be connected to the amygdala both in emotion regulation experimental settings (Banks *et al.*, 2007; Lee *et al.*, 2012; Paschke *et al.*, 2016) and during resting-state (Uchida *et al.*, 2014), providing a link for the top-down inhibition of this emotion generation region.

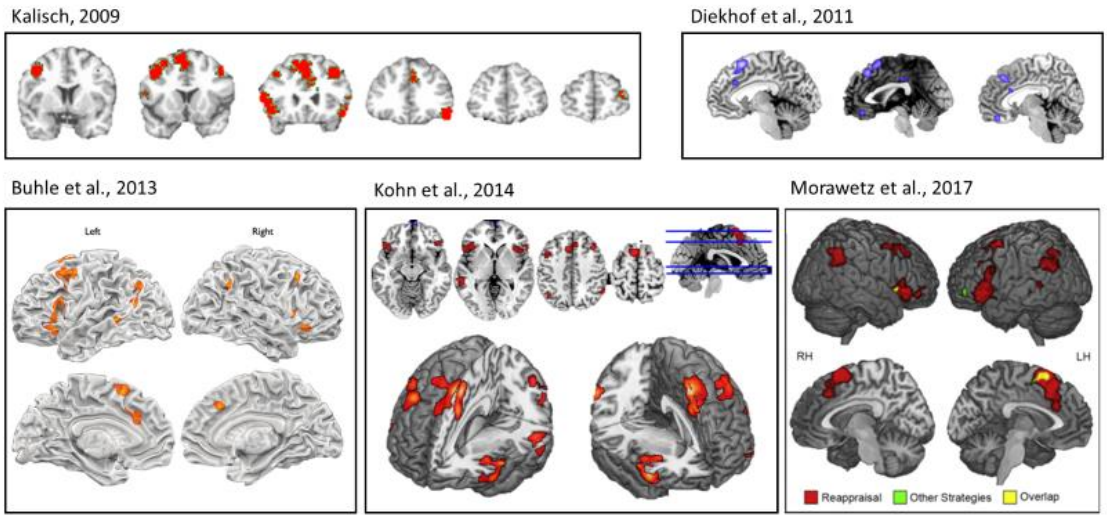

Figure 1.6. Activation results from the different fMRI reappraisal meta-analyses performed to date. It can be observed that a similar pattern of fronto-parietal activations emerges across all of them. Adapted from the figures of each publication.

Goal, strategy, and stimuli-specificity in reappraisal

More interestingly, besides this general pattern of broad activations, recent research provides new insight into the distribution of reappraisal-related activations as a function of **different emotion regulation properties**, such as **emotion regulation goals** (i.e., what outcome one hopes to achieve by regulating, e.g., increasing or decreasing an emotional experience), **strategy** (i.e., the specific subtype of reappraisal one implements, e.g., reinterpretation or distancing), and the **type of stimuli** (e.g., its valence, i.e., whether the stimulus evokes a positive or negative emotional response) (Ochsner, Silvers and Buhle, 2012) (Fig. 1.7.):

- Goal-specificity. Whereas both increase and decrease goals recruit left prefrontal regions, decrease goals have been shown to recruit right prefrontal regions to a greater extent (Ochsner, Silvers and Buhle, 2012). There are two interpretations of this finding. First, it may be that decreasing an emotional response is more difficult than increasing one, and therefore may require additional cognitive control resources (Ochsner *et al.*, 2004). Second, decreasing (but not increasing) an emotional response requires inhibiting the expression of a prepotent appraisal of a stimulus (e.g., as negative) in favor of selecting an alternative reappraisal (e.g., as neutral or even positive), and research shows that the right vlPFC is involved in the selection and/or inhibition of various kinds of responses (Konishi *et al.*, 1999; Lieberman *et al.*, 2007; Aron, Robbins and Poldrack, 2014). Likewise, there is some evidence that increase goals differentially involve anterior portions of the dmPFC. Of the 12 studies reviewed

in Ochsner, Silvers and Buhle (2012) that directly compared increasing an emotion to a control condition where participants responded naturally, six showed increases in anterior dmPFC activation (Ochsner *et al.*, 2004, 2009; Domes *et al.*, 2010; Ichikawa *et al.*, 2011). Of the six that did not, most showed activation in neighboring areas (such as ACC) (Eippert *et al.*, 2007; Van Reekum *et al.*, 2007; New *et al.*, 2009; Urry, 2009; Pitskel *et al.*, 2011; Schulze *et al.*, 2011). Given the role of dmPFC in making judgments about mental states (Mitchell, 2009; Zaki and Ochsner, 2012), and that the majority of reappraisal studies use photographs of people as stimuli, it is likely that these regions support attention to and elaboration of emotional states, intentions, and outcomes of the individuals depicted in these pictures. Finally, whereas increase and decrease goals both seem to modulate the striatum (including both the caudate and putamen), they may differ in the way they modulate the amygdala. On the one hand, decrease goals reliably modulate the amygdala's ventral (corresponding to the basal and lateral amygdala nuclei) and dorsal portions (corresponding to the central nucleus), as well as the extended amygdala (Davis and Shi, 1999; Whalen *et al.*, 2004; Liberzon and Sripada, 2007), which lies between the amygdala and the striatum. On the other hand, increase goals may modulate only the dorsal and extended amygdala. One interpretation of this is that decrease goals influence perceptual and semantic inputs to the amygdala, which come through the basolateral complex, whereas increase goals influence the outputs of the amygdala, which flow from the central nucleus (Ochsner *et al.*, 2002, 2004). This hypothesis would fit with anatomical data showing that the basolateral complex has reciprocal connections with the vlPFC as well as temporal and parietal regions implicated in visuospatial and semantic representation whereas the central nucleus receives inputs from medial prefrontal regions and sends outputs to autonomic centers that implement various components of an emotional response (Aggleton, 2000). However, very few studies have examined increase goals, and thus, conclusions about the goal-specificity of reappraisal-related activations must be considered tentative.

- Strategy-specificity. Reinterpretation seems to differentially call upon vlPFC regions implicated in response selection and inhibition (Thompson-Schill, Bedny and Goldberg, 2005; Badre and Wagner, 2007; Aron, Robbins and Poldrack, 2014). Presumably, this reflects the fact that reinterpretation requires looking up and selecting alternative meanings for stimuli from semantic memory to a greater extent than distancing. Conversely, distancing seems to recruit parietal regions implicated in spatial attention and representation to a greater extent, including perspective taking and the sense of

agency (Gobbini *et al.*, 2007; Chun, Golomb and Turk-Browne, 2011). This may reflect the fact that distancing involves changing the conceptual and spatiotemporal perspective from which stimuli are experienced. In any case, the regions involved in reinterpretation appear to be more strongly left lateralized in prefrontal and temporal cortices, whereas regions involved in distancing appear to be more strongly right lateralized in the PFC. These patterns may reflect the differential dependence of reinterpretation and distancing on linguistic and semantic processes as opposed to spatial and attentional processes, which generally show a left vs. right hemisphere pattern of relative specialization (Ochsner *et al.*, 2004; Gazzaniga, Ivry and Mangun, 2008; Dörfel *et al.*, 2014).

- Valence-specificity. Whereas reappraisal of positive stimuli depends upon left-hemisphere regions, reappraising negative stimuli depends on both hemispheres. These findings might be associated with the fact that, to date, the majority of studies of negative emotion involve decreasing goals. As noted earlier, decreasing goals may require more cognitive resources than increase goals, including placing greater demands on selection/inhibitory functions associated with the right vlPFC (Aron, Robbins and Poldrack, 2014). Also, reappraising negative stimuli typically modulates activity in the amygdala and less commonly activity in the striatum. By contrast, the handful of studies examining reappraisal of positive stimuli more commonly show modulation of the striatum, including the ventral portions associated with reward and reinforcement learning (O'Doherty, 2004; Schultz, 2007). Nonetheless, these conclusions are tentative, because so few studies have examined reappraisal of positive stimuli and, in general, studies of reappraisal have focused on decrease rather than increase goals.
- Stimulus-specificity. To date, most of reappraisal studies have used photographic stimuli pulled from the International Affective Picture System (IAPS) (Lang, Bradley and Cuthbert, 2005), but the emotions elicited by such stimuli may or may not generalize to other contexts. A small number of studies have examined the ability to reappraise the specific emotions elicited by sad, sexual or disgusting videos, scripts that elicit particular emotions, the recollection of autobiographical memories, anticipation of reward or shock, the commission of an error, or other types of stimuli specific to a disorder's symptomatology. Therefore, it is still difficult to draw reliable conclusions about how neural activations might differ as a function of stimulus type.

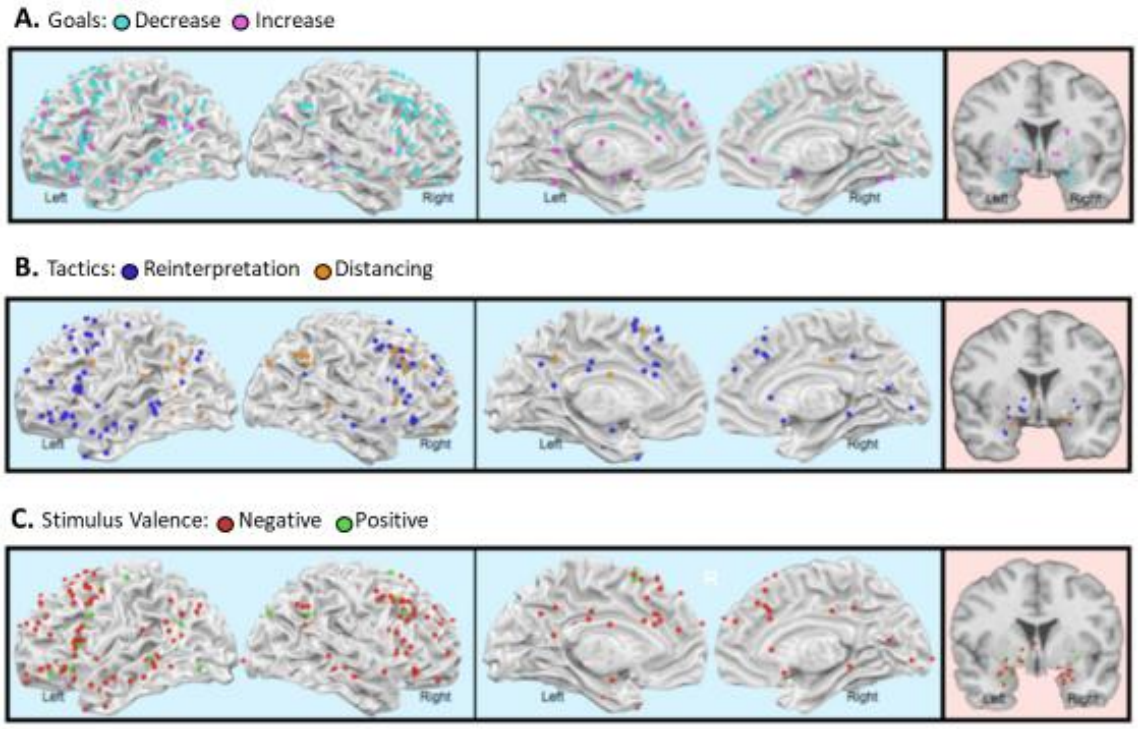

Figure 1.7. Plots of foci as a function of the goals to decrease or increase emotion (A), as a function of the specific reappraisal strategies used (B), or as a function of the valence of the stimuli eliciting the emotions that participants attempted to regulate (C). Blue boxes illustrate regions that are activated during reappraisal (increase>look and decrease>look contrasts). Pink boxes illustrate regions that are deactivated during reappraisal (look>increase and look>decrease contrasts). Adapted from Ochsner, Silvers and Buhle (2012).

Other emotion regulation strategies

The findings described so far relate to reappraisal fMRI studies, but there are also fMRI experiments examining other emotion regulation strategies discussed above, and also the comparison of different strategies. Existing studies of **expressive suppression**, for example, suggest that this strategy is associated with activation of the frontal cortex, similar to reappraisal. However, this strategy is also associated with significant activations of the amygdala and the insula, in contrast with reappraisal (Goldin, McRae, *et al.*, 2009; Hayes *et al.*, 2010; Vanderhasselt *et al.*, 2013). Moreover, in their meta-analysis, Morawetz *et al.*, (2017) examined strategy-specific effects relating either to **attentional deployment** or **response modulation** (which includes expressive suppression) compared to a control condition, although these analyses were rather exploratory given the relative small number of studies using attentional deployment (n = 19) and response modulation (n = 10). Attention-focused emotion regulation resulted in consistent activation of the right AI and the left pre-

supplementary motor area (pre-SMA), while response-focused emotion regulation was associated with converging activation in the right inferior parietal lobule and left vlPFC. Also, in this same meta-analysis, a conjunction analysis was performed between reappraisal and the rest of emotion regulation strategies, demonstrating areas of convergence in the bilateral insula, the left pre-SMA and a small cluster in the left vlPFC. In parallel to what was done in Oschner's et al. (2012) review, in this meta-analysis they also looked at activation differences and similarities according to goal- and stimulus-specificity, but in this case considering all emotion regulation strategies together instead of only in reappraisal (Fig. 1.8.).

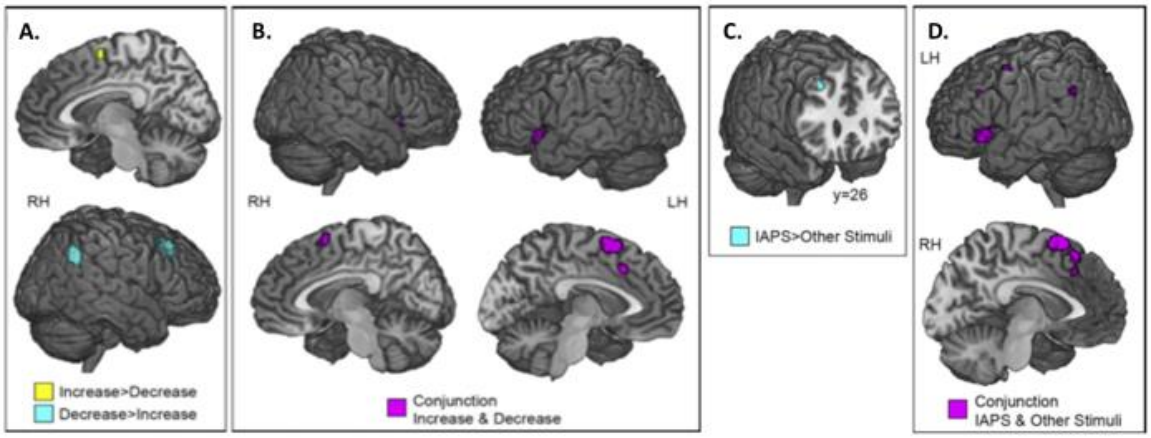

Figure 1.8. Distinct (A) and common (B) neural regions involved in decreasing and increasing emotions. The SMA and the left insula were more active during increasing emotions; the right dorsolateral PFC (dlPFC) and the right inferior parietal lobule during decreasing emotions. The bilateral vlPFC, dmPFC and SMA were active both in decrease and increase conditions. Distinct (C) and common (D) neural regions in response to IAPS pictures and to other stimuli. The right dlPFC was more active in response to IAPS pictures, while no significant clusters were found in response to other stimuli. Left-lateralized regions of convergence included PFC regions (vlPFC, dlPFC, and dmPFC), the inferior parietal lobule, the middle temporal gyrus (MTG) and the pre-SMA. Adapted from Morawetz *et al.* (2017).

Finally, distinctions have also been made regarding the **implicit/explicit axis** presented earlier. Broadly, there appears to be a medial-lateral differentiation between implicit and explicit regulatory processes, with implicit forms of emotion regulation involving vmPFC regions, and explicit forms of regulation involving mainly vlPFC and dlPFC (Gyurak and Etkin, 2014).

1.3. Emotion dysregulation as a transdiagnostic feature of mental health disorders

1.3.1. General deficits in regulating emotions across disorders

For decades, emotion regulation has been explored as an important process in the onset and maintenance of various forms of psychopathology, yet only recently it has been discussed as a transdiagnostic factor for mental health disorders (Kring and Sloan, 2010; Aldao, 2012). Emotion dysregulation may occur when one fails to influence emotion generation in the desired way, and it can take two forms: **emotion-regulation failure** (i.e., not engaging in emotion regulation when it would be helpful to do so) or **emotion misregulation** (i.e., using a form of emotion regulation that is poorly matched to the situation; Gross, 2013). A related concept is that of maladaptive emotion regulation strategies, which refers to when a strategy is either unsuccessful in reducing the unwanted emotional response, or associated with costs that outweigh any benefits of short-term reduction of acute emotions (Campbell-Sills, Ellard and Barlow, 2014). In their meta-analysis, Aldao, Nolen-Hoeksema and Schweizer (2010) identified how different emotion regulation strategies were associated with psychopathology, finding that avoidance, suppression and rumination had a positive association, while problem solving and reappraisal were negatively associated with psychopathology. Nevertheless, as has been outlined above, there is more to emotion regulation than just a simple division between adaptive and maladaptive strategies, and the same is true for its potential relationship with psychopathology. The EPM explained earlier allows for the in-depth exploration of this relationship, in terms of stage-specific difficulties (Fernandez, Jazaieri and Gross, 2016):

- Identification. Whether or not emotion regulation will occur is determined in the identification stage (Sheppes, Suri and Gross, 2015). During this stage, the difference between the current emotional response and the desired emotional response is considered, and the individual determines whether to regulate the current emotional response. Difficulties during this stage have been associated with different forms of psychopathology. For example, individuals who meet criteria for bipolar I disorder (BD), when in manic state, typically report feelings of euphoria and, as a result, are less likely to be interested in downregulating their emotional state. In this case, their emotion regulation goal would be to increase or maintain feelings of euphoria, rather than decreasing the intensity or duration of the euphoria.
- Strategy selection. Different studies have explored the relationship between the problematic selection of emotion-regulation strategies and psychopathology (Aldao, Nolen-Hoeksema and Schweizer, 2010). Studies using both survey-based and

experimental methods have found that individuals with anxiety disorders engage in suppression strategies more than non-anxious individuals (Levitt *et al.*, 2004; Campbell-Sills *et al.*, 2006; Ball *et al.*, 2013; Blalock, Kashdan and Farmer, 2016). Moreover, they have been found to use cognitive reappraisal (Ball *et al.*, 2013; Blalock, Kashdan and Farmer, 2016) and acceptance (Salters-Pedneault *et al.*, 2006) less frequently. With regards to depression, it is characterized by increased use of rumination and less use of reappraisal (Joorman and Siemer, 2014). For example, in their study, Van Meter and Youngstrom (2016) found that depression was more related to a greater tendency to select rumination strategies and a reduced tendency to select strategies such as acceptance and positive reappraisal. Naumann *et al.*, (2016) found that in the context of sadness, women with anorexia and bulimia nervosa, compared to healthy controls (HC), had a greater tendency to employ rumination and suppression and a lower tendency to employ acceptance. Likewise, Goldberg *et al.* (2016) used path analysis in a sample of obsessive-compulsive disorder (OCD) patients and HC to explore the association between emotion regulation strategies and obsessive-compulsive (OC) symptomatology, and found that while reappraisal was associated with reduced presence/severity of OC symptoms (mediated by positive affect and decreased cognitive rigidity), suppression was associated with negative affect, increased cognitive rigidity and increased presence/severity of OC symptoms.

- Implementation. In contrast to studies using self-report to examine the frequency of use of different emotion regulation strategies, other studies have focused on whether a specific disorder is characterized by less effective implementation of adaptive strategies. For example, there is evidence that depressed individuals have an impaired ability to recall happy memories to improve a sad mood (Joormann and Siemer, 2004; Joormann, Siemer and Gotlib, 2007). Thus, while these individuals have identified an emotion regulation goal (i.e., to improve a sad mood) and have selected a strategy (i.e., to recall happy memories), they experience difficulties with the actual implementation of their selected strategy (Joorman and Siemer, 2014). When considering implementation, it is important to take into account the role of emotion regulation flexibility (Aldao, Sheppes and Gross, 2015), which can be defined as the degree of covariation between emotion regulation variability and changes in the environment, where the environment might consist of external events and/or appraisals of emotional reactions to such events. Some forms of psychopathology are associated with decreased flexibility in strategy selection, exhibiting a preference for

selecting a particular set of emotion regulation strategies rather than flexibly selecting strategies according to what would be most adaptive in that specific context. An example of decreased flexibility of emotion regulation can be seen in the context of rituals in individuals with OCD: when experiencing an anxiety-provoking trigger, these individuals tend to engage in ritualized behavior to minimize anxiety, and may prefer this particular strategy over other emotion regulation strategies such as reappraisal or engagement with the anxiety-provoking stimulus (Wang and Bello, 2006).

- Monitoring. At the monitoring stage, individuals decide whether to stop regulating, switch their regulation strategy, or adjust some aspect of their selected strategy (Sheppes, Suri and Gross, 2015). It is at this stage that one can notice that prioritizing short-term goals (e.g., avoidance) over longer-term goals (e.g., gaining skills to manage difficult emotions) is ineffective, a realization that affords the opportunity to modify either the regulation goal or the regulation strategy. Failure to stop a maladaptive strategy or to switch from a maladaptive or inefficient strategy to a more adaptive and efficient one is associated with various forms of psychopathology. For instance, depressed individuals are more likely to employ rumination as an emotion regulation strategy, which is known to negatively affect mood (Nolen-Hoeksema, 2000). Failure to stop rumination once it has started may lead to negative downstream effects, such as increased depressed mood and increased ratings of the self as worthless and incompetent (Nolen-Hoeksema, Morrow and Fredrickson, 1993; Rimes and Watkins, 2005). Difficulties with monitoring can also occur with other forms of psychopathology, such as substance use disorders (SUDs). Individuals who engage in problematic drinking to cope with emotional distress (Abbey, Smith and Scott, 1993) may experience difficulties with the monitoring stage of emotion regulation. More specifically, once they have selected their strategy (drinking) and have implemented it and are experiencing some relief (emotion regulatory goal), there is a point during the monitoring stage at which it would be beneficial to stop or switch strategies, as continuing to drink can lead to dangerous outcomes; failure to do so, whether because of the individual's difficulty with properly monitoring his or her emotion regulation strategy or because alcohol itself may inhibit proper monitoring, can result in these serious negative consequences (Dvorak *et al.*, 2014). In addition to problems with monitoring, they could also fail at selecting and implementing more adaptive strategies because of the higher difficulty of such cognitively demanding strategies (e.g., reappraisal), showing how difficulties at these different stages interact with each other.

Due to the obvious links between psychopathology and emotion regulation deficits, more and more attention has been given to these associations in the past years, and a focus has been put into the transdiagnostic study of these deficits that will be discussed in the following section. Moreover, the neural correlates of emotion regulation in different patient samples have also been examined, and these findings will be discussed in section 1.4. of this introduction.

1.3.2. Emotion regulation in the context of the Research Domain Criteria

Despite major advances in the methods and findings of neuroscience research in recent years, limited advancements have been made in the prevention and treatment of mental illness. One view of why biologically oriented research has failed to yield satisfying results for mental illness is that its research strategies have been aimed at mental illnesses that are inadequately conceptualized. An extreme form of this standpoint is that the putative disorders to be approached are actually "fictive", not referring to actual illnesses (Kozak and Cuthbert, 2016). Current nosologies evolved from a tradition of diagnosis by clinical consensus about observations of patient-reported and clinician-observed behavioral clusters, symptom course, and associated features. The most commonly used diagnostic nosology is the American Psychiatric Association's Diagnostic and Statistical Manual (APA, DSM; American Psychiatric Association, 2013). A fundamental aspect of DSM is that most of the diagnoses derive from sets of symptoms that are individually neither necessary nor sufficient to indicate the disorder. The direct consequence of this is that individuals with widely different characteristics can fall within a single diagnostic class, and at the same time the defining symptom lists for different disorders overlap substantially, so that individuals with different diagnoses can share many symptoms. Another issue is that it is unwarranted to assume that complex higher-order psychological constructs will simply map onto narrower biological mechanisms of psychopathology. Accordingly, simpler, or lower order, phenomena that mediate clinical problems but are not themselves end-state clinical symptoms, would seem more likely candidates for biological elaboration. Narrower psychological constructs such as cognition, emotion, learning, memory, motivation, and perception might be more susceptible to biological analysis than depression, mania, and schizophrenia.

With all these considerations in mind, the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative represents an effort to circumvent the well-documented limitations of psychiatric categories in psychopathology research. The aim is to elaborate a set of psychological constructs linked to behavioral dimensions for which strong evidence exists

for circuits that involve these functions, and relate the extremes of functioning along these dimensions to specified symptoms (i.e., impairment). In the future, mental illness might be considered largely as problems in psychological and related neurobiological systems, rather than as consensually organized clinical phenomena. In this way, the RDoC initiative is intended to uncouple research questions from traditional diagnostic categories that are of limited validity and/or that are too heterogeneously large for productive validation against biological phenomena of smaller granularity.

The psychological constructs that had been proposed in the past years have been organized into five RDoC domains within which individual constructs can be grouped: these domains are Arousal/Modulation, Cognition, Negative Valence, Positive Valence, and Social Processes. Moreover, considering the units of measurement often employed in psychopathology research in various disciplines, a list of analyses levels has been created to help with the elaboration of new constructs. The suggested units are gene, molecule, cell, circuit, physiology (added for measures such as heart rate or cortisol that are not direct measures of circuits per se), behavior, and self-report.

In their commentary, Fernandez, Jazaieri and Gross (2016) consider emotion regulation to be the functional consequence of patterns of interaction among the five existing RDoC domains, that is, an emergent construct. The constructs within the cognitive systems domain regulate the negative valence, positive valence, and arousal and modulatory systems. Furthermore, they propose some empirically based criteria for proposing and testing new RDoC domains, which include being: (1) relevant to multiple disorders (i.e., transdiagnostic) as well as to the full range of normal functioning, (2) not reducible to the more basic (already existing) RDoC domains, and (3) empirically grounded across all of the RDoC units of analysis. Then, they conclude that emotion regulation satisfies these three criteria and, thus, appears to be a suitable candidate for a sixth RDoC domain. Finally, they also review emotion regulation research at each of the levels of analysis in the RDoC matrix (see Table 1.1.), which is summarized in the following:

- Genes. Within the gene unit of analysis, there has been a growing body of literature testing the relationship between certain genes and emotion regulation (see Canli, Ferri and Duman, 2009, for a review). For example, Gilman *et al.* (2015) examined variation in the 5-HTTLPR and emotion responses to a task designed to spontaneously induce emotion regulation. They found that for individuals with two copies of the short allele of this gene, there was diminished downregulation of negative emotion, indicating

that these individuals (relative to those without two copies of the short allele) could be more vulnerable to affective disorders. In a separate study, Miu *et al.* (2013) found evidence for reappraisal as a mediator of the relationship between the 5-HTTLPR gene and social anxiety symptoms, such that individuals with two copies of the short allele reported increased social anxiety symptoms and decreased use of reappraisal.

- Molecules. At the molecular level, several studies have explored the relationship between emotion regulation and molecules such as dopamine (Salgado-Pineda *et al.*, 2005), serotonin (Hariri and Holmes, 2006; Canli and Lesch, 2007; Outhred *et al.*, 2015), oxytocin (Quirin, Kuhl and Düsing, 2011), and cortisol (Lam *et al.*, 2009; Quirin, Kuhl and Düsing, 2011). For example, with regards to serotonin, there is evidence that increasing an individual's amount of serotonin available for absorption via the administration of a selective serotonin reuptake inhibitor facilitates reappraisal of negative stimuli (Outhred *et al.*, 2015), suggesting a close relationship between serotonin and emotion regulation strategies. Moreover, Poon *et al.* (2016) found that low cortisol reactivity and high emotion regulation difficulties tended to relate to higher substance use and externalizing symptoms, and high cortisol reactivity coupled with higher emotion regulation difficulties tended to relate to depressive (but not anxiety) symptoms.
- Cells. Though research on cells specifically relating to emotion regulation is sparse, there is a body of research that sets the stage for investigating the role of cells such as microglia (Walker, Nilsson and Jones, 2013) and cytokines (Miller, Capuron and Raison, 2005) in emotion regulation. For example, in studies conducted on rats exposed to chronic stress or anxiety-provoking situations, there is evidence that stress-induced microglial disturbances may play a role in regulating emotional states (Wohleb *et al.*, 2011; Hinwood *et al.*, 2012). In terms of cytokines, Miller, Capuron and Raison (2005) have explored the ways in which psychological and physical stress influence emotion regulation through their association with immune activation of cytokines such as interferon-alpha.
- Circuits. As reviewed in section 1.2.2. of this introduction, a large number of studies have now examined the neural correlates of various aspects of emotion regulation (Kim and Hamann, 2012; Ochsner, Silvers and Buhle, 2012; Etkin, Büchel and Gross, 2015). Many circuit-based studies of emotion regulation have focused on brain regions such as the dorsolateral and ventrolateral prefrontal cortices (Ochsner *et al.*, 2002; Buhle *et al.*, 2013; Kohn *et al.*, 2014), the ACC (Etkin and Wager, 2007; Etkin, Egner and Kalisch, 2011), the amygdala (Banks *et al.*, 2007; Townsend *et al.*, 2013; Denny *et al.*,

2014), and the insula (Phillips *et al.*, 2003a). Much of this research has focused on the downregulation of emotion-processing regions such as the amygdala by prefrontal systems in the context of negative emotion and reappraisal strategies.

- Physiology. The effects of emotion regulation on physiological measures have been studied using an array of different measures. For example, Gross (1998a) used physiological measures relating to sympathetic activation, somatic activity, and heart rate to assess the differential effects of reappraisal and suppression. Results indicated a lack of elevation in physiological responding when participants reappraised, but increases in multiple indices of sympathetic nervous system activation when participants used suppression. These results are consistent with earlier findings showing that suppression was related to increased sympathetic nervous system activity, decreased somatic activity, decreased heart rate, and increased blinking (Gross and Levenson, 1993). Other studies have focused on physiological effects of emotion regulation strategies in specific contexts. For example, the physiological consequences, measured via several different physiological indices (see the Physiology column of Table 1.1.), of the effects of reappraisal on anger (Mauss *et al.*, 2007), the effects of acceptance and suppression on negative and positive emotion pictures (Dan-Glauser and Gross, 2015), the effects of suppression on disgust (Roberts, Levenson and Gross, 2008), the effects of reappraisal on amusement (Giuliani, McRae and Gross, 2008), and the effects of unconscious reappraisal on a frustrating task (Yuan *et al.*, 2015), among others. In terms of electroencephalography (EEG) measurements, MacNamara, Kotov and Hajcak (2016) assessed the impact of emotional intensity on the late positive potential (LPP), a neurobiological measure assessing event-related potential that is larger for emotional (vs. neutral) stimuli. They found that greater symptoms of major depressive disorder (MDD) were associated with less emotional modulation of the LPP, and greater general anxiety disorder (GAD) symptomatology (controlling for MDD symptoms) was associated with greater negative potentiation of the LPP, suggesting that emotion dysregulation in GAD and MDD may stem from abnormal emotion generation. Rosenthal *et al.* (2016) investigated how individuals diagnosed with borderline personality disorder (BPD) reacted emotionally to personally-relevant (vs. standardized) sounds and found that individuals with BPD, compared to HC, reported higher arousal and lower valence, and heightened skin conductance responses in response to personally-relevant unpleasant sounds. Pupillometry measures have also been used in the context of emotion regulation. For example, Johnstone *et al.* (2007) found that, although MDD patients and HC did not

differ in pupil dilation when trying to decrease negative emotions, MDD patients showed a positive correlation between activation in core emotion circuitry and pupil dilation indicating higher cognitive effort, while HC showed the expected negative correlation between these measures.

- Behavior. Behaviors are typically observed via performances on various tasks designed to elicit emotion and assess how individuals regulate such emotions. Weiss, Thomson and Chan (2014) recently conducted a systematic literature review of emotion regulation measurements in individuals with autism spectrum disorder, and identified several measures of naturalistic observation of emotion regulation. For example, Jahromi, Meek and Ober-Reynolds (2012) conducted a study in which coders coded for 12 emotion regulation strategies in 10-s intervals. Results indicated that children with autism employed more avoidance and venting strategies when faced with frustration. In another study, participants were asked to either reappraise, suppress, or accept their emotion experience after giving an impromptu speech, and results indicated that both reappraising and accepting anxiety were more effective for moderating physiological arousal than suppressing it (Hofmann *et al.,* 2009). Finally, Levitt *et al.* (2004) conducted a study in which participants were exposed to a 5.5% carbon dioxide challenge and asked to either use suppression, acceptance, or neither. Results supported acceptance as a potentially beneficial strategy for reducing both subjective anxiety and avoidance in individuals with panic disorder (PD).
- Self-Report. Self-report assessment tools are ubiquitous in the study of emotion regulation. A plethora of self-report questionnaires focusing on specific aspects of emotion regulation have been used, including questionnaires focusing on difficulties identifying emotions (the Toronto Alexithymia Scale-20, TAS-20; Bagby, Parker and Taylor, 1994; Bagby, Taylor and Parker, 1994), emotion regulation strategies such as reappraisal and suppression (the Emotion Regulation Questionnaire, ERQ; Gross and John, 2003), cognitive strategies such as self-blame, rumination and catastrophizing (the Cognitive Emotion Regulation Questionnaire, CERQ; Garnefski and Kraaij, 2007), and general difficulties in regulating emotions (the Difficulties in Emotion Regulation Scale, DERS; Gratz and Roemer, 2004). In addition to self-report, an emotion regulation interview was recently developed (the Emotion Regulation Interview, ERI; Werner *et al.*, 2011) to assess the frequency and self-efficacy ratings of five strategies (avoid situations, modify situations, distraction, think about the situation differently, and hide visible signs of anxiety). Consistent with the RDoC approach (Cuthbert and Insel, 2013), emotion regulation has been assessed across the full range of functioning. In addition

to studies of clinical samples, emotion regulation has also been studied in many normative, non-clinical samples (Gross and John, 2003; Manser, Cooper and Trefusis, 2012; Goldberg *et al.*, 2016).

- Paradigms. Finally, the study of emotion regulation has incorporated several paradigms that typically involve an emotion induction component followed by an emotion regulation strategy implementation. For example, Gross (1998a) showed participants a film designed to elicit disgust, and then asked participants to either reappraise the situation, suppress their emotional reactions, or simply watch the film (control). Results indicated that both reappraisal and suppression reduced emotion-expressive behavior, and those who reappraised also had lesser increases in disgust experience while watching the film, whereas those who suppressed did not. In other studies (Sheppes *et al.*, 2011), pictures varying in emotion valence and intensity have been used to induce emotional states, including pictures from the IAPS (Lang et al., 2008). The fMRI reappraisal task used in Study 3 and Study 4 of this thesis and further described in section 3.1. would fall into this category.

Table 1.1. Summary of measures that have been used to study emotion regulation across the levels of analysis of the RDoC framework. Adapted from Fernandez, Jazaieri and Gross (2016).

Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
5-HTT	Dopamine	Microglia	Amygdala	Skin conductance	Impromptu speeches	TAS-20	Pictures reappraisal
COMT	Serotonin	Cytokines	PFC	Somatic activity	CO_2 challenge	ERQ	Film clips
Oxytocin receptor gene	Oxytocin		ACC	Finger pulse amplitude	Behavioral observation/ coding systems	CERQ	Emotional Stroop tasks
	Cortisol		Insula	Heart rate		DERS	
				Respiration		ERI	
				Blood pressure			
				Facial EMG			
				EEG			
				Pupillometry			

5-HTT, serotonin transporter gene; COMT, catechol-*O*-methyltransferase gene; PFC, prefrontal cortex; ACC, anterior cingulate cortex; EMG, electromyography; EEG, electroencephalography; CO_2, carbon dioxide; TAS-20, Toronto Alexithymia Scale-20; ERQ, Emotion Regulation Questionnaire; CERQ, Cognitive Emotion Regulation Questionnaire; DERS, Difficulties in Emotion Regulation Scale; ERI, Emotion Regulation Interview.

Bearing in mind all the above-mentioned findings, there is value on studying emotion regulation as a transdiagnostic feature of mental health disorders, and frame it within the context of the RDoC. In the next section, these findings are going to be further supported by

what is already known specifically about the neural correlates of emotion dysregulation in different mental health disorders.

1.4. The neural bases of emotion dysregulation in mental health disorders

According to Phillips' neural model of emotion regulation (Phillips *et al.*, 2003a, 2003b), most mental health conditions could be considered as the consequence of imbalanced interactions between the dorsal and ventral systems of the brain, with the dorsal regulatory network being unable to down-regulate the hyperactive ventral network (Phillips *et al.*, 2003b). According to this model, the ventral system comprises the amygdala, insula, ventral striatum, ventral ACC (vACC), and the vmPFC/medial OFC, while the dorsal system consists of the hippocampus, dorsal ACC (dACC) and dorsal PFC. The ventral system is thought to be involved in recognizing emotionally salient stimuli and generating an emotional state (i.e., bottom-up emotional influences), and the dorsal system in voluntarily regulating these states (i.e., voluntary top-down control of emotions). Despite this, the dorsal-ventral framework, although usefully accounting for much of the data, does not fully reflect that regulation occurs at all levels of the dorsal-ventral axis, instead of just in the dorsal system (Taylor and Liberzon, 2007). For example, as has been already pointed out in HC samples, the vlPFC has been suggested to have a role in the inhibition of negative affect (Ochsner, Silvers and Buhle, 2012; Ochsner and Gross, 2014). Below, findings regarding neural abnormalities during emotion regulation in different mental health disorders are reviewed, in order to see whether they fall into this general pattern of dorsal-ventral dysregulation or if they show more specific abnormalities (these results are summarized in Table 1.2.).

1.4.1. Emotion regulation in mood, anxiety, and obsessive-compulsive disorders

Emotional disorders such as depression and anxiety are estimated by the World Health Organization to be the greatest cause of disability worldwide (Mathers, Lopez and Murray, 2006). Efforts to understand the neurobiological causes of these conditions and potential avenues for treatment are therefore of enormous importance to the general population. Most brain research into mood and anxiety disorders has focused on the bottom-up determinants of emotions, with a focus on subcortical and early sensory processing that generates emotional responses and biases our behavior in an automatic way. For example, much of the focus in anxiety disorders has been on attentional biases toward anxiety-relevant stimuli (MacLeod, Mathews and Tata, 1986; Campbell-Sills, Ellard and Barlow, 2014), generated either through low-level sensory cortex or subcortical structures such as the amygdala, known to play a role in early threat detection. In depression, an extensive literature exists on the role of the

monoaminergic neurotransmitters serotonin, norepinephrine, and dopamine in subcortical and subcortical-cortical networks involved in mood, though, despite all this research, there have been no definitive breakthroughs in understanding the causes of depression (Johnstone and Walter, 2014). For this reason, there might be value on studying not just the bottom-up abnormalities during the generation of emotions, but also the potential deficits in the top-down regulation of these emotions.

In this line, negative emotions such as anxiety and sadness are a normal occurrence in response to adversity in all individuals, but one feature that distinguishes those with mood and anxiety disorders is their inability to regulate certain negative emotions effectively when they arise. Indeed, it might well be argued that the defining feature of many mood and anxiety disorders is the extended duration of emotional episodes rather than their intensity. Cognitive neuroscientists have argued that depression should not be equated with the "down" state itself, but rather with the tendency to enter and get stuck in this state. Thus, the neurobiology of depression should be that of mood reaction and regulation rather than the mood state per se (Holtzheimer and Mayberg, 2011). But, despite the fact that abnormalities in the neural circuitry supporting adaptive regulation of emotions may play a decisive role in determining vulnerability to mood and anxiety disorders (Davidson *et al.*, 2002), only recently have researchers started to explicitly examine this possibility. Below, we discuss the findings separately for mood disorders, anxiety disorders, and OCD.

Mood disorders

The hallmark feature of mood disorders is disordered affect. MDD is defined by sustained negative affect and difficulties experiencing positive affect, while BD is characterized by episodes of depressed but also elevated and/or irritable mood (mania). Despite the fact that disordered affect is the central feature of mood disorders, theories of the onset, maintenance, and recurrence of these disorders have traditionally focused on cognition and behavior but not as much on affect. A closer look at the concept of emotion regulation and the mechanisms that allow understanding individual differences in the ability to regulate affective states may aid us to better comprehend vulnerability to affective disorders and thereby improve treatment approaches (Joorman and Siemer, 2014).

Bipolar disorder

In their review, Phillips, Ladouceur and Drevets (2008) examined the functional neural abnormalities of emotion regulation in patients with BD, differentiating between voluntary and automatic emotion regulation. Regarding voluntary attentional control, findings in PFC regions appeared to be inconsistent, with reduced but also increased activity in different bilateral lateral and dorsal PFC regions in BD compared to healthy adults. Despite this, findings from studies employing voluntary emotion regulation paradigms indicated greater bilateral activity in BD than in healthy adults in these lateral and dorsal PFC regions, together with greater activity in bilateral vmPFC regions implicated in automatic emotion regulation, which may mediate the voluntary emotion regulatory roles of the previous lateral and dorsal PFC regions during voluntary emotion regulation. Structural findings indicated reductions in gray matter (GM) volume and density in lateral and dorsal PFC regions, although there were also inconsistent findings of increased GM volume or no abnormalities in these regions. It is possible that increased activity in lateral PFC regions during voluntary attentional control and voluntary emotion regulation paradigms reflects inefficient utilization of these regions during cognitive control tasks in BD relative to HC.

On the other hand, there have been more consistent findings regarding functional and structural changes in neural regions implicated in automatic emotion regulation in adult BD. Studies employing automatic attentional control paradigms have shown reduced activity predominantly in left-sided vmPFC, both during remission and mania, in BD relative to healthy adults. These functional neuroimaging findings are paralleled by structural neuroimaging findings showing GM structural changes in the left OFC, and abnormal integrity and number of white matter (WM) fibers connecting the left OFC and subcortical limbic regions implicated in emotion processing. Interestingly, increased recruitment of dlPFC in BD compared to healthy adults has been reported during an automatic attentional control paradigm, suggesting the employment of more effortful, voluntary, rather than automatic, regulatory control systems during performance of otherwise automatic control tasks in BD.

The combination of these functional and structural neural abnormalities, which appear to be decreases in activity and GM volume predominantly within left vmPFC regions implicated in automatic emotion regulation, may underlie the mood instability of adult BD. The significance of the laterality of these findings remains unclear, but may suggest a role for the left hemisphere, previously linked with perception of positive emotion (Davidson *et al.*, 1999) in the pathophysiology of BD. These findings indicate that further insights into the neural bases

of mood dysregulation in BD will come especially from studies that employ paradigms that measure the functional integrity of neural regions during performance of automatic emotion regulation paradigms. Moreover, future studies should focus on examination of the relationship between functional and structural abnormalities in these neural regions in adult BD, and the extent to which specific symptom domains, including comorbid anxiety and SUDs, are associated with distinguishable patterns of abnormality in these neural regions.

Major depressive disorder

In their systematic review, Rive *et al.* (2013) also characterized the abnormalities in the neural systems involved in emotion regulation in patients with MDD differentiating between automatic and voluntary emotion regulation. Taken together, they found most differences in the activity of regulatory brain regions between MDD subjects and HC within automatic emotion regulation paradigms. From the twenty-one studies examined, they concluded that additional neuronal resources are recruited by MDD subjects, i.e., the ventral tegmental area (VTA) during automatic behavioral control of rewarding stimuli, the parietal and lateral PFC during automatic attentional control of emotional information, and the dlPFC/vlPFC during automatic cognitive control. These additional resources may be necessary to override strong bottom-up emotional influences, as reflected by reports of limbic hyperactivity (Drevets, 2003), which may occur especially during automatic cognitive control (Abler *et al.*, 2007; Pizzagalli *et al.*, 2009).

Findings of differential neuronal activity in MDD subjects coming from the twenty-three studies of voluntary emotion regulation that they reviewed were less unequivocally conclusive. Nevertheless, they tentatively concluded that MDD subjects are insufficiently capable of compensatory PFC recruitment during voluntary behavioral control and voluntary cognitive control, since activity of PFC regions is at most equal (Beauregard, Paquette and Lévesque, 2006; Erk *et al.*, 2010) but more often decreased in MDD subjects relative to HC (Taylor Tavares *et al.*, 2008; Erk *et al.*, 2010). Finally, there were differential rostral ACC (rACC), dACC and/or subgenual ACC (sgACC) functioning in MDD subjects compared to HC during most regulatory processes, with indications for a relative overrecruitment of the rACC/dACC especially during automatic control.

To reconcile these findings, they speculated that during early, automatic stages of emotion regulation, MDD subjects may be capable of successful emotion regulation, but only by recruiting additional lateral PFC neural resources. This strategy might be mediated by medial prefrontal, especially rACC/dACC functioning. This hypothesis is in line with other neural

models of emotion regulation, demonstrating that the rACC/dACC has a key modulatory function (Drevets, Savitz and Trimble, 2008; Pizzagalli, 2011). During explicit voluntary control, however, when the emotional experience is already ongoing, this strategy of additional recruitment of lateral PFC structures seems to fail, as reflected by abnormally reduced activity in lateral PFC cortices. This hypothesis corresponds with evidence from neurocognitive research, as summarized by Gotlib and Joormann (2010), which points out that MDD subjects have difficulty stopping or inhibiting the processing of negative material especially when this material has already captured one's attention.

Anxiety disorders

Anxiety disorders are a group of mental health disorders characterized by significant feelings of anxiety and fear. Due to the predominance of symptoms of excessive fear, models of anxiety-related attentional bias have proposed that an overly sensitive pre-attentive threat detection system is responsible for drawing attention toward threatening stimuli (Cisler and Koster, 2010). In line with this, elevated amygdala activation in response to threat-relevant information is often measured in high-anxiety individuals, suggesting that attentional biases may have their roots in hyperactive or low-threshold threat detection at a subcortical level. However, heightened amygdala activation is not always found in high-anxiety individuals, in part because amygdala engagement may depend on the specific amygdala nucleus and properties of the threatening stimulus (Etkin *et al.*, 2004). There are also other candidate subcortical regions that might underlie overly sensitive threat detection in anxious individuals, such as the bed nucleus of the stria terminalis (BNST), which plays an important role in sustained, as distinct from transient, forms of vigilance (Walker, Toufexis and Davis, 2003; Somerville *et al.*, 2013).

Nonetheless, it seems likely that anxiety disorders involve more than just hypersensitivity in bottom-up threat detection systems. There is now a large body of evidence showing that highly anxious individuals have deficits in prefrontal circuits that regulate attention and response to threatening stimuli (Cisler and Koster, 2010). Deficits in the performance of working memory tasks in the presence of sustained emotional distractors or anxiety induction in anxious individuals (Shackman *et al.*, 2006) also point to weakened top-down control of emotion, potentially involving the prefrontal network for cognitive control and spontaneous emotion regulation. Using a perceptual discrimination task in the presence of fearful versus neutral facial expressions, Bishop *et al.* (2004) found lower rACC and vlPFC activation in high-anxious compared to low-anxious individuals, and the opposite pattern in the amygdala. This

result is consistent with a model in which rACC detects the need for control over incoming information that conflicts with task demands, and vlFPC is subsequently involved in regulating attention toward task-relevant information and away from threatening, task-irrelevant information. In a later study, Bishop (2009) reported that high trait anxious individuals showed greater interference from non-emotional distractors, along with reduced activation in dlPFC. Thus, elevated trait anxiety is associated with generally reduced lateral PFC-mediated top-down control of attention, resulting in less efficient attentional regulation of distracting emotional information. Coupled with a hypersensitive bottom-up threat detection system, the consequence would be hypervigilance and an inability to disengage from potentially threatening stimuli, which together with the increased tendency for avoidant response in anxiety is consistent with the hypervigilance-avoidance model (Campbell-Sills, Ellard and Barlow, 2014; Johnstone and Walter, 2014).

Besides high-anxiety individuals, hypoactivation of PFC regions during reappraisal of emotional stimuli has also been observed across anxiety disorders (Goldin, Ball, *et al.*, 2009; Goldin, Manber, *et al.*, 2009; New *et al.*, 2009; Ball *et al.*, 2013). Of these, the most consistent neuroimaging findings have been reported for posttraumatic stress disorder (PTSD). A number of studies have shown impaired extinction of conditioned responses to aversive stimuli in PTSD, and hypoactivation in vmPFC/rACC has been reported in response to both trauma-related and non-trauma-related aversive stimuli, as well as during extinction, other emotional and cognitive tasks, and resting baseline (Shin and Liberzon, 2010). Activation in this region also negatively correlates with PTSD symptom severity. All of these results suggest that PTSD is characterized by a disrupted ability to regulate previously conditioned fear responses through the engagement of vmPFC extinction circuitry. Regarding the other anxiety disorders, one recent study (Ball *et al.*, 2013) showed that subjects with GAD and PD who were trained to use cognitive reappraisal displayed decreased dmPFC and dlPFC activation while implementing this strategy. Moreover, PFC activation was inversely related to anxiety severity. In another cognitive reappraisal study (Goldin, Ball, *et al.*, 2009), subjects with social anxiety disorder (SAD) showed increased responses in regions such as the medial PFC and the amygdala, together with a delay in normal cognitive processing in the dlPFC, which only occurred after a temporal lag relative to that in HC. Moreover, dysfunction of neural circuitry supporting cognitive reappraisal may be context-dependent, and exacerbated in the presence of emotional cues that represent the focus of the individual's anxiety disorder. In their study, Goldin, Manber, *et al.* (2009) showed that when regulating responses to images depicting physical threat, no differences emerged between subjects with SAD and HC. However, when

regulating reactions to social threat, subjects with SAD displayed reduced activation in brain regions implicated in cognitive control (dlPFC, dACC), visual attention (medial cuneus, posterior cingulate cortex - PCC), attention (bilateral dorsal parietal lobule), and visual feature detection (bilateral fusiform, superior temporal gyrus - STG). Finally, regarding functional connectivity, increased amygdala-dlPFC connectivity during resting-state has been found in patients with GAD (Etkin *et al.*, 2009).

Finally, there is a possibility that dysfunction may extend beyond regions implicated in cognition and emotion to include regions implicated in processing sensory information and choosing an adaptive behavioral response. Specifically, emotion regulation difficulties across anxiety disorders may be characterized by not only deficits in cortical control of affective responses but also a failure to set in motion appropriate approach- and reward-related behaviors (Etkin *et al.*, 2010).

Obsessive-compulsive disorder

OCD is another chronic and disabling condition that affects 2-3% of the population (Ruscio *et al.*, 2010), characterized by the presence of obsessions (i.e., anxiety-evoking intrusive thoughts, urges, ideas or images) and compulsions, which are ritualistic, repetitive behaviors or mental acts carried out to alleviate anxiety. OC symptoms are increasingly becoming a focus of attention in emotion regulation research, motivated by the fact that difficulties in the cognitive modulation of emotional-related stimuli are a key characteristic of OCD. Cognitive biases are widely accepted to be important factors in the development and maintenance of the disorder (Salkovskis, 1985; Clark and Purdon, 1995), with specific dysfunctional thoughts operating as vulnerability factors in the pathogenesis of OC symptomatology (Abramowitz *et al.*, 2006). It has recently been shown, by means of path analysis, how the habitual use of different emotion regulation strategies can lead to OC symptomatology through mediation by affect and cognitive rigidity (Goldberg *et al.*, 2016). Two pathways emerged: a more adaptive pathway, linking the habitual use of cognitive reappraisal to decreased OC symptomatology, mediated by positive affect and decreased cognitive rigidity; and a less adaptive pathway, linking expressive suppression use to increased OC symptomatology, mediated by negative affect and increased cognitive rigidity.

Despite this, the interrelationships between emotion regulation, affect and OC symptoms are still not fully understood. Standard approaches propose that cortical circuits exert a direct control of emotional expression and experience. But recent research – largely based on OCD-related phenomena- suggests that these associations may not be so straightforward. Instead,

emotional reactivity seems to interact with other aspects of cognition, while cognitive processes may regulate both affect and emotional responses (Taylor and Liberzon, 2007; Arnsten and Rubia, 2012; Ray and Zald, 2012). Additional support to this notion of complex interactions between different systems comes from the neurobiological findings that link OCD and its related dysfunctional cognition with alterations in the cortico-striato-thalamo-cortical loops (updated from the traditional frontostriatal model; Saxena and Rauch, 2000). According to this perspective, OCD is conceptualized as a disorder of self-regulation and behavioral inhibition that involves recurrent projections between the frontal cortex and subcortical structures within the basal ganglia and the thalamus (Harrison *et al.*, 2009; Fontenelle *et al.*, 2011; Pauls *et al.*, 2014). Furthermore, more recent neurobiological models of the disorder place greater emphasis on brain regions outside the cortico-striatal loops that may be critically involved in the pathophysiology of OCD, such as limbic cortico-amygdalar circuitry (Milad and Rauch 2012), and that may account for some of the symptoms characterizing OCD patients that the cortico-striatal model fails to explain (e.g., increased anxiety; Menzies *et al.*, 2008).

Regarding the amygdala, there is considerable evidence indicating hyperactivation in OCD patients during the processing of emotional information. This appears to be the case both with OCD-specific (Breiter *et al.*, 1996; Mataix-Cols *et al.*, 2004; Simon *et al.*, 2010) and generic stimuli, such as emotional faces (Cardoner *et al.*, 2011; Via *et al.*, 2014). Moreover, a general pattern of fronto-subcortical (including fronto-amygdalar) hyper-reactivity has been identified while anticipating and perceiving emotional stimuli; a pattern that is shared by OCD and SAD (Weidt *et al.*, 2016). Likewise, OCD patients show diminished fronto-amygdala connectivity during emotion regulation (de Wit *et al.*, 2015), although, by contrast, increased functional connectivity between the amygdala and the dlPFC has been shown to account for impaired working memory performance in OCD (de Vries *et al.*, 2014). Overall, these findings have been interpreted as suggesting that greater amygdala activation in response to emotional stimuli in OCD may interfere with information processing in cognitive control networks.

Moreover, WM integrity alterations have also been found in several WM tracts, as for example the uncinate fasciculus (a tract that connects the amygdala and the insula) and the inferior fronto-occipital fasciculus (IFOF; a tract that also passes through the amygdala), consistent with the functional findings (Garibotto *et al.*, 2010; Admon *et al.*, 2012; Jayarajan *et al.*, 2012; Benedetti *et al.*, 2013). Finally, two studies have investigated the link between functional and structural connectivity. Admon *et al.* (2012), using a gambling task, showed a deficit in fronto-limbic connectivity both at the functional and structural level, which was also associated with OCD symptom severity. On the other hand, Rus *et al.* (2017) used a negative affect task and

found an increased functional connectivity between the amygdala and parieto-occipital regions, which was related to the structural connectivity estimates between these regions, which in turn were negatively associated with OCD symptom severity.

Even though the literature regarding the neural correlates of emotion regulation in OCD is still scarce as compared to mood and anxiety disorders, preliminary findings point to alterations both in bottom-up and top-down regions, and in the connectivity between them.

1.4.2. Emotion regulation in substance and behavioral addictions

SUDs are complex illnesses, encompassing a host of severe negative physical, economic, and social consequences, and contributing to worldwide disability. With a lifetime prevalence of 35.3% in the general population, individuals with SUDs represent the most prevalent and costly of psychiatric disorders (National Institute of Mental Health (NIMH), 2007; Substance Abuse and Mental Health Services Administration (SAMHSA), 2011). A key feature of SUDs is loss of regulatory control, as is craving, and the regulation of craving (a specific form of emotion regulation that can directly reduce drug use).

A complex relationship exists between emotion regulation and SUDs. On the one hand, acute intoxication can be considered a means of emotion regulation, since people use drugs in part to regulate their current emotional state (i.e., increasing positive affect, ameliorating a preexisting negative state, or decreasing craving). On the other hand, emotion dysregulation in SUDs is both a possible cause for- and a possible consequence of drug use. Emotion dysregulation in childhood and adolescence may be an early risk factor in the development of SUDs. Moreover, an inability to effectively regulate emotions in specific moments may be a proximal causal factor for instances of drug use in individuals who are already suffering from SUDs. Finally, SUDs are marked by deficits in regulation of a specific appetitive state, namely, drug craving, which is at the core of these disorders (Kober, 2014).

Regarding the neural correlates of emotion dysregulation in SUDs, differences in the function and structure of the PFC have been found. With regards to PFC structure, compared to HC, reduced PFC GM density has been found in cigarette smokers (Brody *et al.*, 2004) and cocaine-dependent individuals (specifically the OFC and ACC; Franklin *et al.*, 2002), lower thickness and volume have been reported in various PFC regions in other stimulant users (Daumann *et al.*, 2011; Tabibnia *et al.*, 2011), and lower volume across the PFC has been shown in alcohol-dependent subjects (Fein *et al.*, 2002; Durazzo *et al.*, 2011; Rando *et al.*, 2011). Consistent with these findings, lower measurements of WM integrity (as measured with diffusion tensor imaging -DTI- techniques) in the PFC have been found in individuals with alcohol use disorders

(Pfefferbaum *et al.*, 2009), cocaine-dependent participants (Romero *et al.*, 2010), and in methamphetamine (Alicata *et al.*, 2009) and opiate users (Liu *et al.*, 2008; Bora *et al.*, 2012). Studies investigating brain function during performance of non-affective cognitive control tasks in individuals with SUDs and HC, have consistently found worse performance in SUD individuals compared to HC, along with reduced activity in several PFC regions (such as the dACC, dlPFC, and vlPFC) (Bolla *et al.*, 2004; Eldreth *et al.*, 2004; Hester and Garavan, 2004; Fu *et al.*, 2008; Nestor *et al.*, 2011). In a cognitive reappraisal fMRI task, cocaine users compared to HC showed decreased right vlPFC, PCC, insula and fusiform gyrus activations during emotion regulation, together with decreased functional coupling between the right vlPFC and the amygdala (Albein-Urios *et al.*, 2014). Finally, it is important to highlight that, although some of these abnormalities may precede drug use, the long-term effect of chronic drug use on PFC may further impair emotion regulation in SUDs (Kober, 2014).

Not only SUDs, but also behavioral addictions, are characterized by loss of control over drives or habits, and by persistent preference for immediate rewards at the expense of relative net loss (Clark, 2014). The most commonly studied behavioral addiction is pathological gambling, included now in the DSM-5 under the same category than SUDs (American Psychiatric Association, 2013). Pathological gamblers, compared to HC, have been shown to make significantly less use of reappraisal strategies, more use of suppression strategies, have greater lack of emotional clarity and awareness, and present higher impulsivity (Williams *et al.*, 2012; Torres *et al.*, 2013; Navas *et al.*, 2017). Moreover, during a cognitive reappraisal fMRI task, pathological gamblers showed higher left dlPFC activity during regulation compared to HC, and activity in this region correlated positively with a trait measure of negative urgency (Navas *et al.*, 2017).

Excessive eating can also be considered a form of behavioral addiction, although not recognized in the DSM-5, which shares many features with SUDs (e.g., reward-seeking behavior, impulsivity, craving) as defended by the food addiction model (Volkow *et al.*, 2013; Volkow *et al.*, 2013). Moreover, excessive intake of appetizing and unhealthy foods has been suggested to act as a maladaptive emotion regulation strategy to suppress negative emotions (Hemmingsson, 2014). In addition, negative moods have been found to potentiate brain response to food by influencing mesolimbic circuitry and reward-seeking behavior (Volkow *et al.*, 2013; Rudenga, Sinha and Small, 2013). This suggests that an inability to properly manage negative affective states could be a key aspect in the acquisition and maintenance of excess weight, as those who are unable to manage negative states might be more vulnerable to becoming stressed and consequently seeking relief in the rewarding properties of highly

palatable foods. Then, similar to what is seen in SUDs, overconsumption of rewarding food might in turn lead to changes in the reward circuitry that result in further compulsive food intake (Volkow *et al.*, 2013). Up to date, there is a paucity of studies directly exploring emotion processing and regulation networks in people with excess weight. Despite this, in a HC adolescent sample performing a cognitive reappraisal fMRI task in response to palatable food images, strategies aimed at regulating craving for the food showed increased activation in inhibitory regions (i.e., superior frontal gyrus, vlPFC) and reduced activation in attention-related regions (precuneus and PCC), evidencing the similarities between the regulation of negative emotions and the regulation of craving (Yokum and Stice, 2013). Further research is needed that characterizes the neural correlates of the regulation of negative emotions and/or the regulation of craving in people with excess weight.

Table 1.2. Summary of findings regarding activations in emotion regulation and other related tasks in mental health disorders, as well as structural differences.

		Mood		Anxiety				OCD	Addictions		
Brain Region		**BD**	**MDD**	**GAD**	**SAD**	**PTSD**	**PD**		**SUDs**	**Gambling**	**Excess-weight**
Limbic	Amygdala	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
	Insula								↓		
	Striatum										
PFC	vlPFC		↓↑						↓↓		
	vmPFC	↑↓↓			↑	↓↓↓					
	dlPFC	↑↑↓	↓↑	↓	↓		↓		↓	↑	
	dmPFC			↓	↑		↓				
	ACC		↑		↓	↓↓↓			↓↓		
	OFC	↓							↓		
Other	Parietal		↑		↓						
	Cuneus				↓						
	PCC				↓				↓		
	Fusiform				↓				↓		
	STG				↓						

Purple arrows refer to cognitive reappraisal tasks, green arrows to automatic emotion regulation, red arrows to other type of regulation tasks, and blue arrows to structural data. Amygdala hyperactivation is typically found across tasks and disorders.

PFC, prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; STG, superior temporal gyrus; OCD, obsessive-compulsive disorder; BD, bipolar disorder; MDD, major depressive disorder; GAD, general anxiety disorder; SAD, social anxiety disorder; PTSD, posttraumatic stress disorder; PD, panic disorder; SUB, substance-use disorder.

1.5. Rationale for the study

Emotion regulation is a critical process for dealing appropriately with emotions in our daily lives. An important part of adaptively regulating emotions is being able to maintain a balance between short-term and long-term goals. There are different processes and strategies involved in emotion regulation, which can lead to different affective, cognitive and social outcomes. More importantly, these appear to be altered in mental health disorders, with emotion regulation deficits being a transdiagnostic feature that can be framed within the context of the RDoC.

Several fMRI studies and meta-analyses have shown a consistent pattern of neural activation during emotion regulation in HC, specifically for cognitive reappraisal tasks. This pattern of activations consists on a network of fronto-parietal control regions, which, in turn, down-regulates the limbic system (including the amygdala). Some differences in this general pattern of activation can be found when looking at other strategies, at specific subtypes of reappraisal, or at different regulation goals, for example. Psychiatric populations have also been the subject of research, albeit to a lesser extent. Moreover, patients with mood or anxiety disorders are more commonly assessed in comparison to other disorders. Preliminary findings indicate that the limbic system is overactive and prefrontal regulatory regions are compromised in patients with mental health conditions, showing both hyper and hypoactivations depending on the specific task.

Further research is needed to better characterize whether the same pattern of affected neural activations is observed across different mental health disorders or whether a specific pattern of regional alterations emerges for different disorders, taking into account that most of these show deficits in emotion regulation in one way or another. Moreover, the information coming from task activation studies can be further complemented by using other neuroimaging analysis methods. For example, new insights about these deficits can be obtained by studying the intrinsic patterns of brain functional connectivity, instead of the isolated activation of regions, both during the performance of a task and during rest. Finally, the underlying structural connectivity between brain regions can also shed light on the type of abnormalities that can be found in patients with emotion regulation difficulties, and on whether these structural findings match their functional counterparts.

AIMS AND HYPOTHESES

2. Aims and Hypotheses

2.1. General aims

The overall aim of the present thesis is to provide new insights into the neural correlates of emotion regulation in clinical and healthy control samples. Using different neuroimaging modalities (from functional and structural connectivity, to task activation studies and meta-analysis), we sought to better describe these correlates and their relationship with different emotion regulation strategies by assessing mood, anxiety, and OCD samples in comparison with healthy control subjects, and also excess-weight individuals in comparison to normal-weight subjects. Moreover, we also aimed to describe the neural correlates of emotion regulation strategies outside experimental contexts. The neurobiological underpinnings of the dispositional use of emotion regulation strategies have been comparatively less studied, both in healthy volunteers and clinical samples. We hope that our findings might contribute to expand knowledge of the underlying neurobiology of emotion regulation across conditions and mental health disorders, leading to a better understanding of the commonalities and differences in patient groups with impairments in these processes, and eventually providing new targets for brain-based treatments of emotion regulation deficits.

2.2. Specific aims and hypotheses

The lack of previous research in some of the topics and patient groups included in this thesis has made our studies somehow exploratory. Despite this, we defined specific hypotheses for each study, sometimes pointing to the most probable localization of the expected neuroimaging findings based on previous studies with similar approaches or clinically related patient samples.

STUDY 1: **Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity**

Aims

- To examine, in a sample of healthy volunteers, the association between the resting-state patterns of functional connectivity of the amygdala and trait-like measures of cognitive reappraisal and expressive suppression as assessed by the ERQ.
- To study these patterns of functional connectivity depending on the different amygdala territories, specifically differentiating between basolateral (BLA) and centromedial amygdala (CMA).

Hypotheses

- The use of reappraisal strategies would be associated with a negative coupling between the amygdala and dorsomedial, dorsolateral and ventrolateral frontal regions.
- Due to the paucity of studies on the neurobiological correlates of expressive suppression and on the role of the different amygdala sub-regions, we did not put forward a definite hypothesis about these results, but we hypothesized that differences would be observed compared to reappraisal.
- We expected different patterns of connectivity to emerge from BLA and CMA.

STUDY 2: **Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder**

Aims

- To determine whether there are differences in the resting-state functional connectivity of the left (LA) and right amygdala (RA) in OCD patients versus HC.
- To identify the extent to which abnormal amygdalar resting-state connectivity is associated with disruptions in WM fiber bundles, using DTI estimates.
- To investigate the potential association of both functional and structural connectivity estimates with OCD symptom severity, as well as with the dispositional use of cognitive reappraisal and expressive suppression strategies, as assessed with the ERQ.

Hypotheses

- We expected to find altered functional connectivity in OCD patients between the amygdala and regions implicated in emotion processing and regulation, such as the fronto-parietal network and the insula.
- A differential, asymmetric, pattern of findings was expected for LA and RA.
- Given previous evidence indicating that changes in resting-state connectivity are associated to alterations in structural connectivity, we hypothesized that functional connectivity differences would be related to alterations in the underlying WM microstructure.
- Finally, connectivity patterns were hypothesized to be associated with OCD symptom severity and ERQ sub-scores, with a differential pattern of associations for cognitive reappraisal and expressive suppression.

STUDY 3: **Emotion regulation and excess weight: impaired affective processing characterized by dysfunctional insula activation and connectivity**

Aims

- To compare the brain substrates of emotion regulation in excess-weight individuals versus normal-weight controls.
- To further explore the interaction between emotion generation and emotion regulation systems, by means of a psycho-physiological interaction (PPI) analysis, which assesses changes in the connectivity between these two systems across emotion regulation and generation blocks.
- To explore the complex associations between emotion regulation, body mass index (BMI), impulsivity, approach/avoidance motivation and food addiction by means of path analysis.

Hypotheses

- We hypothesized that excess-weight participants would exhibit heightened reactivity indicated by altered activation in emotion-generation and interoception-related regions when viewing negative stimuli compared to normal-weight controls.
- We expected excess-weight participants to display inefficient down-regulation of negative emotional responses during reappraisal, which would coincide with persistently heightened activation in emotion-generation areas and reduced activity in emotion-regulation areas.
- We expected to find significant associations between the behavioral measures commented above and the areas of dysfunctional activation in the excess-weight group.

STUDY 4: Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies

Aims

- To identify, by means of a meta-analysis of fMRI studies assessing cognitive reappraisal in samples of patients with mood or anxiety disorders, the neural correlates of impaired emotion regulation in these patient populations.
- To explore, in the context of disrupted emotion regulation, the potentially different neurobiological correlates between reinterpretation and distancing reappraisal strategies.

Hypotheses

- We hypothesized that activations in HC (vs. patients) during reappraise blocks would substantially overlap with regions of the prefronto-parietal network previously reported to associate with emotion regulation.
- In the patient group, we expected to find decreased activation of the prefronto-parietal network in combination with an ineffective down-regulation of emotion generation regions (i.e., limbic regions).
- From the scarce literature comparing different reappraisal strategies, we expected distancing to specifically activate parietal regions related to perspective taking and spatial attention, while reinterpretation would be linked to ventral prefrontal regions implicated in response selection and inhibition, along with temporal regions related to linguistic and semantic processing.

METHODOLOGY

3. Methodology

In this section, we describe the different materials, imaging techniques and analysis protocols used across the different studies of this thesis. The description of all the relevant details regarding the different study samples is provided in each of the studies.

3.1. Experimental conditions

3.1.1. Resting-state sequence

During a resting-state paradigm, participants are asked to lay down, either with their eyes open or closed (in our studies, we asked participants to keep their eyes closed), in an awake relaxed state, without performing any task. This paradigm was used for Study 1 and Study 2, and it allows for the study of the intrinsic temporal organization (i.e., functional connectivity or activity synchronization across distinct brain regions) of major brain networks while the participants are not performing any specific task.

3.1.2. Cognitive reappraisal task

This task was used in Study 3 and Study 4. It is an fMRI task in which participants are presented with neutral and negative visual stimuli, typically images from the IAPS (Lang, Bradley and Cuthbert, 2005), but also disorder-specific negative images from other databases when patient samples are used. This task intercalates blocks of neutral images, in which participants are instructed to observe the image (Observe), with negative image blocks, in which participants are instructed either to maintain the negative emotion elicited by the image (Maintain), or to reappraise these negative emotions by means of cognitive reappraisal (reinterpretation, distancing, or both; Reappraise) (Fig. 3.1.). Usually, the contrasts of interest target the comparison between Maintain and Observe in order to capture the brain regions involved in emotion generation, as well as the comparison between Reappraise and Maintain to investigate emotion regulation. An in-scanner behavioral measure is also commonly acquired when using this task. Specifically, participants are asked to self-rate the intensity of the negative emotions experienced after the presentation of each image block, which allows a measure of regulation success by subtracting the average Reappraise from the average Maintain ratings. If regulation is successful, Reappraise ratings should be lower than Maintain ratings and, in consequence, the Success variable is positive.

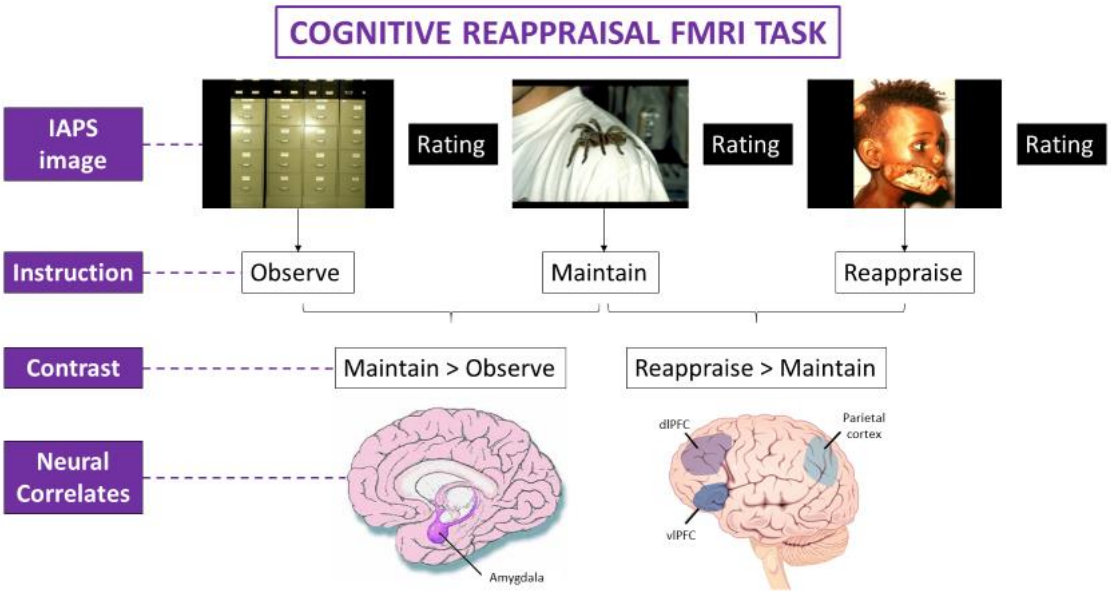

Figure 3.1. Visual representation of the general structure of the cognitive reappraisal fMRI task, the most frequently analyzed contrasts, and the neural correlates associated with them. Across-study differences may be found regarding the type of stimuli, the number of pictures per block, the blocks' duration, and the specific instructions given to participants, among others.

3.2. Questionnaires

3.2.1. Emotion Regulation Questionnaire

The ERQ (Gross and John, 2003) was used in Study 3, and in its Spanish version (Cabello *et al.*, 2013) in Study 1 and Study 2. The ERQ comprises the subscales of expressive suppression and cognitive reappraisal. It consists of 10 items and participants give their answers on a 7-point Likert scale with the endpoints ''strongly disagree'' and ''strongly agree''. Cronbach's α coefficients averaged 0.79 for reappraisal and 0.73 for suppression, and test–retest reliability across 3 months was 0.69 for both scales. The Spanish version of the ERQ also shows adequate internal consistency (Cronbach's α coefficients were α = 0.75 for suppression and α = 0.79 for reappraisal), test–retest reliability (0.66 for suppression and 0.64 for reappraisal over 3 months), and convergent and discriminant validity (Cabello *et al.*, 2013).

3.2.2. Barratt Impulsiveness Scale

The Barratt Impulsiveness Scale (BIS-11; Patton, Stanford and Barratt, 1995) was used in Study 3. It is a questionnaire designed to assess the personality/behavioral construct of impulsiveness, and it includes 30 items that are scored to yield six first-order factors

(attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness). This scale has reported internal consistency coefficients ranging from 0.79 to 0.83 for separate populations of university students, SUD patients, general psychiatric patients, and prison inmates (Patton, Stanford and Barratt, 1995).

3.2.3. Positive and Negative Affect Schedule

The Spanish version (Sandín *et al.*, 1999) of the Positive and Negative Affect Schedule (PANAS; Watson, Clark and Tellegen, 1988) was used in Study 2, which allows to assess positive and negative mood. This is a 20-item self-report measurement of the positive and negative affect experienced during the last 4 weeks.

3.2.4. Yale-Brown Obsessive-Compulsive Scale

The Spanish version (Vega-Dienstmaier *et al.*, 2002) of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman *et al.*, 1989) was used in Study 2. This scale is a clinician-rated, 10-item scale, each item rated from 0 (no symptoms) to 4 (extreme symptoms; total range, 0 to 40), with separate subtotals for severity of obsessions and compulsions. It includes items regarding the amount of time spent on obsessions and compulsions in a day, the distress they provoke and the resistance shown against these.

Other questionnaires like the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960), the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959), the Yale Food Addiction Scale (YFAS; Gearhardt, Corbin and Brownell, 2009), and the Behavioral Inhibition System and Behavioral Activation System scales (Carver and White, 1994), were used in Studies 1 and 3, although these scores were only used for sample characterization, and were not assessed in relation with neuroimaging data.

3.3. Analyses of behavioral data

Behavioral data were analyzed across the studies with the Statistical Package for the Social Sciences (SPSS; Chicago, IL, USA). We conducted independent-sample t-tests to compare quantitative variables between two groups. Moreover, for Study 3, interactions between in-scanner ratings for each condition (Observe, Maintain and Reappraise) and subject groups were evaluated using a 2x3 repeated-measures ANOVA analysis. Pearson correlations were used to check whether relevant relationships existed between the behavioral variables of interest.

A more complex statistical analysis was used in Study 3, i.e., path analysis, which was conducted by means of AMOS 18.0 software. Path analysis is a method used to estimate a set of simultaneous regression equations to explore how a group of variables interrelate in complex patterns. Three types of effects can be distinguished: (1) direct effects, which demonstrate the direct association of one variable with another; (2) indirect effects, which indicate the indirect association of one variable with another via other variables in the model; (3) total effects, which estimate the addition of direct and indirect effects. The first step of this process consists of testing an initial just-identified or saturated model in which the number of free parameters equals the number of known values (i.e., a model with zero degrees of freedom). The following steps consist of performing a trimming of this saturated model by retaining the significant or trend-level significant associations and excluding non-significant paths (Byrne, 2010).

3.4. Magnetic resonance imaging statistical analyses

In the context of the rapid development that has been taking place in cognitive neuroscience since the 1980s, a new technique with superior spatial and temporal resolution emerged, providing an ideal tool for testing many psychological hypotheses. As a consequence, the number of articles using this technique, as well as the refinement and complexity of the methodology and software used, has undergone an exponential increase in the last decades. Remarkable advances in magnetic resonance imaging (MRI) and fMRI have been done ever since, definitely proven it as a highly valuable technique for the study of psychological processes and psychiatric disorders. During the rest of the section, the different MRI and fMRI techniques used in the studies of this thesis are explained in detail (see Fig. 3.2. for a schematic view of the different techniques).

3.4.1. Structural MRI

MRI signal is based on the physical principles of the protons in water when exposed to a magnetic field and a radio frequency pulse. Specifically, spinning protons in a strong magnetic field line up in parallel (or antiparallel) with the magnetic field, reaching equilibrium. When radio frequency pulses (electromagnetic waves) are introduced, protons are disturbed from this equilibrium and some at a low energy state (parallel to the field) will move to the antiparallel (or high energy) position (excitation period). After a short period, they will return to the basal state (relaxation period), emitting photons that correspond to the energy difference between the two states. The amount of time to return to the basal state varies across brain tissue types because of the different concentration of protons, allowing for the

differentiation of GM, WM and cerebrospinal fluid. The changing current during the relaxation period is captured by detector coils, which constitutes the MRI signal (Huettel, Song and McCarthy, 2008). Different types of analyses can be made based on this signal, looking for example at volume differences with voxel-based morphometry (VBM), or at surface properties of the brain. In our case, though, the structural image was used only for registration purposes of the functional images, allowing for better anatomical specificity due to the higher resolution of this image.

Another type of structural image obtained from MRI is diffusion-weighted image (DWI). An application of DWI, DTI, is used to study the organization, coherence and direction of WM tracts. This is conducted by measuring water diffusion through the brain, which is based on the intrinsic random movement of water molecules (Brownian motion). Water tends to diffuse freely when unrestricted (isotropic diffusion, for instance within the ventricles), but water molecules contained in WM tracts are constricted by the limits of the axonal membranes and myelin, and thus they diffuse directionally along the length of the axon (anisotropic diffusion). DTI is obtained by measuring the dephasing of spins of protons (as in other MRI sequences) in the presence of a magnetic field, which varies in space or "gradient". Importantly, this provides a measure of the phase change resulting from the incoherent displacement of the protons along the axis of the gradient (Jones, Knösche and Turner, 2013). Strong magnetic gradients are applied in a minimum of 6 (usually more than 15) non-collinear directions. The measurement can be quantified in each voxel (voxel-based), providing the relative diffusivity of water into directional components for each particular voxel. A reference non-diffusion gradient is also obtained, which contains the information about the diffusion time, gradient duration and gradient strength (b_0 value, usually b_0=1000 in adults). It allows for the obtaining of: (1) quantitative scalar values summarizing different WM properties, (2) a reproduction of tracts by deterministic or probabilistic methods (tractography), and (3) models of whole brain connectivity (connectome approach, which is based on tractography). In quantitative methods, the most commonly retrieved scalar measures are fractional anisotropy (FA) and mean diffusivity (MD). FA ranges between 0 and 1 and expresses the preference of water to diffuse in an anisotropic (1) or isotropic (0) manner. MD (also between 0 and 1) indexes the overall degree of water diffusion, regardless of direction. FA and MD are typically negatively correlated and are considered to be indicators of WM integrity (i.e., axonal ordering, density, degree of myelination), with FA typically being decreased in pathological WM. More specific measures, derived from FA and MD, provide complementary information: axial (AD) and radial diffusivity (RD), which represent either the average diffusion parallel (AD) and perpendicular

(RD) to axonal fibres. AD is allegedly sensitive to changes in axon integrity, while RD is sensitive to myelination. The combined quantification of all these measures is recommended for the appropriate interpretation of WM changes (Huettel, Song and McCarthy, 2008; Jones, Knösche and Turner, 2013). In the context of this thesis, DTI was used in Study 2, specifically to perform probabilistic tractography and to obtain the quantitative WM integrity indicators.

3.4.2. Functional MRI

Amongst some of the benefits of fMRI when compared with other techniques that are typically used for the study of brain function, we can highlight that fMRI is a non-invasive method (e.g., compared to positron emission tomography), with a relatively high spatial resolution, which is a major disadvantage in techniques such as EEG. It is also advantageous since it allows for the possibility to do repeated studies on the same subject. Its first application in psychiatry was reported in 1993 (Breiter *et al.*, 1993), and subsequently, numerous fMRI studies of psychiatric disorders have been conducted, reflecting the increasing enthusiasm in this field. Moreover, thanks to recent advances, fMRI enable us to make analyses of connectivity between different regions of the brain. Considering that psychiatric diseases can be seen as disorders of brain circuitry (Williams, 2016), this type of analysis allows for a deeper understanding of how these circuits may be disrupted and the way this relates to the symptomathology of the disorder.

fMRI is based in the so-called blood-oxygen-level dependent (BOLD) signal, which is an indirect measure of brain activity. Neuronal firing causes a need for more energy intake, and through a process called the hemodynamic response, blood releases oxygen to active neurons at a greater rate than to inactive neurons. This causes a change of the relative levels of oxyhemoglobin and deoxyhemoglobin (oxygenated or deoxygenated blood) that can be detected by MRI on the basis of their differential magnetic susceptibility (Ogawa *et al.*, 1990; Huettel, Song and McCarthy, 2008). Based on these properties, different statistical approaches have been developed to determine which areas of the brain are recruited during a specific psychological process, action or experience:

- Task-based fMRI. Task-based fMRI paradigms use the subtraction of brain activations between two or more different conditions which only differ in the psychological process of interest, to isolate its response. Different types of designs can be used depending on the question being tested, such as block designs, event-related designs and mixed designs (Huettel, Song and McCarthy, 2008). The cognitive reappraisal task described above is an example of a task-based fMRI paradigm using a block design,

which has 3 conditions that are contrasted among each other to isolate the two psychological processes of interest: emotion generation and emotion regulation.

- Psychophysiological interaction analyses. PPI is one of the available modalities to study brain responses to a specific task in the context of functional brain systems, or functionally connected regions, instead of the isolated responses of each region. This approach assesses the influence of a task ("psychological factor") on the strength of functional coupling between the time course of a region of interest (ROI) and the time course of other regions or the rest of the brain ("physiological factor") (Friston *et al.*, 1997). This analysis was used in Study 3 to examine the influence of the cognitive reappraisal task on the functional connectivity between the right AI and the rest of the brain.
- Resting-state functional connectivity analyses. During a resting-state paradigm there are no conditions to be subtracted, instead, the signal obtained is used to investigate synchronous activations between different regions in the absence of a stimulus. Most research focuses on spontaneous low frequency fluctuations (0.01-0.1 Hz) in BOLD signal (Biswal *et al.*, 1995; Huettel, Song and McCarthy, 2008). Several systems have been found to present synchronic fluctuations during rest, which are believed to represent intrinsic operations and a definition of basic brain networks. There are different techniques to explore data-driven patterns of common fluctuation, as for example principal component analysis (PCA) or independent component analysis (ICA). However, it is also possible to explore a specific region within the brain by defining a ROI, which is called a seed, and assess which areas of the brain present common fluctuations with this seed. Also, these intrinsic connectivity patterns can be related to different psychological constructs, and in the context of this thesis, in Study 1 and Study 2, seed-based functional connectivity of the amygdala was inspected in relation to the ERQ subscales.

3.4.3. Neuroimaging meta-analyses

In addition to individual MRI or fMRI studies, different meta-analytical neuroimaging software exists that allow us to combine individual studies (either with structural or functional data) in order to disentangle which results remain significant across studies and which could be false positives (Eickhoff *et al.*, 2012; Radua *et al.*, 2012). One of these, the Anisotropic Effect-Size Signed Differential Mapping (AES-SDM), was used in Study 4 of this thesis. This is a novel neuroimaging meta-analytic approach that is capable of combining tabulated brain hyper/hypoactivation results (i.e., regional peak statistic and coordinate information) with

actual empirical voxel-wise “brain maps” of hyperactivations (or failures of deactivations) and hypoactivations (e.g., statistical parametric maps, SPMs) (Radua *et al.*, 2012, 2014). Put succinctly, the method comprises three major steps. Firstly, whole brain maps of the effect size of the difference between the two groups are recreated separately for each study, either from an SPM or from the reported peak regional coordinate statistics. Secondly, these individual maps are meta-analyzed using the well-established random-effects techniques of standard meta-analyses (and weighing the studies for sample size, intra-study variance and between-study heterogeneity); these models are independently fitted in each voxel, but the statistical significance is derived from a whole-brain permutation test. Thirdly, a set of standard complementary analyses is conducted to further assess the robustness of the main findings.

Recreation of effect-size maps from SPMs is straightforward as it only involves the transformation to Montreal Neurological Institute (MNI) stereotaxic space (in case that they were not already reported in this space) and the voxel-wise conversion of t-values (or alternatively p- or z-values) into effect-sizes. On the other hand, recreation of effect-size maps from peak information is more intensive. Specifically, effect-sizes are directly derived following standard methods in those voxels containing a peak reported in the results table of the original studies, and for the remaining voxels, an effect-size is estimated depending on the distance to close peaks by means of an anisotropic unnormalized Gaussian kernel. This kernel assigns higher effect-sizes to those voxels more correlated with the peak, whereas small effect-sizes are assigned to those that, even if they are neighboring, show only a small correlation at the population level. Both hyperactivations and hypoactivations are represented in the same map in order to correctly analyze those regions with higher between-study heterogeneity i.e., where some studies report hyperactivations and others hypoactivations. Finally, if the t-values of the peak coordinates are unknown, a threshold-based imputation of the effect-size might be conducted. This consists of estimating the mean effect-size of peaks from studies reporting t-values, separately for each type of threshold (e.g., ‘‘corrected p = 0.05’’ and ‘‘uncorrected p = 0.001’’).

In order to test the robustness of the findings, a systematic whole-brain voxel-based jackknife sensitivity analysis is conducted. This consists of repeating the main statistical analysis N times (being N the number of studies included) but discarding one different study at a time, i.e., removing one study and repeating the analyses, then re-including that study and removing another study and repeating the analysis, and so on. The rationale of this test is that if a previously significant brain region remains significant in all or most of the combinations of studies it can be concluded that this finding is highly replicable. Moreover, specific measures

are calculated in order to assess for heterogeneity of effect sizes (the I2 index) and publication bias (Egger's method).

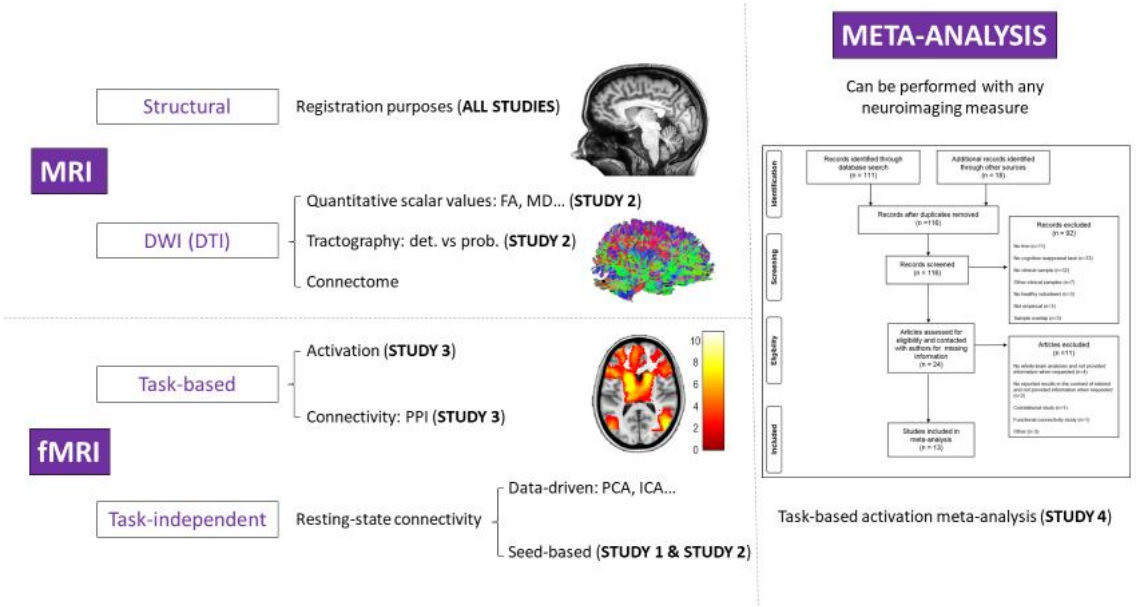

Figure 3.2. Scheme of different neuroimaging analysis techniques, indicating which ones are used in the studies included in this thesis.

3.4.4. Significance thresholding in neuroimaging

The majority of fMRI studies to date have adopted a conventional voxel-based mapping approach based on extensions of the general linear model for time-series analysis (Friston *et al.*, 2007; Huettel, Song and McCarthy, 2008). The basic premise behind such approaches is that the observed fMRI data may be accounted for by a combination of several experimental (or model) parameters (factors) and uncorrelated (or independently distributed) noise. Given the high number of statistical tests performed (one for each voxel) some method of correcting for multiple comparisons has to be applied in order to protect against type I error, leading to the generation of statistically thresholded activation maps related to the experiment at hand. Earlier MRI studies presented uncorrected values with more restrictive thresholds than classical statistical analyses (usually <0.001), but nowadays the use of multiple comparison correction methods such as false discovery rate (FDR) or family-wise error (FWE) corrections has become essential (with other methods such as Bonferroni correction being considered extremely stringent and increasing the probability of type II error).

There are also other correction approaches, as for example the so-called small volume correction, which restricts the number of comparisons to a smaller number of voxels by selecting regions of interest. Another popular approach consists of considering the statistical

significance of a group of voxels in contiguity (cluster) instead of just the significance of each voxel. The idea behind this is that it is less likely for a cluster of voxels to be activated by chance, with the likelihood of a false-positive result decreasing with increasing cluster size. This is a physiologically valid approach, since it is typically not expected for a task to activate one single voxel within the brain (which, after smoothing, might be of $8mm^3$). Although it has some limitations, cluster-based significance allows for keeping relatively relaxed thresholds at the voxel level while compensating this with the number of voxels per cluster required, making it a less conservative correction approach as compared to multiple comparison correction methods. Available software calculate this cluster-threshold based on permutations of groups of voxels with a minimum voxel significance value within a mask containing the number of voxels that are to be analysed (i.e., AlphaSim; Ward, 2000).

Finally, with the increase of computational speed, non-parametric correction methods are becoming more and more popular. Holmes *et al.* (1996) introduced a nonparametric alternative to parametric correction methods based on permutation test theory. This method is conceptually simple, relies only on minimal assumptions, deals with the multiple comparisons issue, and can be applied when the assumptions of a parametric approach are untenable. Essentially, a permutation test builds sampling distribution (called the "permutation distribution") by resampling the observed data. Specifically, we can "shuffle" or permute the observed data, e.g., by assigning different outcome values or labels to each observation from among the set of actually observed outcomes. The probability of an outcome as or more extreme than the one observed, the P-value, is the proportion of statistic values in the permutation distribution greater or equal to that observed. The actual labeling used in the experiment is one of the possible labels, so if the observed statistic is the largest of the permutation distribution, the P-value is 1/N, where N is the number of possible labels of the initial randomization scheme (Nichols and Holmes, 2001). There are several imaging analyses software using non-parametric permutations, and one example is the Threshold-Free Cluster Enhancement (TFCE) technique (Smith and Nichols, 2009) as implemented in the SPM-TFCE toolbox v117 (http://dbm.neuro.uni-jena.de/tfce/).

Different methods for protecting against type I error have been used throughout the studies included in this thesis, reflecting the increasing demands for more conservative corrections in the field (Eklund, Nichols and Knutsson, 2016).

3.4.5. Brain-behavior correlations

One final type of statistical analysis to be mentioned are brain-behavior correlations. Many neuroimaging studies, besides investigating the brain regions that are active or connected during a specific experimental paradigm, aim to further relate these results to behavioral, psychological or physiological constructs of interest. Typically, the results from the neuroimaging analyses are correlated to these other variables of interest (which can come from questionnaires, neuropsychological tests, physiological measures, in-scanner behavioral responses, etc.), in order to check whether there is a general involvement of a brain region during an fMRI task and also with other constructs related to that task. In the context of psychiatric research, a measure that is typically related to neuroimaging results is the severity of the disorder, as in Study 2 of this thesis.

RESULTS

4. Results

4.1. Study 1

Picó-Pérez M, Alonso P, Contreras-Rodríguez O, Martínez-Zalacaín I, López-Solà C, Jiménez-Murcia S, Verdejo-García A, Menchón JM, Soriano-Mas C (2017). **Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity**. Brain Imaging Behav, 12(4):1022-1031. doi: 10.1007/s11682-017-9762-3.

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ORIGINAL RESEARCH

Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity

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Abstract Neuroimaging functional connectivity (FC) analyses have shown that the negative coupling between the amygdala and cortical regions is linked to better emotion regulation in experimental settings. Nevertheless, no studies have examined the association between resting-state cortico-amygdalar FC and the dispositional use of emotion regulation strategies. We aim at assessing the relationship between the resting-state FC patterns of two different amygdala territories, with different functions in the emotion response process, and trait-like measures of cognitive reappraisal and expressive suppression. Forty-eight healthy controls completed the Emotion Regulation Questionnaire (ERQ) and underwent a resting-state functional magnetic resonance imaging acquisition. FC maps of basolateral and centromedial amygdala (BLA/CMA) with different cortical areas were estimated with a seed-based approach, and were then correlated with reappraisal and suppression scores from the ERQ. FC between left BLA and left insula and right BLA and the supplementary motor area (SMA) correlated inversely with reappraisal scores. Conversely, FC between left BLA and the dorsal anterior cingulate cortex correlated directly with suppression scores. Finally, FC between left CMA and the SMA was inversely correlated with suppression. Top-down regulation from the SMA seems to account for the dispositional use of both reappraisal and suppression depending on the specific amygdala nucleus being modulated. In addition, modulation of amygdala activity from cingulate and insular cortices seem to also account for the habitual use of the different emotion regulation strategies.

Keywords Emotion regulation · fMRI · Resting-state · Functional connectivity · Amygdala

Introduction

Emotion regulation refers to the psychological processes by which people influence how they experience and express their emotions (Gross 1998). Emotion regulation can occur

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via different strategies that lead to distinct cognitive processes and behavioral outcomes. Specifically, research has focused on two main strategies: cognitive reappraisal and expressive suppression. Cognitive reappraisal typically appears earlier in the emotion-generation process, and refers to the modification of the initial appraisal of a situation, so as to alter its emotional significance. Expressive suppression consists on inhibiting ongoing emotion-expressive behavior, and it takes place once the emotion has been triggered (Gross 2014, 2015). Gross and John developed a short questionnaire (the Emotion Regulation Questionnaire – ERQ, Gross and John 2003) that evaluates the dispositional use of these two strategies. They observed that frequent use of reappraisal strategies was linked to better control of emotions, interpersonal functioning, and psychological and physical well-being. Conversely, frequent use of suppression strategies was related to poorer control of emotions, worse interpersonal functioning, and greater risk of depression (Gross and John 2003). Later studies have consistently replicated these findings (Hu et al. 2014; Webb et al. 2012).

The neurobiological correlates of emotion regulation have been largely assessed with functional activation measures during experimental tasks. The gold standard for the assessment of the cognitive reappraisal strategy is the Cognitive Reappraisal Task (Ochsner et al. 2002; Phan et al. 2005), which presents participants with images depicting negative emotional content and instruct them to either experience the negative emotion evoked by the images without attempting to modify its impact or downregulate the emotion by means of cognitive reappraisal. Several meta-analyses have examined the neural correlates of the Cognitive Reappraisal Task measured with functional magnetic resonance imaging (fMRI) in healthy participants (Buhle et al. 2013; Diekhof et al. 2011; Kalisch 2009; Kohn et al. 2014). These studies have identified a consistent pattern of cortical activations including the medial, dorsolateral and ventrolateral frontal cortices, as well as the dorsal anterior cingulate cortex (Ochsner et al. 2012). Moreover, cognitive reappraisal-related cortical activity has been shown to modulate the activity of subcortical appraisal structures, such as the amygdala and the insula (Goldin et al. 2009; Wager et al. 2009). Tasks of expressive suppression also present participants with negative affective stimuli, but instruct them to conceal external signs of the emotion rather than reappraise the stimuli (Goldin et al. 2009). The neurobiological correlates of expressive suppression have been much less investigated compared to those of reappraisal. Existing studies suggest that the suppression strategy is associated with activation of the frontal cortex, similar to reappraisal. However, suppression is also associated with significant activations of the amygdala and the insula, at difference with reappraisal (Goldin et al. 2009; Hayes et al. 2010; Vanderhasselt et al. 2013).

Neuroimaging studies have also examined the neurobiological correlates of emotion regulation using functional connectivity approaches. This research has shown that both positive and negative functional connectivity between the amygdala and frontal cortical regions (i.e., negative signal covariance) is linked to better emotion regulation in experimental settings (Banks et al. 2007; Lee et al. 2012; Paschke et al. 2016). In this context, resting-state functional connectivity measures are particularly relevant to unravel the neural correlates of emotion regulation traits or dispositions, as they reflect typical levels of cross-regional coupling (Shehzad et al. 2009). That is, they can be used as biomarkers of the dispositional use of different cognitive and emotional processes (Baur et al. 2013; Kelly et al. 2008), such as emotion regulation. In fitting with this notion, it has been observed that negative resting-state functional connectivity between the amygdala and the medial frontal cortex predicted successful emotion regulation during a cognitive reappraisal task (Uchida et al. 2014). Nevertheless, to date, no studies have examined the association between resting-state cortico-amygdalar functional connectivity and dispositional use of emotion regulation strategies. Consequently, there is also a dearth of knowledge on whether functional connectivity of different functional sub-regions of the amygdala that support different aspects of the emotional response is specifically related to these emotion regulation strategies (Bach et al. 2011; Etkin et al. 2009; Roy et al. 2010; Solano-Castiella et al. 2010). Particularly, the basolateral amygdala (BLA) is believed to be involved in processing high-level sensory input and stimulus-value associations, while the centromedial amygdala (CMA) is involved in generating attentional, vegetative and motor responses (Bzdok et al. 2013). This functional difference between these two amygdala regions has never been assessed in the context of emotion regulation.

The present study is aimed to address the gaps identified above by examining, in a sample of healthy volunteers, the association between the resting-state patterns of functional connectivity of the BLA and the CMA and trait-like measures of cognitive reappraisal and expressive suppression as assessed by the ERQ. Based on existing literature, we focused our analyses on the functional connectivity of the different amygdala territories with frontal, cingulate and insular cortices, which have been robustly shown to be related to emotion regulation (Cutuli 2014; Ochsner and Gross 2014; Ochsner et al. 2012). We anticipated that the use of reappraisal strategies would be associated with a negative coupling between the amygdala and dorsomedial, dorsolateral and ventrolateral frontal regions. Due to the paucity of studies on the neurobiological correlates of expressive suppression and on the role of the different amygdala subregions, we do not put forward a definite hypothesis about these results.

Table 1 Sample characteristics and behavioral measure results

	Healthy controls ($n=48$), Mean (SD)
Age	39.56 (9.64)
Gender (male/female)	25/23
ERQ reappraisal[a]	4.73 (0.98)
ERQ suppression[a]	3.01 (1.15)
PANAS positive ($n=22$)	31.5 (6.51)
PANAS negative ($n=22$)	18 (5.52)

SD Standard Deviation

[a]ERQ scores were standardized by means of dividing the mean score of each subscale by the corresponding number of items (6 for reappraisal and 4 for suppression)

Method

Participants

Forty-eight healthy participants (23 females), aged 19 to 56 years (mean: 39.56, S.D.: 9.64), and without any history of psychiatric or neurological illnesses participated in the study (Table 1). Specifically, participants were screened using the Structured Clinical Interview for DSM-IV non-patient version (SCID-NP) (First et al. 2002) prior to inclusion in the study. Exclusion criteria included: 1) presence or past history (in the previous 6 months) of psychoactive substance abuse or dependence, 2) intellectual disability, 3) presence or past history of any severe medical condition, and 4) any contraindication to MRI scanning. Written informed consent was obtained from all participants after a complete description of the study, which was performed in accordance with the Declaration of Helsinki and approved by Bellvitge Hospital's ethical committee.

Behavioral assessment

Subjects were administered the Spanish version of the ERQ (Cabello et al. 2013) on the same day of scanning. The ERQ comprises the subscales of expressive suppression and cognitive reappraisal (Gross and John 2003). The ERQ consists of 10 items and participants give their answers on a 7-point Likert scale with the endpoints ''strongly disagree'' and ''strongly agree''. The Spanish version of the ERQ shows adequate internal consistency (Cronbach's α coefficients were $\alpha=0.75$ for Suppression and $\alpha=0.79$ for Reappraisal), test–retest reliability (0.66 for Suppression and 0.64 for Reappraisal over 3 months), and convergent and discriminant validity (Cabello et al. 2013). In our sample, Cronbach's α values were 0.72 and 0.71 for the reappraisal and suppression subscales, respectively.

In addition, a subset of the sample ($n=22$) was administered the Spanish version (Sandín et al. 1999) of the Positive and Negative Affect Schedule (PANAS; Watson et al. 1988), which allowed to assess positive and negative mood. This is a 20-item self-report measurement of the positive and negative affect experienced during the last 4 weeks.

Image acquisition and preprocessing

Participants were scanned in a 1.5 T Signa Excite system (General Electric, Milwaukee, Wisconsin) equipped with an eight-channel phased-array head coil and single-shot echo-planar imaging software. Functional sequences consisted of gradient recalled acquisition in the steady state (repetition time, 2000 msec; echo time, 50 msec; and pulse angle, 90°) in a 24-cm field of view, with a 64×64 pixel matrix (in-plane resolution of 3.75×3.75 mm) and a slice thickness of 4 mm (interslice gap, 1 mm). Twenty-two interleaved sections, parallel to the anterior-posterior commissure line, were acquired to generate 120 whole-brain volumes, excluding four initial dummy volumes. For anatomical references, a T1-weighted anatomical scan was also acquired. Specifically, we used a three-dimensional fast spoiled gradient inversion-recovery prepared sequence with 130 contiguous slices (repetition time, 11.8 msec; echo time, 4.2 msec; flip angle, 15°) in a 30-cm field of view, with a 256×256 pixel matrix (in-plane resolution of 1.17×1.17 mm) and a slice thickness of 1.2 mm.

Imaging data were transferred and processed on a Microsoft Windows platform running MATLAB version 7 (R2012a) (The MathWorks Inc, Natick, Massachusetts). Preprocessing was performed using statistical parametric mapping software (SPM8 v6313) (http://www.fil.ion.ucl.ac.uk/spm/). Motion correction was performed by aligning (within participant) each time series to the mean image volume using a least-squares minimization and a 6-parameter (rigid body) spatial transformation. Translation and rotation estimates (x, y, z) were required to be less than 2 mm and 2°, respectively, for all participants. The realigned functional sequences were then coregistered to each participant's respective anatomical scan that had been previously coregistered to the SPM-T1 template. Next, DARTEL (Ashburner 2007) was used to create a study-specific template from anatomical scans, and a two-step normalization was applied to the coregistered functional images. Firstly, normalization parameters (i.e., the flowfields) from subject's space to DARTEL template, estimated for the anatomical scans, were applied to functional time-series. Secondly, functional images were normalized to MNI space. During this process, images were resliced to a 2 mm isotropic resolution and smoothed using a Gaussian filter (full-width at half-maximum, 8 mm). All images were routinely inspected for potential normalization artifacts.

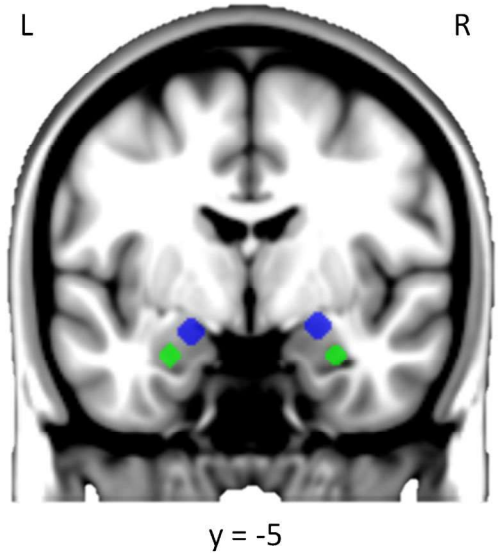

Fig. 1 Amygdala seeds centered at $x=-26$, $y=-5$, $z=-23$ (left BL), $x=29$, $y=-3$, $z=-23$ (right BL), $x=-19$, $y=-5$, $z=-15$ (left CM), and $x=23$, $y=-5$, $z=-13$ (right CM). Blue = CMA; Green = BLA

Data analysis

Seed extraction

The selection of the seed regions of interest was based in previous studies, and corresponded to amygdala subdivisions shown to have distinct whole-brain functional connectivity patterns (Baur et al. 2013). Signal extraction was performed using MarsBaR region-of-interest toolbox (Brett et al. 2002) in Montreal Neurological Institute stereotaxic space. As in previous research of our group with these same regions of interest (Cano et al. 2016), seeds were defined in both hemispheres as 3.5 mm radial spheres centered at: left basolateral amygdala ($x=-26$, $y=-5$, $z=-23$), right basolateral amygdala ($x=29$, $y=-3$, $z=-23$), left centromedial amygdala[1] ($x=-19$, $y=-5$, $z=-15$) and right centromedial amygdala ($x=23$, $y=-5$, $z=-13$) (Fig. 1). Importantly, all these coordinates were spatially separated between each other by at least 8 mm (1 FWHM), according to the formula:

$$\sqrt{\left((x1\text{-}x2)^2 + (y1\text{-}y2)^2 + (z1\text{-}z2)^2\right)}$$

where (x1 y1 z1 & x2 y2 z2) refer to the coordinates of any two voxels in MNI space. This ensured we were obtaining specific functional connectivity maps for each seed region of interest. Importantly, since signal artifacts have been typically described in the amygdala region, we ensured both at the group and the individual level that our images provided an adequate coverage of this region. Sample images illustrating such coverages can be found in Supplementary Figure 1.

First level analysis

A general lineal model (GLM) was created for each hemisphere, which included the two amygdala-seed time series as predictors, and, as nuisance covariates, the three translation and three rotation estimates from the movement correction step plus three covariates corresponding to the white matter, cerebrospinal fluid (CSF) and whole brain signal estimates. These global signal measurements are thought to reflect a combination of physiological processes (i.e., cardiac and respiratory fluctuations), and therefore, were included in the GLM to control for such factors. Specifically, from the anatomical scans we obtained the white matter and CSF tissue probability maps, that were eroded to keep voxels with a probability of at least 0.8 or 0.6 of being white matter or CSF, respectively. Such tissue-specific masks were then binarized to create nuisance variable masks, together with a binary mask for whole brain signal, which was the sum of the white matter and CSF masks plus a gray matter mask. Across the time-series, nuisance signals were derived from each mask by averaging signal from all in-mask voxels. Moreover, a high-pass filter set at 128 s was used to remove low frequency drifts of less than approximately 0.008 Hz. Prior to model estimation, each of the nine nuisance covariates were orthogonalized (using an iterative Gram-Schmidt method) and then removed from each seed's time series by linear regression, resulting in a general linear model that comprised the two "noise-cleaned" seeds and the nine orthogonal nuisance variables, which ensured each seed's time-series reflected its unique variance. Contrast images were generated for each subject by estimating the regression coefficient between all brain voxels and each seed's time series. Such contrast images were then carried over to second level analyses. Due to the recent debate regarding the use of global-signal regression (GSR) (Saad et al. 2012), the analyses were repeated without including global signal as a nuisance covariate.

Second level analysis

Multiple regression models were performed for each of the amygdala seeds including the two ERQ subscales (reappraisal and suppression) as predictors of interest. To increase the sensitivity and specificity of our analyses, second-level analyses were restricted to a 17,391-voxel mask encompassing different regions of the frontal lobe (i.e., inferior frontal, middle frontal, superior frontal, medial

[1] In the study of Baur et al. (2013) from where we based the selection of our coordinates, centromedial and superficial subregions were pooled into one combined ROI, such that this ROI and the BLA ROI were nearly equally sized.

Table 2 Functional connectivity results

Seed	ERQ scale	Contrast	Region	BA	MNI coordinates (x,y,z)	Ke[a]	pFWE
Left BLA	Reappraisal	Negative	Left insula	13	−36, 18, 0	54	0.015
Right BLA	Reappraisal	Negative	SMA	6	−2, −6, 48	53	0.037
	Suppression	Positive	dACC	24	4, −2, 38	154	0.003
					−2, 14, 28	224	0.008
Left CMA	Suppression	Negative	SMA	6	12, −14, 60	17	0.031

Regions showing an association between their connectivity with amygdala seeds and the scores in the ERQ ($p < 0.05$ TFCE FWE-corrected). A mask including several frontal regions, the cingulate gyrus and the bilateral insula was used

BA Broadmann Area, *BLA* basolateral amygdala, *CMA* centromedial amygdala, *dACC* dorsal anterior cingulate cortex, *ERQ* Emotion Regulation Questionnaire, *MNI* Montreal Neurological Institute, *SMA* supplementary motor area

[a]Cluster extent in voxels

frontal and orbital gyri), the cingulate gyri and the insulae. This mask was created with the Wake Forest University Pick-atlas toolbox (Maldjian et al. 2003). Moreover, results were also inspected at the whole-brain level to detect potential significant findings in other regions outside the mask. Finally, exploratory analyses were also performed to explore for potential interactions with sex.

Significance thresholding

To correct for multiple comparisons across our volume of interest (significant threshold set at $p < 0.05$, Family-Wise Error (FWE) corrected), voxel-wise non-parametric permutation testing (Nichols and Holmes 2001) with 5000 permutations was performed using the Threshold-Free Cluster Enhancement (TFCE) technique (Smith and Nichols 2009) as implemented in the SPM-TFCE toolbox v117 (http://dbm.neuro.uni-jena.de/tfce/).

Results

Behavioural results

The mean ERQ sub-scores are presented in Table 1. As can be seen, participants reported using reappraisal strategies to a greater extent than suppression strategies ($t(47) = 8.21$, $p < 0.0005$). PANAS sub-scores are also presented in Table 1. The subset of participants that were administered this questionnaire showed higher experience of positive affect as compared to negative affect ($t(21) = 8.09$, $p < 0.0005$). Pearson correlations between ERQ and PANAS subscales reported no significant associations (r values ranging between −0.03 and 0.31, minimum $p = 0.15$).

Functional connectivity results

BLA and CMA seeds showed different patterns of functional connectivity. These results are presented in Supplementary Figure 2.

Regarding the correlations between FC of the different amygdala seeds and ERQ sub-scores, these results are summarized in Table 2 and detailed below.

Cognitive reappraisal

Reappraisal scores were inversely correlated with the FC between the right BLA and the supplementary motor area (SMA), and between the left BLA and the left anterior insula (AI). These results are presented in Fig. 2. On the other hand, we found no significant correlations between reappraisal scores and FC of the CMA.

Expressive suppression

Suppression scores were positively correlated with the FC between the right BLA and the dorsal anterior cingulate cortex (dACC). Moreover, suppression scores correlated inversely with the FC between the left CMA and the SMA. These results are presented in Fig. 3.

Analyses without GSR

The abovementioned regions remained significant when repeating the analyses without GSR, and also new associations arose. These results can be found in Supplementary Table 1.

Whole-brain results and exploratory analyses

When repeating the above analyses at the whole-brain level, we observed a significant positive association

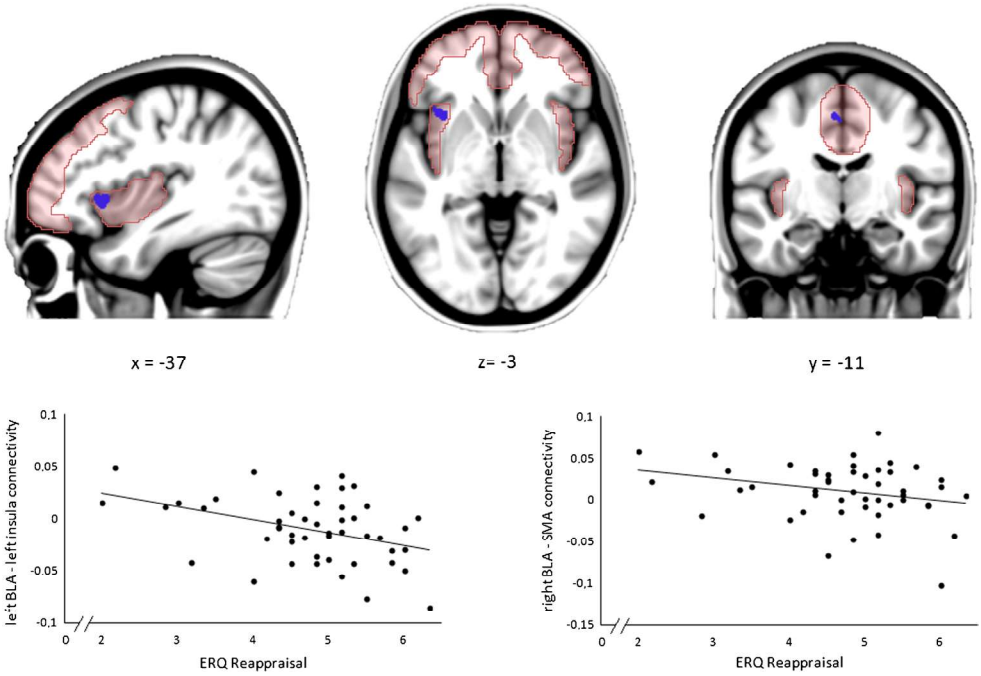

Fig. 2 Top: Brain regions which functional connectivity with BLA was related to reappraisal scores. Shaded red = volume of interest; Blue = voxels of negative correlation with reappraisal scores. Bottom: Scatter plots depicting the relationship between functional connectivity estimates and ERQ reappraisal scores

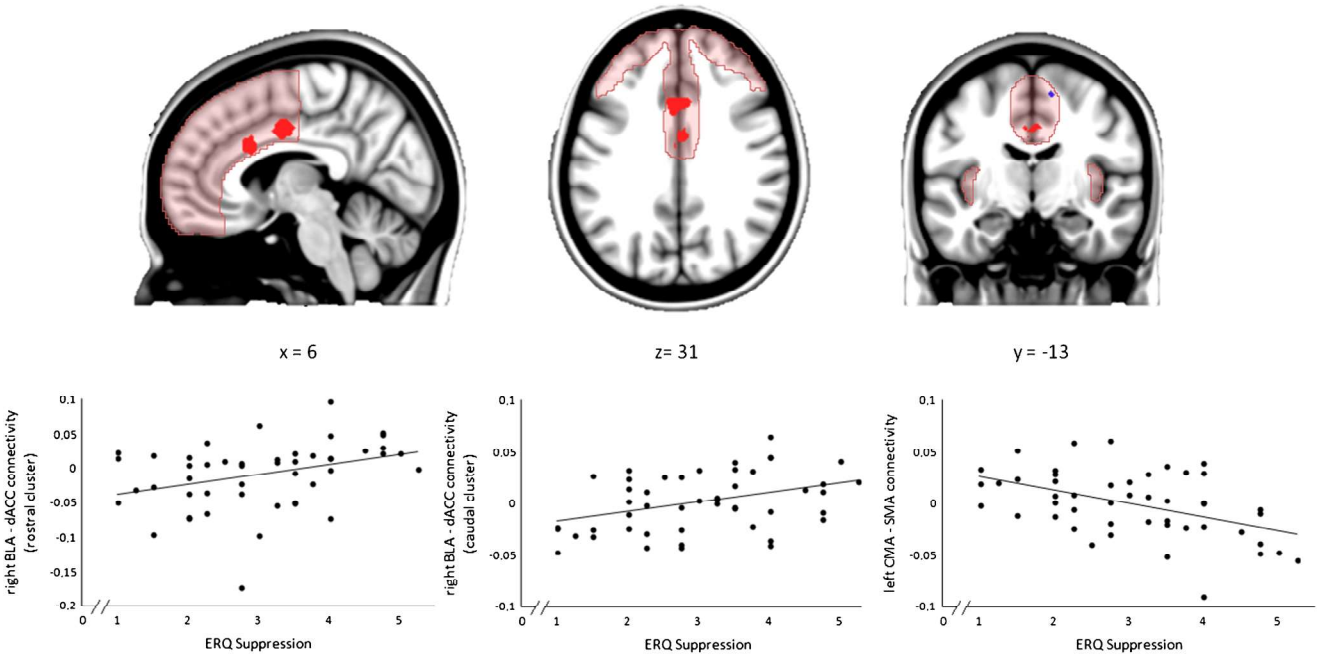

Fig. 3 Top: Brain regions which functional connectivity with BLA and CMA was related to suppression scores. Shaded red = volume of interest; Blue = voxels of negative correlation with suppression scores; Red = voxels of positive correlation with suppression. Bottom: Scatter plots depicting the relationship between functional connectivity estimates and ERQ suppression scores

between suppression scores and the FC between the right BLA and the right supramarginal gyrus (see Supplementary Table 2). Finally, we also explored for potential interactions with the sex of the participants, finding no significant results.

Brain-behavioral correlations

Signal from the peak maxima of significant clusters from the above analyses was extracted and entered in the SPSS matrix to perform correlations with PANAS subscales.

None of these correlations were significant after Bonferroni correction.

Discussion

This is the first study to evaluate the association between resting-state cortico-amygdalar functional connectivity and the dispositional use of emotion regulation strategies. Overall, and in partial agreement with previous research in experimental settings, we have observed that the use of emotion regulation strategies is associated with a significant negative coupling between the amygdala and the frontal cortex. Specifically, the functional connectivity between the BLA and the SMA and the insula is negatively associated with use of cognitive reappraisal strategies. Conversely, higher connectivity between the BLA and the dACC is linked to the use of emotional suppression. With regard to the CMA, the limbic sub-region responsible for the generation of the emotional output, negative connectivity with the SMA is also linked to emotional suppression. These results will be discussed in the following paragraphs in relation with previous research.

The finding of higher negative connectivity between the right BLA and the SMA linked to reappraisal strategies is consistent with previous studies using laboratory-based measures of emotion regulation. This pattern of negative connectivity between limbic regions and dorso-medial frontal regions has been reported in association with reappraisal success (Uchida et al. 2014). Likewise, in an fMRI study using a face processing task, self-reported reappraisal was negatively correlated with amygdala activity and positively correlated with activity in the dorso-medial frontal cortex, while activity from these two regions was also negatively correlated (Drabant et al. 2010). Our cluster, however, was more caudally located, extending from the caudal pre-SMA to the SMA. The pre-SMA has been classically involved in stop-signal inhibition (Aron and Poldrack 2006), and its more caudal division has been specifically associated with response inhibition, as opposed to the activation of its rostral part, associated with conflict processing (Sharp et al. 2010). Interestingly, activation of the caudal pre-SMA and the SMA has also been observed during emotional suppression (Vanderhasselt et al. 2013). Overall, these previous results indicate that the caudal pre-SMA and the SMA are critical for motor response inhibition, which may also entail the suppression of emotional responses. Our results suggest that this brain region is also relevant for non-motor regulatory processes, such as cognitive reappraisal, by exerting a top-down inhibitory control over the BLA, which function critically accounts for the early processing and association of sensory and affective input (Bzdok et al. 2013).

The finding of negative connectivity between the left BLA and the ipsilateral anterior insular cortex linked to cognitive reappraisal resonates with findings from research with clinical populations. A recent study among patients with post-traumatic stress disorder enrolling in cognitive behavioral therapy showed that decreased reappraisal related functional connectivity between the amygdala and the insula predicted better treatment outcomes (Cisler et al. 2016). Our finding may also be interpreted in the context of the relationship between cognitive reappraisal and decreased levels of anxiety, as previous reports have shown that the BLA-insula functional connectivity is positively correlated with the state sub-scale of the State-Trait Anxiety Inventory (STAI) (Baur et al. 2013). Neural activity in the anterior insula is believed to underlie the conscious representation of emotional bodily states (i.e., interoception) (Craig 2009), and importantly, such activity may represent not only recent past and current, but also predicted bodily states (Verdejo-Garcia et al. 2012). Therefore, one possible explanation for our findings is that, in the early phases of the emotion response, activity in the anterior insula may promote the selection of the most appropriate reappraisal strategy in front of a particular aversive scenario via an 'as-if' representation of bodily states, consequently dampening BLA reactivity.

Emotional suppression was associated with an increased coupling between the BLA and the dACC. The coupling between these structures is consistent with the general role of the dACC in anxiety processes (Etkin et al. 2011), and, in particular, in the conscious appraisal of threatening stimuli (Kalisch and Gerlicher 2014) and the expression of sympathetic autonomic fear responses (Milad et al. 2007). Likewise, our group has recently described that the dACC mediates the association between trait and state anxiety (Harrison et al. 2015). Therefore, co-activation of the BLA and the dACC may be necessary for the generation of the negative emotional response that antecedes the use of emotion suppression strategies.

Finally, the increased negative connectivity between the same caudal pre-SMA/SMA region discussed above and the CMA predicted a greater use of suppression strategies. Therefore, the same top-down inhibitory processes, involving the caudal pre-SMA/SMA cortex, relate to both emotion regulation strategies. The neurobiological differences between these two strategies probably depend on the specific amygdala region being inhibited, with downregulation of BLA activity associated with cognitive reappraisal, and downregulation of CMA activity associated with emotional suppression. Moreover, this differential inhibition of two different amygdala territories has been proposed to take place at different moments of the emotional response: regulation of the BLA should occur at early stages of the emotional response to inhibit the links between sensory and affective information, whereas control of CMA activity may take place at later stages to suppress emotional output (Bzdok et al. 2013).

It is important to note that previous research on the neural correlates of emotion regulation has identified significant activations in other (mainly prefrontal) regions not reported here. For example, decreased connectivity between the amygdala and the ventromedial prefrontal cortex has been linked to the use of suppression strategies (Johnstone et al. 2007). In this sense, it could be argued that we should have also identified amygdala connectivity with these other cortical regions, but it is important to bear in mind that all these findings have been obtained in experimental contexts (i.e., during emotion induction), while we used a dispositional/trait measure of emotional regulation strategies. The lack of findings involving the lateral prefrontal cortex, a region that has been also typically associated with cognitive reappraisal (Buhle et al. 2013; Kohn et al. 2014), should be also interpreted in this context.

The results of this study have to be interpreted in the context of the following limitations. Firstly, it is not easy to distinguish between the two different amygdala territories assessed here with the spatial resolution of our fMRI acquisitions. Nevertheless, Bzdok et al. (2013) demonstrated in their study that the spatial resolution of common neuroimaging protocols like ours is enough for delineating functional compartments within tiny brain structures such as the amygdala. Moreover, we have observed distinct patterns of functional connectivity for BLA and CMA nuclei (see Supplementary Figure 2). Secondly, the study was conducted in healthy participants, and future studies should address their clinical relevance in the context of emotion dysregulation and mood and anxiety disorders (Zilverstand et al. 2016), where measurements of emotional suppression should probably be better represented than in healthy control samples. Thirdly, we only assessed trait affect, which have been shown to correlate with emotion regulation strategies in other studies (Gross and John 2003), in a subset of participants. Therefore, the potential effect of such variable on our findings cannot be totally ruled out, although we have not observed any significant correlation between PANAS and ERQ scores in the subset of participants assessed. Moreover, by means of path analysis, we have previously shown that, indeed, trait affect variables seem to depend on emotion regulation capacities rather than influence them (Goldberg et al. 2016). Finally, we assessed emotion regulation strategies with a retrospective self-report measure. Although previous research has shown that ERQ scores predict relevant real-life outcomes such as well-being and depressive symptomatology (Gross and John 2003), future research can benefit from real-time and real-life assessment approaches, such as ecological momentary assessments.

In conclusion, this is the first study to establish the association between the dispositional use of emotion regulation strategies and the resting-state functional connectivity of two functional sub-regions of the amygdala, a pivotal region for emotion processing. Our results are relevant to expand the knowledge of the neurobiological underpinnings of dispositional emotional regulation strategies. The present findings may be informative for ascertaining how people deal with emotions in real-life contexts, which should be of utmost interest for future studies assessing the neurobiological correlates of emotional dysregulation in clinical populations with ecological approaches.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. *Journal of Neuroscience, 26*(9), 2424–33.

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage, 38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Bach, D. R., Behrens, T. E., Garrido, L., Weiskopf, N., & Dolan, R. J. (2011). Deep and superficial amygdala nuclei projections revealed in vivo by probabilistic tractography. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience, 31*(2), 618–623. https://doi.org/10.1523/JNEUROSCI.2744-10.2011.

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Luan Phan, K. (2007). Amygdala-frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience, 2*(4), 303–312. https://doi.org/10.1093/scan/nsm029.

Baur, V., Hänggi, J., Langer, N., & Jäncke, L. (2013). Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. *Biological Psychiatry, 73*(1), 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox [abstract] Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. Available on CD-ROM in NeuroImage, Vol. 16, No 2.

Buhle, J. T., Silvers, J. a, Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., et al. (2013). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex*, 1–10. https://doi.org/10.1093/cercor/bht154.

Bzdok, D., Laird, A. R., Zilles, K., Fox, P. T., & Eickhoff, S. B. (2013). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. *Human Brain Mapping, 34*(12), 3247–3266. https://doi.org/10.1002/hbm.22138.

Cabello, R., Salguero, J. M., Fernández-Berrocal, P., & Gross, J. J. (2013). A Spanish adaptation of the emotion regulation questionnaire. *European Journal of Psychological Assessment, 29*(4), 234–240. https://doi.org/10.1027/1015-5759/a000150.

Cano, M., Cardoner, N., Urretavizcaya, M., Martínez-Zalacaín, I., Goldberg, X., Via, E., et al. (2016). Modulation of limbic and prefrontal connectivity by electroconvulsive therapy in treatment-resistant depression: a preliminary study. *Brain Stimulation, 9*(1), 65–71. https://doi.org/10.1016/j.brs.2015.08.016.

Cisler, J. M., Sigel, B. A., Kramer, T. L., Smitherman, S., Vanderzee, K., Pemberton, J., & Kilts, C. D. (2016). Modes of large-scale brain network organization during threat processing and post-traumatic stress disorder symptom reduction during TF-CBT among adolescent girls. *PloS One, 11*(8), e0159620. https://doi.org/10.1371/journal.pone.0159620.

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

Cutuli, D. (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. *Frontiers in Systems Neuroscience, 8*(September), 1–6. https://doi.org/10.3389/fnsys.2014.00175.

Diekhof, E. K., Geier, K., Falkai, P., & Gruber, O. (2011). Fear is only as deep as the mind allows. A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. *NeuroImage, 58*(1), 275–285. https://doi.org/10.1016/j.neuroimage.2011.05.073.

Drabant, E. M., Mcrae, K., Manuck, S. B., Hariri, A. R., & James, J. (2010). Individual differences in typical reappraisal use predict amygdala and prefrontal responses. *Biological Psychiatry, 65*(5), 367–373. https://doi.org/10.1016/j.biopsych.2008.09.007. Individual.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences, 15*(2), 85–93. https://doi.org/10.1016/j.tics.2010.11.004.

Etkin, A., Prater, K. E., Schatzberg, A. F., Menon, V., & Greicius, M. D. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Archives of General Psychiatry, 66*(12), 1361–1372. https://doi.org/10.1001/archgenpsychiatry.2009.104.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured clinical interview for DSM-IV-TR Axis I disorders, research version, non-patient edition. (SCID-I/NP). New York: Biometrics Research, New York State Psychiatric Institute.

Goldberg, X., Cardoner, N., Alonso, P., López-Solà, C., Real, E., Hernández-Ribas, R., et al. (2016). Inter-individual variability in emotion regulation: pathways to obsessive-compulsive symptoms. *Journal of Obsessive-Compulsive and Related Disorders, 11*(October), 105–112. https://doi.org/10.1016/j.jocrd.2016.10.002.

Goldin, P. R., McRae, K., Ramel, W., & Gross, J. J. (2009). The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biological Psychiatry, 63*(6), 577–586.

Gross, J. J. (1998). The emerging field of emotion regulation: an integrative review. *Review of General Psychology, 2*(3), 271–299. https://doi.org/10.1037/1089-2680.2.3.271.

Gross, J. J. (2014). Emotion regulation: Conceptual and empirical foundations. In J. J. Gross (Ed.), *Handbook of emotion regulation* (2nd edn., pp. 3–20). New York: The Guilford Press.

Gross, J. J. (2015). The extended process model of emotion regulation: elaborations, applications,and future directions. *Psychological Inquiry, 26*(1), 130–137. https://doi.org/10.1080/1047840X.2015.989751.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology, 85*(2), 348–362. https://doi.org/10.1037/0022-3514.85.2.348.

Harrison, B. J., Fullana, M. A., Soriano-Mas, C., Via, E., Pujol, J., Martínez-Zalacaín, I., et al. (2015). A neural mediator of human anxiety sensitivity. *Human Brain Mapping, 36*(10), 3950–3958. https://doi.org/10.1002/hbm.22889.

Hayes, J. P., Morey, R. A., Petty, C. M., Seth, S., Smoski, M. J., McCarthy, G., & Labar, K. S. (2010). Staying cool when things get hot: emotion regulation modulates neural mechanisms of memory encoding. *Frontiers in Human Neuroscience, 4*, 230. https://doi.org/10.3389/fnhum.2010.00230.

Hu, T., Zhang, D., Wang, J., Mistry, R., Ran, G., & Wang, X. (2014). Relation between emotion regulation and mental health: a meta-analysis review. *Psychological Reports, 114*(2), 341–362. https://doi.org/10.2466/03.20.PR0.114k22w4.

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007). Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience, 27*(33), 8877–8884. https://doi.org/10.1523/JNEUROSCI.2063-07.2007.

Kalisch, R. (2009). The functional neuroanatomy of reappraisal: time matters. *Neuroscience and Biobehavioral Reviews, 33*(8), 1215–1226. https://doi.org/10.1016/j.neubiorev.2009.06.003.

Kalisch, R., & Gerlicher, A. M. V. (2014). Making a mountain out of a molehill: on the role of the rostral dorsal anterior cingulate and dorsomedial prefrontal cortex in conscious threat appraisal, catastrophizing, and worrying. *Neuroscience & Biobehavioral Reviews, 42*, 1–8. https://doi.org/10.1016/j.neubiorev.2014.02.002.

Kelly, A. M. C., Uddin, L. Q., Biswal, B. B., Castellanos, F. X., & Milham, M. P. (2008). Competition between functional brain networks mediates behavioral variability. *NeuroImage, 39*(1), 527–537. https://doi.org/10.1016/j.neuroimage.2007.08.008.

Kohn, N., Eickhoff, S. B., Scheller, M., Laird, A. R., Fox, P. T., & Habel, U. (2014). Neural network of cognitive emotion regulation—an ALE meta-analysis and MACM analysis. *NeuroImage, 87*, 345–355. https://doi.org/10.1016/j.neuroimage.2013.11.001.

Lee, H., Heller, A. S., van Reekum, C. M., Nelson, B., & Davidson, R. J. (2012). Amygdala-prefrontal coupling underlies individual differences in emotion regulation. *NeuroImage, 62*(3), 1575–1581. https://doi.org/10.1016/j.neuroimage.2012.05.044.

Maldjian, J., Laurienti, P., Kraft, R., & Burdette, J. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage, 19*(3), 1233–1239.

Milad, M. R., Quirk, G. J., Pitman, R. K., Orr, S. P., Fischl, B., Rauch, S. L., et al. (2007). A role for the human dorsal anterior cingulate cortex in fear expression. *Biological Psychiatry, 62*(10), 1191–1194. https://doi.org/10.1016/j.biopsych.2007.04.032.

Nichols, T. E., & Holmes, A. P. (2001). Nonparametric permutation tests for {PET} functional neuroimaging experiments: a primer with examples. *Human Brain Mapping, 15*(1), 1–25. https://doi.org/10.1002/hbm.1058.

Ochsner, K., SIlvers, J., & Buhle, J. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Annals of the New York Academy of Sciences, 1252*, 1–35. https://doi.org/10.1111/j.1749-6632.2012.06751.x.

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of

emotion. *Journal of Cognitive Neuroscience, 14*(8), 1215–1229. https://doi.org/10.1162/089892902760807212.

Ochsner, K. N., & Gross, J. J. (2014). The neural bases of emotion and emotion regulation: A valuation perspective. In J. J. Gross (Ed.), *Handbook of emotion regulation* (2nd edn., pp. 23–42). New York: The Guilford Press.

Paschke, L. M., Dörfel, D., Steimke, R., Trempler, I., Magrabi, A., Ludwig, V. U., et al. (2016). Individual differences in self-reported self-control predict successful emotion regulation. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsw036.

Phan, K. L., Fitzgerald, D. a., Nathan, P. J., Moore, G. J., Uhde, T. W., & Tancer, M. E. (2005). Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. *Biological Psychiatry, 57*(3), 210–219. https://doi.org/10.1016/j.biopsych.2004.10.030.

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, a M. C., Uddin, Q. L., Gotimer, K., et al. (2010). Functional connectivity of the human amygdala using resting state fMRI. *NeuroImage, 45*(2), 614–626. https://doi.org/10.1016/j.neuroimage.2008.11.030.Functional.

Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., & Cox, R. W. (2012). Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain Connectivity, 2*(1), 25–32. https://doi.org/10.1089/brain.2012.0080.

Sandín, B., Chorot, P., Lostao, L., Joiner, T. E., Santed, M. A., & Valiente, R. M. (1999). Escalas PANAS de afecto positivo y negativo: validacion factorial y convergencia transcultural. *Psicothema*. ISSN 0214-9915.

Sharp, D. J., Bonnelle, V., De Boissezon, X., Beckmann, C. F., James, S. G., Patel, M. C., & Mehta, M. A. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proceedings of the National Academy of Sciences of the United States of America, 107*(13), 6106–11. https://doi.org/10.1073/pnas.1000175107.

Shehzad, Z., Kelly, A. M. C., Reiss, P. T., Gee, D. G., Gotimer, K., Uddin, L. Q., et al. (2009). The resting brain: unconstrained yet reliable. *Cerebral Cortex, 19*(10), 2209–2229. https://doi.org/10.1093/cercor/bhn256.

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage, 44*(1), 83–98. https://doi.org/10.1016/j.neuroimage.2008.03.061.

Solano-Castiella, E., Anwander, A., Lohmann, G., Weiss, M., Docherty, C., Geyer, S., et al. (2010). Diffusion tensor imaging segments the human amygdala in vivo. *NeuroImage, 49*(4), 2958–2965. https://doi.org/10.1016/j.neuroimage.2009.11.027.

Uchida, M., Biederman, J., Gabrieli, J. D. E., Micco, J., De Los Angeles, C., Brown, A., et al. (2014). Emotion regulation ability varies in relation to intrinsic functional brain architecture. *Social Cognitive and Affective Neuroscience, 10*(12), 1738–1748. https://doi.org/10.1093/scan/nsv059.

Vanderhasselt, M. A., Baeken, C., Van Schuerbeek, P., Luypaert, R., & De Raedt, R. (2013). Inter-individual differences in the habitual use of cognitive reappraisal and expressive suppression are associated with variations in prefrontal cognitive control for emotional information: an event related fMRI study. *Biological Psychology, 92*(3), 433–439. https://doi.org/10.1016/j.biopsycho.2012.03.005.

Vanderhasselt, M.-A., Kühn, S., & De Raedt, R. (2013). Put on your poker face": neural systems supporting the anticipation for expressive suppression and cognitive reappraisal. *Social Cognitive and Affective Neuroscience, 8*(8), 903–910. https://doi.org/10.1093/scan/nss090.

Verdejo-Garcia, A., Clark, L., & Dunn, B. D. (2012). The role of interoception in addiction: a critical review. *Neuroscience & Biobehavioral Reviews, 36*(8), 1857–1869. https://doi.org/10.1016/j.neubiorev.2012.05.007.

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. a., & Kevin, N. (2009). Neural mechanisms of emotion regulation: evidence for two independent prefrontal-subcortical pathways. *Neuron, 59*(6), 1037–1050. https://doi.org/10.1016/j.neuron.2008.09.006.Neural.

Watson, D., Clark, L., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063–1070. https://doi.org/10.1037/0022-3514.54.6.1063.

Webb, T. L., Miles, E., & Sheeran, P. (2012). Dealing with feeling: a meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. *Psychological Bulletin, 138*(4), 775–808. https://doi.org/10.1037/a0027600.

Zilverstand, A., Parvaz, M. A., & Goldstein, R. Z. (2016). Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2016.06.009.

Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity

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Results

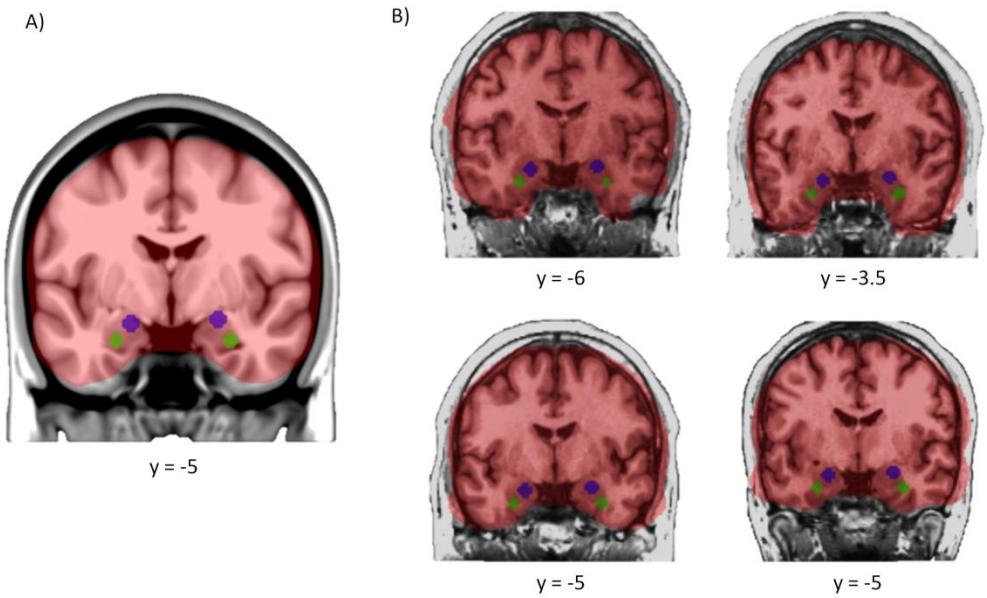

Figure S1. BLA (green) and CMA (blue) seeds overlaid on A) an anatomical template depicting a group-level functional map coverage (shaded red), and B) the anatomical image and functional map coverage (shaded red) of four representative subjects.

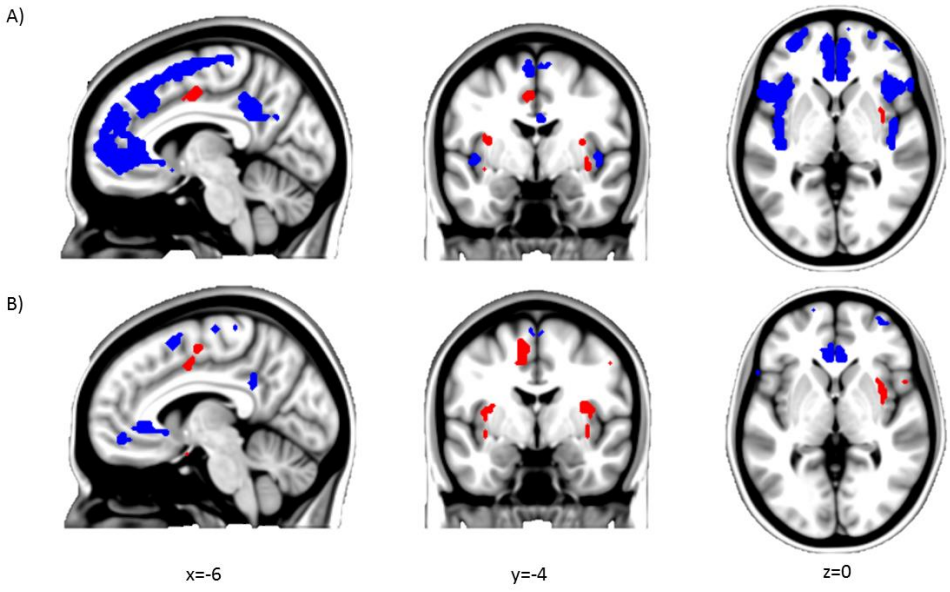

Figure S2. Functional connectivity patterns of BLA (A) and CMA seeds (B). Positive correlations are depicted in red, and negative correlations in blue. x, y and z refer to medial-lateral, rostro-caudal and dorso-ventral coordinates in normalized MNI space. Significance threshold was set at $p<0.005$, uncorrected.

Supplementary Table 1. Associations between ERQ scores and amygdala functional connectivity patterns without using global signal regression.

Seed	ERQ scale	Contrast	Region	BA	MNI coordinates (x, y, z)	Ke[a]	pFWE
Left BLA	Reappraisal	Negative	Left insula[b]	47	-36, 18, -2	123	0.009
			dACC	33	6, 10, 26	227	0.016
Right BLA	Reappraisal	Negative	SMA[b]/dACC	6	0, -8, 50	1686	0.001
			Left insula	13	-32, 18, -2	72	0.029
	Suppression	Positive	dACC[b]	24	-4, 12, 24	74	0.039
Left CMA	Suppression	Negative	SMA[b]	6	10, -8, 52	246	0.011

Regions showing significant correlations between functional connectivity with amygdala seeds and ERQ scores ($p<0.05$ TFCE FWE-corrected). A mask including several frontal regions, the cingulate gyrus and the bilateral insula was used. Abbreviations: BA, Broadmann Area; BLA, basolateral amygdala; CMA, centromedial amygdala; dACC, dorsal anterior cingulate cortex; ERQ, Emotion Regulation Questionnaire; MNI, Montreal Neurological Institute; SMA, supplementary motor area. [a]Cluster extent in voxels; [b]Regions showing significant results also when controlling for global signal regression.

Supplementary Table 2. Associations between ERQ scores and amygdala functional connectivity patterns at the whole brain level.

Seed	ERQ scale	Contrast	Region	BA	MNI coordinates (x, y, z)	Ke[a]	pFWE
Right BLA	Suppression	Positive	Right supramarginal gyrus	40	62, -34, 28	31	0.018

Results are significant at $p<0.05$ TFCE FWE-corrected. Abbreviations: BA, Broadmann Area; BLA, basolateral amygdala; ERQ, Emotion Regulation Questionnaire; MNI, Montreal Neurological Institute. [a]Cluster extent in voxels.

4.2. Study 2

Picó-Pérez M, Ipser J, Taylor P, Alonso P, López-Solà C, Real E, Segalàs C, Roos A, Menchón JM, Stein DJ, Soriano-Mas C (2018**). Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder.** *In press.*

Intrinsic functional and structural connectivity of emotion regulation networks in obsessive-compulsive disorder

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Abstract

Despite emotion regulation being altered in patients with obsessive-compulsive disorder (OCD), no studies have investigated its relation to multimodal amygdala connectivity. We compared cortico-limbic functional and structural connectivity between OCD patients and healthy controls (HC), and correlated this with the dispositional use of emotion regulation strategies and with OCD severity.

OCD patients (n=73) and HC (n=42) were assessed for suppression and reappraisal strategies using the Emotion Regulation Questionnaire (ERQ) and for OCD severity using the Y-BOCS. Resting-state functional magnetic resonance imaging (rs-fMRI) connectivity maps were generated using subject-specific left (LA) and right amygdala (RA) masks. We identified between-group differences in amygdala whole-brain connectivity, and evaluated the moderating effect of ERQ strategies. Significant regions and amygdala seeds were used as targets in probabilistic tractography analysis.

Patients scored higher in suppression and lower in reappraisal. We observed higher rs-fMRI RA – right post-central gyrus (PCG) connectivity in HC, and in patients this was correlated with symptom severity. Reappraisal scores were associated with higher negative LA – left insula connectivity in HC, and suppression scores were negatively associated with LA – precuneus and angular gyri connectivity in OCD. Structurally, patients showed higher mean diffusivity in tracts connecting the amygdala with the other targets.

RA – PCG connectivity is diminished in patients, while disrupted emotion regulation is related to altered amygdala connectivity with the insula and posterior brain regions. Our results are the first showing, from a multimodal perspective, the association between amygdala connectivity and specific emotional processing domains, emphasizing the importance of amygdala connectivity in OCD pathophysiology.

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and disabling condition that affects 2-3% of the population (Ruscio et al. 2010), characterized by the presence of obsessions (i.e., anxiety-evoking intrusive thoughts, ideas or images or pathological urges) and compulsions, which are ritualistic, repetitive behaviours or mental acts carried out to alleviate anxiety. OCD is seen as being strongly linked to cortico-striatal circuitry abnormalities (Menzies et al. 2008), an idea that has received empirical support from functional and structural connectivity studies (Harrison et al. 2009; Fontenelle et al. 2011). However, the cortico-striatal model fails to account for some of the symptoms characterizing OCD patients (e.g., increased anxiety (Menzies et al. 2008)). Accordingly, more recent neurobiological models of the disorder place greater emphasis on brain regions outside the cortico-striatal loops that may be critically involved in the pathophysiology of OCD, such as limbic cortico-amygdalar circuitry (Milad and Rauch 2012).

The amygdala has a role in mediating fear and anxiety processes (LeDoux 2000). Its function has been well characterized in relation to trait and state anxiety (Baur et al. 2013), as well as in relation to anxiety disorders (Roy et al. 2013; Hahn et al. 2011). The amygdala is also a key neural component underlying emotion regulation processes (Banks et al. 2007; Lee et al. 2012) and strategies (Goldin, McRae, et al. 2009). For instance, insulo-amygdalar functional connectivity has been shown to be associated with the habitual use of cognitive reappraisal strategies (which consist of modifying the initial appraisal of a situation to alter its emotional significance, and which are considered to be adaptive), while connectivity between the amygdala and the supplementary motor area has been shown to be related with both cognitive reappraisal and expressive suppression (which consists of inhibiting ongoing emotion-expressive behaviour and which is considered to be maladaptive) (Picó-Pérez et al. 2017).

There is considerable evidence indicating that the amygdala is hyperactive in OCD patients when processing emotional information. This appears to be the case both with OCD-specific (Simon et al. 2010; Breiter et al. 1996; Mataix-Cols et al. 2004) and generic stimuli, such as emotional faces (Cardoner et al. 2011; Via et al. 2014). Moreover, studies have identified a general pattern of fronto-subcortical (including fronto-amygdalar) hyper-reactivity while anticipating and perceiving

emotional stimuli; a pattern that is shared by OCD and social anxiety disorder (SAD) patients (Weidt et al. 2016). Likewise, OCD patients show diminished fronto-amygdala connectivity during emotion regulation (de Wit et al. 2015), although, by contrast, increased functional connectivity between the amygdala and dorso-lateral prefrontal cortex (dlPFC) has been shown to account for impaired working memory performance in OCD (de Vries et al. 2014). Overall, these findings have been interpreted as suggesting that greater amygdala activation in response to emotional stimuli in OCD may interfere with information processing in cognitive control networks.

Regarding white matter (WM) integrity, alterations in the uncinate fasciculus (a tract that connects the amygdala and the insula) have been reported in different studies with OCD samples, showing decreased fractional anisotropy (FA) (Admon et al. 2012; Benedetti et al. 2013) and increased mean (MD) and radial diffusivity (RD) in adult patients (Benedetti et al. 2013; Jayarajan et al. 2012), but increased FA in adolescent patients (Zarei et al. 2011). Moreover, differences in the inferior fronto-occipital fasciculus (IFOF), a tract that also passes through the amygdala, have been consistently found. In adult OCD patients decreased FA and increased MD have been reported (Benedetti et al. 2013; Garibotto et al. 2010), while in adolescent samples RD (Jayarajan et al. 2012) and FA increases (Gruner et al. 2012; Zarei et al. 2011) have been found. These changes in neural diffusion reflect neuronal impairment that likely contributes to structural connectivity alterations.

Despite the existence of both functional and structural amygdala connectivity alterations in OCD, and that the potential association between these may be informative about the nature of amygdala alterations in OCD, only two studies have investigated the link between these two measurements. Admon et al. (2012), using a gambling task, showed a deficit in fronto-limbic connectivity both at the functional and structural level, which was also associated with OCD symptom severity. On the other hand, Rus et al. (2017) used a negative affect task and found an increased functional connectivity between the amygdala and parieto-occipital regions, which was related to the structural connectivity estimates between these regions, which in turn were negatively associated with OCD symptom severity. To date, however, no studies have investigated multimodal connectivity alterations in OCD in relation with emotion regulation,

although, as stated above, this may be underpinned by amygdala networks (Ochsner, Silvers, and Buhle 2012) and patients with OCD have shown decreased emotion regulation abilities, with difficulties in engaging in cognitive reappraisal strategies (Goldberg et al. 2016).

In this study, we aimed to determine whether there are differences in the resting-state functional magnetic resonance imaging (rs-fMRI) connectivity of the left (LA) and right amygdala (RA) in OCD patients versus healthy controls (HC). We also aimed to identify the extent to which abnormal amygdalar resting-state connectivity is associated with disruptions in WM fibre bundles, using diffusion-tension imaging (DTI) estimates. Given evidence that changes in the structural connectivity of the brain correspond to alterations in resting-state connectivity (van den Heuvel et al. 2009; Hermundstad et al. 2013), we hypothesized that functional connectivity differences would be related to alterations in the underlying WM microstructure. Finally, we also investigated the potential association of both functional and structural connectivity estimates with OCD symptom severity, as well as with anticipated group differences in the dispositional use of cognitive reappraisal and expressive suppression strategies, as assessed using the Emotion Regulation Questionnaire (ERQ).

Materials and Methods

Participants

134 subjects (86 OCD patients and 48 HC) participated in the study, of which 19 were excluded for different reasons, including excessive motion (2 patients and 2 HC) or preprocessing artifacts in functional data (4 patients and 3 HC), or problems with the DTI sequence acquisition (7 patients and 1 HC). The final sample was made up of 73 OCD patients (30 females, mean age ± SD = 37.74 ± 10.19 years) and 42 HC (20 females, mean age ± SD = 39.43 ± 9.79 years) (see Table 1 for further details). Details on inclusion and exclusion criteria are shown in the Supplementary Material.

Behavioural assessment

Subjects were administered the Spanish version of the ERQ (Cabello et al. 2013) on the same

day of the scan, which comprises the subscales of expressive suppression and cognitive reappraisal (Gross and John 2003). Further information on this scale can be found in the Supplementary Material. In addition, depressive symptoms were evaluated both in patients and controls by means of the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), and anxiety symptoms with the 14-item Hamilton Anxiety Rating Scale (HARS) (Hamilton 1959). Finally, in the patient group, global severity of OCD symptoms was assessed by means of the clinician-administered version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al. 1989).

Image acquisition and preprocessing

Image acquisition parameters are presented in the Supplementary Material. RS-fMRI BOLD data were preprocessed using afni_proc.py in AFNI v16.1.04 (Cox 1996) (http://afni.nimh.nih.gov/), after discarding the first 4 volumes to allow for stabilization of tissue magnetization. Diffusion-weighed imaging (DWI) data were visually inspected for motion and dropout slices, with individual volumes discarded (subjects were excluded when <14 volumes remained), and TORTOISE V2.5.2 (Pierpaoli et al. 2010) and the fat_proc* programs in AFNI were subsequently used for the preprocessing. Information regarding the specific preprocessing steps followed can be found in the Supplementary Material.

Resting-state data analyses

Seed extraction and first-level analyses

Subject-specific left (LA) and right amygdala (RA) masks were extracted from T1w anatomical images using the segmentation algorithm from FreeSurfer. These masks were subsequently mapped to the MNI152 template space and the voxel average time series of the preprocessed, resting-state BOLD time-series was calculated for each. Whole-brain connectivity maps were generated for each subject by correlating voxel-wise time-series with the mean signal inside each amygdala mask. To better approximate distributional properties upon which subsequent statistical tests are based, the Fisher-Z transform was subsequently applied to the correlation coefficients; however, to aid interpretability, all connectivity estimates are reported as Pearson's correlation

coefficients in this paper.

Second-level analyses and thresholding

To illustrate the regions functionally connected with the amygdala seeds, we computed group-specific one-sample t-tests using statistical parametric mapping software (SPM12 v6685) (http://www.fil.ion.ucl.ac.uk/spm/), adjusting for subject level estimates of motion. Whole-brain two-sample t-tests were conducted to compare the connectivity maps between HC and OCD groups. ERQ subscales were also included as covariates of interest, in interaction with group, to examine their potential relationship with amygdala connectivity.

Data were analysed at the whole-brain level, and the SPM cluster thresholding correction was used, requiring an uncorrected p-voxel of 0.001, and a family-wise error (FWE) corrected p-cluster of 0.05. Eigenvariates from regions with between-group connectivity differences were extracted and entered into an SPSS v21 (IBM Corporation, Armonk, NY) data matrix to assess correlations between connectivity and the severity of OCD symptoms. Pearson correlations were used, and assumptions of normality and homoscedascity were met in all analyses, unless otherwise noted.

DTI analyses

Target placement

Regions for which significant between-group differences in amygdalar functional connectivity were observed, or for which connectivity was associated with ERQ scores, were selected as targets together with amygdala seeds for the subsequent tractography analysis. Details about this placement are presented in the Supplementary Material.

Probabilistic tractography

WM regions of interest (referred to hereafter as WM-ROIs) connecting pairs of resting-state targets were identified using probabilistic tractography, as implemented in AFNI's FATCAT utility toolkit (Taylor and Saad 2013). FATCAT efficiently finds connections within networks and provides

quantitative measures for all identified WM-ROIs. DTI parameter (FA and first eigenvector) uncertainty maps for probabilistic tracking were calculated with FATCAT 3dDWUncert using 50 iterations (Taylor and Saad 2013). Parameters for probabilistic tracking were 5 seed points per voxel, 1000 Monte Carlo iterations, and a threshold fraction of 0.001, and, at each iteration, the algorithm found locations of tracts connecting pairs of targets. Standard propagation parameters for this algorithm were used: 60º maximum angle of propagation confined to voxels with FA>0.2.

Here we report FA and MD for each WM-ROI, as calculated by FATCAT, as well as the volume of the tracts. Tract volume was standardized with reference to the whole-brain volume (fractional volume of tract (fNV)). Only those WM-ROIs found between the same targets in >85% of subjects were selected for further analysis.

Results

Behavioral results

The mean ERQ sub-scores are presented in Table 1. OCD patients scored significantly higher than HC in suppression ($t = 3.10$, $df = 104.20$, $p < .005$), while HC scored significantly higher in reappraisal ($t = -4.79$, $df = 107.36$, $p < .0005$). Also, OCD patients scored significantly higher than HC both in the HDRS ($t = 10.35$, $df = 94.3$, $p < .0005$) and the HARS ($t = 10.06$, $df = 95.88$, $p < .0005$). HDRS and HARS scores were not, however, significantly associated with the ERQ.

Resting-state functional connectivity results

One-sample functional connectivity patterns

Similar whole-brain patterns of functional connectivity were evident for LA and RA seeds, as illustrated in Figure 1 in the Supplementary Material.

Functional connectivity differences

Between-group connectivity comparisons revealed higher connectivity in HC between RA and the right post-central gyrus (PCG) (Table 2, Figure 2). Moreover, the connectivity between these two regions was significantly correlated with Y-BOCS scores in the patient group ($r=.305$, $p=.009$).

Functional connectivity associations with the ERQ

A group interaction effect was found in the association between reappraisal use and LA-left posterior insula connectivity, primarily due to a negative association between reappraisal and functional connectivity between these two regions in HCs. On the other hand, there was a negative association between suppression and functional connectivity between the LA and the precuneus and the bilateral angular gyri in the OCD group (Table 2, Figure 3).

Structural connectivity results

Distribution of tracts

The following WM-ROIs connecting the amygdala and the resting-state clusters arising from the above analyses were identified in at least 85% of participants: (1) the left uncinate fasciculus, connecting LA and left insula targets; (2) the left IFOF, connecting LA and left angular gyrus targets; (3) the right IFOF, connecting RA and right angular gyrus targets; and (4) the right cortico-spinal tract, connecting RA with the right PCG. An example of the WM-ROIs from a representative subject can be found in Figure 4.

Differences in DTI parameters

A multivariate analysis comparing FA, MD and fNV between HC and OCD patients was performed for each of the WM-ROIs, including age and sex as covariates. Groups significantly differed in the left uncinate fasciculus (OCD patients N = 69, HC N = 42, $F(3, 105) = 3.26$, $p = .024$), the right IFOF (OCD patients N = 67, HC N = 38, $F(3, 99) = 3.78$, $p = .013$) and the right cortico-spinal tract (OCD patients N = 66, HC N = 36, $F(3, 96) = 3.3$, $p = .023$), with a trend towards a significant difference observed for the left IFOF as well (OCD patients N = 69, HC N = 39, $F(3, 102) = 2.5$, $p = .064$). According to post-hoc tests, group differences were driven in all tracts by higher MD in the OCD group. Moreover, in patients, lower FA was found in the left uncinate fasciculus, and higher fNV in the right cortico-spinal tract (Table 3).

Associations between DTI parameters and the ERQ

No associations were observed between any of the DTI parameters and reappraisal or suppression scores, both within and across groups.

Associations with pharmacological, clinical and sociodemographic data

Use of medication did not influence the abovementioned results. Likewise, we did not observe any association between functional connectivity results and depression or anxiety scores (HDRS and HARS, respectively). Conversely, DTI estimates from the left uncinate fasciculus were correlated with depression and anxiety scores. Finally, greater age was significantly associated with lower FA across the entire sample as well as within each group for all WM-ROIs (further details about these analyses are presented in Supplementary Material).

Discussion

Our study showed a reduced functional connectivity between the RA and the right PCG in OCD patients, and the connectivity between these regions was found to correlate positively with symptom severity. Moreover, at the structural level, OCD patients displayed higher MD and fNV in the right cortico-spinal tract connecting these regions. Regarding correlations with ERQ scores, a group interaction effect was found in the association between reappraisal use and LA-left posterior insula connectivity, primarily due to a negative association between reappraisal use and functional connectivity between these regions in the HC group. On the other hand, we also observed a negative association between suppression scores and functional connectivity of the LA with the precuneus and bilateral angular gyri specifically in the OCD group. Finally, although we did not find associations between ERQ and DTI parameters within the tracts connecting these regions, we did observe between-group differences in MD and FA involving the left uncinate fasciculus and the right IFOF.

The reduced functional connectivity observed in OCD patients between the RA and the right PCG can reflect altered emotional processing. The PCG forms part of the somatosensory cortex, which serves to integrate somatosensory information with emotional input from the amygdala and, together with the amygdala and right visual cortices, has been found to be important for linking perception of emotional stimuli to motivation (Adolphs et al. 2000; Adolphs 2001). The right

somatosensory cortex, for instance, has been shown to be active during the processing of incongruent somatosensory-emotional information (i.e., incongruent facial and voice expressions) (Klasen et al. 2011). Indeed, previous research in OCD patients has shown decreased functional connectivity in networks comprising the post-central gyrus (Moreira et al. 2017; Gürsel et al. 2018). In addition, the altered functional connectivity between the somatosensory cortex and the amygdala seems to be underpinned by an abnormal pattern of structural connectivity between these regions, since we observed increased MD in the right cortico-spinal tract, in agreement with previous reports in other OCD samples (Fontenelle et al. 2011). This finding, together with the greater volume of this tract observed in OCD, indicates that patients may have relatively more crossing fibers between the RA and the PCG, and, therefore, show less efficient connectivity between the regions. Anyhow, although functional connectivity between the RA and the right somatosensory cortex was decreased in OCD, such decreased connectivity correlated significantly with symptom severity, suggesting the presence of a compensatory mechanism aimed at ameliorating disrupted emotional processing.

In HCs, negative connectivity between the LA and the insula was associated with increased use of cognitive reappraisal strategies. This result is consistent with a previous study from our group where the anterior insula showed negative connectivity with the amygdala in healthy subjects with increasing use of reappraisal strategies (Picó-Pérez et al. 2017). Neural activity in the insula underlies the conscious representation of emotional bodily states (i.e., interoception) (Craig 2009), and, in the early phases of the emotion response, activity in the insula may promote the selection of the most appropriate reappraisal strategy in front of an aversive scenario via an ‘as-if’ representation of bodily states (Verdejo-Garcia, Clark, and Dunn 2012), which in turn may engage prefronto-parietal regulatory regions to finally dampen amygdala reactivity. Our data suggests that such mechanisms are altered in OCD patients. Moreover, patients showed higher MD and lower FA in the left uncinate fasciculus connecting these regions, which can be interpreted as decreased structural integrity of this tract. Previous studies have also found increased diffusivity (Jayarajan et al. 2012) and decreased FA (Admon et al. 2012) in this tract in patients with OCD. Although we did not find direct associations between ERQ scores and structural data, it may be

speculated that structural integrity of the uncinatus is necessary to develop adaptive emotional responses in response to anxiety-invoking scenarios.

OCD patients also showed a negative association between the dispositional use of suppression strategies and functional connectivity between the LA and a set of parietal clusters involving the angular gyri and the precuneus. Such negative association between suppression and parieto-limbic connectivity may reflect the regulatory role of the parietal cortex on limbic activity during the deployment of suppression strategies, which were preferentially observed in patients. Indeed, activity in the angular gyri and the precuneus has previously been reported in the use of suppression strategies (Goldin, Manber, et al. 2009; Dörfel et al. 2014; Hayes et al. 2010). Previous studies in OCD samples, however, have shown disrupted functional and structural connectivity between the amygdala and posterior cortical regions (Rus et al. 2017). Therefore, an alternative explanation for our findings is that disrupted parieto-limbic connectivity may be associated with a preferential use of dysfunctional emotional regulation strategies (i.e., suppression). In agreement with these notions, we also observed increased MD in the IFOF of OCD patients, which concurs with other results showing abnormalities in parietal white matter (Kitamura et al. 2006) and decreased FA and increased MD in the bilateral IFOF connecting the amygdala with the parietal cortex in OCD (Benedetti et al. 2013; Garibotto et al. 2010).

Notably, previous research on the neural correlates of emotion regulation has identified significant activations in other (mainly prefrontal) regions (Buhle et al. 2013; Kohn et al. 2014) not reported here. For example, de Wit et al. (2015) showed decreased activity in the left dlPFC and increased activity in the dmPFC of OCD patients during emotion regulation. In this sense, it could be argued that we should have also identified alterations in amygdala connectivity with these other regions, but it is important to bear in mind that those findings stemmed from task-activation studies, in experimental contexts (i.e., during emotion induction), while we used a dispositional/trait measure of emotional regulation.

This research has several strengths. To date, this is the study evaluating the largest OCD dataset with a multimodal neuroimaging approach, and the first study to assess the neurobiological correlates of dispositional emotion regulation strategies in OCD. Combining multiple units of

analysis to investigate the neurobiological correlates of brain disorders permits a deeper understanding of the mechanistic effects accounting for disrupted behaviors. Overall, when alterations in functional connectivity are paralleled by structural connectivity disruptions, brain pathologies may be associated with the direct links between pairs of structures. Conversely, if such structural connectivity alterations are not observed, functional network level alterations may be better suspected. Nevertheless, it is also important to note that variables such as developmental stage and spatial proximity might moderate these relationships (Bennett and Rypma 2013). Limitations of the current study should also be acknowledged. This includes the use of a 1.5T scanner, the assessment of a limited number of diffusion directions (N = 25), and the acquisition of non-isotropic voxels. Nevertheless, it is important to mention that previous DTI studies have shown reliability across different magnet strengths (i.e., 1.5T vs. 3T (Teipel et al. 2011; Grech-Sollars et al. 2015)). Moreover, in our study, DTI analyses were secondary in relation to functional assessments, which were performed with standard EPI sequences. Likewise, we observed some associations between the structural connectivity estimates from the left uncinate fasciculus and depressive and anxiety symptoms that may have partially contributed to our pattern of findings. Finally, most patients were on medication. Pharmacological treatment has been suggested to be a significant confounder in functional connectivity studies (Posner et al. 2014), although it is not wholly clear in what direction this might bias our results. In any case, it is important to note that treatment doses in our OCD sample were stable during the three months preceding the fMRI, and we did not find any relationship between our imaging findings and pharmacological treatment.

Conclusion

In conclusion, we have shown that functional and structural connectivity of the amygdala with the somatosensory cortex is disrupted in patients with OCD. While such alterations do not underpin the preferential use of suppression regulation strategies observed in these patients, the neural correlates of disrupted emotion regulation include both altered connectivity with posterior brain regions as well as between the amygdala and the insula. This study is the first taking specific emotional processing domains into account while using a multimodal perspective, and our

findings emphasize the importance of integrating the role of amygdala connectivity in OCD pathophysiology.

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References

Admon, Roee, Maya Bleich-Cohen, Ronit Weizmant, Michael Poyurovsky, Sarit Faragian, and Talma Hendler. 2012. “Functional and Structural Neural Indices of Risk Aversion in Obsessive-Compulsive Disorder (OCD).” *Psychiatry Research - Neuroimaging* 203 (2–3): 207–13. https://doi.org/10.1016/j.pscychresns.2012.02.002.

Adolphs, R, H Damasio, D Tranel, G Cooper, and R Damasio. 2000. “A Role for Somatosensory Cortices in the Visual Recognition of Emotion as Revealed by Three-Dimensional Lesion Mapping.” *The Journal of Neuroscience* 20 (7): 2683–90. https://doi.org/123123123.

Adolphs, Ralph. 2001. “The Neurobiology of Social Cognition.” *Current Opinion in Neurobiology* 11: 213–39. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15667456.

Banks, Sarah J., Kamryn T. Eddy, Mike Angstadt, Pradeep J. Nathan, and K. Luan Phan. 2007. “Amygdala-Frontal Connectivity during Emotion Regulation.” *Social Cognitive and Affective Neuroscience* 2 (4): 303–12. https://doi.org/10.1093/scan/nsm029.

Baur, Volker, Jürgen Hänggi, Nicolas Langer, and Lutz Jäncke. 2013. “Resting-State Functional and Structural Connectivity within an Insula-Amygdala Route Specifically Index State and Trait Anxiety.” *Biological Psychiatry* 73 (1): 85–92. https://doi.org/10.1016/j.biopsych.2012.06.003.

Benedetti, Francesco, Chiara Giacosa, Daniele Radaelli, Sara Poletti, Elena Pozzi, Sara Dallaspezia, Andrea Falini, and Enrico Smeraldi. 2013. “Widespread Changes of White Matter Microstructure in Obsessive–compulsive Disorder: Effect of Drug Status.” *European Neuropsychopharmacology* 23 (7): 581–93. https://doi.org/10.1016/J.EURONEURO.2012.07.002.

Breiter, Hans C., Scott L. Rauch, Kenneth K. Kwong, John R. Baker, Robert M. Weisskoff, David N. Kennedy, Adair D. Kendrick, et al. 1996. “Functional Magnetic Resonance Imaging of Symptom Provocation in Obsessive-Compulsive Disorder.” *Archives of General Psychiatry* 53 (7): 595. https://doi.org/10.1001/archpsyc.1996.01830070041008.

Buhle, Jason T, Jennifer a Silvers, Tor D Wager, Richard Lopez, Chukwudi Onyemekwu, Hedy Kober, Jochen Weber, and Kevin N Ochsner. 2013. “Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies.” *Cerebral Cortex (New York, N.Y.: 1991)*, 1–10. https://doi.org/10.1093/cercor/bht154.

Cabello, Rosario, José M. Salguero, Pablo Fernández-Berrocal, and James J. Gross. 2013. “A Spanish Adaptation of the Emotion Regulation Questionnaire.” *European Journal of Psychological Assessment* 29 (4): 234–40. https://doi.org/10.1027/1015-5759/a000150.

Cardoner, Narcís, Ben J. Harrison, Jesús Pujol, Carles Soriano-Mas, Rosa Hernández-Ribas, Marina López-Solá, Eva Real, et al. 2011. “Enhanced Brain Responsiveness during Active Emotional Face Processing in Obsessive Compulsive Disorder.” *The World Journal of Biological Psychiatry* 12 (5): 349–63. https://doi.org/10.3109/15622975.2011.559268.

Cox, R W. 1996. “AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages.” *Computers and Biomedical Research* 29 (29): 162–73. https://doi.org/10.1006/cbmr.1996.0014.

Craig, A. D. 2009. “How Do You Feel — Now? The Anterior Insula and Human Awareness.” *Nature Reviews Neuroscience* 10 (1): 59–70. https://doi.org/10.1038/nrn2555.

Dörfel, Denise, Jan Peter Lamke, Falk Hummel, Ullrich Wagner, Susanne Erk, and Henrik Walter. 2014. “Common and Differential Neural Networks of Emotion Regulation by Detachment, Reinterpretation, Distraction, and Expressive Suppression: A Comparative FMRI Investigation.” *NeuroImage* 101: 298–309. https://doi.org/10.1016/j.neuroimage.2014.06.051.

Fontenelle, Leonardo F, Ivanei E Bramati, Jorge Moll, Mauro V Medlowicz, Ricardo de Oliveira-Souza, and Fernanda Tovar-Moll. 2011. “White Matter Changes in OCD Revealed by Diffusion Tensor Imaging.” *CNS Spectrums* 16 (May): 101–9. https://doi.org/10.1017/S1092852912000.

Garibotto, V., P. Scifo, A. Gorini, Clarke R. Alonso, S. Brambati, L. Bellodi, and D. Perani. 2010. “Disorganization of Anatomical Connectivity in Obsessive Compulsive Disorder: A Multi-Parameter Diffusion Tensor Imaging Study in a Subpopulation of Patients.” *Neurobiology of Disease* 37 (2): 468–76. https://doi.org/10.1016/J.NBD.2009.11.003.

Goldberg, X., N. Cardoner, P. Alonso, C. López-Solà, E. Real, R. Hernández-Ribas, S. Jiménez-Murcia, et al. 2016. “Inter-Individual Variability in Emotion Regulation: Pathways to Obsessive-Compulsive Symptoms.” *Journal of Obsessive-Compulsive and Related Disorders* 11 (October): 105–12. https://doi.org/10.1016/j.jocrd.2016.10.002.

Goldin, Philippe, Tali Manber, Shabnam Hakimi, Turhan Canli, and James J Gross. 2009. “Neural Bases of Social Anxiety Disorder: Emotional Reactivity and Cognitive Regulation During Social and Physical Threat.” *Arch Gen Psychiatry* 66 (2): 170–80.

https://doi.org/10.1001/archgenpsychiatry.2008.525.

Goldin, Philippe, Kateri McRae, Wiveka Ramel, and James J Gross. 2009. “The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion.” *Biological Psychiatry* 63 (6): 577–86.

Goodman, Wayne K., Lawrence H. Price, Steven A. Rasmussen, Carolyn Mazure, Roberta L. Fleischmann, Candy L. Hill, George R. Heninger, and Dennis S. Charney. 1989. “The Yale-Brown Obsessive Compulsive Scale.” *Archives of General Psychiatry* 46 (11): 1006. https://doi.org/10.1001/archpsyc.1989.01810110048007.

Grech-Sollars, Matthew, Patrick W Hales, Keiko Miyazaki, Felix Raschke, Daniel Rodriguez, Martin Wilson, Simrandip K Gill, et al. 2015. “Multi-Centre Reproducibility of Diffusion MRI Parameters for Clinical Sequences in the Brain.” *NMR in Biomedicine* 28 (4): 468–85. https://doi.org/10.1002/nbm.3269.

Gross, James J, and Oliver P John. 2003. “Individual Differences in Two Emotion Regulation Processes: Implications for Affect, Relationships, and Well-Being.” *Journal of Personality and Social Psychology* 85 (2): 348–62. https://doi.org/10.1037/0022-3514.85.2.348.

Gruner, Patricia, An Vo, Toshikazu Ikuta, Katie Mahon, Bart D Peters, Anil K Malhotra, Aziz M Uluğ, and Philip R Szeszko. 2012. “White Matter Abnormalities in Pediatric Obsessive-Compulsive Disorder.” *Neuropsychopharmacology* 37 (12): 2730–39. https://doi.org/10.1038/npp.2012.138.

Gürsel, Deniz A., Mihai Avram, Christian Sorg, Felix Brandl, and Kathrin Koch. 2018. “Frontoparietal Areas Link Impairments of Large-Scale Intrinsic Brain Networks with Aberrant Fronto-Striatal Interactions in OCD: A Meta-Analysis of Resting-State Functional Connectivity.” *Neuroscience & Biobehavioral Reviews*, February. https://doi.org/10.1016/j.neubiorev.2018.01.016.

Hahn, Andreas, Patrycja Stein, Christian Windischberger, Andreas Weissenbacher, Christoph Spindelegger, Ewald Moser, Siegfried Kasper, and Rupert Lanzenberger. 2011. “Reduced Resting-State Functional Connectivity between Amygdala and Orbitofrontal Cortex in Social Anxiety Disorder.” *NeuroImage* 56 (3): 881–89. https://doi.org/10.1016/J.NEUROIMAGE.2011.02.064.

Hamilton, M. 1959. “The Assessment of Anxiety States by Rating.” *The British Journal of Medical Psychology* 32 (1): 50–55. http://www.ncbi.nlm.nih.gov/pubmed/13638508.

Hamilton, M. 1960. “A Rating Scale for Depression.” *Journal of Neurology, Neurosurgery, and*

Psychiatry 23 (1): 56–62. http://www.ncbi.nlm.nih.gov/pubmed/14399272.

Harrison, Ben J., Carles Soriano-Mas, Jesus Pujol, Hector Ortiz, Marina López-Solà, Rosa Hernández-Ribas, Joan Deus, et al. 2009. “Altered Corticostriatal Functional Connectivity in Obsessive-Compulsive Disorder.” *Archives of General Psychiatry* 66 (11): 1189. https://doi.org/10.1001/archgenpsychiatry.2009.152.

Hayes, Jasmeet Pannu, Rajendra A Morey, Christopher M Petty, Srishti Seth, Moria J Smoski, Gregory McCarthy, and Kevin S Labar. 2010. “Staying Cool When Things Get Hot: Emotion Regulation Modulates Neural Mechanisms of Memory Encoding.” *Frontiers in Human Neuroscience* 4: 230. https://doi.org/10.3389/fnhum.2010.00230.

Hermundstad, Ann M, Danielle S Bassett, Kevin S Brown, Elissa M Aminoff, David Clewett, Scott Freeman, Amy Frithsen, et al. 2013. “Structural Foundations of Resting-State and Task-Based Functional Connectivity in the Human Brain.” *Proceedings of the National Academy of Sciences of the United States of America* 110 (15): 6169–74. https://doi.org/10.1073/pnas.1219562110.

Heuvel, Martijn P. van den, René C.W. Mandl, René S. Kahn, and Hilleke E. Hulshoff Pol. 2009. “Functionally Linked Resting-State Networks Reflect the Underlying Structural Connectivity Architecture of the Human Brain.” *Human Brain Mapping* 30 (10): 3127–41. https://doi.org/10.1002/hbm.20737.

Jayarajan, Rajan Nishanth, Ganesan Venkatasubramanian, Biju Viswanath, Y.C. Janardhan Reddy, Shoba Srinath, Mandapatti K. Vasudev, and Channapatna R. Chandrashekar. 2012. “White Matter Abnormalities in Children and Adolescents with Obsessive-Compulsive Disorder: A Diffusion Tensor Imaging Study.” *Depression and Anxiety* 29 (9): 780–88. https://doi.org/10.1002/da.21890.

Kitamura, H., T. Shioiri, T. Kimura, M. Ohkubo, T. Nakada, and T. Someya. 2006. “Parietal White Matter Abnormalities in Obsessive-Compulsive Disorder: A Magnetic Resonance Spectroscopy Study at 3-Tesla.” *Acta Psychiatrica Scandinavica* 114 (2): 101–8. https://doi.org/10.1111/j.1600-0447.2006.00858.x.

Klasen, M., C. A. Kenworthy, K. A. Mathiak, T. T. J. Kircher, and K. Mathiak. 2011. “Supramodal Representation of Emotions.” *Journal of Neuroscience* 31 (38): 13635–43. https://doi.org/10.1523/JNEUROSCI.2833-11.2011.

Kohn, N., S.B. Eickhoff, M. Scheller, A.R. Laird, P.T. Fox, and U. Habel. 2014. “Neural Network of

Cognitive Emotion Regulation — An ALE Meta-Analysis and MACM Analysis." *NeuroImage* 87: 345–55. https://doi.org/10.1016/j.neuroimage.2013.11.001.

LeDoux, J E. 2000. "Emotion Circuits in the Brain." *Annual Review of Neuroscience* 23 (January): 155–84. https://doi.org/10.1146/annurev.neuro.23.1.155.

Lee, Hyejeen, Aaron S Heller, Carien M van Reekum, Brady Nelson, and Davidson. 2012. "Amygdala-Prefrontal Coupling Underlies Individual Differences in Emotion Regulation." *NeuroImage* 62 (3): 1575–81. https://doi.org/10.1016/j.neuroimage.2012.05.044. Amygdala-prefrontal.

Mataix-Cols, David, Sarah Wooderson, Natalia Lawrence, Michael J. Brammer, Anne Speckens, and Mary L. Phillips. 2004. "Distinct Neural Correlates of Washing, Checking, and Hoarding SymptomDimensions in Obsessive-Compulsive Disorder." *Archives of General Psychiatry* 61 (6): 564. https://doi.org/10.1001/archpsyc.61.6.564.

Menzies, Lara, Samuel R. Chamberlain, Angela R. Laird, Sarah M. Thelen, Barbara J. Sahakian, and Ed T. Bullmore. 2008. "Integrating Evidence from Neuroimaging and Neuropsychological Studies of Obsessive-Compulsive Disorder: The Orbitofronto-Striatal Model Revisited." *Neuroscience and Biobehavioral Reviews* 32 (3): 525–49. https://doi.org/10.1016/j.neubiorev.2007.09.005.

Milad, Mohammed R., and Scott L. Rauch. 2012. "Obsessive-Compulsive Disorder: Beyond Segregated Cortico-Striatal Pathways." *Trends in Cognitive Sciences* 16 (1): 43–51. https://doi.org/10.1016/J.TICS.2011.11.003.

Moreira, P S, P Marques, C Soriano-Mas, R Magalhães, N Sousa, J M Soares, and P Morgado. 2017. "The Neural Correlates of Obsessive-Compulsive Disorder: A Multimodal Perspective." *Translational Psychiatry* 7 (8): e1224. https://doi.org/10.1038/tp.2017.189.

Ochsner, Kevin, Jennifer Silvers, and Jason Buhle. 2012. "Functional Imaging Studies of Emotion Regulation: A Synthetic Review and Evolving Model of the Cognitive Control of Emotion." *Ann N Y Acad Sci* 1252: 1–35. https://doi.org/10.1111/j.1749-6632.2012.06751.x.

Picó-Pérez, Maria, Pino Alonso, Oren Contreras-Rodríguez, Ignacio Martínez-Zalacaín, Clara López-Solà, Susana Jiménez-Murcia, Antonio Verdejo-García, José M. Menchón, and Carles Soriano-Mas. 2017. "Dispositional Use of Emotion Regulation Strategies and Resting-State Cortico-Limbic Functional Connectivity." *Brain Imaging and Behavior*. https://doi.org/10.1007/s11682-017-9762-3.

Pierpaoli, C., L. Walker, M. O. Irfanoglu, A. Barnett, P. Basser, L-C. Chang, C. Koay, et al. 2010.

"TORTOISE: An Integrated Software Package for Processing of Diffusion MRI Data." *ISMRM 18th Annual Meeting* Stockholm (Sweden): #1597.

Posner, Jonathan, Rachel Marsh, Tiago V Maia, Bradley S Peterson, Allison Gruber, and H Blair Simpson. 2014. "Reduced Functional Connectivity within the Limbic Cortico-Striato-Thalamo-Cortical Loop in Unmedicated Adults with Obsessive-Compulsive Disorder." *Human Brain Mapping* 35 (6): 2852–60. https://doi.org/10.1002/hbm.22371.

Roy, Amy K, Julie L Fudge, Clare Kelly, Justin S A Perry, Teresa Daniele, Christina Carlisi, Brenda Benson, et al. 2013. "Intrinsic Functional Connectivity of Amygdala-Based Networks in Adolescent Generalized Anxiety Disorder." *Journal of the American Academy of Child and Adolescent Psychiatry* 52 (3): 290–299.e2. https://doi.org/10.1016/j.jaac.2012.12.010.

Rus, Oana Georgiana, Tim Jonas Reess, Gerd Wagner, Claus Zimmer, Michael Zaudig, and Kathrin Koch. 2017. "Functional and Structural Connectivity of the Amygdala in Obsessive-Compulsive Disorder." *NeuroImage Clinical* 13: 246–55. https://doi.org/10.1016/j.nicl.2016.12.007.

Ruscio, A M, D J Stein, W T Chiu, and R C Kessler. 2010. "The Epidemiology of Obsessive-Compulsive Disorder in the National Comorbidity Survey Replication." *Molecular Psychiatry* 15 (1): 53–63. https://doi.org/10.1038/mp.2008.94.

Simon, Daniela, Christian Kaufmann, Kathrin Müsch, Eva Kischkel, and Norbert Kathmann. 2010. "Fronto-Striato-Limbic Hyperactivation in Obsessive-Compulsive Disorder during Individually Tailored Symptom Provocation." *Psychophysiology* 47 (4): 728–38. https://doi.org/10.1111/j.1469-8986.2010.00980.x.

Taylor, Paul A, and Ziad S Saad. 2013. "FATCAT: (An Efficient) Functional And Tractographic Connectivity Analysis Toolbox." *Brain Connectivity* 3 (5): 523–35. https://doi.org/10.1089/brain.2013.0154.

Teipel, Stefan J., Sigrid Reuter, Bram Stieltjes, Julio Acosta-Cabronero, Ulrike Ernemann, Andreas Fellgiebel, Massimo Filippi, et al. 2011. "Multicenter Stability of Diffusion Tensor Imaging Measures: A European Clinical and Physical Phantom Study." *Psychiatry Research: Neuroimaging* 194 (3): 363–71. https://doi.org/10.1016/J.PSCYCHRESNS.2011.05.012.

Verdejo-Garcia, Antonio, Luke Clark, and Barnaby D. Dunn. 2012. "The Role of Interoception in Addiction: A Critical Review." *Neuroscience & Biobehavioral Reviews* 36 (8): 1857–69. https://doi.org/10.1016/j.neubiorev.2012.05.007.

Via, Esther, Narcís Cardoner, Jesús Pujol, Pino Alonso, Marina López-Solà, Eva Real, Oren Contreras-Rodríguez, et al. 2014. “Amygdala Activation and Symptom Dimensions in Obsessive-Compulsive Disorder.” *The British Journal of Psychiatry : The Journal of Mental Science* 204 (1): 61–68. https://doi.org/10.1192/bjp.bp.112.123364.

Vries, Froukje E. de, Stella J. de Wit, Danielle C. Cath, Ysbrand D. van der Werf, Vionne van der Borden, Thomas B. van Rossum, Anton J.L.M. van Balkom, Nic J.A. van der Wee, Dick J. Veltman, and Odile A. van den Heuvel. 2014. “Compensatory Frontoparietal Activity During Working Memory: An Endophenotype of Obsessive-Compulsive Disorder.” *Biological Psychiatry* 76 (11): 878–87. https://doi.org/10.1016/J.BIOPSYCH.2013.11.021.

Weidt, S., J. Lutz, M. Rufer, A. Delsignore, N. J. Jakob, U. Herwig, and A. B. Bruehl. 2016. “Common and Differential Alterations of General Emotion Processing in Obsessive-Compulsive and Social Anxiety Disorder.” *Psychological Medicine* 46 (07): 1427–36. https://doi.org/10.1017/S0033291715002998.

Wit, S. J. de, Y. D. van der Werf, D. Mataix-Cols, J. P. Trujillo, P. van Oppen, D. J. Veltman, and O. A. van den Heuvel. 2015. “Emotion Regulation before and after Transcranial Magnetic Stimulation in Obsessive Compulsive Disorder.” *Psychological Medicine* 45 (14): 3059–73. https://doi.org/10.1017/S0033291715001026.

Zarei, Mojtaba, David Mataix-Cols, Isobel Heyman, Morgan Hough, Joanne Doherty, Linda Burge, Louise Winmill, Sunita Nijhawan, Paul M. Matthews, and Anthony James. 2011. “Changes in Gray Matter Volume and White Matter Microstructure in Adolescents with Obsessive-Compulsive Disorder.” *Biological Psychiatry* 70 (11): 1083–90. https://doi.org/10.1016/J.BIOPSYCH.2011.06.032.

Tables

Table 1. Demographic and clinical characteristics of the sample.

	OCD (n=73), Mean (SD)	HC (n=42), Mean (SD)	Statistic[c]	p-value
Age	37.74 (10.19)	39.43 (9.79)	-0.86	.38
Gender (male/female)	43/30	22/20	0.462	.56
Handedness (R/L)[a]	59/4	32/5	1.46	.28
ERQ Reappraisal[b]	3.6 (1.49)	4.76 (1.07)	-4.79	<.0005
ERQ Suppression[b]	3.78 (1.58)	2.96 (1.2)	3.1	<.005
HDRS	10.27 (5.65)	2.04 (2.2)	10.35	<.0005
HARS	12.41 (7.16)	2.56 (2.51)	10.06	<.0005
Age at onset of OCD	20.9 (8.43)	-	-	-
Y-BOCS Total	22.14 (6.35)	-	-	-
Pharmacological treatment	**N (%)**			
Medication free	6 (8.21)	-	-	-
SSRIs	24 (32.87)	-	-	-
Fluoxetine, 20-80 mg/d	13 (17.8)	-	-	-
Escitalopram, 10-20 mg/d	5 (6.84)	-	-	-
Sertraline, 200 mg/d	3 (4.1)	-	-	-
Fluvoxamine, 200-300 mg/d	2 (2.73)	-	-	-
Paroxetine, 40 mg/d	1 (1.36)	-	-	-
Clomipramine, 75-300 mg/d	8 (10.95)	-	-	-
SSRIs with Clomipramine	12 (16.43)	-	-	-
SSRIs combinations	1 (1.36)	-	-	-
Antipsychotic augmentations	22 (30.13)	-	-	-
Comorbidities	**N (%)**			
No	45 (61.6)	-	-	-
Major Depressive Disorder	10 (13.7)	-	-	-
General Anxiety Disorder	3 (4.1)	-	-	-
Eating Disorder	3 (4.1)	-	-	-
Tics	3 (4.1)	-	-	-
Panic Disorder	2 (2.7)	-	-	-
Dysthymia	2 (2.7)	-	-	-
OCD Personality Disorder	2 (2.7)	-	-	-
ADHD	1 (1.4)	-	-	-
Agoraphobia	1 (1.4)	-	-	-
Gambling Disorder	1 (1.4)	-	-	-

HC healthy controls, *OCD* obsessive-compulsive disorder patients, *SD* Standard Deviation, *ERQ* Emotion Regulation Questionnaire, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *Y-BOCS* Yale-Brown Obsessive-Compulsive Scale, *ADHD* Attention Deficit Hyperactivity Disorder.

[a]Handedness had n=63 in the OCD group and n=37 in the HC group, the HDRS and the HARS n=25 in the HC group, and age at onset of OCD n=72.

[b]ERQ scores were standardized by means of dividing the mean score of each subscale by the corresponding number of items (6 for reappraisal and 4 for suppression).

[c]Student's t-test for quantitative variables and χ^2 test for qualitative ones.

Table 2. Resting-state functional connectivity results.

Seed	ERQ scale	Contrast	Region	MNI coordinates (x, y, z)	Ke[a]	t-statistic
RA	-	HC > OCD	Right post-central gyrus	39, -27, 57	51	4.57
LA	Reappraisal	HC < OCD	Left posterior insula	-45, -6, 9	90	5.77
LA	Suppression	OCD -	Precuneus	9, -66, 39	400	5.16
			Right angular gyrus	30, -63, 57	123	4.65
			Left angular gyrus	-30, -69, 33	52	4.19

Regions showing between-group differences in amygdala connectivity, or in its association with ERQ scores ($p < .05$ FWE-cluster corrected).

LA left amygdala, *RA* right amygdala, *HC* healthy controls, *OCD* obsessive-compulsive disorder patients, *ERQ* Emotion Regulation Questionnaire, *MNI* Montreal Neurological Institute.

Table 3. Structural connectivity differences.

WM-ROI	DTI parameter	F-statistic	p-value	Direction of findings
Left uncinate fasciculus	FA	4.09	.046	OCD < HC
	MD	7.61	.007	OCD > HC
	fNV	0.14	.703	-
Right IFOF	FA	0.79	.374	-
	MD	10.86	.001	OCD > HC
	fNV	0.04	.829	-
Right cortico-spinal tract	FA	0.04	.834	-
	MD	6.75	.011	OCD > HC
	fNV	4.71	.032	OCD > HC

Regions showing a between-group difference in the DTI parameters of the WM-ROIs, according to post-hoc analysis.

WM-ROI white-matter region of interest, *DTI* diffusion tensor image, *IFOF* inferior fronto-occipital fasciculus, *FA* fractional anisotropy, *MD* mean diffusivity, *fNV* fractional volume of tracts, *HC* healthy controls, *OCD* obsessive-compulsive disorder patients.

Figures

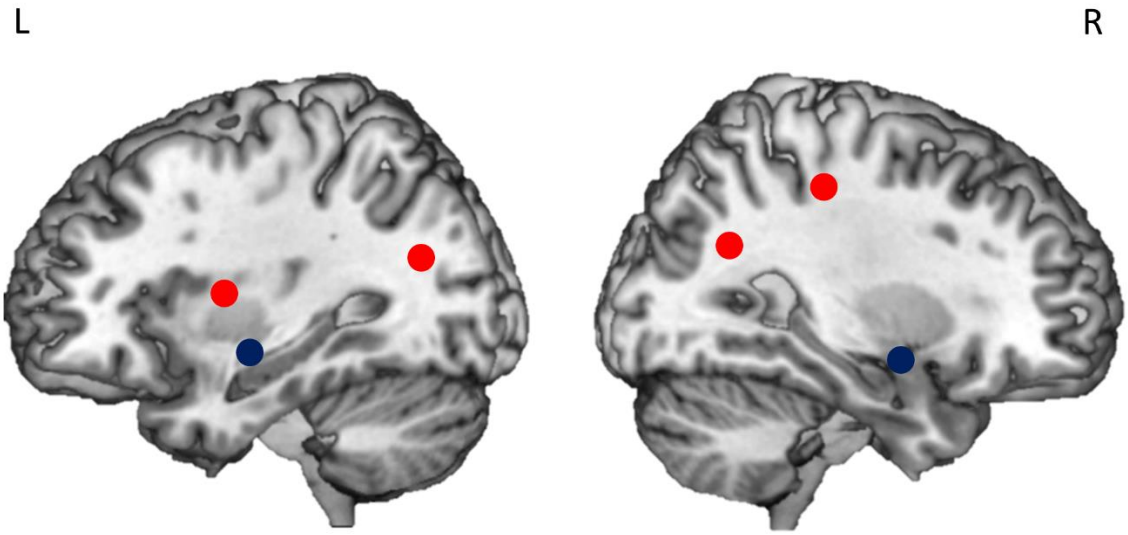

Fig. 1. Placement of DTI targets based on resting-state functional connectivity results (in MNI space). LA and RA are shown in blue, and the rest of the targets in red. L=Left, R=Right.

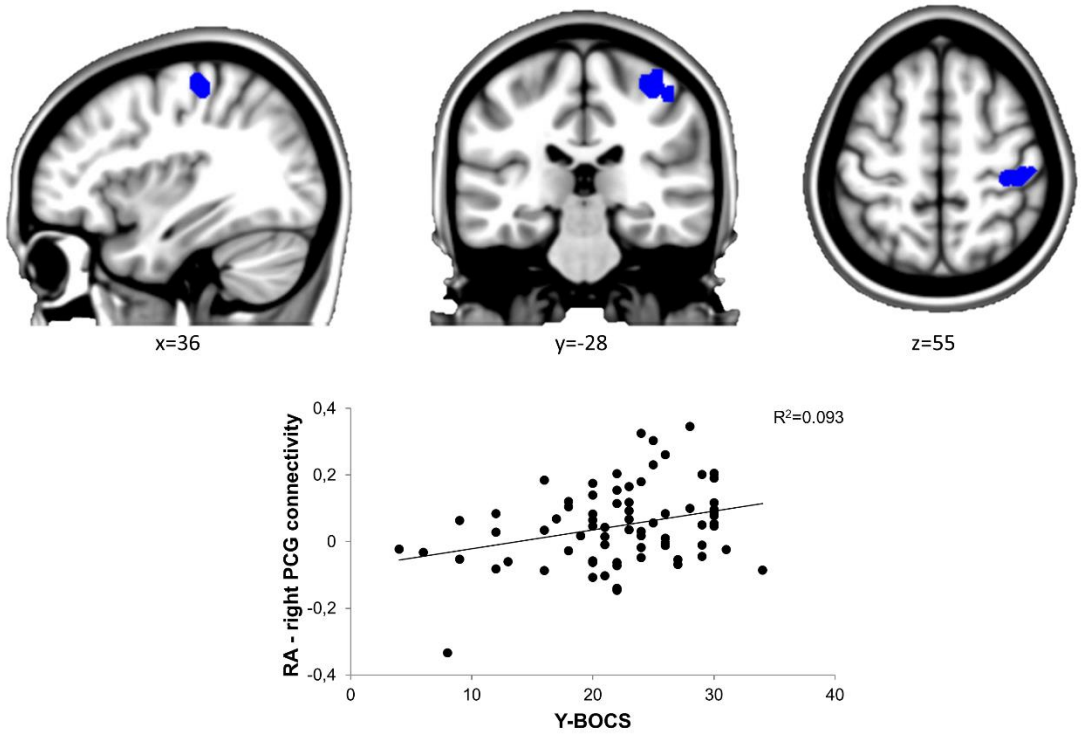

Fig. 2. Between-group functional connectivity differences. RA – right PCG connectivity was significantly higher in HC than in OCD patients, and connectivity values were positively correlated with Y-BOCS scores in the OCD group.

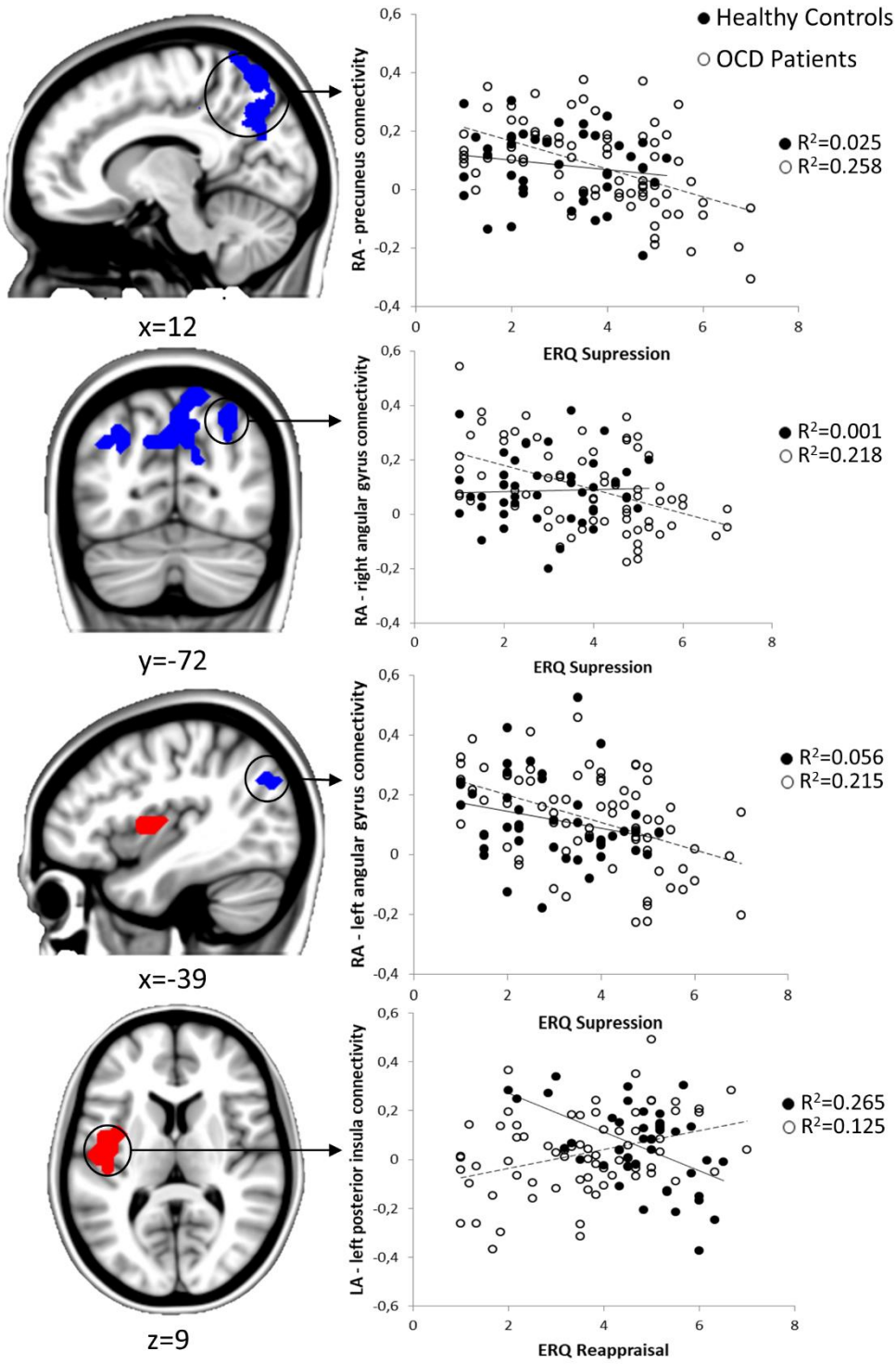

Fig. 3. Functional connectivity associations with the ERQ. Left: Regions showing an association with cognitive reappraisal (left posterior insula) are shown in red, while regions showing an association with suppression (precuneus and bilateral angular gyri) are shown in blue. Right: Scatter plots depicting the relationship between functional connectivity estimates and corresponding ERQ scores for both groups.

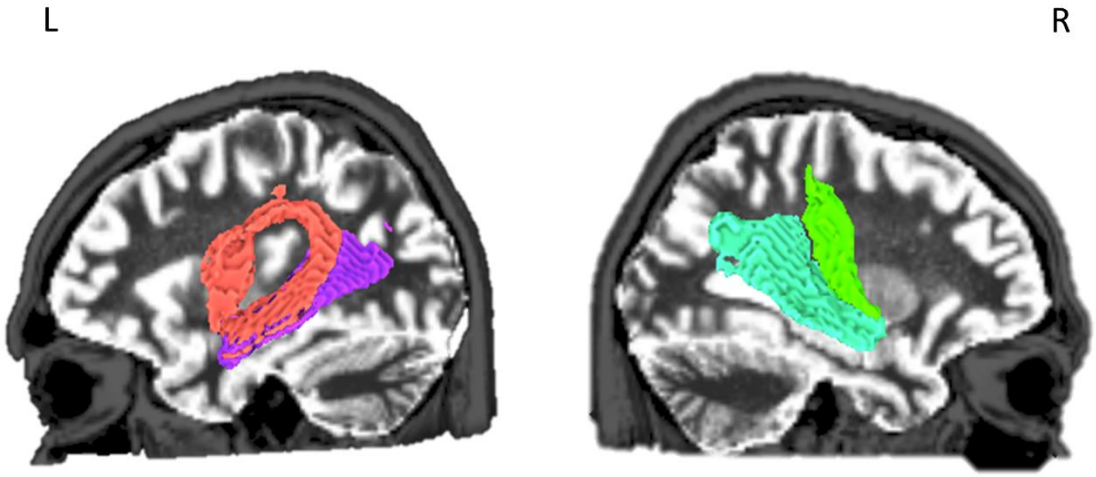

Fig. 4. Example of the WM-ROIs consistently found between the probabilistic tractography targets from a representative subject (in subject DW space). The left uncinate fasciculus is shown in red, the left IFOF in purple, the right IFOF in light blue, and the right cortico-spinal tract in green. L=Left, R=Right.

Supplementary Material

Methods

Participants

Subjects with obsessive-compulsive disorder (OCD) were recruited from the OCD Clinic and Research Unit of Bellvitge University Hospital (Barcelona, Spain). Patients were interviewed by two psychiatrists with extensive experience in OCD (PA and CS), and the Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-IV) was used to confirm the diagnosis. All patients met DSM-IV criteria for OCD for at least one year, and had been stably medicated for at least a 3-month period prior to the MRI. Exclusion criteria included: 1) age under 18 or over 65, 2) presence or past history (in the previous six months) of psychoactive substance abuse or dependence, 3) intellectual disability, 4) neurological disease comorbidity, except for tic disorder, 5) present or past history of psychotic disorders, 6) presence or past history of any other serious medical condition, and 7) any contraindication to MRI scanning. Comorbidity with other Axis I disorders was not considered an exclusion criterion provided that OCD was the primary diagnosis and the reason for seeking medical assistance.

Healthy controls were recruited from the same sociodemographic environment and constituted a comparable sample in terms of age, gender and handedness (see Table 1). Prior to inclusion, each control participant underwent the Structured Clinical Interview for DSM-IV non-patient version (SCID-NP) (First et al. 2002) to exclude presence or past history of any psychiatric disorder. Otherwise, identical exclusion criteria were applied to both patient and control groups. Written informed consent was obtained from all participants after a complete description of the study, which was performed in accordance with the Declaration of Helsinki (2013) and approved by Bellvitge Hospital's ethical committee.

Behavioural assessment

The Emotion Regulation Questionnaire (ERQ) consists of 10 items, with participants providing responses on a 7-point Likert scale anchored by the statements ''strongly disagree'' and ''strongly

agree''. Previous validation of the Spanish version of the ERQ demonstrated that it has adequate internal consistency (Cronbach's α coefficients were α = .75 for suppression and α = .79 for reappraisal), test–retest reliability (.66 for Suppression and .64 for Reappraisal over 3 months), and convergent and discriminant validity with "Big Five" personality traits (Cabello et al. 2013).

Image acquisition and preprocessing

Participants were scanned using a 1.5T Signa Excite system (General Electric, Milwaukee, Wisconsin) equipped with an eight-channel phased-array head coil and single-shot echo-planar imaging (EPI) software. Functional sequences consisted of a gradient recalled acquisition in the steady state (repetition time, 2000 msec; echo time, 50 msec; and pulse angle, 90°) in a 24-cm field of view, with a 64 × 64 pixel matrix (in-plane resolution of 3.75 × 3.75 mm) and a slice thickness of 4 mm (interslice gap, 1 mm). Twenty-two interleaved sections, parallel to the anterior-posterior commissure line, were acquired for each of the 120 whole-brain volumes. A high resolution T1-weighted anatomical scan was also acquired to facilitate registration of the EPI and diffusion-tensor imaging (DTI) data into standard space. Specifically, we used a three-dimensional fast spoiled gradient inversion-recovery prepared sequence with 130 contiguous slices (repetition time, 11.8 msec; echo time, 4.2 msec; flip angle, 15°) in a 30-cm field of view, with a 256 × 256 pixel matrix (in-plane resolution of 1.17 × 1.17 mm) and a slice thickness of 1.2 mm. Finally, diffusion-weighted scans were obtained using spin-echo single-shot echo-planar sequences of 25 directions with a b-value of 1000 s/mm^2, together with a single non–diffusion weighted volume. Twenty-six slices were acquired parallel to the anterior-posterior commissure (repetition time, 8300 msec; echo time, 94 msec; and pulse angle, 90°) in a 26-cm field of view, with a 128 x 128 acquisition matrix reconstructed into a 256 x 256 matrix.

Resting-state fMRI (rs-fMRI) BOLD data were preprocessed with a pipeline specified using afni_proc.py tool (see Table S1 for details). Outlying data points in each voxel's time-series were subsequently truncated using the default implementation of 3dDespike. The echo-planar images (EPI) were placed into the MNI152 standard space at a 3mm isotropic spatial resolution through the application of a linear affine warping matrix generated by the registration of each subject's T1-weighted (T1w) volume into MNI space. Motion correction was implemented as part of the same

step (thereby minimizing data smoothing), using displacement parameters generated by aligning the EPI time-series to the mean EPI volume. Alignment quality was confirmed through visual inspection. Participants for whom it was not possible to retain at least 95% (3.8 minutes) of rs-fMRI data after flagging high motion volumes, defined as those displaced relative to the preceding volume by more than 0.3 mm, were excluded from the analysis. Finally, mean, linear, quadratic and cubic temporal trends, as well as the 6 rigid-body motion parameter estimates and their first-order derivatives, were subsequently removed from the EPI time-series for each participant. The influence of physiological noise was addressed through regressing out both the mean BOLD signal from lateral ventricle masks, as well as a localized signal estimate from subject-specific WM masks, as part of the Anaticor preprocessing pipeline (Jo et al. 2013). Skull removal from the T1w prior to registration, and the generation of WM and ventricle masks was performed using FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/).

Regarding the preprocessing of the diffusion-weighed imaging (DWI) data, the DIFFPREP module in TORTOISE V2.5.2 (Pierpaoli et al. 2010) was used to compute distortion corrections for subject motion, eddy currents and basic EPI distortions. The fat_proc* programs in AFNI were used to invert the contrast of the T1w images to imitate that of T2-weighted images solely for providing an anatomical reference volume within TORTOISE (see the Appendix of Taylor et al. (2016)). Finally, the preprocessed DWIs were exported to AFNI for diffusion tensor (DT) and associated parameter fitting, and the remaining analyses.

DTI analyses

Target placement

Target spheres for probabilistic tractography were placed as close as possible to significant resting-state functional connectivity clusters (average distance: 15.7 mm, range: 10.4 mm to 24.7 mm) whilst simultaneously maximizing white-matter (WM) coverage. A total of 4 targets were employed for tractography (see Results section in the main manuscript), together with left (LA) and right amygdala (RA) seeds. Specifically, one target was placed near the left posterior insula, another one near the right post-central gyrus, and considering the big cluster extending from the

precuneus to the bilateral angular gyri, two bilateral targets were placed in intermediate locations between these regions (see Figure 1 and Supplementary Table 2 for the target placement and coordinates). These targets were generated in MNI space after which they were transformed to each subject's DW space and doubled in volume to ensure adequate WM coverage.

Results

Associations with pharmacological, clinical and sociodemographic data

Partial correlations were performed with medication use as control variable. The correlation between RA – right post-central gyrus functional connectivity and the Y-BOCS remained significant (r=.323, p=.006), and also between suppression and the functional connectivity between the LA and the precuneus (r=-.494, p<.0005) and the bilateral angular gyri (left: r=-.462, p<.0005; right: r=-.457, p<.0005). Moreover, we performed multivariate analyses in order to check if medication status was influencing DTI parameters in any of the identified tracts, and none of the models reached statistical significance.

The association of depressive (measured with the Hamilton Depression Rating Scale - HDRS) and anxious (Hamilton Anxiety Rating Scale - HARS) symptoms with imaging findings within our patient group was also checked. There were no correlations between either the HDRS or the HARS and our functional connectivity results. Moreover, the associations between ERQ and functional connectivity estimates were still significant when controlling for HDRS and HARS scores through partial correlations. Conversely, DTI estimates from the left uncinate fasciculus were correlated with depressive symptoms (FA: r=-.327, p=.006; fNV: r=-.373, p=.002), and to a lesser extent with anxious symptoms (FA: r=-.302, p=.012; r=-.259, p=.032). No further correlations were observed for the rest of white matter tracts.

There was a significant association between age and the fractional anisotropy (FA) values of the different tracts in the expected direction. Specifically, for the healthy controls group age was negatively correlated with FA from the left uncinated fasciculus (r=-.459, p=.002) and the bilateral inferior fronto-occipital fasciculus (IFOF) (left: r=-.389, p=.014; right: r=-.411, p=.01), and in the patients group it correlated negatively with FA from the bilateral IFOF (left: r=-.471, p<.0005; right:

r=-.421, p<.0005). When looking at the entire sample together, age was also negatively correlated with FA from the left uncinated fasciculus (r=-.266, p=.005), the bilateral IFOF (left: r=-.421, p<.0005; right: r=-.410, p<.0005) and the right cortico-spinal tract (r=-.207, p=.037). These findings indicate a measure of reliability of the DTI data, since the inverse association between age and FA values is a highly consistent result in the DTI literature (Pfefferbaum et al. 2000; Pfefferbaum and Sullivan 2003).

Tables

Table S1. The afni_proc.py command used in AFNI (Cox 1996).

```
afni_proc.py                                                                    \
        -subj_id <subjid>                                                       \
        -dsets <absolute path to +orig RS-fMRI BOLD dataset>                    \
        -copy_anat <absolute path to subject-specific MPRAGE T1 dataset>        \
        -do_block despike tshift align tlrc volreg blur mask regress           \
        -anat_has_skull no                                                      \
        -volreg_base_ind 60                                                     \
        -volreg_align_e2a                                                       \
        -volreg_tlrc_warp                                                       \
        -regress_censor_motion 0.3                                              \
        -regress_censor_outliers 0.1                                            \
        -mask_segment_anat yes                                                  \
        -tlrc_base <absolute path to AFNI's MNI_avg152T1+tlrc template>         \
        -blur_size 6                                                            \
        -tcat_remove_first_trs 4                                                \
        -regress_anaticor                                                       \
        -regress_apply_mot_types demean deriv                                   \
        -regress_ROI CSFe                                                       \
        -regress_RSFC                                                           \
        -regress_run_clustsim no                                                \
        -regress_est_blur_errts                                                 \
        -mask_apply group
```

Subject-specific information substituted for arguments in brackets.

The -regress_censor_outliers and -regress_censor_motion arguments were provided to afni_proc.py to generate the desired censor files, for QC purposes. No regression of censored timepoints was actually conducted in the final model.

Table S2. MNI coordinates of the DTI targets.

Target	MNI coordinates (x, y, z)
Left Amygdala	-33, -5, -11
Right Amygdala	33, -5, -11
Left posterior insula	-31, -5, 9
Left angular gyrus	-30, -69, 21
Right angular gyrus	30, -63, 26
Right post-central gyrus	26, -27, 48

MNI Montreal Neurological Institute.

Figures

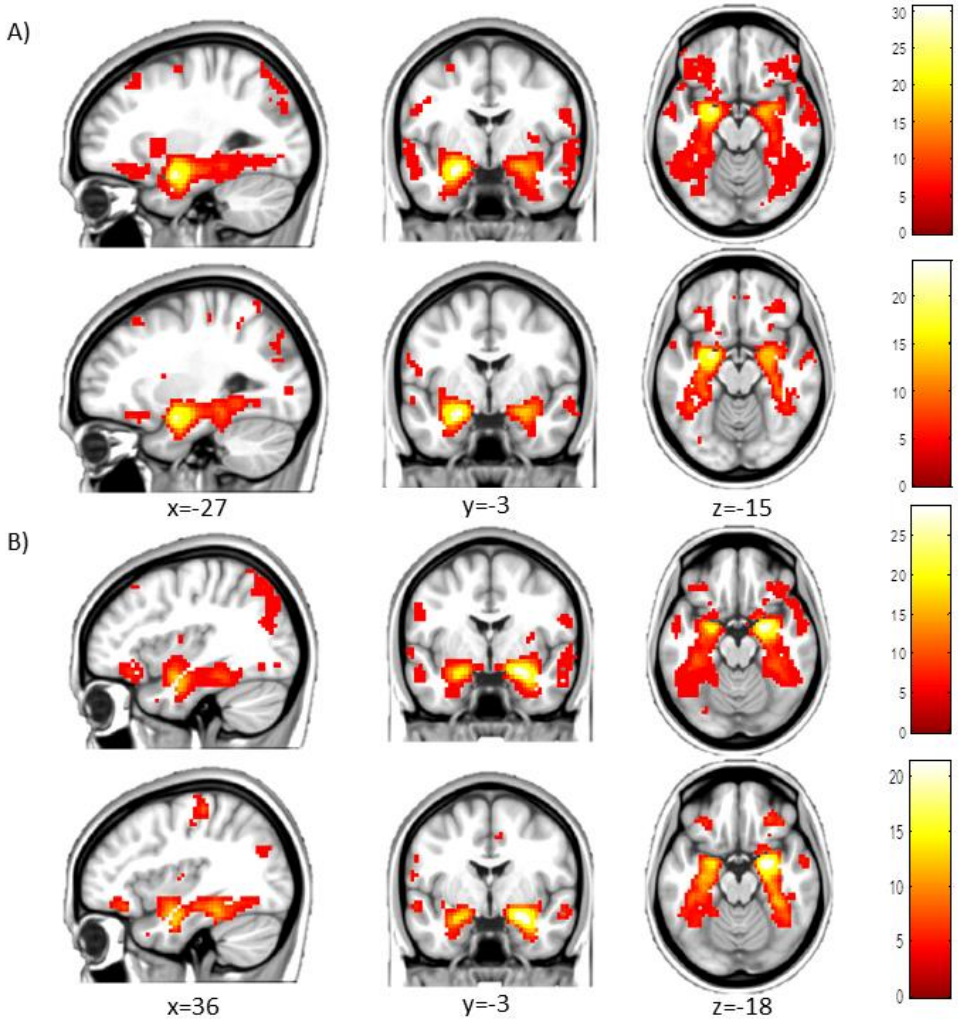

Figure S1. Whole-brain functional connectivity patterns of LA (A) and RA (B) seeds for OCD patients (top row) and for HC (bottom row). The brains are displayed in neurological orientation (left = left). The scale on the right is shaded according to the magnitude of the voxel-wise t-statistics. No statistically significant negative correlations were observed for either group. x, y and z refer to medial-lateral, rostro-caudal and dorso-ventral coordinates in normalized MNI space. Significance threshold was set at p<.05, FWE-corrected.

References

Cabello, Rosario, José M. Salguero, Pablo Fernández-Berrocal, and James J. Gross. 2013. “A Spanish Adaptation of the Emotion Regulation Questionnaire.” *European Journal of Psychological Assessment* 29 (4): 234–40. https://doi.org/10.1027/1015-5759/a000150.

Cox, R W. 1996. “AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages.” *Computers and Biomedical Research* 29 (29): 162–73. https://doi.org/10.1006/cbmr.1996.0014.

First, Michael B., Robert L. Spitzer, Miriam Gibbon, and Janet B. W. Williams. 2002. “Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition. (SCID-I/NP).” In *New York: Biometrics Research*. New York State Psychiatric Institute.

Jo, Hang Joon, Stephen J Gotts, Richard C Reynolds, Peter A Bandettini, Alex Martin, Robert W Cox, and Ziad S Saad. 2013. “Effective Preprocessing Procedures Virtually Eliminate Distance-Dependent Motion Artifacts in Resting State FMRI.” *Journal of Applied Mathematics* 2013 (May). NIH Public Access. https://doi.org/10.1155/2013/935154.

Pfefferbaum, Adolf, and Edith V. Sullivan. 2003. “Increased Brain White Matter Diffusivity in Normal Adult Aging: Relationship to Anisotropy and Partial Voluming.” *Magnetic Resonance in Medicine* 49 (5). Wiley Subscription Services, Inc., A Wiley Company: 953–61. https://doi.org/10.1002/mrm.10452.

Pfefferbaum, Adolf, Edith V. Sullivan, Maj Hedehus, Kelvin O. Lim, Elfar Adalsteinsson, and Michael Moseley. 2000. “Age-Related Decline in Brain White Matter Anisotropy Measured with Spatially Corrected Echo-Planar Diffusion Tensor Imaging.” *Magnetic Resonance in Medicine* 44 (2). John Wiley & Sons, Inc.: 259–68. https://doi.org/10.1002/1522-2594(200008)44:2<259::AID-MRM13>3.0.CO;2-6.

Pierpaoli, C., L. Walker, M. O. Irfanoglu, A. Barnett, P. Basser, L-C. Chang, C. Koay, et al. 2010. “TORTOISE: An Integrated Software Package for Processing of Diffusion MRI Data.” *ISMRM 18th Annual Meeting* Stockholm (Sweden): #1597.

Taylor, Paul A, A Alhamud, Andre van der Kouwe, Muhammad G Saleh, Barbara Laughton, and Ernesta Meintjes. 2016. “Assessing the Performance of Different DTI Motion Correction Strategies in the Presence of EPI Distortion Correction.” *Human Brain Mapping* 37 (12). NIH Public Access: 4405–24. https://doi.org/10.1002/hbm.23318.

“World Medical Association Declaration of Helsinki.” 2013. *JAMA* 310 (20). American Medical Association: 2191. https://doi.org/10.1001/jama.2013.281053.

4.3. Study 3

Steward T*, Picó-Pérez M*, Mata F, Martínez-Zalacaín I, Cano M, Contreras-Rodríguez O, Fernández-Aranda F, Yucel M, Soriano-Mas C, Verdejo-García A (2016). **Emotion regulation and excess weight: impaired affective processing characterized by dysfunctional insula activation and connectivity.** PLoS One 11(3):e0152150. *Shared first Authorship.

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RESEARCH ARTICLE

Emotion Regulation and Excess Weight: Impaired Affective Processing Characterized by Dysfunctional Insula Activation and Connectivity

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Data Availability Statement: Because this study contains confidential information from participants, such as brain images and information from medical and psychological records, unrestricted distribution of the data was not allowed by the Ethics Committee that evaluated our study (approval number CF13/2459 – 2013001307). However, the anonymized data set may be requested by contacting the corresponding author of the article at csoriano@idibell.cat.

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Abstract

Emotion-regulation strategies are understood to influence food intake. This study examined the neurophysiological underpinnings of negative emotion processing and emotion regulation in individuals with excess weight compared to normal-weight controls. Fifteen participants with excess-weight (body mass index >25) and sixteen normal-weight controls (body mass index 18–25) performed an emotion-regulation task during functional magnetic resonance imaging. Participants were exposed to 24 negative affective or neutral pictures that they were instructed to Observe (neutral pictures), Maintain (sustain the emotion elicited by negative pictures) or Regulate (down-regulate the emotion provoked by negative pictures through previously trained reappraisal techniques). When instructed to regulate negative emotions by means of cognitive reappraisal, participants with excess weight displayed persistently heightened activation in the right anterior insula. Decreased responsivity was also found in right anterior insula, the orbitofrontal cortex and cerebellum during negative emotion experience in participants with excess weight. Psycho-physiological interaction analyses showed that excess-weight participants had decreased negative functional coupling between the right anterior insula and the right dlPFC, and the bilateral dmPFC during cognitive reappraisal. Our findings support contentions that excess weight is linked to an abnormal pattern of neural activation and connectivity during the experience and regulation of negative emotions, with the insula playing a key role in these alterations. We posit that ineffective regulation of emotional states contributes to the acquisition and preservation of excess weight.

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Introduction

Worldwide, the number of people with excess weight has increased from 857 million in 1980, to 2.1 billion in 2013 [1]. The increase in incidence of overweight and obesity is particularly high during young adulthood [2] and is of concern given that earlier onset of obesity is associated with poorer recovery and outcomes [3]. Interventions that solely focus on correcting the imbalance between caloric intake and energy expenditure have proved to be ineffective and are frequently characterized by momentary weight loss followed by weight gain once treatment has ended [4], indicating the presence of underlying maintenance factors. To this end, a growing body of evidence has established a robust link between negative affect, coping styles and increased weight [5].

It has been suggested that chronic negative affective states result in the acquisition of maladaptive coping strategies such as the excess intake of appetizing and unhealthy foods to suppress negative emotions [6]. An indirect causality model is supported by evidence showing that individuals with high body mass index (BMI) show a stronger association between chronic stress and weight gain compared to low-BMI individuals who experience stress to a similar extent [7]. In addition, negative moods have been found to potentiate brain response to food [8] by influencing mesolimbic circuitry and reward-seeking behavior [9]. More specifically, imaging studies have linked obesity to a reduction of dopamine striatal D2 receptors [10], and to decreased prefrontal metabolism in the ortbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) [11]. Other research, in a wide range of different populations, has found that dysfunction in these two aforementioned regions results in alterations in salience attribution and inhibitory control, respectively [12,13]. Overall, this suggests that an inability to properly value and manage negative affective states could be a key aspect in the acquisition and maintenance of excess weight as those who are unable to manage negative states might be more vulnerable to becoming stressed and consequently seeking relief in the rewarding properties of highly palatable foods [14]. Furthermore, weight-based discrimination is highly prevalent in society [15] and has been positively associated with negative attitudes towards weight problems and low self-esteem, thus further aggravating negative mood states and encouraging harmful food intake in these populations [16].

To date there is a paucity of studies exploring emotion processing and regulation networks in people with excess weight. However, researchers have found that the neural systems involved in managing emotions and in regulating appetitive responses to palatable foods highly overlap [17,18]. As the presence of stressors and negative emotions are inevitable facets of everyday life, the way one regulates negative affect can shape eating behavior [19]. Emotion regulation refers to the set of distinct, goal-based strategies by which individuals attempt to control how they experience (i.e., the nature, timing and reactivity to) these emotions [20]. Typically, the most studied emotion regulation strategy in brain-imaging studies has been cognitive reappraisal, which involves reinterpreting the meaning of affective stimuli in order to modify their emotional intensity [21]. During reappraisal, prefrontal control systems are understood to modulate activity in affect systems as a function of one's regulatory goals and the nature of emotions being regulated [22]. Specifically, the dorsolateral prefrontal cortex (dlPFC) is known to support the manipulations and cognitive demands of appraisals via working memory whereas the ventrolateral prefrontal cortex (vlPFC) involves the selection and/or inhibition of appraisal resources [23–25]. Furthermore, the dorsomedial prefrontal cortex (dmPFC) assists in monitoring and providing the meaning of changing emotional states while the ventromedial prefrontal cortex (vmPFC) modulates activity in regions linked to emotional responses, such as the amygdala and the insula [26–28].

Reappraisal has been so widely studied due to the fact that its cognitive and physiological costs are lower than other emotion-regulation strategies (e.g. expressive suppression and distraction) and that it is highly effective at regulating affect and physiological arousal [29,30]. Indeed, the use of ineffective or maladaptive emotion-regulation strategies, such as expressive suppression [31], over adaptive strategies like reappraisal has been found to lead to increased food intake [32]. However, no studies to date have explored the neural substrates of emotion regulation by means of cognitive reappraisal in people with excess weight.

In this study, we used functional magnetic resonance imaging (fMRI) to compare the brain substrates of emotion regulation in excess-weight individuals versus normal-weight controls. A modified version of the original cognitive reappraisal task designed by Phan et al. [33] was used to assess emotion regulation. This task [34] has been shown to activate the brain networks involved in the generation of a negative emotional state [21,35–37] (i.e., insula and amygdala), as well as in the employment of cognitive emotion-regulation strategies (i.e., prefrontal cortex) [22,23,38,39]. To further explore the interaction between emotion generation and emotion regulation systems, we also performed a psycho-physiological interaction (PPI) analysis and assessed changes in the connectivity between these two systems across emotion regulation and generation blocks.

On the basis of previous literature [9,22] we hypothesized that excess-weight participants would exhibit heightened reactivity indicated by altered activation in emotion-generation and interoception-related regions when viewing negative stimuli compared to normal-weight controls. Additionally, we expected excess-weight participants to display inefficient down-regulation of negative emotional responses during reappraisal, and that this would coincide with persistently heightened activation in emotion-generation areas and reduced activity in emotion-regulation areas. Moreover, since emotion regulation [40], impulsivity [41], approach/avoidance motivation [42] and food addiction [43] are key trait and state characteristics that contribute to the acquisition and maintenance of excess weight and related affective alterations, and in agreement with theoretical accounts about the associations between these factors [44], we expected to find a complex interaction between behavioral measure results assessing these traits and areas of dysfunctional activation in the excess-weight group. These complex associations were subsequently explored by means of path analysis.

Methods

Participants

Participants were recruited through community notice boards at Monash University, Melbourne, Australia. Potential participants were invited to complete an online survey that assessed their eligibility to participate in a neuroimaging study on emotions and weight. Written and signed informed consent was obtained from all subjects after they were provided with a complete description of the study, which was reviewed and approved by the Monash University Human Research Ethics Committee (approval number CF13/2459–2013001307).

Young adults from both sexes were eligible for the study if they met the following inclusion criteria: (i) aged between 18 and 24; (ii) BMI ranges between 18 and 40 (people with a BMI higher than 40 were excluded from the study due to potential confounding metabolic variables). BMI was calculated from measurements of height and weight obtained using standardized procedures and equipment (Seca 700 Mechanical Column Scale) at the Monash Biomedical Imaging Centre (MBI), and calculated using the following formula: weight (kg)/height (m^2). Participants with a BMI between 18 and 25 were placed in the normal-weight group and participants with a BMI greater than 25 were placed in the excess-weight group. The exclusion criteria were: (i) current comorbid medical conditions associated with excess weight

Table 1. Sample characteristics and behavioral measure results.

	Excess weight	Normal weight	Statistic
	(n = 14)	(n = 14)	*(p-value)*
Age	21.71 ± 1.81	21.21 ± 1.42	**-0.811 (.425)**
Male/female	6/8	6/8	**χ^2 = 0.00 (1)**
Weight (kg)	90.03 ± 15.44	60.79 ± 9.36	**-6.059 (0.000)**
BMI	31.85 ± 4.70	20.94 ± 1.64	**-8.194 (0.000)**
Height (m)	1.68 ± 0.09	1.70 ± 0.09	**0.517 (0.610)**
Education Level*	5.43 ± 0.85	5.07 ± 0.28	**χ^2 = 4.16 (0.125)**
Emotion Regulation Questionnaire (ERQ)**			
Cognitive reappraisal score	22.54 ± 7.49	23.71 ± 5.62	**0.464 (0.188)**
Expressive suppression score	18.77 ± 4.97	21.07 ± 4.25	**1.297 (0.194)**
Barratt Impulsiveness Scale (BIS-11)			
Total score	47.29 ± 11.23	37.79 ± 5.25	**-2.868 (0.008)**
Attentional	16.79 ± 3.64	12.50 ± 2.65	**-3.559 (0.001)**
Motor	20.64 ± 5.108	19.57 ± 3.005	**-0.676 (0.505)**
Non-planning	9.86 ± 4.294	5.71± 3.197	**-2.896 (0.008)**
Yale Food Addiction Scale (YFAS)			
YFAS symptom count	2.71 ± 1.94	1.93 ± 0.99	**-1.349 (0.189)**
The Behavioral Inhibition System and Behavioral Activation System			
Behavioral Inhibition System score	39.14 ± 5.947	38.93 ± 4.938	**-0.104 (0.918)**
Behavioral Activation System score	17.71 ± 2.585	16.71 ± 2.091	**-1.125 (0.271)**

Data are means ±SD;

* 1: No formal education 2: Did not complete high school 3: Completed high school 4: Diploma 5: Undergraduate degree/currently completing 6: Undergraduate degree/completed 7: Postgraduate degree/currently completing 8: Postgraduate completed

** Excess weight n = 13 *statistic* = t-values unless otherwise indicated.

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(e.g., type II diabetes, hypertension); (ii) history of a psychiatric disorder or current psychiatric symptoms (e.g., depression); (iii) history of head trauma or neurological illness involving the central nervous system; and (iv) MRI contraindications (e.g. piercings, etc.).

Fifteen excess-weight participants and sixteen normal-weight controls participated in the study. Results from two participants (one normal-weight control and one excess-weight participant) were excluded due to excessive movement during image acquisition, as were the results from an additional normal-weight participant for failure to carry out the reappraisal task. The final sample thus consisted of 14 excess-weight subjects and 14 normal-weight controls (6 males and 8 females for both groups). Demographic and behavioral data from the study participants are summarized in Table 1.

Procedures

Eligible participants were scheduled for image acquisition after a light meal (breakfast or lunch), between 8 a.m. and 2 p.m., at the Monash Biomedical Imaging facility (MBI). Participants were weighed and measured and briefly interviewed about their medical history to confirm they met inclusion criteria. Participants were given task instructions ahead of the scanner session and trained to decrease the intensity of their emotions through cognitive reappraisal techniques such as distancing and reinterpretation [34]. After the general training on reappraisal techniques, all participants performed a brief rehearsal of maintenance and reappraisal

strategies using trial images. Only after successful rehearsal were the participants entered into the scanner.

fMRI task: cognitive reappraisal task

We used a modified version of the original cognitive reappraisal task designed by Phan et al. [33]. This task has been used to study emotion regulation in different psychiatric populations as well as in healthy controls [21,34]. The task consisted of presenting a series of blocks displaying neutral or negative picture stimuli that participants were instructed to (1) Observe (to passively observe neutral pictures); (2) Maintain (to actively pay attention to 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 means of previously trained cognitive reappraisal techniques). Task instructions and visual stimuli were presented through an MRI-compatible angled mirror system and using Presentation® software (Version 0.70, www.neurobs.com) (see Fig 1).

We used 24 stimuli that were extracted from the International Affective Picture System [45]: eight neutral pictures (e.g. household objects), which were presented in the Observe condition and 16 highly unpleasant, arousing pictures (e.g. mutilations) in the Maintain and Regulate conditions. Specifically, it consisted of 12 blocks: four blocks for each condition. Instructions (Observe, Maintain or Regulate) were pseudo-randomized throughout the task to avoid the induction of sustained mood states. Each block began with the instructive prompt (Observe, Maintain or Regulate) presented in the middle of the screen for 4 seconds. After the prompt, participants viewed two different pictures of equal valence for 10 seconds each. After the presentation of the second picture of each block, the intensity of the negative emotion experienced was self-rated by participants on a 1–5 number scale (1 being 'neutral' and 5 being 'extremely negative'). These in-scanner ratings were recorded through an fMRI-compatible response pad (Lumina–Cedrus Corporation).

Each block was followed by 10 seconds of baseline during which a cross fixation was presented on the screen to minimize carryover effects. Further descriptions of our task procedures have been reported elsewhere [34].

Stimuli. The images were selected according to International Affective Picture System normative values for valence and arousal [45]; mean valence values were 5.79 (0.71), 2.53 (0.69), 2.66 (0.68) and mean arousal values were 4.28 (0.73), 6.44 (0.46) and, 6.40 (0.60) for images included in the Observe, Maintain, and Regulate conditions, respectively. Pairwise

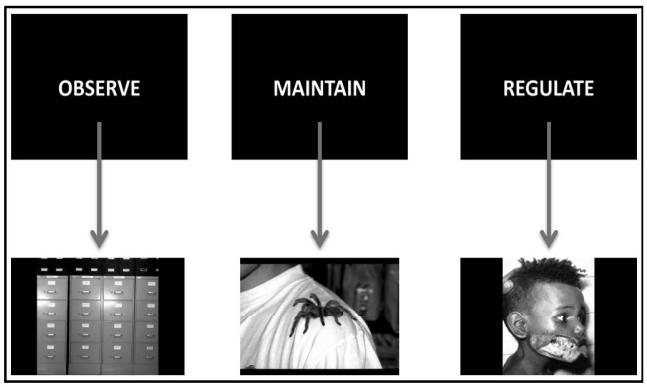

Fig 1. fMRI task. Example images for Observe, Maintain and Regulate conditions.

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comparisons showed that Maintain and Regulate did not differ between them in valence or arousal ($P > 0.7$), whereas both differed from the Observe values in valence and arousal ($P < 0.001$).

Outside-scanner behavioral measures

Further behavioral measures were obtained through the use of different scales in order to characterize emotion regulation ability, food addiction severity, impulsiveness, and inhibition/approach behavior (Table 1). Specifically, participants were administered the Emotion Regulation Questionnaire (ERQ), the Barratt Impulsiveness Scale (BIS-11), the Yale Food Addiction Scale (YFAS) and the Behavioral Inhibition System and Behavioral Activation System scales. Further details about these tasks and their psychometric properties can be found in S1 File.

Image acquisition and preprocessing

We used a 3.0 Tesla Siemens Skyra MRI scanner, equipped with a 32-channel head coil. During acquisition, a $T2^*$-weighted echo-planar imaging (EPI) was obtained [repetition time (TR) = 2000 ms, echo time (TE) = 37 ms, field of view (FOV) = 228 x 228 mm, 76 x 76 matrix, flip angle = 90°, 34 axial slices of 3-mm thickness, 234 scans]. A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (192 slices, TR = 2300 ms, TE = 2.07 ms, flip angle = 9°, FOV = 240 x 225, 1 mm^3 voxels) was also obtained for anatomical reference.

Imaging data were transferred and processed using MATLAB version R2009a (The MathWorks Inc, Natick, MA, USA). Pre-processing was performed using statistical parametric mapping software (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/). Motion correction was performed by aligning (within participant) each time series to the mean image volume using a least-squares minimization and a 6-parameter (rigid body) spatial transformation. Translation and rotation estimates (x, y, z) were required to be less than 2 mm or 2° for each participant respectively. The realigned functional sequences were subsequently coregistered to each participant's anatomical scan, which had been previously coregistered and normalized to the SPM-T1 template. Normalization parameters were then applied to the coregistered functional images, which were then resliced to a 2mm isotropic resolution. Finally, spatial smoothing was carried out by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm).

Statistical Analyses

Behavioral data analyses. We conducted independent-sample t-tests to compare the two groups on relevant variables (Table 1). Interactions between in-scanner ratings for each condition (Observe, Maintain and Regulate) and subject groups were evaluated using a 2x3 repeated-measures ANOVA analysis. Participants' self-reported success in lowering their in-scanner negative emotion intensity was calculated by subtracting the means of participants' Regulate ratings from the means of participants' Maintain ratings. This value is referred to as Success and was compared between groups using an independent-sample t-test. Behavioral data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS; Chicago, IL, USA).

fMRI, main task effects: first-level analyses. Two contrasts of interest were defined at first-level (single-subject) analysis: (1) Maintain/Observe and (2) Regulate/Maintain. The first contrast was carried out to index brain activations associated with negative emotion generation, whereas the second contrast indexed brain activations associated with cognitive reappraisal [21,23,37,39]. Conditions were modeled for the 20 seconds that the images were on the screen and did not include instruction and rating periods. The BOLD response at each voxel

was convolved with the SPM8 canonical hemodynamic response function using a 128-s high-pass filter.

fMRI, main task effects: second-level analyses. Between-group comparisons were conducted with two-sample t-tests using group (normal-weight vs. excess-weight) as the main factor. Keeping in mind our previously stated hypothesis regarding specific regions involved in the generation and processing of negative emotions, analyses were conducted utilizing a bilateral amygdala and insula mask for the Maintain/Observe comparison. This restriction of search regions was designed with the WFU_PICKAtlas [46].

A bilateral prefrontal region mask was created for the Regulate/Maintain contrast as this region has been implicated in the employment of reappraisal strategies [22,38]. Analyses were also conducted for this contrast using the emotion-generation mask in order to compare to what degree participants were able to shift from one task (Maintain) to another (Regulate). Additional analyses were carried out using masks generated by extracting and conjoining areas from one-sample (excess-weight and normal-weight) activations for each contrast.

Peak activations derived from the two main fMRI contrasts were extracted and entered into an SPSS data matrix to assess their relationship with behavioral measures and perform path analyses.

Psychophysiological interactions analysis. In order to explore the task-induced connectivity between the brain regions activated during the fMRI task, we conducted a psychophysiological interactions (PPI) analysis using SPM8 [47]. Here, we explored the impact of the two contrasts of interest (the 'psychological' factor) on the strength of time-course correlations between our empirically obtained ROI with all the other regions of the brain (the 'physiological' factor). To perform the first-level analysis (subject-level), the ROI was drawn from the set of regions showing group differences in the two contrasts from task activation analyses (Maintain/Observe and Regulate/Maintain). Since there was only one region showing group differences in both contrasts (the right anterior insula), we chose this area as our ROI. Each seed was defined as 5-mm radial spheres using MarsBaR region-of-interest toolbox [48] in MNI stereotaxic space with the coordinates derived from the peak maxima in each contrast: x = 42, y = 10, z = -12 in the case of Maintain/Observe, and x = 38, y = 18, z = -16 in the case of Regulate/Maintain.

Functional connectivity maps were estimated for the selected seed of each contrast by including our signal of interest (seed) together with the nuisance signals (CSF, white matter and global brain signal) as predictors of interest or no interest, respectively, in whole-brain linear regression analyses. A high-pass filter set at 128 seconds was used to remove low-frequency drifts of less than approximately 0.008 Hz. Contrast images were generated for each subject by estimating the regression coefficient between the seed time series and each brain voxel signal. Resulting images were then included in a two-sample t-test model for each of the contrasts (second-level) to assess for between-group effects.

Significance thresholding. In SPSS analyses significance threshold was set at $p<0.05$. In all SPM analyses (including PPI) statistical significance was determined by a combination of voxel-level and cluster-extent thresholds, using the AlphaSim algorithm as implemented in the SPM REST toolbox (http://resting-fmri.sourceforge.net/) [49]. The minimum spatial cluster extent (KE) to satisfy a family-wise error (FWE) rate correction of $pFWE < .05$ varied over the different contrasts. Input parameters to AlphaSim included a voxel-level probability of $p<0.01$, a rmm of 5, a FWHM corresponding to the actual smoothing of the data after model estimation, and a mask volume that depended on the mask being applied (ranging from 6417 to 20225 voxels for task activation analyses, and consisting on a whole-brain mask of 140825 voxels for the PPI analysis). As a result, for task activation analyses we obtained cluster-extent

thresholds ranging from 44 to 158 voxels, while for the PPI analysis the thresholds were of 361 (Maintain/Observe) and 545 (Regulate/Maintain) voxels in order to satisfy a pFWE < .05.

Emotion processing and reappraisal model

We used Pearson correlations to check whether complex relationships existed between BMI, fMRI task activation results and behavioral variables, as a preliminary step before conducting path analysis. Path analysis was carried out with maximum likelihood estimation to test both the direct and indirect predictive effect of participant BMI on these variables. This method is further explained in S1 File.

Results

Behavioral results

In-scanner behavioral measures. Interactions between in-scanner negative emotion intensity ratings for each condition (Observe, Maintain and Regulate) and subject groups were evaluated using a 2x3 repeated-measures ANOVA analysis. A main effect of condition was found ($F(2,52) = 165.65$, $p<0.001$) and planned comparisons showed that Maintain differed from Observe, indicating successful negative emotion induction during this condition for both groups (Maintain>Observe: $F(1,26) = 319.68$, $p<0.001$). Moreover, planned comparisons contrasting Regulate and Maintain also showed differences between the two conditions (Maintain>Regulate $F(1,26) = 56.97$, $p<0.001$) indicating successful emotion regulation. No main effect of group was found ($F(1,26) = 0.234$, $p>0.05$). Finally, there was an interaction effect between condition and group ($F(2,52) = 4.599$, $p = 0.014$). We performed independent-sample t-tests to further interpret this interaction, and these showed no differences between the groups in Observe or Regulate ratings ($p>0.05$ in all cases). Interestingly, ratings for normal-weight subjects during Maintain were significantly higher than for excess-weight subjects ($p = 0.043$) (Table 2, Fig 2).

Using Success values, independent-sample t-tests showed that normal-weight subjects more effectively lowered their reported negative emotion intensity rating during Regulate compared to their excess-weight counterparts ($p = 0.012$).

Outside-scanner behavioral measures. Total Barratt Impulsiveness Scale (BIS-11) scores were higher for excess-weight subjects compared to normal-weight controls ($p = 0.008$), indicating higher levels of impulsive behavior in the former. Additional examination found that excess-weight scores in BIS-11 Attentional and Non-planning 2nd order factors were greater than those of normal-weight (Table 1).

Table 2. In-scanner Negative Emotion Ratings.

In-scanner Negative	Excess weight	Normal weight	*t*
Emotion Ratings	(n = 14)	(n = 14)	*(p-value)*
Observe	1.17 ± 0.32	1.07 ± 0.18	**-1.098 (0.115)**
Maintain	3.09 ± 0.67	3.57 ± 0.52	**2.124 (0.043)**
Regulate	2.48 ± 0.71	2.29 ± 0.49	**-0.942 (0.355)**
Success	0.60 ± 0.64	1.29 ± 0.69	**2.70 (0.012)**

Data are means ±SD, 1–5 number scale (1 being "neutral" and 5 being "extremely negative").

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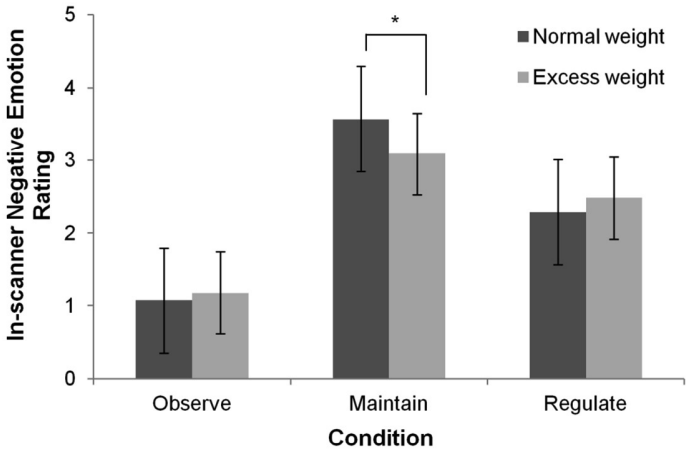

Fig 2. In-Scanner Negative Emotion Intensity Ratings. Mean (95% Confidence Interval) in-scanner negative emotion ratings elicited during each condition (Observe, Maintain and Regulate) (n = 28) *p<0.05.

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fMRI task activations

Results regarding the common activations from both groups for the two main contrasts are provided in S1 File.

Maintain/Observe. A direct between-groups comparison utilizing an emotion-generation mask showed that normal-weight subjects had increased activation in the right insula compared to excess-weight subjects. Comparisons using a mask generated by extracting and combining areas from one-sample activations also found greater activation in the left OFC and the bilateral cerebellar vermis in normal-weight subjects than in excess-weight subjects (Table 3, Fig 3a and 3b).

Regulate/Maintain. No between-group differences using the emotion-regulation mask passed significance threshold. However, a direct between-groups comparison using the emotion-generation mask showed that excess-weight subjects had greater activation in the right anterior insula compared to normal-weight controls (Table 3, Fig 3c).

Table 3. Neuroimaging Results.

			MNI				
	Region	**Side**	**(x)**	**(y)**	**(z)**	**k***	***t***
Maintain>Observe							
(Normal weight>Excess weight)							
With Emotion-Generation Mask	Anterior Insula	R	42	10	-14	242	3.95
With One-Sample Mask	Cerebellar Vermis	L/R	-2	-42	-8	1084	3.66
			4	-48	-8		3.50
	Orbitofrontal Cortex	L	-34	34	-10	174	3.58
Regulate>Maintain							
(Excess weight>Normal weight)							
With Emotion- Generation Mask	Anterior Insula	R	38	18	-16	50	4.34

Regions showing significant activations during Maintain/Observe for the normal-weight group more than the excess-weight group; and regions showing significant activations during Regulate/Maintain in excess-weight>normal-weight. An emotion-generation mask including the amygdala and the insula and a mask created including one-sample activated areas from both groups were used

* Cluster extent in voxels.

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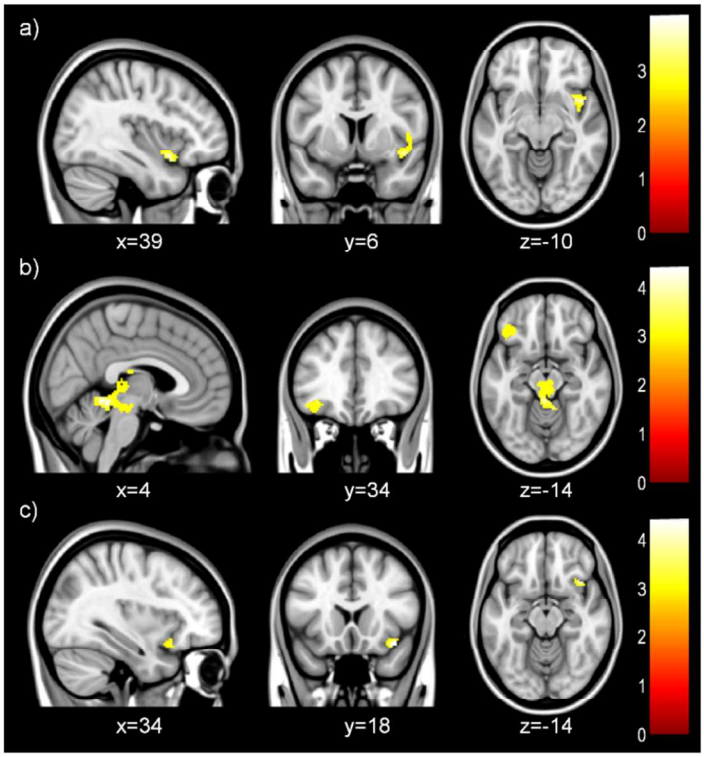

Fig 3. Neuroimaging Results. Between-group differences during negative emotion maintenance (Maintain/Observe) in normal-weight versus excess-weight participants. An emotion generation mask (a) and a mask consisting of combined one-sample results (b) were used. Between-group differences during negative emotion reappraisal (Regulate/Maintain) in excess-weight versus normal-weight participants (c). An emotion generation mask consisting of the amygdala and insula was used.

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PPI Analyses

Seed selection. Task-induced functional connectivity analyses were performed to explore whether specific regions showing significant between-group differences in the main task contrasts were abnormally connected with other regions of the brain. Among the clusters showing significant between-group differences, we selected the right insula, which showed greater activation in normal-weight versus excess-weight participants during Maintain/Observe, and greater activation in excess-weight versus normal-weight subjects during Regulate/Maintain (see Table 3 and Fig 3).

Group differences in Maintain/Observe. No significant between-group differences were found for this contrast.

Group differences in Regulate/Maintain. In normal-weight participants, as compared to those with excess-weight, the right insula seed showed significantly increased negative functional coupling with the right dlPFC, and the bilateral dmPFC (Table 4, Fig 4).

Emotion processing and reappraisal model

Significant correlations between BMI, right insula activations during Maintain/Observe and Regulate/Maintain, BIS-11 2nd Order Attentional scores, and in-scanner Maintain and Success ratings suggested the existence of complex pathways between them and were further tested with path analysis. The whole set of correlations used for the path analysis can be found in S1 File.

Table 4. PPI Results.

			MNI				
	Region	**Side**	**(x)**	**(y)**	**(z)**	**k***	***t***
Regulate>Maintain (Normal weight<Excess weight)							
	dlPFC	R	36	44	34	882	**5.18**
	dmPFC	L	-20	-12	42	1416	**4.73**
	dmPFC	R	28	-6	46	1031	**3.82**

Regions showing a significant anticorrelation with the right insula seed during Regulate/Maintain in the normal-weight group compared to the excess-weight group at the whole-brain level

* Cluster extent in voxels.

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Different models were tested (see S1 File) and the final model obtained is summarized in Fig 5, and was considered to best represent the observed relationships between the variables. This model provided good fit and all direct effects were highly significant. Specifically, increased BMI was directly associated with decreased right insula activity during Maintain/Observe and with heightened right insula activity during Regulate/Maintain. Accordingly, increased right insula activity during Maintain/Observe was found to directly predict lower BIS-11 2nd Order Attentional scores, and these in turn predicted higher in-scanner negative emotion ratings during Maintain. Subsequently, higher in-scanner Maintain ratings directly predicted greater Success scores. Finally, increased Regulate/Maintain insula activity was associated with lower Success ratings.

The exploration of the squared multiple correlations showed that Model 3 accounted for 26% of the variance of right insula activation during Maintain/Observe, 47% of right insula activation during Regulate/Maintain, 21% of BIS-11 2nd Order Attentional scores and 19% and 57% of in-scanner Maintain negative emotion ratings and Success, respectively.

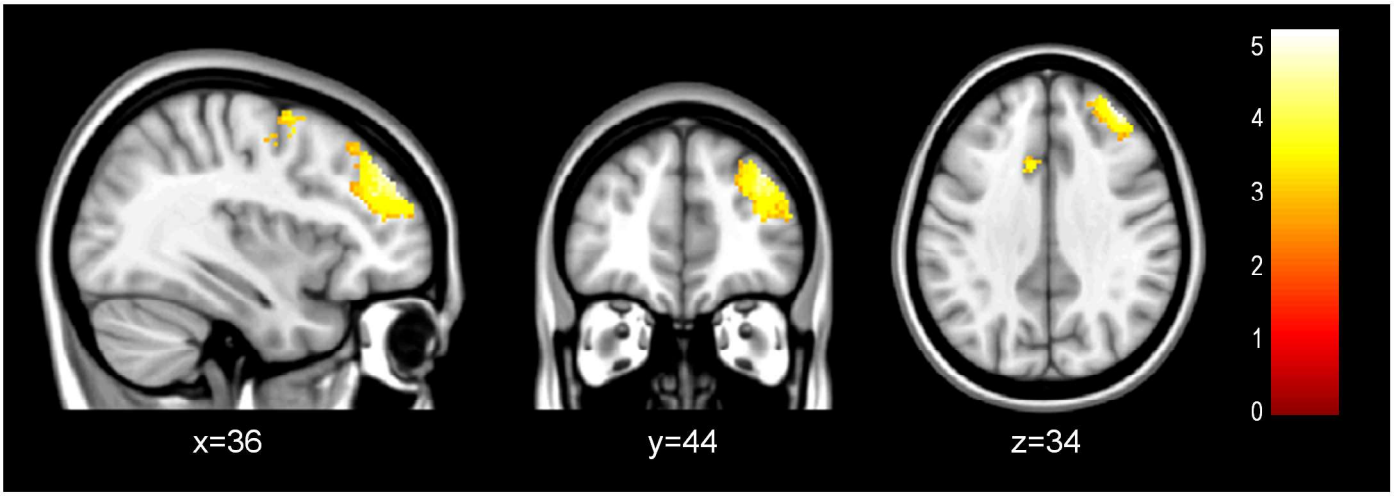

Fig 4. PPI Results. Regions showing different patterns of connectivity with the right insula seed between normal-weight individuals compared to excess-weight participants during reappraisal (Regulate>Maintain), with normal-weight subjects presenting a significant anticorrelation between the right insula and the PFC regions shown.

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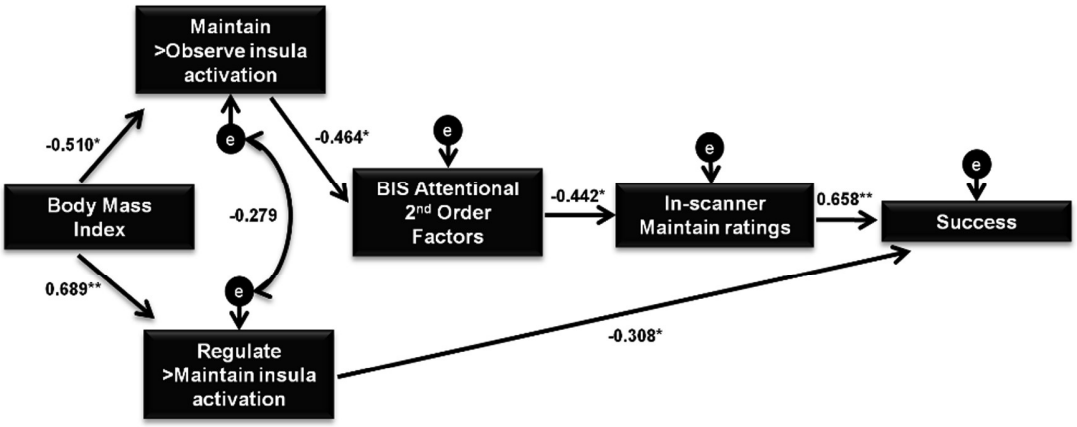

Fig 5. Final Path Analysis Model. Model 3 was the best representation of the observed relationship between variables and examined the complex associations between Body Mass Index (BMI), neuroimaging results and behavioral data. BIS-11 = Barratt Impulsiveness Scale; Standardized regression weights for direct effects are shown *p<0.05 **p<0.001.

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Further information regarding model fitting of path analysis and the indirect associations of the final model can be found in S1 File.

Discussion

In this study, we aimed to compare the neural substrates of negative emotion processing and emotion regulation in people with excess weight using fMRI. Our main finding showed that excess-weight subjects displayed decreased insula activation when experiencing negative emotions and increased activation when instructed to regulate these emotions using cognitive reappraisal. This is in keeping with our hypothesis that participants with excess weight would display persistently heightened activation in emotion-generation brain regions during reappraisal. Contrary to our original hypothesis, participants with excess weight did not show hyperactivation in the insula and amygdala during negative emotion experience nor did we find hypoactivation in prefrontal regions during reappraisal. Notwithstanding, PPI connectivity analyses found that excess-weight participants had reduced negative connectivity between the right anterior insula and prefrontal regions during cognitive reappraisal compared to normal-weight controls. Decreased activation in the OFC and cerebellum during negative emotion experience was also found in excess-weight subjects.

The somatic marker hypothesis (SMH) argues for a mechanism by which emotional processes can steer (or bias) behavior via physiological markers [50]. The key idea of this hypothesis is that somatic marker signals influence the higher-order processing of affective stimuli and choices, at multiple levels of operation, some of which occur overtly (consciously) and some of which occur covertly (non-consciously). This theory uploads that "cognitive operations, regardless of their content, depend on support processes such as attention, working memory and emotion" and that body states serve as a form of dispositional knowledge to guide reasoning and decision making [51]. Our results suggest that excess weight may be linked to a decreased ability to allocate attentional resources to engage physiological "feedback/warning" markers when facing negative-emotion-inducing stimuli [52]. This conclusion is supported by the findings of our path analysis, which found that increased BMI was directly associated with decreased right insula activity during the Maintain-Observe contrast and that this decrease in right insula activation predicted poor attentional impulsiveness performance on the BIS-11

and lower in-scanner negative emotion ratings. The insula is ascribed to a vast number of functional properties, including gustatory processing [53], and serves as a crossroads for integrating homeostatic feedback with expected outcomes [54]. By acting as a "preferential clearinghouse" for such interoceptive markers, disrupted insula activation in excess-weight participants could lead to an adverse physiological state that adjusts the tendency to direct focal attentional resources in one direction over another. This is in line with the findings of our previous studies showing that excess weight is associated with insula dysfunctions relevant to the perception of interoceptive signals [55] and the anticipation of risky choices [56].

When instructed to use emotion regulation, our study found that excess weight subjects did not lower right anterior insula activity to the same extent as normal-weight control subjects. The anterior insula is known to be involved in the secondary processing of emotional experience through the integration of interoceptive signals with external context [28,54], a key aspect of successful cognitive reappraisal [38]. This is suggestive of the notion that excess-weight participants may be less able to engage the optimal brain circuitry needed to exert effective down-regulation of emotion-generation regions as high BMI correlated with increased activity in the right anterior insula during emotion regulation and consequently predicted poorer reappraisal performance. This correlation dovetails with another study using real-time fMRI (rtfMRI) which found that participants with an increased BOLD signal in the insula rated aversive pictures more negatively compared to those having a decreased signal [57]. Moreover, our PPI analyses found reduced negative connectivity between the right anterior insula and the dlPFC and the dmPFC in participants with excess weight during Regulate/Maintain. The dmPFC and the dlPFC are ascribed to the monitoring of emotional states and the use of working memory to model appraisals, respectively [23,24]. This finding indicates that excess-weight participants may be unable to exert effective regulation of emotional responses via prefrontal regions when facing negative stimuli.

We also found that excess-weight subjects had decreased activation in the OFC when experiencing negative emotions compared to normal-weight subjects. The OFC is critically involved in the evaluation of affective feedback and related cognitive control functions, such as value-based decision-making [58]. Decreased OFC activation in this group when experiencing emotions could be indicative of abnormal evaluation of negative stimuli and hence could hamper efforts to restrain unhealthy food choices [9]. Likewise, excess-weight participants displayed lower bilateral cerebellar vermis activation during the Maintain-Observe contrast compared to normal-weight controls. fMRI evidence suggests that the cerebellar vermis serves as a node in the corticolimbic network and is involved in detecting, integrating and filtering emotional information [59]. As patients with lesions to this specific area of the cerebellum exhibit a flattening of affect, excess-weight participants' deceased activation of this region when exposed to negative images could be responsible for their diminished in-scanner behavioral response during Maintain.

There are several limitations to the present study. Firstly our sample size was rather modest and all data were collected from young, college-educated individuals. Future studies should aim to include participants from a wider range of different ages and social backgrounds. Secondly, our study failed to find differences in neural activation in prefrontal regions either within or between groups, at difference with previous studies [22,38], though we did find differences regarding task-induced prefronto-limbic connectivity. We propose that this discrepancy is related to the fact that prefrontal regions continue to undergo development far into young adulthood [60], and thus it is possible that this sample of young adults did not utilize frontal control over subcortical regions in the same way a more heterogeneous, older sample would have [61]. Gaining a better understanding of prefrontal development is of importance as other studies have found that adolescents display hypo-responsivity of inhibitory regions while

anticipating intake of sugary drinks [62]. Finally, possible differentiating activation patterns among subjects with binge eating disorder (BED) were not examined. This distinction warrants further research since emotion-regulation deficits are a widely used explanation for the development and maintenance of BED [63].

Taken together, these results demonstrate for the first time the differential patterns of brain activation during emotion generation and regulation in individuals with excess weight: these patterns are suggestive of poorer perception of interoceptive signals when experiencing emotions and less effective down-regulation of the emotion-generation network during reappraisal. This study adds neurobiological support to the abundance of evidence demonstrating that difficulties in emotion regulation influence eating and lead to increased food intake [32,63]. Our results reinforce the pertinence of developing novel treatment interventions aimed at improving emotion regulation strategies, impulsiveness and focal attention in individuals with excess weight or at risk of becoming overweight [64,65].

Supporting Information

S1 File. Supporting Information.
(DOCX)

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Author Contributions

Conceived and designed the experiments: CSM AVG. Performed the experiments: FM. Analyzed the data: MPP TS IMZ MC CSM OCR. Contributed reagents/materials/analysis tools: MC IMZ OCR. Wrote the paper: CSM FFA MY AVG TS MPP.

References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014; 384: 766–781. doi: 10.1016/S0140-6736(14)60460-8 PMID: 24880830
2. Lowe MR, Annunziato RA, Markowitz JT, Didie E, Bellace DL, Riddell L, et al. Multiple types of dieting prospectively predict weight gain during the freshman year of college. Appetite. 2006; 47: 83–90. doi: 10.1016/j.appet.2006.03.160 PMID: 16650913
3. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. Int J Obes. Nature Publishing Group; 2011; 35: 891–898. doi: 10.1038/ijo.2010.222
4. Mark AL. Dietary Therapy for Obesity Is a Failure and Pharmacotherapy Is the Future: a Point of View. Clin Exp Pharmacol Physiol. 2006; 33: 857–862. doi: 10.1111/j.1440-1681.2006.04454.x PMID: 16922821
5. Roberts C, Connan F, Treasure J, Troop N, Campbell IC. The effects of stress on body weight: biological and psychological predictors of change in body mass index (BMI) in a non-clinical female population. Obes Res. 2007; 15: 3045–3056.
6. Hemmingsson E. A new model of the role of psychological and emotional distress in promoting obesity: conceptual review with implications for treatment and prevention. Obes Rev. 2014; 15: 769–779. doi: 10.1111/obr.12197 PMID: 24931366
7. Block JP, He Y, Zaslavsky AM, Ding L, Ayanian JZ. Psychosocial Stress and Change in Weight Among US Adults. Am J Epidemiol. 2009; 170: 181–192. doi: 10.1093/aje/kwp104 PMID: 19465744
8. Rudenga KJ, Sinha R, Small DM. Acute stress potentiates brain response to milkshake as a function of body weight and chronic stress. Int J Obes. Nature Publishing Group; 2013; 37: 309–316. doi: 10.1038/ijo.2012.39

9. Volkow ND, Wang G-J, Tomasi D, Baler RD. Obesity and addiction: neurobiological overlaps. Obes Rev. 2013; 14: 2–18. doi: 10.1111/j.1467-789X.2012.01031.x PMID: 23016694
10. De Weijer BA, van de Giessen E, van Amelsvoort TA, Boot E, Braak B, Janssen IM, et al. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. EJNMMI Res. 2011; 1: 37. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3265412&tool=pmcentrez&rendertype=abstract doi: 10.1186/2191-219X-1-37 PMID: 22214469
11. Volkow ND, Wang G-J, Telang F, Fowler JS, Thanos PK, Logan J, et al. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. Neuroimage. 2008; 42: 1537–43. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2659013&tool=pmcentrez&rendertype=abstract doi: 10.1016/j.neuroimage.2008.06.002 PMID: 18598772
12. Grabenhorst F, Rolls ET, Bilderbeck A. How cognition modulates affective responses to taste and flavor: top-down influences on the orbitofrontal and pregenual cingulate cortices. Cereb Cortex. 2008; 18: 1549–59. Available: http://www.ncbi.nlm.nih.gov/pubmed/18056086 PMID: 18056086
13. Potegal M. Temporal and frontal lobe initiation and regulation of the top-down escalation of anger and aggression. Behav Brain Res. 2012; 231: 386–95. Available: http://www.ncbi.nlm.nih.gov/pubmed/22085875 doi: 10.1016/j.bbr.2011.10.049 PMID: 22085875
14. Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav. 2005; 86: 773–95. Available: http://www.ncbi.nlm.nih.gov/pubmed/16289609 PMID: 16289609
15. Durso LE, Latner JD. Understanding self-directed stigma: development of the weight bias internalization scale. Obesity (Silver Spring). 2008; 16 Suppl 2: S80–6. Available: http://www.ncbi.nlm.nih.gov/pubmed/18978768
16. Friedman KE, Reichmann SK, Costanzo PR, Zelli A, Ashmore JA, Musante GJ. Weight stigmatization and ideological beliefs: relation to psychological functioning in obese adults. Obes Res. 2005; 13: 907–16. Available: http://www.ncbi.nlm.nih.gov/pubmed/15919845 PMID: 15919845
17. Yokum S, Stice E. Cognitive regulation of food craving: effects of three cognitive reappraisal strategies on neural response to palatable foods. Int J Obes (Lond). 2013; 37: 1565–70. doi: 10.1038/ijo.2013.39
18. Siep N, Roefs A, Roebroeck A, Havermans R, Bonte M, Jansen A. Fighting food temptations: the modulating effects of short-term cognitive reappraisal, suppression and up-regulation on mesocorticolimbic activity related to appetitive motivation. Neuroimage. 2012; 60: 213–20. Available: http://www.ncbi.nlm.nih.gov/pubmed/22230946 doi: 10.1016/j.neuroimage.2011.12.067 PMID: 22230946
19. Raspopow K, Matheson K, Abizaid A, Anisman H. Unsupportive social interactions influence emotional eating behaviors. The role of coping styles as mediators. Appetite. Elsevier Ltd; 2013; 62: 143–149. doi: 10.1016/j.appet.2012.11.031
20. Gross JJ. The emerging field of emotion regulation: An integrative review. Rev Gen Psychol. 1998; 2: 271–299. doi: 10.1037/1089-2680.2.3.271
21. Ochsner KN, Bunge SA, Gross JJ, Gabrieli JDE. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J Cogn Neurosci. 2002; 14: 1215–29. doi: 10.1162/089892902760807212 PMID: 12495527
22. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci. 2012; 1251: E1–E24. doi: 10.1111/j.1749-6632.2012.06751.x PMID: 23025352
23. Buhle JT, Silvers JA, Wager TD, Lopez R, Onyemekwu C, Kober H, et al. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb Cortex. 2014; 24: 2981–90. doi: 10.1093/cercor/bht154 PMID: 23765157
24. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. Neuron. 2008; 59: 1037–50. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2742320&tool=pmcentrez&rendertype=abstract doi: 10.1016/j.neuron.2008.09.006 PMID: 18817740
25. Golkar A, Lonsdorf TB, Olsson A, Lindstrom KM, Berrebi J, Fransson P, et al. Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. PLoS One. 2012; doi: 10.1371/journal.pone.0048107
26. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci. 2006; 7: 268–77. Available: http://www.ncbi.nlm.nih.gov/pubmed/16552413 PMID: 16552413
27. Ochsner KN, Ray RR, Hughes B, McRae K, Cooper JC, Weber J, et al. Bottom-up and top-down processes in emotion generation: common and distinct neural mechanisms. Psychol Sci. 2009; 20: 1322–31. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2858766&tool=pmcentrez&rendertype=abstract doi: 10.1111/j.1467-9280.2009.02459.x PMID: 19883494

28. Zaki J, Davis JI, Ochsner KN. Overlapping activity in anterior insula during interoception and emotional experience. Neuroimage. 2012; 62: 493–9. Available: http://www.ncbi.nlm.nih.gov/pubmed/22587900 doi: 10.1016/j.neuroimage.2012.05.012 PMID: 22587900

29. Gross JJ. Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. J Pers Soc Psychol. 1998; 74: 224–37. Available: http://www.ncbi.nlm.nih.gov/pubmed/9457784 PMID: 9457784

30. Yuan J, Long Q, Ding N, Lou Y, Liu Y, Yang J. Suppression dampens unpleasant emotion faster than reappraisal: Neural dynamics in a Chinese sample. Sci China Life Sci. 2015; 58: 480–91. Available: http://www.ncbi.nlm.nih.gov/pubmed/25316046 doi: 10.1007/s11427-014-4739-6 PMID: 25316046

31. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol. 2003; 85: 348–362. doi: 10.1037/0022-3514.85.2.348 PMID: 12916575

32. Svaldi J, Tuschen-Caffier B, Lackner HK, Zimmermann S, Naumann E. The effects of emotion regulation on the desire to overeat in restrained eaters. Appetite. Elsevier Ltd; 2012; 59: 256–263. doi: 10.1016/j.appet.2012.04.016

33. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. Biol Psychiatry. 2005; 57: 210–219. doi: 10.1016/j.biopsych.2004.10.030 PMID: 15691521

34. Albein-Urios N, Verdejo-Román J, Asensio S, Soriano-Mas C, Martínez-González JM, Verdejo-García A. Re-appraisal of negative emotions in cocaine dependence: dysfunctional corticolimbic activation and connectivity. Addict Biol. 2014; 19: 415–426. doi: 10.1111/j.1369-1600.2012.00497.x PMID: 22978709

35. Goldin PR, McRae K, Ramel W, Gross JJ. The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion. Biol Psychiatry. 2008; 63: 577–86. doi: 10.1016/j.biopsych.2007.05.031 PMID: 17888411

36. Perlman G, Simmons AN, Wu J, Hahn KS, Tapert SF, Max JE, et al. Amygdala Response and Functional Connectivity During Emotion Regulation: A Study of 14 Depressed Adolescents. J Affect Disord. 2012; 29: 997–1003.

37. Diekhof EK, Geier K, Falkai P, Gruber O. Fear is only as deep as the mind allows: a coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. Neuroimage. 2011; 58: 275–85. doi: 10.1016/j.neuroimage.2011.05.073 PMID: 21669291

38. Frank DW, Dewitt M, Hudgens-Haney M, Schaeffer DJ, Ball BH, Schwarz NF, et al. Emotion regulation: Quantitative meta-analysis of functional activation and deactivation. Neurosci Biobehav Rev. Elsevier Ltd; 2014; 45: 202–211. doi: 10.1016/j.neubiorev.2014.06.010

39. Etkin A, Büchel C, Gross JJ. The neural bases of emotion regulation. Nat Rev Neurosci. 2015; 16: 693–700. doi: 10.1038/nrn4044 PMID: 26481098

40. Vandewalle J, Moens E, Braet C. Comprehending emotional eating in obese youngsters: the role of parental rejection and emotion regulation. Int J Obes (Lond). 2014; 38: 525–30. Available: http://www.ncbi.nlm.nih.gov/pubmed/24418843

41. Leehr EJ, Schag K, Brückmann C, Plewnia C, Zipfel S, Nieratschker V, et al. A Putative Association of COMT Val(108/158)Met with Impulsivity in Binge Eating Disorder. Eur Eat Disord Rev. 2015; doi: 10.1002/erv.2421

42. Müller A, Claes L, Wilderjans TF, de Zwaan M. Temperament subtypes in treatment seeking obese individuals: a latent profile analysis. Eur Eat Disord Rev. 2014; 22: 260–6. Available: http://www.ncbi.nlm.nih.gov/pubmed/24809764 doi: 10.1002/erv.2294 PMID: 24809764

43. Meule A, Hermann T, Kübler A. Food addiction in overweight and obese adolescents seeking weight-loss treatment. Eur Eat Disord Rev. 2015; 23: 193–8. Available: http://www.ncbi.nlm.nih.gov/pubmed/25778000 doi: 10.1002/erv.2355 PMID: 25778000

44. Singh M. Mood, food, and obesity. Front Psychol. 2014; 5: 925. doi: 10.3389/fpsyg.2014.00925 PMID: 25225489

45. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS); Instruction manual and effective ratings. The Center for Research in Psychophysiology, University of Florida. Tech Rep. 2001;A–5.

46. Maldjian J, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage. 2003; 19: 1233–1239. doi: 10.1016/S1053-8119(03)00169-1 PMID: 12880848

47. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage. 1997; 6: 218–29. doi: 10.1006/nimg.1997.0291 PMID: 9344826

48. Brett M, Anton JL, Valabregue R, Poline JB. Region of interest analysis using an SPM toolbox. Neuroimage. 2002; 16: 497.

49. Song X-W, Dong Z-Y, Long X-Y, Li S-F, Zuo X-N, Zhu C-Z, et al. REST: A Toolkit for Resting-State Functional Magnetic Resonance Imaging Data Processing. PLoS One. 2011; 6: e25031. doi: 10.1371/journal.pone.0025031 PMID: 21949842

50. Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci. 1996; 351: 1413–20. Available: http://www.ncbi.nlm.nih.gov/pubmed/8941953 PMID: 8941953

51. Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex. 2000; 10: 295–307. doi: 10.1093/cercor/10.3.295 PMID: 10731224

52. Verdejo-García A, Verdejo-Román J, Rio-Valle JS, Lacomba J, Lagos FM, Soriano-Mas C. Dysfunctional involvement of emotion and reward brain regions on social decision making in excess weight adolescents. Hum Brain Mapp. 2015; 36: 226–237. doi: 10.1002/hbm.22625 PMID: 25168709

53. Wagner A, Aizenstein H, Frank GK, Figurski J, May JC, Putnam K, et al. Neural correlates of habituation to taste stimuli in healthy women. Psychiatry Res Neuroimaging. 2006; 147: 57–67. doi: 10.1016/j.pscychresns.2005.11.005 PMID: 16806849

54. Nelson SM, Dosenbach NUF, Cohen AL, Wheeler ME, Schlaggar BL, Petersen SE. Role of the anterior insula in task-level control and focal attention. Brain Struct Funct. 2010; 214: 669–80. doi: 10.1007/s00429-010-0260-2 PMID: 20512372

55. Mata F, Verdejo-Roman J, Soriano-Mas C, Verdejo-Garcia A. Insula tuning towards external eating versus interoceptive input in adolescents with overweight and obesity. Appetite. Elsevier Ltd; 2015; 93: 24–30. doi: 10.1016/j.appet.2015.03.024

56. Delgado-Rico E, Soriano-Mas C, Verdejo-Román J, Río-Valle JS, Verdejo-García A. Decreased insular and increased midbrain activations during decision-making under risk in adolescents with excess weight. Obesity. 2013; 21: 1662–1668. doi: 10.1002/oby.20375 PMID: 23723089

57. Lawrence EJ, Su L, Barker GJ, Medford N, Dalton J, Williams SCR, et al. Self-regulation of the anterior insula: Reinforcement learning using real-time fMRI neurofeedback. Neuroimage. 2014; 88: 113–124. doi: 10.1016/j.neuroimage.2013.10.069

58. Fellows LK. Orbitofrontal contributions to value-based decision making: evidence from humans with frontal lobe damage. Ann N Y Acad Sci. 2011; 1239: 51–58. doi: 10.1111/j.1749-6632.2011.06229.x PMID: 22145875

59. Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, et al. Distinct Cerebellar Contributions to Intrinsic Connectivity Networks. J Neurosci. 2009; 29: 8586–8594. doi: 10.1523/JNEUROSCI.1868-09.2009 PMID: 19571149

60. Vink M, Derks JM, Hoogendam JM, Hillegers M, Kahn RS. Functional differences in emotion processing during adolescence and early adulthood. Neuroimage. Elsevier Inc.; 2014; 91: 70–76. doi: 10.1016/j.neuroimage.2014.01.035

61. McRae K, Gross JJ, Weber J, Robertson ER, Sokol-Hessner P, Ray RD, et al. The development of emotion regulation: An fMRI study of cognitive reappraisal in children, adolescents and young adults. Soc Cogn Affect Neurosci. 2012; 7: 11–22. doi: 10.1093/scan/nsr093 PMID: 22228751

62. Burger KS, Stice E. Neural responsivity during soft drink intake, anticipation, and advertisement exposure in habitually consuming youth. Obesity. 2014; 22: 441–450. doi: 10.1002/oby.20563 PMID: 23836764

63. Leehr EJ, Krohmer K, Schag K, Dresler T, Zipfel S, Giel KE. Emotion regulation model in binge eating disorder and obesity—a systematic review. Neurosci Biobehav Rev. Elsevier Ltd; 2015; 49: 125–134. doi: 10.1016/j.neubiorev.2014.12.008

64. Lavender JM, Green D, Anestis MD, Tull MT, Gratz KL. Negative Affect, Negative Urgency, Thought Suppression, and Bulimic Symptoms: A Moderated Mediation Analysis in a Sample at-Risk for Bulimic Symptoms. Eur Eat Disord Rev. 2015; 23: 246–250. doi: 10.1002/erv.2351 PMID: 25783752

65. Tchanturia K, Doris E, Fleming C. Effectiveness of Cognitive Remediation and Emotion Skills Training (CREST) for Anorexia Nervosa in Group Format: A Naturalistic Pilot Study. Eur Eat Disord Rev. 2014; 22: 200–205. doi: 10.1002/erv.2287 PMID: 24616049

Supporting Information

Emotion regulation and excess weight: impaired affective processing characterized by dysfunctional insula activation

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Methods

Outside-scanner behavioral measures

The Emotion Regulation Questionnaire (ERQ) is designed to assess individual differences in the habitual use of two emotion regulation strategies: cognitive reappraisal and expressive suppression [1]. Cognitive reappraisal is defined as an active, cognitive strategy where situations are reappraised so that their emotional impact is lessened or strengthened, whereas expressive suppression is defined as a response-focused strategy where behavioral reactions or emotional expressions are concealed by means of restraining or inhibiting external facial or bodily signs of emotion. This 10-item questionnaire is commonplace in studies of ER and has presented good psychometric properties. It has demonstrated adequate to good internal consistency and temporal stability [2,3] as well as good convergent and discriminant validity [4].

The Barratt Impulsiveness Scale (BIS-11) [5] is a questionnaire designed to assess the personality/behavioral construct of impulsiveness. It is one of the most widely used instruments for the assessment of impulsiveness and includes 30 items that are scored to yield six first-order factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness). This scale has reported internal consistency coefficients ranging from 0.79 to 0.83 for separate populations of university students, substance-abuse patients, general psychiatric patients, and prison inmates [5].

The Yale Food Addiction Scale (YFAS) is a 25-point questionnaire, based on DSM-IV codes for substance dependence criteria, to assess food addiction in individuals [6]. It has been developed to identify those who are most likely to exhibit markers of substance dependence

with the consumption of high fat/high sugar foods and assesses clinically significant impairment or distress from eating. The YFAS has exhibited adequate internal reliability, and showed good convergent validity with measures of similar constructs and good discriminant validity relative to related but dissimilar constructs [7].

The Behavioral Inhibition System and Behavioral Activation System scales are designed to assess dispositional sensitivity to the behavioral inhibition system and the behavioral activation or behavioral approach system [8]. The Behavioral Activation System is related to motivations to seek out positive experiences and is commonly referred to as approach motivation, whereas the Behavioral Inhibition System is sensitive to signs of fear-inducing stimuli and is commonly referred to as avoidance motivation. This 20-item questionnaire uses a 4-point scale and examines individual differences in the sensitivity of these systems. This questionnaire has displayed satisfactory psychometric properties and all the subscales have been reported to have satisfactory internal consistencies, α's ranging from .66 to .76, and two-month test–retest reliabilities, r's ranging from .59 to .69 [8].

Emotion processing and reappraisal model

Path analysis is a method used to estimate a set of simultaneous regression equations to explore how a group of variables interrelate in complex patterns. Three types of effects can be distinguished: (1) direct effects, which demonstrate the direct association of one variable with another; (2) indirect effects, which indicate the indirect association of one variable with another via other variables in the model; (3) total effects, which estimate the addition of direct and indirect effects. The first step of this process consists of testing an initial just-identified or saturated model in which the number of free parameters equals the number of known values (i.e., a model with zero degrees of freedom). The following steps consist of

performing a trimming of this saturated model by retaining the significant or trend-level significant associations and excluding non-significant paths. [9]

Path analysis was conducted by means of AMOS 18.0 software and the significance of indirect effects was tested using a bootstrapping method [10]. Model fit was assessed using the following indices: i) Chi-square statistic (X2), which acts as a measure of misfit where non-significant values imply a good fit of the model to the data; ii) goodness of fit index (GFI), which indicates the proportion of the variance in the sample variance-covariance matrix that is accounted for by the model (expected to be greater than 0.95); iii) root mean square error of approximation (RMSEA), which estimates the lack of fit compared to the saturated model (where values up to 0.05 indicate a good fit); and iv) comparative fit index (CFI), which compares the fit of the proposed model to a null model where none of the variables are related between each other (with values greater than 0.95 indicating a good fit).

Results

Imaging Results

Common Task Activations

Widespread activations were found in bilateral posterior sensory regions, the thalamus, the insula, the amygdala, the cerebellum and regions of the midbrain and prefrontal cortex (Fig S1a) for both groups during Maintain>Observe.

On the other hand, activations were found in the left precentral gyrus in both groups during Regulate>Maintain (Fig S1b), as well as deactivations in the left posterior insula and the cuneus (Fig S1c).

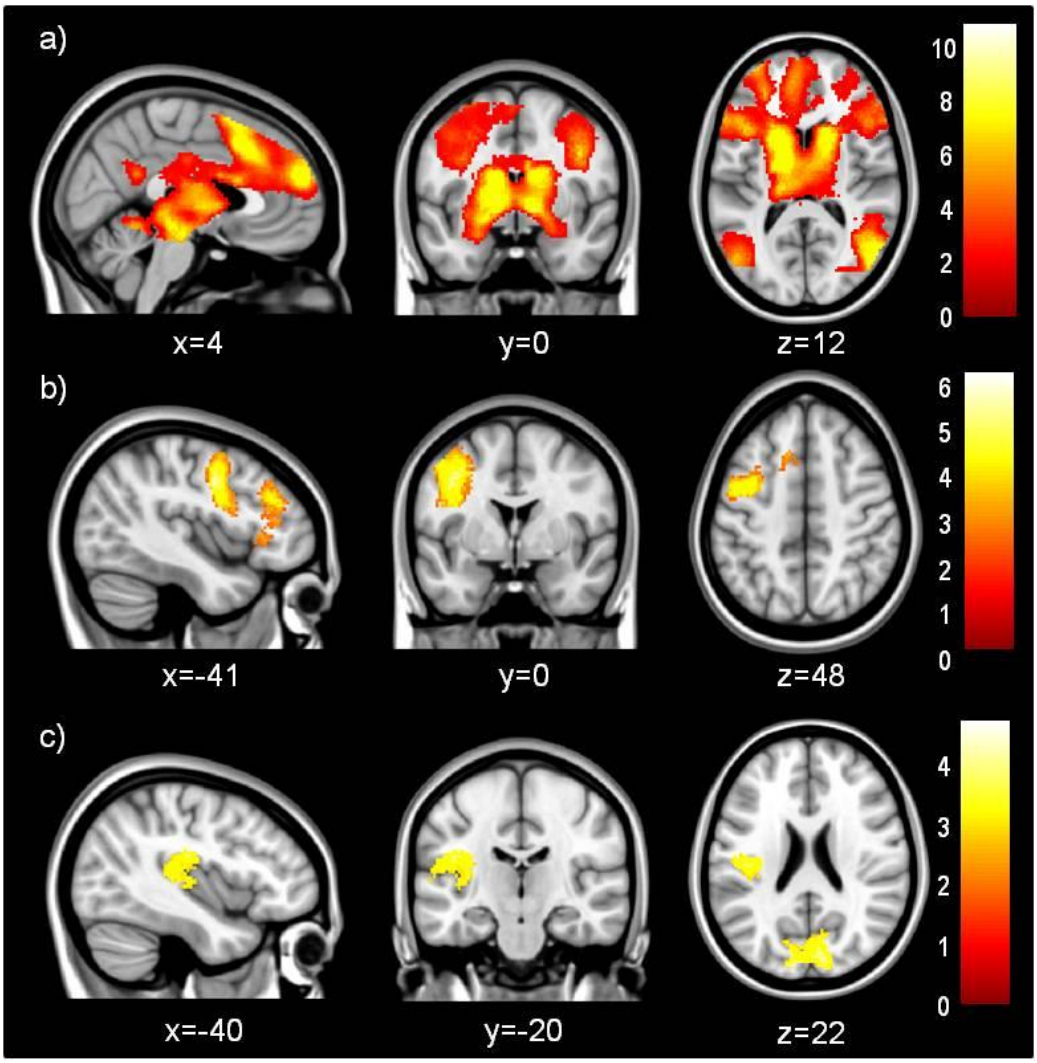

Figure S1. Areas showing increased activation in both normal-weight and excess-weight participants during (a) negative emotion maintenance (Maintain>Observe) and (b) reappraisal (Regulate>Maintain), and (c) areas showing decreased activation during reappraisal (Maintain>Regulate).

Path analysis

In order to not distort path analysis results, data from one participant was excluded due to outlying imaging results during Maintain>Observe.

	BMI	**Maintain >Observe insula activation**	**Regulate >Maintain insula activation**	**BIS-11 Attentional 2nd Order Factor**	**In-scanner Maintain ratings**	**Success**
BMI	1					
Maintain>Observe insula activation	-0.510**	1				
Regulate>Maintain insula activation	0.689**	-0.525**	1			
BIS-11 Attentional 2nd Order Factor	0.408*	-0.464*	0.363	1		
In-scanner Maintain ratings	-0.287	0.143	-0.182	-0.442*	1	
Success	-0.401*	0.340	-0.421*	-0.398*	0.703**	1

Table S1. Pearson's correlations between Body Mass Index (BMI), right insula activations during Maintain>Observe and Regulate>Maintain, Barratt Impulsiveness Scale (BIS-11) Attentional 2nd Order Factor

Model trimming

Model 1 (Fig S2) provided good fit statistics (Table S2) and the direction of the associations was in agreement with BMI having a predictive effect on imaging results and behavioral outcomes. However, a lack of statistical significance of the regression weights that connected BMI, behavioral and imaging results directly with in-scanner reappraisal Success ratings showed that the model was overcomplicated. Therefore, we analyzed a second model (Model 2) that excluded these non-significant associations.

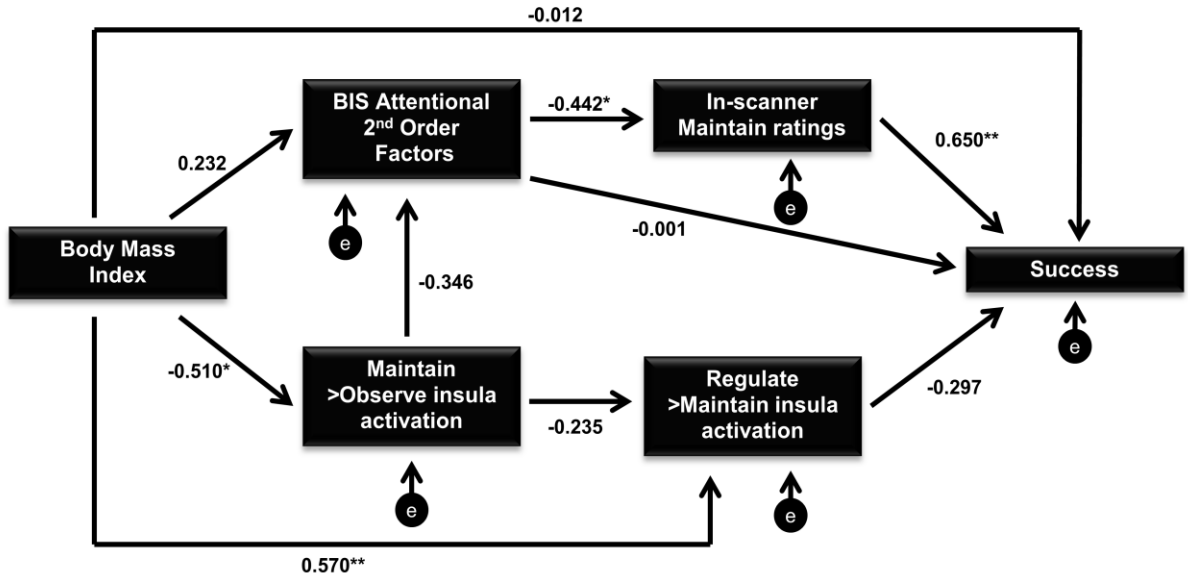

Figure S2. Model 1, which explored all significant correlations between Body Mass Index (BMI), behavioral and imaging variables. Lack of statistical significance of some of the explored effects suggest that the model may be overcomplicated. Standardized regression weights for direct effects are shown *p<0.05 **p<0.001.

Values indicative of good fit	X^2	p value	df	GFI >0.95	RMSEA <0.05	CFI >0.95
Model 1	1.833	.872	5	0.978	0	1
Model 2	3.187	.922	8	0.961	0	1
Model 3	3.187	.922	8	0.961	0	1

Table S2. Model fit indices for tested models: X^2 chi-square statistic, df degrees of freedom, GFI goodness of fit index, RMSEA root mean square error of approximation, CFI comparative fit index.

Model 2 showed an improved fit to the data. Still, the regression weight directly linking the right insula peak for Maintain>Observe and the right insula peak for Regulate>Maintain was non-significant. Consequently, we analyzed a more parsimonious model that excluded this non-significant association.

Indirect associations between variables

The best fitting model, model 3, showed that increased BMI was indirectly associated with higher BIS-11 2nd order Attentional scores (standardized indirect effect = 0.237, p=0.010), decreased in-scanner negative emotion ratings during Maintain (standardized indirect effect = -0.105, p=0.010) and decreased Success scores (standardized indirect effect = -0.281, p=0.026). Increased right insula activation during Maintain>Observe indirectly predicted higher in-scanner negative emotion ratings during Maintain (standardized indirect effect = 0.205, p=0.010) and also indirectly predicted increased Success scores (standardized indirect effect = 0.135, p=0.010). Lastly, higher BIS-11 2nd order Attentional scores showed an indirect, negative effect on Success scores (standardized indirect effect = -0.291, p=0.010).

References

1. Gross JJ, John OP (2003) Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 85: 348–362.
2. Sala M, Molina P, Abler B (2012) Measurement invariance of the Emotion Regulation Questionnaire (ERQ). A cross-national validity study. European Journal of Developmental Psychology 9: 6.
3. Batistoni S, Ordonez T (2013) Emotional Regulation Questionnaire (ERQ): psychometric indicators and affective relations in an elderly sample. Psicol Reflex Crit 26: 10-18.
4. Ioannidis CA, Siegling AB (2015) Criterion and incremental validity of the emotion regulation questionnaire. Front Psychol 6: 247.
5. Patton JH, Stanford MS, Barratt ES (1995) Factor Structure of the Barratt Impulsiveness Scale. Journal of Clinical Psychology 768–774.
6. Gearhardt AN, Corbin WR, Brownell KD (2009) Food Addiction An Examination of the Diagnostic Criteria for Dependence. J Addict Med 3: 42–45.
7. Gearhardt AN, Corbin WR, Brownell KD (2009) Preliminary validation of the Yale Food Addiction Scale. Appetite 52: 430–436.
8. Carver CS, White TL (1994) Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales. J Pers Soc Psychol 67: 319–333.
9. Byrne BM. Structural Equation Modeling with AMOS. 2nd ed. New York: 2010.

10. Shrout PE, Bolger N (2002) Mediation in experimental and nonexperimental studies: new procedures and recommendations. Psychol Methods 7: 422-445.

4.4. Study 4

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Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies

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ABSTRACT

Emotion regulation by means of cognitive reappraisal has been widely studied with functional magnetic resonance imaging (fMRI). To date, several meta-analyses of studies using cognitive reappraisal tasks in healthy volunteers have been carried out, but no meta-analyses have yet been performed on the fMRI data of clinical populations with identified alterations in emotion regulation capacity.

We provide a comprehensive meta-analysis of cognitive reappraisal fMRI studies in populations of patients with mood or anxiety disorders, yielding a pooled sample of 247 patients and 262 controls from thirteen independent studies. As a distinguishing feature of this meta-analysis, original statistical brain maps were obtained from six of these studies.

Our primary results demonstrated that patients with mood and anxiety disorders recruited the regulatory fronto-parietal network involved in cognitive reappraisal to a lesser extent in comparison to healthy controls. Conversely, they presented increased activation in regions that may be associated with the emotional experience (i.e., insula, cerebellum, precentral and inferior occipital gyri) and in regions whose activation may be the consequence of compensatory mechanisms (i.e., supramarginal gyri and superior parietal lobule). Moreover, activations in the left ventrolateral prefrontal cortex and the left superior temporal gyrus were associated with reinterpretation emotion regulation strategies, whereas medial frontal and parietal activations were associated with the deployment of distancing strategies.

The regions revealed by this meta-analysis conform to a pattern of dysfunctional brain activation during cognitive reappraisal common to mood and anxiety disorders. As such, this neural pattern may reflect a transdiagnostic feature of these disorders.

1. Introduction

Throughout our day-to-day lives we are confronted with situations that trigger negative emotions. The unpleasantness of the emotion or contextual factors can lead us to try to change the way we feel. To this end, we draw upon an inherent human capacity: emotion regulation. Emotion regulation has been defined as the processes by which individuals influence their emotions, when they have them, and how they experience and express these emotions (Gross, 1998a). There are several ways to carry out emotion regulation, but not all are equally adaptive. An emotion regulation strategy is considered maladaptive if it is unsuccessful in reducing emotional response or if it is associated with costs that potentially outweigh the short-term benefits brought about by diminishing acute emotions. Conversely, an emotion regulation strategy is considered adaptive if it decreases subjective distress and/or physiological arousal while maintaining one's ability to pursue meaningful short- and long-term goals (Campbell-Sills et al., 2014).

Emotion regulation strategies are classified according to when their

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primary effect appears during the emotion-generative process (Gross, 1998a). Thus, antecedent-focused strategies are those acting before emotional responses have been completely generated, while response-focused strategies are those put into practice after the full development of the emotional response. Overall, antecedent-focused strategies are considered more adaptive than response-focused strategies (Gross, 1998b). An example of an antecedent-focus strategy which has been widely studied is cognitive reappraisal. This strategy has been associated with decreased sympathetic nervous system activity and enhanced cognitive control of emotions, leading to decreased levels of negative affect and higher levels of positive emotions. Successful employment of this strategy subsequently brings about better interpersonal functioning along with physical and psychological well-being (Gross, 1998b; Gross and John, 2003; Webb et al., 2012; Gross, 2014; Hu et al., 2014). Importantly, several studies have shown that many patients with psychiatric disorders have difficulties in using cognitive reappraisal, and it has been suggested that ineffective emotion regulation may represent a transdiagnostic feature of mood and anxiety disorders (Campbell-Sills et al., 2006). Specifically, behavioral studies show a wide range of emotion regulation deficits in these patients, featuring the more frequent use of maladaptive strategies such as expressive suppression or less awareness and acceptance of emotions (Aldao et al., 2010, Cutuli, 2014, Ehring et al., 2008, Görlach et al., 2016). Likewise, neuroimaging studies show structural and functional abnormalities in the prefrontal cortex circuits related with top-down inhibitory control, which is necessary to deploy cognitive reappraisal strategies. This coincides with hyperreactivity in limbic structures implicated in emotion generation (Etkin and Wager, 2007; Phillips et al., 2008; Rive et al., 2013). Moreover, such inefficient use of cognitive reappraisal strategies may have relevant consequences not only for the development and maintenance of mental health alterations, but also for treatment response. Thus, Cognitive Behavioral Therapy (CBT), the most frequently used psychotherapy technique for these disorders (Beck, 2005), is tightly linked to improving cognitive reappraisal abilities (Taylor and Liberzon, 2007). For instance, it has been shown that, after treatment with CBT, patients with social anxiety disorder improve their performance on a cognitive reappraisal task, both at the behavioral and neurobiological level (Goldin et al., 2013).

The neurofunctional correlates of cognitive reappraisal have been widely studied with functional magnetic resonance imaging (fMRI). Emotion regulation paradigms typically expose subjects to stimuli of negative emotional content (e.g., images or videos), and although experiments differ in trial timelines, they generally alternate between task-blocks or trials in which participants are instructed to experience the negative emotions evoked by the images (i.e., maintain condition) with others in which participants are instructed to reduce the intensity of evoked negative emotions via cognitive reappraisal (i.e., reappraise condition) (Ochsner et al., 2002; Phan et al., 2005). Maintain is the most common control condition, and subjects are characteristically instructed to not down-regulate the evoked emotion, similarly to what was reported in Ochsner et al. (2002). Likewise, regarding the reappraise condition, in most studies participants are instructed to use distancing or reinterpretation as reappraisal strategies. The former refers to rationalizing the content of a situation by adopting the perspective of an uninvolved observer (e.g., when viewing a scene depicting a wounded person, presuming that the person is actually an actor). The latter refers to changing the meaning of stimuli in order to view the outcome of a situation in a more positive light (e.g., deciding that an image of weeping people outside a church is actually of a wedding instead of a funeral) (Ochsner et al., 2012; Dörfel et al., 2014).

The results of reviews and meta-analyses on the neurofunctional correlates of cognitive reappraisal in healthy volunteers have been rather homogenous. Regulating negative affective states involves activation of the prefronto-parietal network, and at times, the middle temporal gyrus. These prefronto-parietal activations are accompanied by significant deactivations of the limbic subcortical network (Kalisch, 2009; Diekhof et al., 2011; Ochsner et al., 2012; Buhle et al., 2013; Kohn et al., 2014; Etkin et al., 2015). More specifically, the regions consistently recruited as part of the prefronto-parietal network are the dorsolateral, medial and ventrolateral prefrontal cortices, the dorsal anterior cingulate cortex and the inferior parietal lobule. Notably, these regions have been traditionally associated with cognitive processes such as conflict monitoring, selective attention, working memory, mental state attribution, response selection and inhibition and semantic processing (Pessoa et al., 2003; Wager and Smith, 2003; Botvinick et al., 2004; Thompson-Schill et al., 2005; Aron et al., 2014). All of these processes are believed to be relevant for implementing successful cognitive reappraisal (Ochsner and Gross, 2014). Likewise, down-regulated regions in the limbic network commonly include the amygdala, the ventral striatum and the insula, regions associated with the detection of arousing and potentially threatening stimuli, reward processing and the integration of information about body states, respectively (Craig, 2003; Haber and Knutson, 2010; Morrison and Salzman, 2010).

Although the cognitive reappraisal paradigm has also been extensively used in clinical populations to study the neurobiological correlates of altered emotion regulation capacity, to our knowledge, only one review (Zilverstand et al., 2016) has been conducted to summarize this information and no meta-analysis has been performed to provide a comprehensive description of the neurobiological commonalities underlying emotion regulation deficits across different mental health conditions. The aim of the present study is to identify, by means of a meta-analysis of fMRI studies assessing cognitive reappraisal in samples of patients with mood or anxiety disorders, the neural correlates of impaired emotion regulation. We specifically focused on mood and anxiety as disorders where concurring emotion regulation alterations have been consistently described (Campbell-Sills et al., 2006; Aldao et al., 2010). Our analyses were centered on comparing reappraise and maintain blocks during the presentation of images of negative emotional content in order to identify regions presenting both increased and decreased activation during cognitive reappraisal. Moreover, we explored the differences between reinterpretation and distancing strategies.

We hypothesized that activations in healthy controls (vs. patient group) during reappraise blocks would substantially overlap with previously reported regions in the prefronto-parietal network (Buhle et al., 2013; Diekhof et al., 2011; Kalisch, 2009; Kohn et al., 2014). In the patient group, we expected to find decreased activation of the prefronto-parietal network in combination with an ineffective down-regulation of emotion generation regions (i.e., limbic regions). Likewise, from the sparse literature comparing different reappraisal strategies, we expected distancing to specifically activate parietal regions related to perspective taking and spatial attention, while reinterpretation would be linked to ventral prefrontal regions implicated in response selection and inhibition, along with temporal regions related to linguistic and semantic processing (Ochsner et al., 2012; Dörfel et al., 2014).

2. Methods

2.1. Literature search and study selection

A comprehensive literature search using PubMed and Google Scholar was conducted of English-language, peer-reviewed fMRI studies on cognitive reappraisal in human clinical samples published until December 2016. The search terms were: 'fMRI', 'reappraisal' or 'cognitive reappraisal', 'clinical sample' or 'anxiety' or 'depression' and their combinations. In addition, manual searches were conducted within review articles and via the reference lists of individual studies. If any studies contained participant group overlap, only the first reported study was included. If not originally reported, the corresponding authors of the identified studies were asked to provide additional details

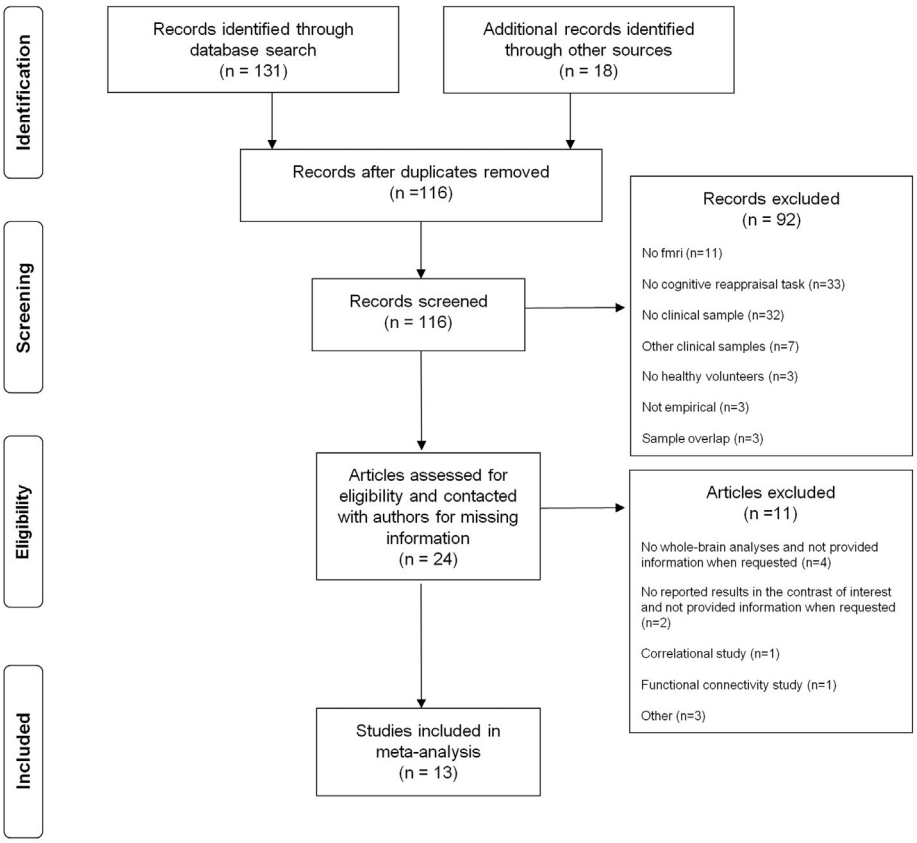

Fig. 1. PRISMA flow diagram. Note: PRISMA = Preferred reporting items for systematic reviews and meta-analyses (http://www.prismastatement.org/).

and whole-brain results when necessary and possible. The literature search identified 116 articles after removing duplicates (Fig. 1).

We selected studies comparing BOLD response during a cognitive reappraisal task between a clinical and a matched healthy sample. Specifically, we included studies in which patients and controls were presented with negative visual stimuli (either images with general negative content from the International Affective Picture System – IAPS (Lang et al., 2005), or disorder-specific negative images from other databases) and with instructions to reappraise these images by means of reinterpretation, distancing, or both. This task intercalates blocks in which participants are instructed to maintain the negative emotion elicited by the image, and blocks in which participants are instructed to reappraise. Our contrast of interest was the comparison of these two conditions (Reappraise vs. Maintain). We selected studies using samples diagnosed with mood or anxiety disorders according to DSM-IV criteria (American Psychiatric Association, 2000) for our main analysis (Table 1).

Studies were excluded if they were correlational or connectivity studies, rather than task activation analyses. We also excluded studies from which, after contact with the authors, peak information or statistic parametric maps (SPMs) could not be retrieved, or that did not report whole-brain statistical results, and/or in which statistical thresholds varied across the assessment of different brain regions (Fig. 1).

Thirteen studies could be included in our main analysis. We were able to retrieve the original empirical SPMs of the contrast of interest for six data sets included in the main analysis, substantially increasing the statistical power (Radua et al., 2012). For the remaining seven studies, peaks coordinates and effect sizes were extracted and coded from the original publication or from supplementary data provided by corresponding authors.

The literature search, decisions on inclusion and data extraction were all performed independently by two of the authors (M.P.-P. & T.S.) and compared by dummy-coding all studies according to the inclusion criteria. Cohen's Kappa was computed to quantify inter-rater agreement, ranging between 0.655 and 0.940. All disagreements were resolved by discussion. For each data set, variables regarding age, gender, the cognitive reappraisal strategy used and stimulus material were also extracted (Table 1). Further information regarding the specific task instructions given to participants and trial timelines is summarized in Supplementary Tables 1 and 2.

2.2. Meta-analytic approach

Functional activation differences between patients and controls were meta-analyzed using Anisotropic Effect-Size Signed Differential Mapping (AES-SDM) software, version 4.13 (www.sdmproject.com) (Radua et al., 2012; Radua et al., 2014). This method, which has been validated and used in several structural and functional MRI studies, creates a brain map of the effect size of the difference between the two groups (patients vs. controls) of each study (either from SPMs or from peak information) and afterwards conducts a voxel-wise random-effects meta-analysis (weighing the studies for sample size, intra-study variance and between-study heterogeneity) (Radua and Mataix-Cols, 2009; Radua et al., 2010; Radua et al., 2012; Radua et al., 2014) (see Supplementary material). In one study (Goldin et al., 2009), we retrieved two contrasts from the same sample (Reappraise > Maintain using non-specific stimuli, and Reappraise > Maintain using disorder-specific stimuli), and the results from these contrasts were combined before inclusion in the main analysis.

To assess the robustness of the findings, we conducted a jackknife sensitivity analysis (Radua and Mataix-Cols, 2009) (see Supplementary material). The I^2 index and Egger's method were used to assess for heterogeneity of effect sizes and publication bias, respectively.

We also conducted an exploratory analysis to investigate the potential differences depending on the specific reappraisal strategy used by comparing those studies instructing to use distancing with those instructing to use reinterpretation, excluding studies that let the subject choose which strategy to use or did not give specific instructions (n = 3

Table 1
Characteristics of the 13 cognitive reappraisal fMRI data sets included in the meta-analysis.

Author	Disorder	Clinical sample		Healthy sample		Cognitive reappraisal strategy used	Stimulus material
		N (female)	Age, y, Mean (SD)	N (female)	Age, y, Mean (SD)		
Dillon and Pizzagalli, 2013	Major depressive disorder	12 (7)	31.00 (8.20)	24 (12)	34.42 (14.93)	Distancing	Negative images (IAPS)
Gaebler et al., 2014	Social anxiety disorder	21 (16)	30. 5 (7.17)	23 (18)	30.0 (7.99)	Distancing	Negative images (IAPS)
Goldin et al., 2009	Social anxiety disorder	15 (9)	31.6 (9.7)	17 (9)	32.1 (9.3)	Reinterpretation and distancing	Harsh facial expressions and violent scenes[a]
Greening et al., 2014	Major depressive disorder	19 (13)	26.79 (11.4)	19 (13)	27.63 (11.0)	Reinterpretation	Sad images (IAPS)
Johnstone et al., 2007	Major depressive disorder	21 (13)	33 (12)	18 (11)	28 (12)	Reinterpretation and distancing	Negative images (IAPS)
Kanske et al., 2012	Remitted major depressive disorder	23 (16)	43.65 (10.12)	25 (18)	43.88 (11.21)	Reinterpretation and distancing	Negative images (IAPS)
Morris et al., 2012	Bipolar disorder I	13 (5)	41 (3)	15 (9)	35 (2)	Distancing	Negative images (IAPS)
New et al., 2009	Post-traumatic stress disorder	14 (14)	38.7 (11.2)	14 (14)	31.7 (10.3)	Reinterpretation	Negative images (IAPS)
Perlman et al., 2012	Adolescent major depressive disorder	14 (6)	15.7 (1.5)	14 (6)	15.1 (1.6)	Reinterpretation	Negative images (IAPS)
Sheline et al., 2009	Major depressive disorder	20 (12)	34 (9.4)	21 (15)	35 (7.3)	Reinterpretation and distancing	Negative images (IAPS)
Smoski et al., 2013	Remitted major depressive disorder	18 (14)	24.8 (4.7)	19 (12)	27.9 (6.3)	Reinterpretation and distancing	Sad images (IAPS + other normed set)
Townsend et al., 2013	Bipolar disorder I	30 (11)	37.9 (12.6)	26 (11)	35.5 (12.4)	Reinterpretation	Negative images (IAPS)
Ziv et al., 2013	Social anxiety disorder	27 (12)	31.1 (7.6)	27 (13)	32.6 (9.5)	Reinterpretation	Anger and contempt faces

Abbreviations: SD, standard deviation; IAPS, International Affective Picture System.
[a] In the study by Goldin et al., contrasts from both types of stimuli were combined.

for distancing and $n = 5$ for reinterpretation). Finally, complementary meta-analyses were performed after excluding a study that only included women (New et al., 2009), a study using an adolescent sample (Perlman et al., 2012), studies that used disorder-specific stimuli (studies included $n = 9$), and studies with most or all patients taking medication (studies included $n = 11$). We also explored for potential differences between studies with anxiety and depression samples ($n = 4$ for anxiety and $n = 9$ for depression), and performed a meta-regression analysis to evaluate the effect of different trial durations on our findings.

Statistical significance was assessed with AES-SDM default thresholds (voxel-level $P < 0.005$ uncorrected, peak SDM-Z > 1, minimum extent 10 contiguous voxels), as previous simulations indicate that this threshold provides an optimal balance between sensitivity and false-positive rate (Radua et al., 2012). Results are reported in Montreal Neurological Institute (MNI) space.

3. Results

3.1. Included studies and sample characteristics

The final sample consisted of thirteen independent data sets reporting a healthy control vs. patient contrast including a total of 247 patients (148 females, mean age of 32.75 years, s.d. = 11.32) and 262 controls (161 females, mean age of 32.20 years, s.d. = 11.48) (Table 1). Patient diagnoses included major depressive disorder (MDD) (5 studies), remitted MDD (2 studies), bipolar disorder (2 studies), social anxiety disorder (3 studies) and post-traumatic stress disorder (1 study). Regarding medication use, only four studies included patients under medication, and from these, in only one (Morris et al., 2012) were all subjects medicated. In the remaining 3 studies, the percentage of medicated patients was 19% (Gaebler et al., 2014), 39% (Kanske et al., 2012), and 70% (Townsend et al., 2013).

Ten out of these thirteen studies reported having collected the subjective ratings of the emotion being experienced during the cognitive reappraisal task (typically these ratings are recorded at the end of each Maintain and Reappraise block, and then compared in order to confirm that subjects were performing the task). Even though we could not obtain access to the totality of these data and therefore not conduct quantitative analyses with them, it is worth noting that, of these ten studies, eight found no significant between-group differences in these ratings while only two found significant differences, indicating that in the majority of studies patients subjectively reported being able to reappraise negative emotions during the task to the same extent as healthy controls.

3.2. Primary meta-analytic results

Six large clusters were mapped as consistently demonstrating higher functional activations during cognitive reappraisal in patients compared to healthy controls. The major regions comprising these clusters were: (1) the bilateral precentral gyrus; (2) the left supramarginal gyrus; (3) the left anterior insula; (4) the cerebellum; (5) the left inferior occipital gyrus (IOG); and (6) the superior parietal lobule (SPL). We also note the relevant involvement of smaller regions including the right fusiform gyrus, the left middle occipital gyrus (MOG), the right supramarginal gyrus, the posterior midcingulate cortex, the right rolandic operculum, the right posterior insula, the right inferior frontal gyrus (IFG), the left caudate and the bilateral postcentral gyrus (Fig. 2, Table 2).

Four large regional clusters were also mapped as consistently demonstrating higher significant activations during cognitive reappraisal in healthy controls compared to patients. These clusters comprised the following regions: (1) the posterior cingulate cortex (PCC), extending into the precuneus; (2) the bilateral dorsomedial prefrontal cortex (dmPFC); (3) the bilateral angular gyrus; and (4) the left ventrolateral prefrontal cortex (vlPFC). We also note the relevant involvement of smaller regions including the right middle temporal gyrus (MTG), the anterior midcingulate cortex, the left putamen and the cuneus (Fig. 2, Table 2).

Our robustness analyses indicated that most results were highly replicable and that there was neither substantial heterogeneity nor evidence of potential publication bias in the main results (see Table 2).

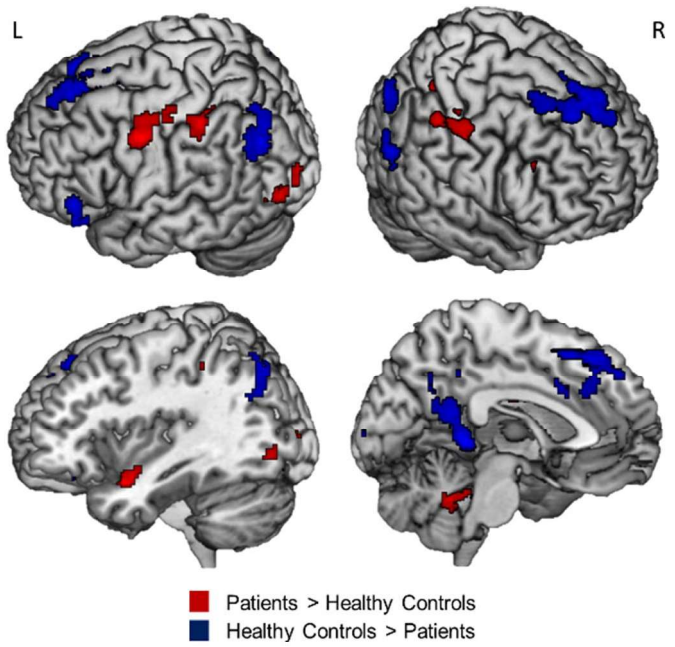

Fig. 2. Significant brain functional activations for the Patients > Controls (red) and Controls > Patients (blue) comparisons determined by meta-analysis. Results are displayed at $p < 0.005$ (cluster size ≥ 10 voxels). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

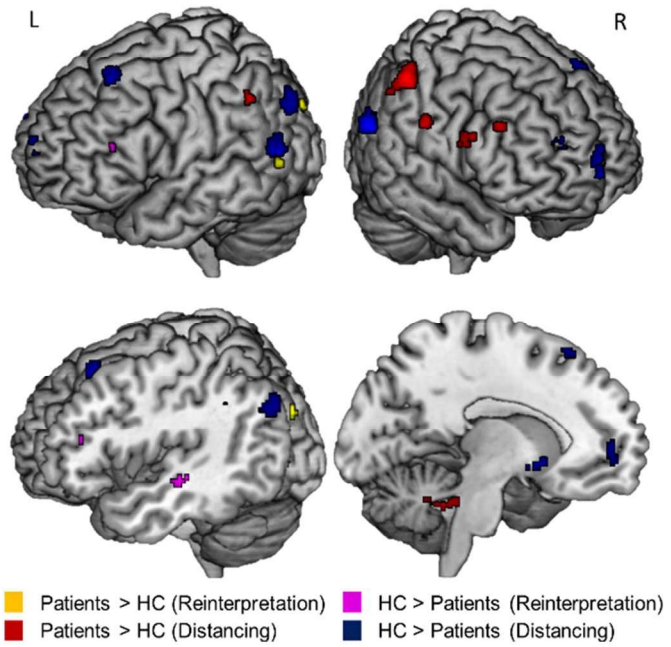

Fig. 3. Comparison of significant brain functional activations for patients and controls depending on the reappraisal strategy used. Colors refer to: Patients > Controls Reinterpretation (yellow), Patients > Controls Distancing (red), Controls > Patients Reinterpretation (purple) and Controls > Patients distancing (blue). Results are displayed at $p < 0.005$ (cluster size ≥ 10 voxels). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Comparison of reappraisal strategies

Regarding the exploratory comparison between distancing and reinterpretation studies, we found some overlap among the regions displaying increased activation in healthy controls, although there were also regions of specific activation for each strategy. The left vlPFC and the left superior temporal gyrus (STG) were specifically activated in reinterpretation studies, while the bilateral angular gyrus, the ventromedial prefrontal cortex (vmPFC), the left MTG, the left precuneus, the bilateral MFG, the PCC, the left caudate and the left inferior temporal gyrus (ITG) were active in distancing studies. As per regions showing increased activation in the clinical group, the left MTG and the

Table 2
Results of meta-analysis for the Patients > Controls and Controls > Patients contrasts during cognitive reappraisal: regional differences in activation at $p < 0.005$, $z > 1$ and cluster size > 10 voxels.

Comparison	Region	Number of voxels	MNI coordinates (x,y,z)	SDM-Z	Voxel P	I^2	JK	Egger test p
Patients > Controls	Left precentral gyrus	200	−52,−2,42	2.388	0.000035703	0%	13/13	0.375
	Left supramarginal gyrus	109	−44,−36,48	2.177	0.000152230	0%	13/13	0.393
	Left anterior insula	98	−40,6,−20	2.257	0.000087440	0%	13/13	0.820
	Cerebellum, vermic lobule X	174	−6,−52,−28	2.073	0.000289619	0%	12/13	0.497
	Right precentral gyrus	123	42,−16,34	2.221	0.000115395	0%	12/13	0.945
	Left inferior occipital gyrus	86	−34,−80,−6	2.264	0.000084102	0%	12/13	0.467
	Right superior parietal lobule	55	26,−48,50	2.305	0.000065565	0%	12/13	0.677
	Left middle occipital gyrus	21	−32,−92,2	1.936	0.000629008	0%	11/13	0.666
	Right fusiform gyrus	25	42,−6,−34	1.998	0.000449419	0%	10/13	0.765
	Right supramarginal gyrus	23	56,−30,48	2.022	0.000389874	0%	10/13	0.231
	Left caudate	14	−18,−10,24	1.814	0.001201749	0%	9/13	0.988
	Right inferior frontal gyrus	14	38,24,26	1.662	0.002571642	0%	9/13	0.780
	Posterior midcingulate cortex	12	10,6,48	1.862	0.000940323	0%	9/13	0.425
	Right posterior insula	11	38,−8,14	1.622	0.003091931	0%	9/13	0.035
	Right postcentral gyrus	14	40,−26,48	1.716	0.001970708	1.37%	8/13	0.354
	Right rolandic operculum	12	50,0,12	1.756	0.001611292	0%	8/13	0.037
	Left postcentral gyrus	15	−44,−18,56	1.633	0.002938330	0%	4/13	0.163
Controls > Patients	Posterior cingulate cortex/precuneus	953	−4,−38,2	−2.731	0.000006378	3.23%	13/13	0.775
	Left dorsomedial prefrontal cortex	576	−6.32,48	−2.601	0.000020027	8.61%	13/13	0.735
	Left angular gyrus	269	−42,−72,34	−2.429	0.000066340	0%	13/13	0.264
	Left ventrolateral prefrontal cortex	62	−54,36,−2	−2.453	0.000055134	0%	12/13	0.859
	Right middle temporal gyrus	51	56,−60,18	−2.359	0.000102818	0%	11/13	0.675
	Anterior midcingulate cortex	28	−10,18,28	−2.354	0.000107050	0%	11/13	0.049
	Left cuneus	10	0,−98,8	−2.100	0.000493467	0%	11/13	0.905
	Right dorsomedial prefrontal cortex	66	16,20,50	−2.007	0.000824511	13.48%	10/13	0.741
	Right angular gyrus	62	44,−70,48	−2.222	0.000248015	0%	10/13	0.904
	Left putamen	15	−26,14,−4	−1.985	0.000930309	0%	10/13	0.138

Abbreviations: MNI, Montreal Neurological Institute; SDM, Signed Differential Mapping; P, *p*-value; I^2, Percentage of variance attributable to study heterogeneity; JK, Jackknife Sensitivity Test.

superior occipital gyrus (SOG) were specifically associated with reinterpretation, and the bilateral supramarginal gyri, the cerebellum, the right postcentral gyrus, the right IFG, the left insula (anterior and posterior), the right anterior insula and the right fusiform gyrus were associated with studies instructing the use of distancing (see Fig. 3 and Supplementary Table 3).

3.4. Complementary meta-analyses

The results of these analyses are fully described in Supplementary material. Overall, results from the primary meta-analysis were not significantly affected when we excluded studies that only included women or adolescents and when excluding studies with medication (see Supplementary Fig. 1), while some differences were found for the patients' group when excluding studies with disorder-specific stimuli (see Supplementary Table 4 and Supplementary Fig. 2). Also, when independently comparing healthy controls studies with depression and anxiety samples, and when directly contrasting these two clinical groups, we found no regions specifically associated to any of the groups. These results, however, should be interpreted with caution (see Results section of the Supplementary material). Finally, in a meta-regression analysis we observed that some of our main findings were significantly influenced by trial duration (see Supplementary Table 5).

4. Discussion

To our knowledge, this is the first meta-analysis of functional neuroimaging studies assessing emotion regulation by means of a cognitive reappraisal task in clinical populations. In the clinical group, our primary analysis showed a decreased activation of cortical regions typically engaged by healthy controls during cognitive reappraisal, such as the PCC, the dmPFC, the angular gyri and the left vlPFC. By contrast, patients presented increased activations in other cortical regions such as the precentral and supramarginal gyri, the left IOG and the SPL, together with the cerebellar vermis and the left anterior insula. These results indicate that dysfunction in the cortical network responsible for the cognitive control of negative emotions may be a characteristic feature of mood and anxiety disorders, and that aberrant hyperactivation may appear in other regions as a consequence of, or to compensate for, such impaired cortical control of emotions.

The regions deficiently engaged by patient populations are responsible for a variety of cognitive processes relevant for emotion regulation. The dmPFC, whose cluster extended to the dorsal anterior cingulate cortex, and the angular gyri are relevant regions for the allocation of attentional resources and monitoring emotional experiences (Pessoa et al., 2003; Botvinick et al., 2004). Relatedly, the vlPFC has a preponderant role in response selection and inhibition (Aron et al., 2014), particularly in the inhibition of emotional appraisals (Wager et al., 2009). Findings from our meta-analysis therefore suggest that emotion regulation alterations in mood and anxiety disorders may be partly a consequence of ineffective management of attentional and inhibitory resources. Moreover, hypoactivation of the retrosplenial and posterior cingulate cortices may indicate deficient use of mnemonic, abstract and planning resources (Leech et al., 2012; Bird et al., 2015), all important for the deployment of successful emotion regulation strategies. In addition, deficient activation of the PCC, in combination with the results of the angular gyri, supports previous research indicating that the default mode network (DMN), the brain system responsible for inward attention (Raichle, 2015), is critically involved in cognitive reappraisal (Diekhof et al., 2011; Kohn et al., 2014). Correspondingly, functional alterations in the DMN have consistently been reported in subjects with mood or anxiety disorders (Mulders et al., 2015; Peterson et al., 2014).

According to previous literature (Campbell-Sills et al., 2014; Johnstone and Walter, 2014; Kober, 2014) hypoactivation in the dorsolateral prefrontal cortex (dlPFC) in clinical populations could be expected, but this was not the case in our findings. The dlPFC is a critical region for carrying out certain executive functions (Wager and Smith, 2003), and in the context of emotion regulation, it is involved in the active manipulation of information to reappraise emotional stimuli (Ochsner et al., 2012). There are two potential explanations for our lack of significant findings. Firstly, although this region has been reported as hypoactivated in a recent review of neuroimaging studies in mood and anxiety samples (Zilverstand et al., 2016), it may well be that the apparent hypoactivation of this region across studies do not reach statistical significance when submitted to evaluation with strict meta-analytical techniques. In parallel, compensatory hyperactivations of the dlPFC in particular groups of subjects may have cast a shadow on the suspected hypoactivation of this brain region. Such compensatory hyperactivation has been reported in depression samples during executive testing, allowing cognitive performance to remain unaltered (Fitzgerald et al., 2008; Matsuo et al., 2007). It is feasible that this could also occur in the context of cognitive reappraisal.

When focusing on regions where the clinical groups showed hyperactivation in relation to healthy controls, a differentiation could be made between those areas putatively associated with the emotional experience and areas whose activation may be the consequence of a compensatory mechanism. The former group includes activations in the cerebellar vermis and the left anterior insula, but also in cortical regions such as the precentral gyri and the left IOG (Zaki et al., 2012; Seehausen et al., 2014; Strata, 2015; Wiggins et al., 2016). The cerebellar vermis has been associated with the acquisition of fear learning and the expression of autonomic and motor responses of emotions (Strata et al., 2011; Strata, 2015). The anterior insula is involved, among other processes, in the secondary processing of emotional experience through the integration of interoceptive signals with external context (Craig, 2003; Zaki et al., 2012). The increased insula activation reported here is therefore likely reflecting the unsuccessful reappraisal of emotional content and the consequent increase in emotion-related physiological markers (Wiens, 2005). Regarding the abovementioned cortical regions, hyperactivity in the left IOG is likely to reflect greater attention to negative emotional stimuli (Wiggins et al., 2016), while increased activation of the precentral gyri should be understood in the context of the role of this region in emotion experience (Hajcak et al., 2007), more specifically in the preparation of motor responses when facing emotional stimuli (Hardee et al., 2017). Overall, this pattern of hyperactivations seem to reflect increased perceptual processing of emotional stimuli leading to amplified physiological and motor responses and increased physiological feedback.

By contrast, the supramarginal gyri and the SPL have been described as crucial for inhibitory control during cognitive reappraisal of negatively valenced stimuli (Buhle et al., 2013; Ochsner and Gross, 2014), and therefore the increased activation of these two regions in clinical groups observed here may be interpreted as compensatory to account for impaired activation in other cortical areas (i.e., the fronto-parietal network described above involving the dmPFC, the vlPFC, the angular gyri and the PCC). Interestingly, activation of the supramarginal gyrus during cognitive reappraisal has been shown to be predictive of response to CBT in subjects with anxiety disorders (Ball et al., 2014).

It is also important to note that we did not observe increased activation in the amygdala in clinical populations. This finding partially concurs with the results of a previous systematic review, in which amygdala hyperactivity was only observed in samples of patients with mood, but not anxiety, disorders (Zilverstand et al., 2016). Even though the amygdala has classically been considered as the core region of the emotional brain (LeDoux, 2000), its function is, in all likelihood, more substantial in particular emotional contexts, such as fear learning acquisition by means of implicit learning (Ohman and Mineka, 2001). Indeed, its role in the conscious appraisal of emotions has recently been cast into doubt (LeDoux, 2014).

The specific emotion regulation strategy used by participants had a significant effect on our results. In reinterpretation studies, the most

significant differences were observed in the left vlPFC and the left STG, while in distancing studies these were located in parietal regions (angular gyri and PCC). The existence of such differential patterns of activation between reinterpretation and distancing strategies has already been proposed in previous reports (Ochsner et al., 2004; Ochsner et al., 2012). These reports postulate that reinterpretation relies on regions involved in response selection and inhibition, and semantic processing, whereas distancing is more related to brain areas linked to perspective taking and the sense of agency. Moreover, the left lateralization of reinterpretation findings has been also suggested to indicate a greater involvement of linguistic and semantic processes in the deployment of this emotion regulation strategy (Ochsner et al., 2012). Concerning regions displaying hyperactivation in the clinical groups, it is of interest to observe how in reinterpretation studies such results were limited to perceptual visual regions, whereas in distancing studies increased activations extended through different cortical and subcortical regions, involving those previously classified as related with the emotional experience and those associated with compensatory mechanisms. Future studies will have to elucidate whether such findings may be interpreted as evidence of the superior capacity of reinterpretation strategies to downregulate negative emotional experiences.

The general pattern of altered activations by patients with mood and anxiety disorders was not significantly affected when we controlled for the effect of particular subgroups of patients, such as women, adolescents, or patients on medication. Moreover, we did not observe differences between studies assessing mood or anxiety samples. Likewise, when we excluded studies using disorder-specific stimuli from the analysis, the pattern of hypoactivated regions in the clinical group was not altered. Decreased activation within this network may be underpinning both disorder-specific and unspecific alterations in emotion regulation, which therefore could have a pervasive frequency in different contexts of the patients' life. Contrarily, the pattern of abnormally hyperactivated regions in clinical populations was partially modified. Findings in the precentral gyri, for instance, were no longer significant, which, in line with our previous argumentation, may be interpreted as a less marked empathic response when facing unspecific emotional stimuli. In the same vein, the lack of significant hyperactivation in IOG seem to suggest that more perceptive and attentional resources are typically devoted to disorder-relevant stimuli, although significant hyperactivations when facing unspecific stimuli were observed in other second-order visual regions, such as the right MOG. Finally, for unspecific stimuli, compensatory hyperactivations were limited to the supramarginal gyri, but were not observed in the SPL, which likely reflects that the neural resources needed to manage disturbing images vary as a function of one's personal relevance to the stimuli. Lastly, trial duration significantly influenced some of our results, and therefore further research is warranted to ascertain the particular temporal dynamics of the different brain regions involved in emotion regulation.

It also should be mentioned that, although impaired emotion regulation capacity in these samples have repeatedly been identified through different measures (neuroimaging, physiological and psychopathological) (Campbell-Sills et al., 2014; Johnstone and Walter, 2014; Joorman and Siemer, 2014), no significant differences between patient and control groups were found in subjective negative emotion ratings during the fMRI task in the different studies analyzed. This result is best understood as reflecting the limitations of intra-scanner behavioral assessments, social desirability effects or impaired self-awareness of emotional experience, as recently suggested by Zilverstand et al. (2016). Unfortunately, due to the lack of sufficient data, we could not perform a meta-regression analysis between behavioral and neuroimaging data.

Methodological strengths of the current study include the use of a novel meta-analytic method combining the positive features of standard (non-neuroimaging) meta-analytic methods (i.e. the inclusion of full information from a given study, represented here by SPMs) with those from typical neuroimaging coordinate approaches (i.e. the greater availability of data coming from reported coordinate results). In this sense, we were able to include six original contrast maps that allowed us to better estimate the results associated with our comparison of interest. Within the limitations, we have to disclose those inherently linked to meta-analysis, such as the inclusion of studies with different statistical thresholds. Although our method provides an excellent control for false positives, it is more difficult to avoid false negative results. Moreover, despite providing an optimal balance between sensitivity and false positive rate, the default AES-SDM statistical thresholds were based on uncorrected *P*-values, which may also be seen as a limitation (Radua et al., 2012). Moreover, our strict study selection criteria resulted in a limited number of studies being included in our analysis. This specially hampered additional analyses, such as the comparison between emotion regulation strategies. Further, our results are limited to clinical populations with mood or some particular anxiety disorders, and thus we cannot generalize our findings to other anxiety disorders not included in the meta-analysis (such as specific phobia or panic disorders) or other clinical samples. Finally, other factors important for emotion regulation were not considered in this meta-analysis. For example, it would be of interest to pinpoint potential differences in the timing of regulatory responses between clinical samples and healthy controls, and to disentangle the differential benefits of using reinterpretation vs. distancing strategies.

In conclusion, patients with mood or anxiety disorders show a different pattern of brain activation from healthy controls when carrying out a cognitive reappraisal task. Specifically, patients are not able to recruit some of the fronto-parietal regions (i.e., the dmPFC, the vlPFC, the angular gyri and the PCC) implicated in the top-down regulation of negative emotions. Even though no differences between patients and controls in behavioral ratings were found, increased activation in regions involved in the emotional experience, such as the anterior insula and the cerebellar vermis, indicate that whichever strategy patients may have used was not effective on a neurobiological level. We can therefore consider that a transdiagnostic brain network exists which may be considered as a target for future interventions aimed at increasing emotion regulation capacities in patients with mood or anxiety disorders.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2017.06.001.

References

Aldao, A., Nolen-Hoeksema, S., Schweizer, S., 2010. Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin. Psychol. Rev. 30, 217–237. http://dx.doi.org/10.1016/j.cpr.2009.11.004.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental

Disorders, 4th ed. http://dx.doi.org/10.1176/appi.books.9780890423349.
Aron, A.R., Robbins, T.W., Poldrack, R.A., 2014. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn. Sci. 18, 177–185. http://dx.doi.org/10.1016/j.tics.2013.12.003.
Ball, T.M., Stein, M.B., Ramsawh, H.J., Campbell-Sills, L., Paulus, M.P., 2014. Single-subject anxiety treatment outcome prediction using functional neuroimaging. Neuropsychopharmacology 39, 1254–1261. http://dx.doi.org/10.1038/npp.2013.328.
Beck, A.T., 2005. The current state of cognitive therapy: a 40-year retrospective. Arch. Gen. Psychiatry 62 (9), 953. http://dx.doi.org/10.1001/archpsyc.62.9.953.
Bird, C.M., Keidel, J.L., Ing, L.P., Horner, A.J., Burgess, N., 2015. Consolidation of complex events via reinstatement in posterior cingulate cortex. J. Neurosci. 35, 14426–14434. http://dx.doi.org/10.1523/JNEUROSCI.1774-15.2015.
Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn. Sci. 8, 539–546. http://dx.doi.org/10.1016/j.tics.2004.10.003.
Buhle, J.T., Silvers, J. a, Wager, T.D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., Ochsner, K.N., 2013. Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cereb. Cortex 1–10. http://dx.doi.org/10.1093/cercor/bht154.
Campbell-Sills, L., Barlow, D.H., Brown, T.A., Hofmann, S.G., 2006. Effects of suppression and acceptance on emotional responses of individuals with anxiety and mood disorders. Behav. Res. Ther. 44, 1251–1263. http://dx.doi.org/10.1016/j.brat.2005.10.001.
Campbell-Sills, L., Ellard, K.K., Barlow, D.H., 2014. Emotion regulation in anxiety disorders. In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. The Guilford Press, pp. 393–412.
Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13, 500–505.
Cutuli, D., 2014. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Front. Syst. Neurosci. 8, 1–6. http://dx.doi.org/10.3389/fnsys.2014.00175.
Diekhof, E.K., Geier, K., Falkai, P., Gruber, O., 2011. Fear is only as deep as the mind allows. A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect. NeuroImage 58, 275–285. http://dx.doi.org/10.1016/j.neuroimage.2011.05.073.
Dillon, D.G., Pizzagalli, D.A., 2013. Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. Psychiatry Res. 212, 99–107. http://dx.doi.org/10.1016/j.pscychresns.2013.01.001.
Dörfel, D., Lamke, J.P., Hummel, F., Wagner, U., Erk, S., Walter, H., 2014. Common and differential neural networks of emotion regulation by detachment, reinterpretation, distraction, and expressive suppression: A comparative fMRI investigation. NeuroImage 101, 298–309. http://dx.doi.org/10.1016/j.neuroimage.2014.06.051.
Ehring, T., Fischer, S., Schnülle, J., Bösterling, A., Tuschen-Caffier, B., 2008. Characteristics of emotion regulation in recovered depressed versus never depressed individuals. Personal. Individ. Differ. 44, 1574–1584. http://dx.doi.org/10.1016/j.paid.2008.01.013.
Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am. J. Psychiatry 164, 1476–1488. http://dx.doi.org/10.1176/appi.ajp.2007.07030504.Functional.
Etkin, A., Büchel, C., Gross, J.J., 2015. The neural bases of emotion regulation. Nat. Rev. Neurosci. 16, 693–700. http://dx.doi.org/10.1038/nrn4044.
Fitzgerald, P.B., Srithiran, A., Benitez, J., Daskalakis, Z.Z., Oxley, T.J., Kulkarni, J., Egan, G.F., 2008. An fMRI study of prefrontal brain activation during multiple tasks in patients with major depressive disorder. Hum. Brain Mapp. 29, 490–501. http://dx.doi.org/10.1002/hbm.20414.
Gaebler, M., Daniels, J.K., Lamke, J., Fydrich, T., Walter, H., 2014. Behavioural and neural correlates of self-focused emotion regulation in social anxiety disorder. J. Psychiatry Neurosci. 39, 249–258. http://dx.doi.org/10.1503/jpn.130080.
Goldin, P.R., Manber, T., Hakimi, S., Canli, T., Gross, J.J., 2009. Neural bases of social anxiety disorder: emotional reactivity and cognitive regulation during social and physical threat. Arch. Gen. Psychiatry 66, 170–180. http://dx.doi.org/10.1001/archgenpsychiatry.2008.525.
Goldin, P.R., Ziv, M., Jazaieri, H., Hahn, K., Heimberg, R., Gross, J.J., 2013. Impact of cognitive behavioral therapy for social anxiety disorder on the neural dynamics of cognitive reappraisal of negative self-beliefs. JAMA Psychiatry 70, 23945981. http://dx.doi.org/10.1001/jamapsychiatry.2013.234.Impact.
Görlach, M.G., Kohlmann, S., Shedden-Mora, M., Rief, W., Westermann, S., 2016. Expressive suppression of emotions and overeating in individuals with overweight and obesity. Eur. Eat. Disord. Rev. 1–6. http://dx.doi.org/10.1002/erv.2452.
Greening, S.G., Osuch, E.A., Williamson, P.C., Mitchell, D.G.V., 2014. The neural correlates of regulating positive and negative emotions in medication-free major depression. Soc. Cogn. Affect. Neurosci. 9, 628–637. http://dx.doi.org/10.1093/scan/nst027.
Gross, J.J., 1998a. The emerging field of emotion regulation: an integrative review. Rev. Gen. Psychol. 2, 271–299. http://dx.doi.org/10.1037/1089-2680.2.3.271.
Gross, J.J., 1998b. Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. J. Pers. Soc. Psychol. 74, 224–237. http://dx.doi.org/10.1037/0022-3514.74.1.224.
Gross, J.J., 2014. Emotion regulation: conceptual and empirical foundations. In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. The Guilford Press, pp. 3–20.
Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J. Pers. Soc. Psychol. 85, 348–362. http://dx.doi.org/10.1037/0022-3514.85.2.348.
Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26. http://dx.doi.org/10.1038/npp.2009.129.
Hajcak, G., Molnar, C., George, M.S., Bolger, K., Koola, J., Nahas, Z., 2007. Emotion facilitates action: a transcranial magnetic stimulation study of motor cortex excitability during picture viewing. Psychophysiology 44, 91–97. http://dx.doi.org/10.1111/j.1469-8986.2006.00487.x.
Hardee, J.E., Cope, L.M., Munier, E.C., Zucker, R.A., Heitzeg, M.M., 2017. Sex differences in the development of emotion circuitry in adolescents at risk for substance abuse: a longitudinal fMRI study. Soc. Cogn. Affect. Neurosci. 1–11. http://dx.doi.org/10.1093/scan/nsx021.
Hu, T., Zhang, D., Wang, J., Mistry, R., Ran, G., Wang, X., 2014. Relation between emotion regulation and mental health: a meta-analysis review. Psychol. Rep. 114, 341–362. http://dx.doi.org/10.2466/03.20.PR0.114k22w4.
Johnstone, T., Walter, H., 2014. The neural basis of emotion dysregulation. In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. The Guilford Press, pp. 58–75.
Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neurosci. 27, 8877–8884. http://dx.doi.org/10.1523/JNEUROSCI.2063-07.2007.
Joorman, J., Siemer, M., 2014. Emotion regulation in mood disorders. In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. The Guilford Press, pp. 413–427.
Kalisch, R., 2009. The functional neuroanatomy of reappraisal: time matters. Neurosci. Biobehav. Rev. 33, 1215–1226. http://dx.doi.org/10.1016/j.neubiorev.2009.06.003.
Kanske, P., Heissler, J., Schönfelder, S., Wessa, M., 2012. Neural correlates of emotion regulation deficits in remitted depression: the influence of regulation strategy, habitual regulation use, and emotional valence. NeuroImage 61, 686–693. http://dx.doi.org/10.1016/j.neuroimage.2012.03.089.
Kober, H., 2014. Emotion regulation in substance use disorders. In: Handbook of Emotion Regulation. The Guilford Press, pp. 428–446.
Kohn, N., Eickhoff, S.B., Scheller, M., Laird, A.R., Fox, P.T., Habel, U., 2014. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. NeuroImage 87, 345–355. http://dx.doi.org/10.1016/j.neuroimage.2013.11.001.
Lang, P., Bradley, M., Cuthbert, B., 2005. International affective picture system (IAPS): digitized photographs, instruction manual and affective ratings. Tech. Rep. A-6, 2005.
LeDoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23, 155–184. http://dx.doi.org/10.1146/annurev.neuro.23.1.155.
LeDoux, J.E., 2014. Coming to terms with fear. Proc. Natl. Acad. Sci. U. S. A. 111 (8), 2871. http://dx.doi.org/10.1073/pnas.1400335111.
Leech, R., Braga, R., Sharp, D.J., 2012. Echoes of the brain within the posterior cingulate cortex. J. Neurosci. 32, 215–222. http://dx.doi.org/10.1523/JNEUROSCI.3689-11.2012.
Matsuo, K., Glahn, D.C., Peluso, M.A.M., Hatch, J.P., Monkul, E.S., Najt, P., Sanches, M., Zamarripa, F., Li, J., Lancaster, J.L., Fox, P.T., Gao, J.-H., Soares, J.C., 2007. Prefrontal hyperactivation during working memory task in untreated individuals with major depressive disorder. Mol. Psychiatry 12, 158–166. http://dx.doi.org/10.1038/sj.mp.4001894.
Morris, R.W., Sparks, A., Mitchell, P.B., Weickert, C.S., Green, M.J., 2012. Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation. Transl. Psychiatry e90, 2. http://dx.doi.org/10.1038/tp.2012.16.
Morrison, S.E., Salzman, C.D., 2010. Re-valuing the amygdala. Curr. Opin. Neurobiol. 20, 221–230. http://dx.doi.org/10.1016/j.conb.2010.02.007.
Mulders, P.C., van Eijndhoven, P.F., Schene, A.H., Beckmann, C.F., Tendolkar, I., 2015. Resting-state functional connectivity in major depressive disorder: a review. Neurosci. Biobehav. Rev. 56, 330–344. http://dx.doi.org/10.1016/j.neubiorev.2015.07.014.
New, A.S., Fan, J., Murrough, J.W., Liu, X., Liebman, R.E., Guise, K.G., Tang, C.Y., Charney, D.S., 2009. A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and posttraumatic stress disorder. Biol. Psychiatry 66, 656–664. http://dx.doi.org/10.1016/j.biopsych.2009.05.020.
Ochsner, K.N., Gross, J.J., 2014. The neural bases of emotion and emotion regulation: a valuation perspective. In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. The Guilford Press, pp. 23–42.
Ochsner, K.N., Bunge, S.A., Gross, J.J., Gabrieli, J.D.E., 2002. Rethinking feelings: an FMRI study of the cognitive regulation of emotion. J. Cogn. Neurosci. 14, 1215–1229. http://dx.doi.org/10.1162/089892902760807212.
Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D.E., Gross, J.J., 2004. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. NeuroImage 23, 483–499. http://dx.doi.org/10.1016/j.neuroimage.2004.06.030.
Ochsner, K., SIlvers, J., Buhle, J., 2012. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Ann. N. Y. Acad. Sci. 1252, 1–35. http://dx.doi.org/10.1111/j.1749-6632.2012.06751.x.
Ohman, A., Mineka, S., 2001. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol. Rev. 108, 483–522.
Perlman, G., Simmons, A.N., Wu, J., Hahn, K.S., Tapert, S.F., Max, J.E., Paulus, M.P., Brown, G.G., Frank, G.K., Campbell-Sills, L., Yang, T.T., 2012. Amygdala response and functional connectivity during emotion regulation: a study of 14 depressed adolescents. J. Affect. Disord. 139, 75–84. http://dx.doi.org/10.1016/j.jad.2012.01.044.
Pessoa, L., Kastner, S., Ungerleider, L.G., 2003. Neuroimaging studies of attention: from modulation of sensory processing to top-down control. J. Neurosci. 23, 3990–3998.
Peterson, A., Thome, J., Frewen, P., Lanius, R.A., 2014. Resting-state neuroimaging studies: a new way of identifying differences and similarities among the anxiety

disorders? Can. J. Psychiatr. 59, 294–300.
Phan, K.L., Fitzgerald, D.a., Nathan, P.J., Moore, G.J., Uhde, T.W., Tancer, M.E., 2005. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biol. Psychiatry 57, 210–219. http://dx.doi.org/10.1016/j.biopsych.2004.10.030.
Phillips, M., Ladouceur, C., Drevets, W., 2008. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol. Psychiatry 13, 829–857. http://dx.doi.org/10.1038/mp.2008.65.A.
Radua, J., van den Heuvel, O.A., Surguladze, S., Mataix-Cols, D., 2010. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. Arch. Gen. Psychiatry 67, 701–711. http://dx.doi.org/10.1001/archgenpsychiatry.2010.70.
Radua, J., Mataix-Cols, D., 2009. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br. J. Psychiatry 195, 393–402. http://dx.doi.org/10.1192/bjp.bp.108.055046.
Radua, J., Rubia, K., Canales-Rodriguez, E.J., Pomarol-Clotet, E., Fusar-Poli, P., Mataix-Cols, D., 2014. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. Front. Psychiatry 5, 1–8. http://dx.doi.org/10.3389/fpsyt.2014.00013.
Radua, J., Mataix-Cols, D., Phillips, M.L., El-Hage, W., Kronhaus, D.M., Cardoner, N., Surguladze, S., 2012. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur. Psychiatry 27, 605–611. http://dx.doi.org/10.1016/j.eurpsy.2011.04.001.
Raichle, M.E., 2015. The brain's default mode network. Annu. Rev. Neurosci. 38, 433–447. http://dx.doi.org/10.1146/annurev-neuro-071013-014030.
Rive, M.M., van Rooijen, G., Veltman, D.J., Phillips, M.L., Schene, A.H., Ruhé, H.G., 2013. Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci. Biobehav. Rev. 37, 2529–2553. http://dx.doi.org/10.1016/j.neubiorev.2013.07.018.
Seehausen, M., Kazzer, P., Bajbouj, M., Heekeren, H.R., Jacobs, A.M., Klann-Delius, G., Menninghaus, W., Prehn, K., 2014. Talking about social conflict in the MRI scanner: neural correlates of being empathized with. NeuroImage 84, 951–961. http://dx.doi.org/10.1016/j.neuroimage.2013.09.056.
Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M. a, Wang, S., Coalson, R.S., Raichle, M.E., 2009. The default mode network and self-referential processes in depression. Proc. Natl. Acad. Sci. U. S. A. 106, 1942–1947. http://dx.doi.org/10.1073/pnas.0812686106.
Smoski, M.J., Keng, S.-L., Schiller, C.E., Minkel, J., Dichter, G.S., 2013. Neural mechanisms of cognitive reappraisal in remitted major depressive disorder. J. Affect. Disord. 151, 171–177. http://dx.doi.org/10.1016/0277-9536(94)90182-1.
Strata, P., 2015. The emotional cerebellum. Cerebellum 14, 570–577. http://dx.doi.org/10.1007/s12311-015-0649-9.
Strata, P., Scelfo, B., Sacchetti, B., 2011. Involvement of cerebellum in emotional behavior. Physiol. Res. 60.
Taylor, S.F., Liberzon, I., 2007. Neural correlates of emotion regulation in psychopathology. Trends Cogn. Sci. 11, 413–418. http://dx.doi.org/10.1016/j.tics.2007.08.006.
Thompson-Schill, S.L., Bedny, M., Goldberg, R.F., 2005. The frontal lobes and the regulation of mental activity. Curr. Opin. Neurobiol. 15, 219–224. http://dx.doi.org/10.1016/j.conb.2005.03.006.
Townsend, J.D., Torrisi, S.J., Lieberman, M.D., Sugar, C.a., Bookheimer, S.Y., Altshuler, L.L., 2013. Frontal-amygdala connectivity alterations during emotion down-regulation in bipolar i disorder. Biol. Psychiatry 73, 127–135. http://dx.doi.org/10.1016/j.biopsych.2012.06.030.
Wager, T.D., Smith, E.E., 2003. Neuroimaging studies of working memory: a meta-analysis. Cogn. Affect. Behav. Neurosci. 3, 255–274.
Wager, T.D., Davidson, M.L., Hughes, B.L., Lindquist, M. a, Kevin, N., 2009. Neural mechanisms of emotion regulation: evidence for two independent prefrontal-subcortical pathways. Neuron 59, 1037–1050. http://dx.doi.org/10.1016/j.neuron.2008.09.006.Neural.
Webb, T.L., Miles, E., Sheeran, P., 2012. Dealing with feeling: a meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. Psychol. Bull. 138, 775–808. http://dx.doi.org/10.1037/a0027600.
Wiens, S., 2005. Interoception in emotional experience. Curr. Opin. Neurol. 18, 442–447. http://dx.doi.org/10.1097/01.wco.0000168079.92106.99.
Wiggins, J.L., Adleman, N.E., Kim, P., Oakes, A.H., Hsu, D., Reynolds, R.C., Chen, G., Pine, D.S., Brotman, M.A., Leibenluft, E., 2016. Developmental differences in the neural mechanisms of facial emotion labeling. Soc. Cogn. Affect. Neurosci. 11, 172–181. http://dx.doi.org/10.1093/scan/nsv101.
Zaki, J., Davis, J.I., Ochsner, K.N., 2012. Overlapping activity in anterior insula during interoception and emotional experience. NeuroImage 62, 493–499. http://dx.doi.org/10.1016/j.neuroimage.2012.05.012.
Zilverstand, A., Parvaz, M.A., Goldstein, R.Z., 2016. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. Neuroimage. http://dx.doi.org/10.1016/j.neuroimage.2016.06.009.
Ziv, M., Goldin, P.R., Jazaieri, H., Hahn, K.S., Gross, J.J., 2013. Emotion regulation in social anxiety disorder: behavioral and neural responses to three socio-emotional tasks. Biol. Mood Anxiety Disord. 3, 20. http://dx.doi.org/10.1186/2045-5380-3-20.

Supplementary information

Methods

Methodological details of the included studies

Supplementary Table 1. Trial timeline for each of the included studies.

Study	Duration of image presentation (seconds)
Dillon and Pizzagalli, 2013	6
Gaebler et al., 2014	8
Goldin et al., 2009	6
Greening et al., 2014	8
Johnstone et al., 2007	10
Kanske et al., 2012	7
Morris et al., 2012	10
New et al., 2009	12
Perlman et al., 2012	12
Sheline et al., 2009	10
Smoski et al., 2013	9-12
Townsend et al., 2013	4 (x8 images)
Ziv et al., 2013	9

Supplementary Table 2. Instructions given to participants in Maintain and Reappraise conditions.

Study	Instructions
	Maintain
Dillon and Pizzagalli, 2013	Participants were asked to mentally place themselves in scenes as though they were happening now, and vividly imagine all the sensations that would be experienced.
Gaebler et al., 2014	Participants were asked "to be personally affected by the situation" potentially by imagining "to be in the midst of the situation, perceiving smells, noises and movements" or "letting the image grow.
Goldin et al., 2009	Participants were instructed to "just look" without trying to control or modulate their emotional reactivity.
Greening et al., 2014	Participants were asked to identify the feeling associated with the scene and experience whatever feelings come naturally without changing them.
Johnstone et al., 2007	Participants were instructed to maintain their attention to the picture without changing their negative affective experience.
Kanske et al., 2012	Participants attended the content of the picture but did not manipulate the emotional response to it.
Morris et al., 2012	Participants were instructed to maintain their initial subjective emotional response to each image, without alteration.
New et al., 2009	Participants were instructed to maintain their responses.
Perlman et al., 2012	Participants were instructed to "notice what you are feeling without trying to change it" and to "maintain your emotional reaction until the picture disappears."

Sheline et al., 2009	Participants were asked to passively look at negative picture.
Smoski et al., 2013	Participants were instructed not to regulate their emotion response.
Townsend et al., 2013	Subjects were instructed to attend to and naturally experience the emotional state elicited by the images.
Ziv et al., 2013	Participants were asked to react normally without any attempt to control, modify, or regulate any reactions.
	Reappraise
Dillon and Pizzagalli, 2013	Participants were told to imagine that scenes were old, posed photographs being viewed from a distance.
Gaebler et al., 2014	Subjects were told to take the role of a distanced observer, imagining that the depicted situation does not concern you.
Goldin et al., 2009	Instructions were to "regulate" by actively thinking in a way that modifies the interpretation of the stimulus and thus reduces negative reactions ("This does not involve me," "This does not influence me," or "This does not impact me", or "The person will be okay," "The person was not really hurt").
Greening et al., 2014	Participants were told to acknowledge that the scene is negative. However, it does not affect you, things do not stay this bad, and the scene does not reflect the whole world.
Johnstone et al., 2007	Individuals were trained to either view the situation as fake or unreal or imagine that the situation being depicted had a different outcome than the one suggested.
Kanske et al., 2012	Instructions were to decrease any emotional response by reinterpreting the displayed situation, for example, as produced by actors and therefore not real, as meaning something else, or having a different outcome than initially suggested by the picture.
Morris et al., 2012	Instructions were to imagine that the situation was not real or that they were a detached observer.
New et al., 2009	Subjects were instructed to decrease the intensity of their affect by imagining a less negative outcome for the circumstances depicted in the picture.
Perlman et al., 2012	Participants were asked to interpret the image in such a way as minimize their emotional response.
Sheline et al., 2009	Participants were instructed to depersonalize the image such that it did not pertain to them, that the image was not real, and that the outcome of the scene portrayed was positive.
Smoski et al., 2013	Participants were asked to reinterpret the image to reduce its negative tone. Both self-focused and situation-focused reappraisal strategies were permitted.
Townsend et al., 2013	Subjects were instructed to cognitively re-evaluate the image. (Sample instructions: "If you see an image of a snake you might think, 'That snake isn't poisonous—it can't hurt me' ").
Ziv et al., 2013	Participants were instructed to try and down regulate negative emotion reactions by actively reinterpreting the meaning of the emotion inducing stimulus.

Meta-analytic approach

AES-SDM is a novel neuroimaging meta-analytic approach that is capable of combining tabulated brain hyper/hypoactivation results (i.e., regional peak statistic and coordinate information) with actual empirical voxel-wise "brain maps" of hyperactivations (or failures of deactivations) and hypoactivations (e.g., SPMs). Put succinctly, the method comprises three major steps. Firstly, whole brain maps of the effect size of the difference between the two groups are recreated separately for each study, either from an SPM or from the reported peak regional coordinate statistics. Secondly, these individual maps are meta-analyzed using the well-established random-effects techniques of standard meta-analyses; these models are independently fitted in each voxel, but the statistical significance is derived from a whole-brain permutation test. Thirdly, a set of standard complementary analyses is conducted to further assess the robustness of the main findings.

Recreation of effect size maps from SPM maps is straightforward as it only involves the transformation to MNI stereotaxic space (in case that they were not already reported in this space) and the voxel-wise conversion of t-values (or alternatively p- or z-values) into effect sizes. Location of the maximum and minimum activity peaks in the recreated maps was manually checked to identify potential artifacts (e.g. image flip) during the conversion.

On the other hand, recreation of effect size maps from peak information is more intensive. Specifically, effect-sizes are straightforwardly derived following standard methods in those voxels containing a peak reported in the results table of the original studies, and for the remaining voxels, an effect-size is estimated depending on the distance to close peaks by means of an anisotropic unnormalized Gaussian kernel. This kernel assigns higher effect-sizes to those voxels more correlated with the peak, whereas small effect-sizes are assigned to those that, even if they are neighboring, show only a small correlation at the population level. Both hyperactivations and hypoactivations are represented in the same map in order to correctly analyze those regions with higher between-study heterogeneity i.e., where some studies report hyperactivations and others hypoactivations.

Finally, if the t values of the peak coordinates are unknown, a threshold-based imputation of the effect size might be conducted. This consists of estimating the mean effect size of peaks from studies reporting t values, separately for each type of threshold (e.g. ''corrected P = 0.05'' and ''uncorrected P = 0.001'').

Jackknife sensitivity analysis

In order to test the replicability of the results, a systematic whole-brain voxel-based jackknife sensitivity analysis is conducted. This consists of repeating the main statistical analysis 13 times but discarding one different study at a time, i.e. removing one study and repeating the analyses, then re-including that study and removing another study and repeating the analysis, and so on. The rationale of this test is that if a previously significant brain region remains significant in all or most of the combinations of studies it can be concluded that this finding is highly replicable.

Results

Complementary meta-analyses

In the complementary analysis excluding the study that only included women (New et al., 2009), most activations remained significant for the regions showing higher activation in patients compared to healthy controls except for the right posterior insula and the left postcentral gyrus clusters (which were not among the most significant and consistent clusters). All of the remaining activations that were significantly higher in healthy controls compared to patients survived this exclusion. When excluding the study that used an adolescent sample (Perlman et al., 2012), we found that almost all regions of higher activation in the patient sample remained significant except for the left postcentral gyrus cluster. All regions of higher activation in the healthy sample remained significant. Also, when excluding the studies by Morris et al. (2012) and Townsend et al. (2013) (with a high proportion of medicated patients) all the main findings remained significant (see Supplementary Figure 1).

We performed an additional analysis excluding studies that used disorder-specific stimuli instead of pictures of general negative content (Goldin et al., 2009; Greening et al., 2014; Smoski et al., 2013; Ziv et al., 2013). The clusters showing higher activation in healthy controls compared to patients all remained significant expect for the cluster in the left putamen. Regions of higher activation in patients were not as consistent and the following regions maintained significance when excluding the aforementioned studies: the cerebellum, the left supramarginal gyrus, the left anterior insula, the right fusiform, the right rolandic operculum, the right IFG, the left caudate and the left postcentral gyrus. Moreover, new significant regions were found when excluding these studies: the right precentral gyrus showed higher activation in healthy controls, and the right middle frontal gyrus (MFG) and the right MOG had greater activation in patients (see Supplementary Table 4 and Supplementary Figure 2).

When comparing with healthy control studies with anxiety (n=4) and depression (n=9) samples independently most of the findings from our primary meta-analysis remained significant, except for the angular gyrus (healthy controls > patients), the left anterior insula and the cerebellum (patients > healthy controls). These results, however, should be interpreted with caution, since these areas lost their significance in both comparisons (depression vs. controls and anxiety vs. controls), and no significant differences were observed in the direct comparison between the two clinical groups, suggesting that this may be consequence of the limited statistical power of this analysis.

Finally, a meta-regression analysis was performed using the duration of presentation of the stimuli summarized in Supplementary Table 1. The significant regions from this analysis overlapping with our main results are presented in Supplementary Table 5.

Supplementary Table 3. Results of meta-analysis for the Reinterpretation > Distancing and Distancing > Reinterpretation contrasts, both for Patients > Controls and Controls > Patients: regional differences in activation at p<0.005, z>1 and cluster size >10 voxels.

Comparison	Region	Number of voxels	MNI coordinates (x,y,z)	SDM-Z	Voxel P	I^2
Patients > Controls						
Reinterpretation > Distancing	Left MTG	112	-60,-60,12	-2.797	0.000050962	0%
	Left SOG	30	-26,-86,32	-2.725	0.000074506	0%
Distancing > Reinterpretation	Right supramarginal gyrus	112	52,-36,52	2.627	0.000118792	22.13%
	Left cerebellum, lobules IV,V	71	-10,-54,-26	2.345	0.000485003	5.57%
	Right postcentral gyrus	47	64,-12,30	2.406	0.000363946	0%
	Right dlPFC	41	54,14,24	2.184	0.001046836	0%
	Right cerebellum, lobule IX	40	16,-38,-30	2.450	0.000294447	0%
	Left supramarginal gyrus	33	-44,-48,40	2.424	0.000334024	0%
	Cerebellum, vermic lobule IX	33	6,-48,-38	2.296	0.000615656	0%
	Left anterior insula	24	-32,10,-18	2.280	0.000666559	0%
	Left posterior insula	20	-34,-2,14	2.244	0.000789404	0%
	Right IFG	15	42,24,30	2.249	0.000770688	0%
	Right IFG	14	42,10,28	2.051	0.001867592	0%
	Right anterior insula	14	32,30,2	2.049	0.001884341	0%
	Right IFG	11	48,34,10	2.021	0.002124369	0%
	Right fusiform gyrus	10	38,-10,-36	2.054	0.001843929	0%

Controls > Patients						
Reinterpretation > Distancing	Left vlPFC	33	-44,32,18	2.213	0.000917077	0%
	Left STG	25	-44,-22,-4	2.580	0.000153601	0%
Distancing > Reinterpretation	Right angular gyrus	191	54,-62,22	-2.906	0.000027657	0%
	vmPFC	134	0,62,4	-2.630	0.000125110	0%
	Left MTG	112	-60,-60,12	-2.797	0.000050962	0%
	Left precuneus	93	-2,-64,42	-2.869	0.000033975	0%
	Left angular gyrus	78	-42,-74,38	-2.324	0.000558913	0%
	Left MFG	30	-26,28,54	-2.407	0.000376761	0%
	PCC	23	12,-48,28	-2.195	0.001015663	0%
	Left caudate	19	-10,12,-6	-2.273	0.000708580	0%
	Right MFG	12	30,60,24	-2.393	0.000407100	0%
	Left ITG	10	-54,4,-36	-2.228	0.000880957	0%

Abbreviations: MNI, Montreal Neurological Institute; SDM, Signed Differential Mapping; P, p-value; I^2, Percentage of variance attributable to study heterogeneity.

Supplementary Table 4. Results of meta-analysis for the Patients > Controls and Controls > Patients contrasts during cognitive reappraisal when excluding studies using disorder-specific stimuli: regional differences in activation at p<0.005, z>1 and cluster size >10 voxels.

Comparison	Region	Number of voxels	MNI coordinates (x,y,z)	SDM-Z	Voxel P	I^2	Main analysis
Patients > Controls	Left cerebellum, lobules IV-VI	328	-12,-52,-26	2.339	0.000026345	0%	Yes
	Right rolandic operculum	271	54,0,-8	1.938	0.000384808	0%	Yes
	Right cerebellum, lobule IX	203	12,-46,-32	2.179	0.000081360	0%	Yes
	Left supramarginal gyrus	116	-46,-36,50	1.821	0.000788033	0%	Yes
	Left anterior insula	83	-38,6,-18	2.051	0.000192523	0%	Yes
	Left postcentral gyrus	32	-46,-22,56	1.755	0.001151562	0%	Yes
	Right fusiform gyrus	30	42,-6,-32	1.965	0.000327528	0%	Yes
	Left superior parietal lobule	27	-30,-42,42	1.733	0.001301885	0%	Yes
	Right MFG	23	36,52,12	1.797	0.000899732	7.15%	No
	Right MOG	18	40,-84,0	1.646	0.002068639	0%	No
	Left caudate	11	-18,-12,26	1.748	0.001197636	0%	Yes
	Right IFG	11	40,24,26	1.703	0.001523077	0%	Yes
Controls > Patients	Posterior cingulate cortex	825	-2,-48,18	-2.389	0.000028789	5.55%	Yes
	Left angular gyrus	500	-48,-72,34	-2.544	0.000010848	0%	Yes
	Right MTG/angular gyrus	319	52,-62,22	-2.270	0.000062048	11.91%	Yes
	Left dmPFC	122	-6,32,48	-1.874	0.000670910	0%	Yes
	Left vlPFC	57	-40,30,-8	-1.727	0.001445055	9.93%	Yes

Right precental gyrus	49	24,-18,60	-2.234	0.000080407	0%	No
aMCC	45	-10,18,28	-2.213	0.000091553	0%	Yes
Left OFC	34	-38,36,-18	-1.852	0.000759959	0%	Yes
Left cuneus	28	4,-96,10	-1.820	0.000897586	0%	Yes
Left dmPFC	26	-18,38,40	-1.636	0.002258658	0%	Yes
dmPFC	24	-4,32,32	-1.693	0.001707613	0%	Yes
Right dmPFC	16	12,36,52	-1.646	0.002164125	0%	Yes

Abbreviations: MNI, Montreal Neurological Institute; SDM, Signed Differential Mapping; P, p-value; I^2, Percentage of variance attributable to study heterogeneity.

Supplementary Table 5. Results of meta-regression analysis considering the duration of the stimuli overlapping with our main results, both for Patients > Controls and Controls > Patients: regional differences in activation at p<0.005, z>1 and cluster size >10 voxels.

Comparison	Region	Number of voxels	MNI coordinates (x,y,z)	SDM-Z	Voxel P
Patients > Controls					
Higher activation with shorter stimuli	Left precentral gyrus	339	-42, -2, 38	-2.174	0.000046432
	Right SPL	63	30, -48, 52	-1.660	0.000727654
Higher activation with longer stimuli	-				
Controls > Patients					
Higher activation with shorter stimuli	Right angular gyrus	49	46, -70, 42	1.745	0.000867009
Higher activation with longer stimuli	Left vlPFC	125	-32, 28, -12	-1.814	0.000294149
	Left dmPFC	26	-4, 40, 52	-1.635	0.000815392

Abbreviations: MNI, Montreal Neurological Institute; SDM, Signed Differential Mapping; P, p-value.

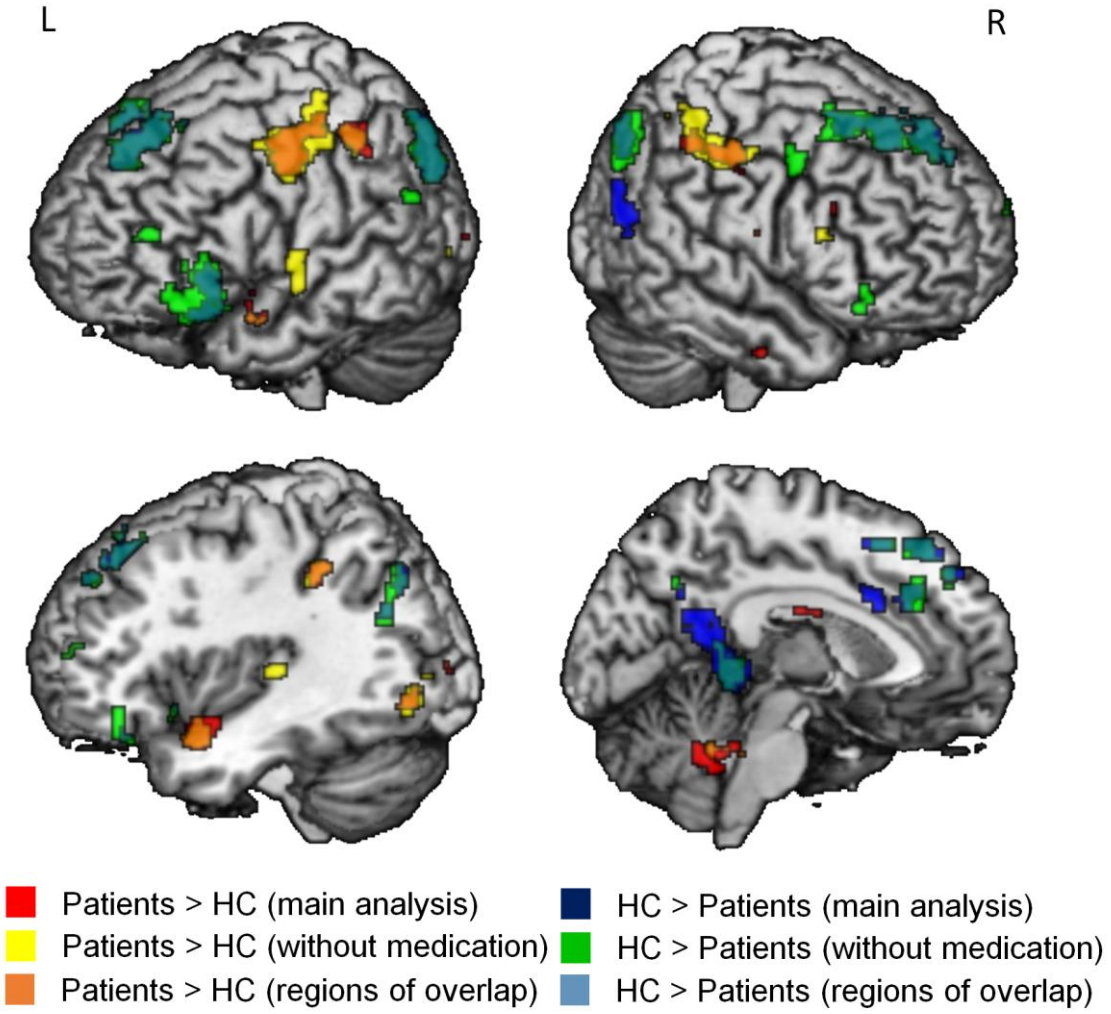

Figure S1. Comparison of significant functional brain activations in the Patients > Controls (red) and Controls > Patients (blue) contrasts in the primary meta-analysis and when excluding studies with more than 50% of participants taking medication (yellow for Patients > Controls and green for Controls > Patients). Regions of overlap between both meta-analyses are shown in orange (Patients > Controls) and light blue (Controls > Patients). Results are displayed at $p<0.005$ (cluster size $\geqslant$10 voxels).

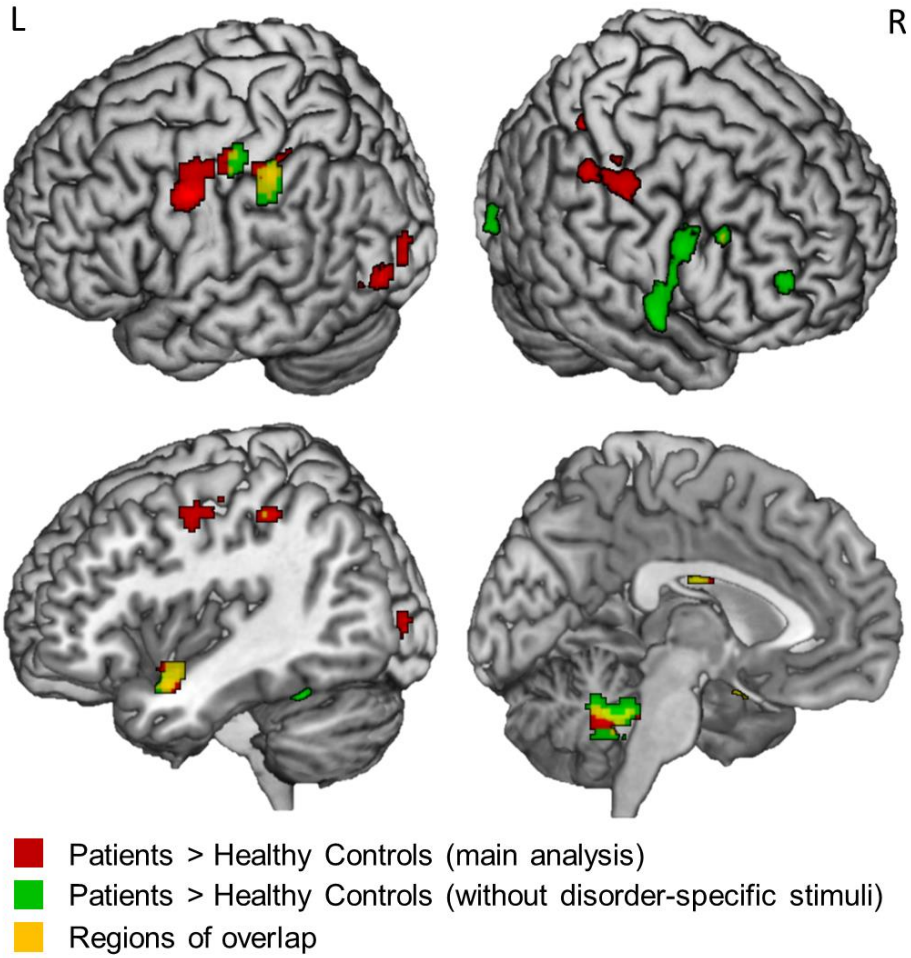

Figure S2. Comparison of significant functional brain activations in the Patients > Controls contrast in the primary meta-analysis (red) and when excluding studies using disorder-specific stimuli (green). Regions of overlap between both meta-analyses are shown in yellow. Results are displayed at $p<0.005$ (cluster size $\geqslant$10 voxels).

References

Dillon, D.G., Pizzagalli, D.A., 2013. Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. Psychiatry Res 212, 99–107. doi:10.1016/j.pscychresns.2013.01.001

Gaebler, M., Daniels, J.K., Lamke, J., Fydrich, T., Walter, H., 2014. Behavioural and neural correlates of self-focused emotion regulation in social anxiety disorder. J Psychiatry Neurosci 39, 249–258. doi:10.1503/jpn.130080

Goldin, P.R., Manber, T., Hakimi, S., Canli, T., Gross, J.J., 2009. Neural Bases of Social Anxiety Disorder: Emotional Reactivity and Cognitive Regulation During Social and Physical Threat. Arch Gen Psychiatry 66, 170–180. doi:10.1001/archgenpsychiatry.2008.525

Greening, S.G., Osuch, E. a, Williamson, P.C., Mitchell, D.G. V, 2014. The neural correlates of regulating positive and negative emotions in medication-free major depression. Soc. Cogn. Affect. Neurosci. 9, 628–37. doi:10.1093/scan/nst027

Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neurosci. 27, 8877–8884. doi:10.1523/JNEUROSCI.2063-07.2007

Kanske, P., Heissler, J., Schönfelder, S., Wessa, M., 2012. Neural correlates of emotion regulation deficits in remitted depression: The influence of regulation strategy, habitual regulation use, and emotional valence. Neuroimage 61, 686–693. doi:10.1016/j.neuroimage.2012.03.089

Morris, R.W., Sparks, a, Mitchell, P.B., Weickert, C.S., Green, M.J., 2012. Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation. Transl. Psychiatry 2, e90. doi:10.1038/tp.2012.16

New, A.S., Fan, J., Murrough, J.W., Liu, X., Liebman, R.E., Guise, K.G., Tang, C.Y., Charney, D.S., 2009. A Functional Magnetic Resonance Imaging Study of Deliberate Emotion Regulation in Resilience and Posttraumatic Stress Disorder. Biol. Psychiatry 66, 656–664. doi:10.1016/j.biopsych.2009.05.020

Perlman, G., Simmons, A.N., Wu, J., Hahn, K.S., Tapert, S.F., Max, J.E., Paulus, M.P., Brown, G.G., Frank, G.K., Campbell-Sills, L., Yang, T.T., 2012. Amygdala Response and Functional Connectivity During Emotion Regulation: A Study of 14 Depressed Adolescents. J Affect Disord 139, 75–84. doi:doi:10.1016/j.jad.2012.01.044

Sheline, Y.I., Barch, D.M., Price, J.L., Rundle, M.M., Vaishnavi, S.N., Snyder, A.Z., Mintun, M. a, Wang, S., Coalson, R.S., Raichle, M.E., 2009. The default mode network and self-referential processes in depression. Proc. Natl. Acad. Sci. U. S. A. 106, 1942–1947. doi:10.1073/pnas.0812686106

Smoski, M.J., Keng, S.-L., Schiller, C.E., Minkel, J., Dichter, G.S., 2013. Neural mechanisms of cognitive reappraisal in remitted major depressive disorder. J Affect Disord 151, 171–177. doi:10.1016/0277-9536(94)90182-1

Townsend, J.D., Torrisi, S.J., Lieberman, M.D., Sugar, C. a., Bookheimer, S.Y., Altshuler, L.L., 2013. Frontal-Amygdala connectivity alterations during emotion downregulation in bipolar i disorder. Biol. Psychiatry 73, 127–135. doi:10.1016/j.biopsych.2012.06.030

Ziv, M., Goldin, P.R., Jazaieri, H., Hahn, K.S., Gross, J.J., 2013. Emotion regulation in social anxiety disorder: behavioral and neural responses to three socio-emotional tasks. Biol. Mood Anxiety Disord. 3, 20. doi:10.1186/2045-5380-3-20

GENERAL DISCUSSION

5. General Discussion

The present section summarizes and presents a general discussion of the findings from the different studies of this thesis. The discussion will also focus on the implications for future research on the study of emotion regulation across mental health disorders and the development of novel treatment approaches for psychiatric patients. Comments on the general limitations and an overall conclusion will be also provided.

5.1. Summary of key findings

The present thesis aimed at identifying functional and structural alterations within the brain networks underlying emotion reactivity and regulation in mood and anxiety disorders, OCD, and excess-weight individuals, by using both functional and anatomical magnetic resonance approaches. Emotion regulation is fundamental to promoting normal socialization, interpersonal interactions, successful decision-making and, overall, to self-regulate behavior appropriately according to the context. An adequate emotion regulation response relies on the correct balance within specific brain networks that contain emotional, cognitive and perceptual elements that respond to and integrate the emotional information to successfully guide behavior.

Our first study was aimed at characterizing the intrinsic functional connectivity patterns related to the habitual use of two emotion regulation strategies, namely, cognitive reappraisal and expressive suppression. Despite the amount of literature studying functional activations during cognitive reappraisal fMRI tasks (and to a lesser extent during suppression), previous studies looking at resting-state patterns of connectivity and emotion regulation strategies use were scarce or non-existent, and for this reason we decided to first look at a HC sample in order to characterize the “normal” pattern of associations. Moreover, we were interested in differentiating between amygdala sub-regions, due to the putatively different functions associated with them. We found that the functional connectivity between the BLA and the SMA and the insula was negatively associated with the use of cognitive reappraisal strategies. Conversely, higher connectivity between the BLA and the dACC was linked to the use of suppression. With regard to the CMA, the limbic sub-region responsible for the generation of the emotional output, negative connectivity with the SMA was also linked to emotional suppression. Our findings supported the idea that the use of emotion regulation strategies is associated with significant negative coupling between the amygdala and the frontal cortex,

and that different patterns emerge in association with cognitive reappraisal and with expressive suppression.

Next, in the second study, we looked at these patterns of resting-state intrinsic functional connectivity and their relationship with ERQ scales in patients with OCD, further complementing it with DTI measures and tractography. Our study showed reduced functional connectivity between the RA and the right post-central gyrus (PCG) in OCD patients, and the connectivity between these regions was found to correlate positively with symptom severity. Moreover, on the structural level, OCD patients displayed higher MD and fractional volume (fNV) in the right cortico-spinal tract connecting these regions. Regarding correlations with ERQ scores, a group interaction effect was found in the association between reappraisal use and LA-left insula functional connectivity, primarily due to a negative association between reappraisal use and connectivity between these regions in the HC group, as was found for BLA in Study 1. On the other hand, we also observed a negative association between suppression scores and functional connectivity of the LA with the precuneus and bilateral angular gyri specifically in the OCD group. Finally, although we did not find associations between ERQ and DTI parameters within the tracts connecting these regions, we did observe between-group differences in MD and FA involving the left uncinate fasciculus and the right IFOF. In this study, the neural correlates of disrupted emotion regulation included both altered connectivity with posterior brain regions as well as between the amygdala and the insula, emphasizing the importance of integrating the role of amygdala connectivity in OCD pathophysiology.

In study 3 we used the more classical approach of looking at activation and connectivity during the cognitive reappraisal fMRI task, but including a group of participants with excess weight, who had not been studied in the past using this task. Our main finding showed that excess-weight subjects displayed decreased insula activation when experiencing negative emotions and increased activation when instructed to regulate these emotions using cognitive reappraisal. This is in keeping with our hypothesis that participants with excess weight would display persistently heightened activation in emotion generation brain regions during reappraisal. Contrary to our original hypothesis, participants with excess weight did not show hyperactivation in the insula and amygdala during negative emotion experience nor did we find hypoactivation in prefrontal regions during reappraisal. Notwithstanding, PPI connectivity analyses found that excess-weight participants had reduced negative connectivity between the right insula and the dlPFC during cognitive reappraisal compared to normal-weight controls. Decreased activation in the OFC and the cerebellum during negative emotion experience was also found in excess-weight subjects. Regarding the findings of the path analysis, increased

BMI was directly associated with decreased right insula activity during the Maintain>Observe contrast, and this decrease in right insula activation predicted poor attentional impulsiveness performance on the BIS-11, which in turn predicted lower in-scanner ratings of emotional experience during Maintain blocks, which finally predicted lower success in down-regulating emotions. At the same time, BMI was also directly associated with increased right insula activation during the Regulate>Maintain contrast, which in turn also predicted lower success measures. These findings are suggestive of poorer perception of interoceptive signals when experiencing emotions and less effective down-regulation of the emotion generation network during reappraisal.

Finally, in the last study, we aimed at characterizing a pattern of shared neural alterations in different mental health disorders when performing the cognitive reappraisal fMRI task. At first, all mental health disorders were considered, but due to the high amount of variability among them and the disparate number of studies in other less well-studied disorders, in the end we decided to only focus on mood and anxiety disorders. Our primary analysis was of the Reappraise>Maintain contrast, and the clinical group showed a decreased activation of cortical regions typically engaged by HC during cognitive reappraisal, such as the PCC, the dmPFC, the angular gyri and the left vlPFC. By contrast, patients presented increased activations in other cortical regions such as the precentral and supramarginal gyri, the left inferior occipital gyrus (IOG) and the superior parietal lobule (SPL), together with the cerebellar vermis and the left AI. These results indicate that dysfunction in the cortical network responsible for the cognitive control of negative emotions may be a characteristic feature of mood and anxiety disorders, and that aberrant hyperactivation may appear in other regions as a consequence of, or to compensate for, such impaired cortical control of emotions. Moreover, a differential pattern of activations emerged as a result of the specific reappraisal strategy being used by participants. In reinterpretation studies, the most significant differences between patients and HC were observed in the left vlPFC and the left STG, while in distancing studies, these were located in parietal regions (angular gyri and PCC), in line with our hypotheses.

Across these four studies we were able to characterize the existence of different patterns of brain activation and connectivity in the different patient samples as compared to HC, and in the different types of emotion regulation strategies. Some differences and commonalities among the patient samples could be observed, which will be described next and are visually summarized in Figure 5.1.

5.1.1. Common alterations across the studied samples

The **insula** is the region where alterations were found across all of our clinical samples and analysis methods. The insula is involved, among other processes, in the secondary processing of emotional experience through the integration of interoceptive signals with external context (Craig, 2003; Zaki, Davis and Ochsner, 2012). It also acts as an intermediate regulatory region that, when faced with negative-emotion-inducing stimuli, recruits the prefronto-parietal control network (Nelson *et al.*, 2010). A decreased activation of the insula during the experience of negative emotions might reflect a decreased ability to allocate attentional resources to engage necessary physiological feedback markers, eventually leading to less regulatory engagement (Verdejo-García *et al.*, 2015). On the other hand, increased insula activation during regulation likely reflects the unsuccessful reappraisal of emotional content and the consequent increase in emotion-related physiological markers (Wiens, 2005).

Moreover, alterations were also found regarding insular connectivity. A pattern of negative connectivity (anticorrelated regions) was found between the insula and the dlPFC in the normal-weight control group during the regulation of negative emotions, probably reflecting the control that higher-order, top-down regulatory regions exert over the insula once this region has accomplished its signaling function. In comparison to the normal-weight group, this pattern was found to be altered in excess-weight individuals. Additionally, at the level of resting-state intrinsic functional connectivity, a pattern of negative connectivity between the insula and the amygdala was found to be associated with higher cognitive reappraisal use in HC but not in OCD patients, giving further emphasis to the involvement of the insula at all levels of emotion processing. It could be that in the early phases of the emotion response, activity in the insula promotes the selection of the most appropriate reappraisal strategy when facing a particular aversive scenario via an “as-if” representation of bodily states, consequently dampening amygdala reactivity (Verdejo-Garcia, Clark and Dunn, 2012). Then, the association between these two regions would be more consolidated in those individuals making greater use of reappraisal strategies (and absent in OCD patients). As a final remark, both MD and FA were found to be altered in OCD patients in the WM tract connecting the amygdala and the insula, that is, the uncinate fasciculus, indicating higher diffusion and less integrity of this tract.

In conclusion, we were able to find a region that not only is affected across all the samples studied, but also across the different domains of neuroimaging analysis. This suggests that perhaps the focus should be shifted from deficits in the more classic bottom-up (i.e., the amygdala) and top-down (i.e., PFC) regions to intermediate integrative hubs such as the insula.

5.1.2. Differential alterations across the studied samples

Substantial differences also emerged across our different samples. Our main finding refers to the hypoactivation expected in the **prefronto-parietal control network**, which was only found in the meta-analysis of mood and anxiety disorders. For these patient groups, decreased activation during reappraisal was found in the dmPFC, the vlPFC, the PCC and the angular gyrus, consistent with our hypothesis and with the preliminary findings of individual reappraisal studies with these patient samples. Regrettably, this pattern of observations was not found in excess-weight individuals, where the main alteration was limited to the insula. There may be several reasons for this lack of findings. First, these were subjects with excess-weight but they were not a diagnosed patient group, and although individuals with these characteristics have been shown to have emotion regulation problems, their deficits might not be as severe as in mood and anxiety disorders. This deficit might be one of properly identifying emotions and allocating attentional resources to them, and not a more general shortcoming with regulatory control. Second, the individuals of this study were younger as compared to the mean age of the subjects included in the meta-analysis. It is well-known that PFC regions continue to undergo development far into young adulthood (Vink *et al.*, 2014), and thus it is possible that this sample of young adults (both normal-weight and excess-weight subjects) did not utilize frontal control over subcortical regions in the same way than an older sample would have (McRae *et al.*, 2012), thereby decreasing our chances to find significant differences between the groups. Finally, it is worth mentioning that although activation differences were not found in the PFC for our excess-weight sample, there was a finding of decreased negative connectivity between the insula and the dlPFC in this group, reflecting that the proper cross-talk between the PFC and the insula might indeed be affected.

The same lack of PFC results was encountered in the OCD patient group, which had a more comparable mean age. In this group, the results were circumscribed to posterior regions of the brain, showing a pattern of alterations that was not initially expected. It is important to bear in mind that our approach in this study was significantly different from task-activation studies done in experimental contexts, where PFC activation (and hypoactivation in patients) is typically found. In this case, we used a trait measure of emotional regulation combined with intrinsic functional connectivity at rest, so the different results obtained, although complementary, cannot be directly compared. Despite this, in Study 1 performed on HC, an association was indeed found between the use of suppression strategies and the connectivity between the amygdala and a PFC region (the dACC), showing that this more indirect approach is also able to capture PFC involvement in emotion regulation. One relevant difference

between Study 1 and Study 2 is that amygdalar sub-territories were explored in the former but not in the latter, since we decided to sacrifice this information in favor of a subject-specific anatomical definition of the amygdala performed with the FreeSurfer segmentation algorithm, which does not allow for segmenting the amygdala into its sub-divisions. Despite this, the finding of amygdala-insular connectivity associated with cognitive reappraisal was replicated in Study 2, showing again the robustness of this region's involvement in emotion regulation processes. One interpretation of our lack of PFC findings is that OCD patients may not have PFC deficits in relation with emotion regulation, or at least not as evident as in mood and anxiety disorder patients. Instead, their deficits could be more localized within posterior regions of the brain related with somatosensory processing and perspective-taking. We speculate that their pattern of disrupted parieto-limbic connectivity may be associated with a preferential use of dysfunctional emotional regulation strategies, such as suppression. Although they may not lack the necessary PFC resources to engage in reappraisal, they still may have difficulties with flexibly selecting the most adaptive strategy according to their context, becoming trapped in the use of maladaptive strategies. It is important to remember that our functional connectivity findings were further supported by consistent results in structural connectivity, finding higher diffusion in OCD patients in those tracts connecting the regions that showed differences between the HC and the OCD patient group.

Finally, two other regions were specifically found to have decreased activation during the experience of negative emotions in excess-weight individuals: the **OFC** and the **cerebellum**. The OFC, as it was mentioned in the introduction, is critically involved in the contextual valuation of emotions, while the cerebellum has also been shown to be involved in detecting, integrating and filtering emotional information (Strata, Scelfo and Sacchetti, 2011; Strata, 2015). The interpretation of these findings dovetails with the interpretation of the insula, and despite not analyzing the Maintain>Observe contrast in our meta-analysis, we can hypothesize that at least cerebellar activity might show the same pattern, with this activation being increased during the regulation period in mood and anxiety disorder patients as compared to HC. Likewise, mood and anxiety disorder patients also showed increased activation as compared to HC during regulation in the IOG, which may again reflect greater attention given to negative emotional stimuli (Wiggins *et al.*, 2016), and in other prefronto-parietal regions, which may be recruited to compensate for their deficits, recruitment that may not be necessary in excess-weight individuals.

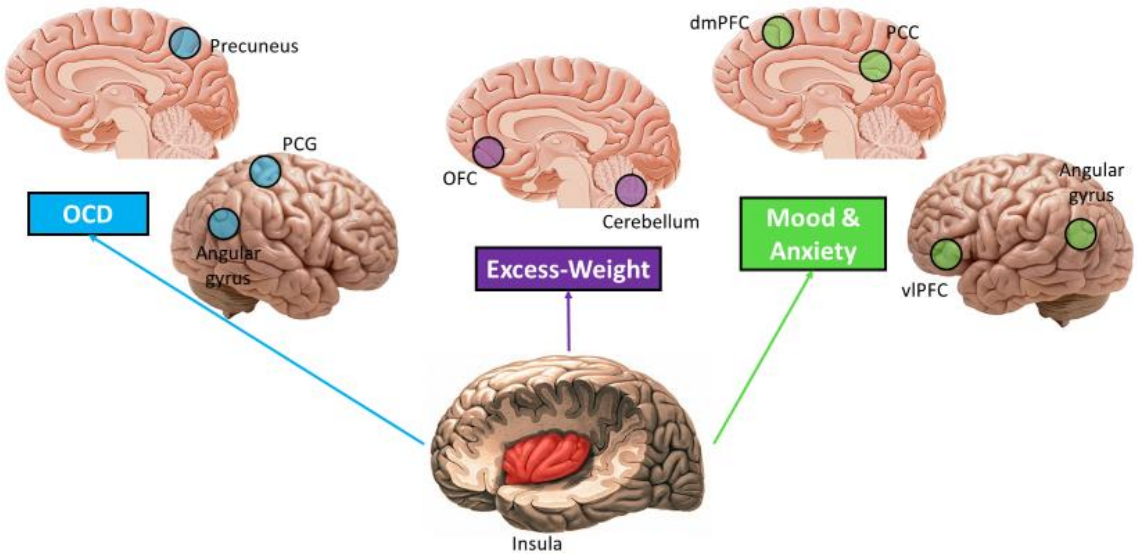

Figure 5.1. Visual representation of the main results of the 4 studies, showing the regions specifically altered in each sample as well as the insula, whose alteration is shared across samples.

5.2. Implications for future research

The present thesis has attempted to approach the study of the neurobiological bases of emotion regulation by using an integrative view, including different neuroimaging modalities as well as different patient groups. The four studies presented herein constitute a step forward in the characterization of how the brain responds to emotional situations and regulates them, and how changes in this response pattern may compromise flexible and advantageous behaviors across different pathologies.

We bring this thesis to an end by discussing some future lines of research in the field of emotion regulation and mental health disorders. In the first place, up to date, most of the literature has been cross-sectional, but more longitudinal studies are needed to clarify the directionality of the relationships between the variables related to emotion regulation and mental health disorders. In this vein, an important question is whether difficulties in emotion regulation are a risk factor for disorders' onset or a mere epiphenomenon of these disorders. Such knowledge should help in identifying the most optimal strategies for treatment and prevention of mental health disorders.

Regarding treatment, individual-level interventions could be designed to teach people healthier emotion regulation patterns (Gross and Muñoz, 1995), with more specific interventions targeting individuals who have clinical diagnoses (Campbell-Sills, Ellard and Barlow, 2014; Joorman and Siemer, 2014). Actually, many of our pharmacological and

psychosocial interventions for psychiatric disorders already have an emotion regulation component, but much remains to be learned about how exactly each type of intervention influences particular aspects of emotion regulation. Moreover, there are many psychological interventions with an increasing focus on emotion regulation training, particularly within the context of third generation therapies (Carvalho *et al.*, 2017), such as acceptance and commitment therapy (ACT; Hayes, Strosahl and Wilson, 2012), emotion regulation therapy (Mennin and Fresco, 2014), dialectical behavior therapy (Neacsiu, Bohus and Linehan, 2014), attentional bias modification (MacLeod and Grafton, 2014), affect regulation training (Berking and Schwarz, 2014), and mindfulness training (Farb *et al.*, 2014). Although these interventions have shown promise for the treatment of different disorders, it is also possible to improve emotion regulation using technical devices that alter activity in brain regions that are involved in emotion regulation processes. This is the case for brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS) (Ochsner and Gross, 2014). But there are several problems with these techniques: their exact mechanism of action remains unknown, they are invasive (DBS has only been used in very severe treatment-resistant patients), and in the case of rTMS and tDCS, subcortical regions cannot be targeted. By contrast, neurofeedback (NFB) has emerged as a non-invasive technique that overcomes some of these issues. First developed for EEG, this technique uses real-time information from the brain to deliver feedback to the subjects in order to help them train the process being learned. In the past years, its use has increased also in fMRI experiments, and it has been tested to help train cognitive reappraisal strategies, with some promising results (Sarkheil *et al.*, 2015; Zilverstand *et al.*, 2015). Despite this, much research is still needed for us to be able to see NFB as an ecological and cost-effective treatment for mental health disorders, and this will probably be achieved by combining EEG and fMRI NFB approaches.

A final consideration regarding treatment is that, as we have seen in the results of this thesis, different neural correlates of emotion dysregulation may emerge in different patient samples. Or, to be consistent with the RDoC framework, the different neural patterns observed may relate to different processes and deficits, with some of these being common across disorders, but not all of them. This is relevant when choosing an appropriate treatment, which ideally should be individually customized and neurobiologically informed, and not solely based on diagnosis. In this sense, taking into account our findings, we venture to put forward the following recommendations:

- In the case of OCD, perhaps their training should be aimed at improving flexible switching between strategies, identifying which is more appropriate as a function of the context.
- In the case of excess-weight individuals, training should be mainly aimed at improving emotional awareness. This appears to be a crucial rate-limiting factor for successfully regulating emotions (Barrett *et al.*, 2001), and, according to our results, excess-weight individuals could already be failing at this point, thereby making it more difficult to regulate emotions as a result.
- In the case of mood and anxiety disorders, their pattern of deficits encompassed the typical fronto-parietal control network. In this line, one interesting open issue is whether non-affective cognitive control training yields transferable gains to improve control over affective stimuli (Schweizer, Hampshire and Dalgleish, 2011). Moreover, until patients develop the necessary cognitive resources to apply more complex strategies such as reappraisal, other less demanding strategies can be initially trained (i.e., distraction; Sheppes *et al.*, 2011).
- Finally, since all groups of patients showed some kind of alteration in the insula, probably all of them would benefit from improving emotion recognition and awareness, since this is a necessary step before any emotion regulation strategy may be applied.

5.3. Limitations

The results obtained in the studies included in this thesis have to be considered within the context of some methodological limitations. Besides the specific limitations of each study, described in detail in each publication, there are some general limitations applicable to all current results.

The most important limitation when including patient samples relates to pharmacological treatment. Most of the OCD patients were under medication in Study 2, as was the case for patients from some of the studies in our meta-analysis (Study 4). Pharmacological treatment has been suggested as a likely confounder, especially in functional connectivity studies (Posner *et al.*, 2014), although it is not wholly clear in what direction it might bias results. Despite this, it is important to note that treatment doses in OCD patients were stable during the three months preceding the fMRI, and we did not find any relationship between our findings and pharmacological treatment (see Supplementary Material of Study 2 and Study 4).

Moreover, all of our studies were cross-sectional, which does not allow for the establishment of causality relationships between relevant variables and their neural correlates. It would be interesting for future studies to assess if the neural alterations described in our studies persist after symptom recovery, as well as if they precede the disorder's onset and therefore may anticipate it.

Finally, as has been already mentioned, cognitive reappraisal and expressive suppression strategies do not comprehensively represent all emotion regulation strategies, so generalization of our findings is limited to specific types of strategies. Moreover, the focus of attention is recently being moved from the oversimplification of adaptive/maladaptive strategies to the study of flexibly changing between strategies, which probably reflects the deficits found in patients with mental health disorders more accurately. Nevertheless, it is well known that the patient groups assessed here do have problems in applying cognitive reappraisal and tend to make use of suppression when faced with negative emotions.

A similar limitation in the generalizability of our findings is that we exclusively focused on the regulation of negative emotions. However, the study of the regulation of positive emotions is equally important, as for example the regulation of reward processing. This may be critical in groups of individuals with impulsivity problems, such as excess-weight subjects, but also in patients featuring anhedonia, a symptom typically found in depressive disorders. It would be of great interest to ascertain whether the same or different neural correlates emerge for deficits in regulating negative and positive emotions, as this would also shed light in how treatments should be customized for these patient groups.

CONCLUSIONS

6. Conclusions

We draw the following conclusions from the work presented in this thesis:

- The dispositional use of cognitive reappraisal and expressive suppression in HC subjects shows different neural correlates, with reappraisal use being related to BLA-insular and SMA intrinsic functional connectivity, and suppression use being associated to BLA-dACC and CMA-SMA functional connectivity.
- Results across the different studies support the notion of a primary functional alteration in the insula across OCD, mood and anxiety disorders, and excess-weight individuals, a region that is critically involved in emotional awareness and valuation.
- OCD patients show decreased functional and structural connectivity between the RA and the right PCG. Moreover, the association between amygdala's intrinsic functional connectivity and habitual reappraisal and suppression use is altered in comparison with HC, with microstructural alterations in underlying WM tracts connecting these regions.
- Excess-weight individuals show decreased attentional involvement during the experimentation of emotions, and increased emotional reactivity during emotion regulation, as indicated by decreased insula, OFC, and cerebellum activity during the Maintain>Observe contrast, and increased insula activity during the Regulate>Maintain contrast.
- Other alterations in mood and anxiety disorders encompass decreased activations in the prefronto-parietal regulatory network during cognitive reappraisal, as well as increased activations in attentional and parietal compensatory regions.
- According to our findings, there are deficits in emotion regulation shared across different disorders, in line with the transdiagnostic RDoC framework, although there are also specific deficits for different disorder groups, which further emphasizes the need of subject-wise brain-based treatments targeting individual needs.

RESUM

7. Summary in Catalan

Resum en català

1. INTRODUCCIÓ

1.1. La regulació emocional

Les emocions formen una part essencial de les nostres vides. Ens ajuden a dirigir l'atenció cap a les característiques rellevants del nostre ambient, optimitzen els nostres inputs sensorials, ajusten la pressa de decisions, preparen la resposta comportamental, faciliten les interaccions socials, i milloren la memòria episòdica (Gross, 2014). Tot i així, les emocions també poden perjudicar-nos, especialment quan el seu tipus, intensitat, o duració no és apropiat per a una situació concreta. En moments així, recorrem a una habilitat inherentment humana: la regulació emocional.

S'han proposat diferents models de regulació emocional al llarg dels anys, i l'interès en aquest camp ha crescut exponencialment a les últimes dècades. Un model àmpliament utilitzat en l'estudi de la regulació de les emocions és el del *procés de regulació emocional* (Gross, 1998b). Segons aquest model, hi ha cinc moments temporals en els quals els individus podem regular les nostres emocions, representant cinc famílies de processos de regulació emocional: selecció de la situació, modificació de la situació, desplegament atencional, modificació cognitiva, i modulació de resposta. Aquestes famílies es distingeixen pel moment temporal en el procés de generació d'emocions en el qual tenen el seu impacte principal, permetent distingir de manera general entre estratègies enfocades a l'antecedent, que són aquelles que tenen lloc a l'inici del procés de generació d'emocions (selecció de la situació, modificació de la situació, desplegament atencional i modificació cognitiva), i estratègies enfocades a la resposta, que són aquelles que tenen lloc cap al final del procés de la generació d'emocions (modulació de resposta).

Una de les estratègies que més s'ha estudiat és la reavaluació cognitiva, un tipus d'estratègia de modificació cognitiva que consisteix en canviar la manera en què avaluem una situació per modificar el seu significat emocional, ja sigui canviant la manera en què pensem sobre la situació o sobre la nostra capacitat de gestionar les exigències emocionals. Podem trobar dos tipus de sub-estratègies de reavaluació cognitiva: la reinterpretació, que consisteix en canviar el significat de l'estímul de manera que el resultat de la situació sigui més positiu (p.e., decidir que una imatge de gent plorant fora d'una església fa referència a una boda i no a un funeral);

i el distanciament, que consisteix en racionalitzar el contingut d'una situació adoptant la perspectiva d'un observador objectiu (p.e., al veure una escena d'una persona ferida, imaginar-se que la persona en realitat és una actriu). Un altra estratègia que també s'ha estudiat molt és la supressió expressiva, que forma part de les estratègies de modulació de resposta i consisteix en intentar inhibir l'expressió de les emocions.

A més, els diferents tipus d'estratègies poden tindre diferents conseqüències, tant a curt com a llarg termini. Les dos estratègies que més sovint s'han comparat són la reavaluació cognitiva i la supressió expressiva, trobant que l'ús d'estratègies de supressió comporta una disminució en l'experiència d'emocions positives però no negatives (Gross and Levenson, 1993, 1997; Gross, 1998a), un augment en la resposta del sistema nerviós simpàtic (Gross and Levenson, 1993, 1997; Gross, 1998a; Harris, 2001; Demaree *et al.*, 2006), i una major activació en regions del cervell involucrades en la generació d'emocions com l'amígdala (Goldin, McRae, *et al.*, 2009). D'altra banda, l'ús d'estratègies de reavaluació s'ha vist vinculat a una disminució en l'experiència d'emocions negatives i un augment en les positives (Gross, 1998a; Ray *et al.*, 2010; Lieberman *et al.*, 2011; Szasz, Szentagotai and Hofmann, 2011; Wolgast, Lundh and Viborg, 2011; Feinberg *et al.*, 2012), cap impacte o una disminució en la resposta del sistema nerviós simpàtic (Gross, 1998a; Wolgast, Lundh and Viborg, 2011; Kim and Hamann, 2012; Shiota and Levenson, 2012), i una menor activació en regions del cervell involucrades en la generació d'emocions com l'amígdala (Ochsner and Gross, 2008; Ochsner *et al.*, 2004; Goldin *et al.*, 2009; Kanske *et al.*, 2011) i l'estriat ventral (Staudinger *et al.*, 2009).

1.2. Correlats neurals de la regulació emocional

En els últims anys s'ha fet un gran esforç en intentar entendre els mecanismes neurobiològics que hi ha sota la generació i regulació d'emocions, mitjançant l'ús de tècniques de neuroimatge. La majoria d'estudis de ressonància magnètica funcional (RMf) s'han centrat en estudiar l'estratègia de reavaluació cognitiva. Així, gràcies a diferents estudis individuals i meta-anàlisis s'ha vist que hi ha diferents sistemes neurals implicats en general i aplicar reavaluacions, que formen una xarxa prefronto-parietal de control de dalt-a-baix (Ochsner and Gross, 2005). En primer lloc, l'escorça prefrontal dorsolateral (dlPFC per les sigles en anglès) i posterior, junt amb regions parietals inferiors generalment implicades en atenció selectiva i memòria de treball, s'utilitzarien per dirigir l'atenció cap a les característiques de l'estímul rellevants per la reavaluació i al mateix temps mantenir en la ment els objectius de la reavaluació i el contingut de les pròpies reavaluacions (Miller, 2000; Wager and Smith, 2003; Wager, Jonides and Reading, 2004). En segon lloc, les regions dorsals de l'escorça cingulada

anterior (ACC per les sigles en anglès) implicades en la supervisió del rendiment poden ajudar a monitoritzar fins a quin punt les pròpies reavaluacions estan modificant de la manera esperada la resposta emocional (Botvinick, Cohen and Carter, 2004). En tercer lloc, les regions de l'escorça prefrontal ventrolateral (vlPFC per les sigles en anglès) implicades en seleccionar respostes apropiades amb els objectius i inhibir respostes no apropiades i en recuperar informació de la memòria semàntica, s'utilitzarien per a seleccionar deliberadament una nova reavaluació de l'estímul apropiada tenint en compte l'avaluació inicial que es tenia de l'estímul (Thompson-Schill, Bedny and Goldberg, 2005; Badre and Wagner, 2007). Finalment, tenint en compte que la reavaluació comporta centrar-se en el propi estat emocional o en el d'altres i interpretar-lo o reinterpretar-lo, regions de l'escorça prefrontal dorsomedial (dmPFC per les sigles en anglès) implicades en l'atribució d'estats mentals també poden trobar-se actives durant la reavaluació cognitiva (Olsson and Ochsner, 2008; Mitchell, 2009). Pel que fa a les regions que són modulades per la reavaluació cognitiva, es tractaria de regions involucrades en la generació de les emocions, com és el cas de l'amígdala, i en menor measura l'estriat ventral, l'ínsula, i l'escorça prefrontal ventromedial (vmPFC per les sigles en anglès) (Ochsner and Gross, 2005, 2008).

D'altra banda, pel que fa a la supressió expressiva, s'ha estudiat menys en el context de la RMf, però els estudis actuals suggereixen que, mentre que aquesta estratègia també està associada a una activació de l'escorça prefrontal, també es donaria una activació de l'amígdala i l'ínsula, diferenciant-se així de la reavaluació cognitiva (Goldin, McRae, *et al.*, 2009; Hayes *et al.*, 2010; Vanderhasselt *et al.*, 2013).

1.3. Dèficits de regulació emocional en els trastorns psiquiàtrics

Durant dècades s'ha explorat la regulació emocional com un procés rellevant en l'inici i el manteniment de diferents tipus de psicopatologies, i de manera més recent s'ha considerat un possible factor transdiagnòstic als trastorns psiquiàtrics (Kring and Sloan, 2010; Aldao, 2012). Els pacients de diferents trastorns tenen problemes amb la correcta identificació de les emocions, la selecció d'una estratègia de regulació emocional adequada, la implementació d'aquestes estratègies, i la supervisió de que estiguin aplicant-se correctament (Fernandez, Jazaieri and Gross, 2016). Per exemple, aquests subjectes fan menor ús d'estratègies de reavaluació cognitiva, considerades més adaptatives degut a les conseqüències ja mencionades, i més ús d'estratègies de supressió expressiva, considerades menys adaptatives (Aldao, Nolen-Hoeksema and Schweizer, 2010). És per això que recentment s'ha proposat la regulació emocional com a un nou domini en el marc de referència dels *Research Domain*

Criteria (RDoC) del *National Institute for Mental Health* (NIMH), ja que aquesta és rellevant en múltiples trastorns i també en l'ampli rang del funcionament normal, no és reductible als dominis més bàsics ja existents al RDoC, i conté evidència empírica a través de les diferents unitats d'anàlisi definides al RDoC (gens, molècules, cèl·lules, circuits, fisiologia, comportament, qüestionaris auto-administrats, i paradigmes).

A més, des del punt de vista dels correlats neurals de la regulació emocional, aquests també s'han vist afectats a diferents trastorns psiquiàtrics (Johnstone and Walter, 2014). D'acord amb el model neural de la regulació emocional de Phillips (Phillips *et al.*, 2003a, 2003b), la majoria de trastorns psiquiàtrics poden considerar-se com la conseqüència d'un mal balanç en la interacció entre els sistemes ventrals i dorsals del cervell, amb la xarxa regulatòria dorsal essent incapaç de disminuir la hiperactivació de la xarxa ventral. El sistema ventral comprendria l'amígdala, l'ínsula, l'estriat ventral, l'ACC ventral, i el vmPFC/escorça orbitofrontal medial (OFC), mentre que el sistema dorsal estaria format per l'hipocamp, l'ACC dorsal, i l'escorça prefrontal (PFC) dorsal. Tot i així, aquest model dorsal-ventral no pot explicar la totalitat dels dèficits trobats, ja que trobem que també hi ha regions ventrals que exercirien funcions regulatòries sobre les emocions (p.e., el vlPFC, com s'ha comentat anteriorment) (Taylor and Liberzon, 2007). Alteracions en l'activació i la connectivitat del PFC i l'amígdala, entre altres regions, s'han trobat a diferents trastorns psiquiàtrics, com per exemple en els trastorns afectius (Phillips, Ladouceur and Drevets, 2008; Rive *et al.*, 2013), d'ansietat (Campbell-Sills, Ellard and Barlow, 2014), el trastorn obsessiu-compulsiu (TOC; de Wit *et al.*, 2015), i també en el trastorn per l'ús de substàncies (Kober, 2014), en joc patològic (Navas *et al.*, 2017), i en individus amb excés de pes (Volkow *et al.*, 2013).

1.4. Motivació de l'estudi

La regulació emocional és un procés críticament necessari per gestionar de manera apropiada les emocions en el nostre dia a dia. Hi ha diferents estratègies de regulació emocional que comporten diferents conseqüències afectives, cognitives i socials. Encara més important, aquestes pareixen estar afectades als trastorns psiquiàtrics, essent els dèficits de regulació emocional una característica transdiagnòstica que pot ser considerada en el context del RDoC.

Diferents estudis i meta-anàlisis de RMf han mostrat un patró consistent d'activació neural durant la regulació emocional en controls sans (principalment en tasques de reavaluació cognitiva), que consisteix en una xarxa prefronto-parietal de regions regulatòries, que s'encarrega de regular a la baixa l'activació del sistema límbic (incloent l'amígdala). En comparació, als trastorns psiquiàtrics trobem una menor quantitat d'estudis de neuroimatge i

regulació emocional, havent-se estudiat principalment en trastorns afectius i d'ansietat. Resultats preliminars indiquen que el sistema límbic podria estar hiperactiu i les regions regulatòries prefrontals es trobarien alterades, amb híper i hipo-activacions en funció de la tasca.

Es necessiten més estudis per poder determinar si s'observa el mateix patró d'activacions neurals afectades en diferents trastorns psiquiàtrics, o si hi ha un patró específic per cada trastorn, tenint en compte que en la majoria de trastorns predominen els dèficits de regulació emocional d'una manera o altra. A més, la informació que tenim provinent d'estudis d'activació durant una tasca també es pot complementar utilitzant altres mètodes d'anàlisis en neuroimatge. Per exemple, més informació sobre aquests dèficits es podria obtenir estudiant els patrons intrínsecs de connectivitat funcional entre regions, en compte de l'activació aïllada d'aquestes, tant durant l'execució d'una tasca com durant el repòs. Finalment, la connectivitat estructural subjacent també pot ajudar a clarificar el tipus d'alteracions que es troben en pacients amb dificultats en la regulació de les emocions, i si aquestes alteracions estructurals es corresponen amb les dades funcionals.

2. OBJECTIUS

L'objectiu general d'aquesta tesi és oferir noves dades respecte als correlats neurals de la regulació emocional en mostres clíniques i controls sans. Utilitzant diferents modalitats de neuroimatge (des de connectivitat estructural i funcional, fins estudis d'activació en tasca i meta-anàlisis), esperem oferir una millor descripció d'aquests correlats i la seua relació amb diferents estratègies de regulació emocional, avaluant mostres de pacients amb trastorns afectius, d'ansietat, i TOC en comparació amb controls sans, així com individus amb excés de pes en comparació amb individus amb pes normal.

Estudi 1:

- Examinar, en una mostra de controls sans, l'associació entre els patrons de connectivitat funcional de l'amígdala durant el repòs i l'ús habitual de la reavaluació cognitiva i la supressió expressiva mesurat amb el Qüestionari de Regulació Emocional (ERQ per les sigles en anglès).
- Estudiar aquests patrons de connectivitat funcional depenent dels diferents territoris de l'amígdala, específicament diferenciant entre l'amígdala basolateral (BLA per les sigles en anglès) i l'amígdala centromediana (CMA per les sigles en anglès).

Estudi 2:

- Determinar si hi ha diferències en la connectivitat funcional en repòs de l'amígdala esquerra (LA per les sigles en anglès) i l'amígdala dreta (RA per les sigles en anglès) entre pacients amb TOC i controls sans.
- Identificar si la connectivitat funcional alterada de l'amígdala s'associa amb alteracions en els tractes de matèria blanca, utilitzant tècniques d'imatge per tensor de difusió (DTI per les sigles en anglès).
- Investigar l'associació entre la connectivitat funcional i estructural i la severitat dels símptomes de TOC, així com l'ús habitual d'estratègies de reavaluació cognitiva i supressió expressiva mesurades amb l'ERQ.

Estudi 3:

- Comparar els correlats neurals en una tasca de reavaluació cognitiva entre individus amb excés de pes i individus amb pes normal.
- Explorar la interacció entre els sistemes de generació i regulació de les emocions utilitzant anàlisis d'interacció psicofisiològica (PPI per les sigles en anglès), el qual avalua els canvis en la connectivitat entre aquests sistemes durant les condicions d'experimentar i de regular emocions.
- Explorar les associacions complexes entre la regulació emocional, la impulsivitat, la motivació d'apropament/evitació i l'addicció al menjar, mitjançant l'ús d'anàlisis de camins (*path analysis*).

Estudi 4:

- Identificar, mitjançant un meta-anàlisi d'estudis de RMf utilitzant una tasca de reavaluació cognitiva en pacients amb trastorns afectius o d'ansietat, els correlats neurals dels dèficits de regulació emocional en aquestes mostres.
- Explorar, en el context de la regulació emocional alterada, els correlats neurobiològics potencialment diferents entre les estratègies de reinterpretació i de distanciament.

3. METODOLOGIA

El conjunt de mètodes utilitzats per explorar els correlats neurals de la regulació emocional en les mostres descrites es presenta a continuació.

3.1. Condicions experimentals

- Seqüència en estat de repòs: Els participants estan desperts però sense realitzar cap tasca, en un estat de relaxació, i amb els ulls oberts o tancats (tancats en els nostres estudis). S'ha utilitzat als Estudis 1 i 2.
- Tasca de reavaluació cognitiva: És una tasca de RMf on als participants se'ls presenten una sèrie d'estímuls visuals amb contingut neutre o negatiu, i se'ls demana o bé que observen les imatges neutres (bloc Observar), que experimenten les emocions provocades per les imatges negatives (bloc Experimentar), o que intenten regular les emocions provocades per les imatges negatives (bloc Reavaluar). Aquesta tasca s'ha utilitzat als Estudis 3 i 4.

3.2. Qüestionaris

El qüestionari més rellevant en el context de la regulació emocional que s'ha utilitzat és l'ERQ (Gross and John, 2003), i s'ha utilitzat als Estudis 1, 2 (la versió espanyola; Cabello *et al.*, 2013) i 3. Aquest qüestionari avalua l'ús habitual d'estratègies de reavaluació cognitiva i supressió expressiva, i consisteix en 10 ítems als quals els participants han de respondre en una escala de 7 punts tipus Likert.

3.3. Anàlisis de dades de comportament

Per analitzar les dades de comportament dels diferents estudis s'ha utilitzat el paquet estadístic per les ciències socials (SPSS per les sigles en anglès; Chicago, IL, USA). A més, en l'Estudi 3, s'ha utilitzat el software AMOS 18.0 per realitzar el *path analysis* (Byrne, 2010).

3.4. Anàlisis d'imatge per ressonància magnètica (RM)

- RM estructural: A tots els estudis les imatges estructurals s'han utilitzat per ajudar en el corregistre de les imatges funcionals, permetent així una millor especificitat anatòmica gràcies a la major resolució d'aquesta imatge. D'altra banda, a l'Estudi 2 s'ha utilitzat altre tipus d'imatge estructural derivada de la RM, la imatge de difusió (DWI per les sigles en anglès), que mitjançant el DTI permet estudiar l'organització, coherència i direcció dels tractes de matèria blanca.
- RM funcional: La RMf està basada en la senyal depenent del nivell d'oxigenació de la sang (BOLD per les sigles en anglès), una mesura indirecta d'activitat cerebral. A partir de les propietats d'aquesta senyal, poden derivar-se diferents aproximacions estadístiques per determinar quines àrees del cervell s'utilitzen durant un procés psicològic específic. En concret, s'ha utilitzat la RMf basada en una tasca (la de

reavaluació cognitiva) als Estudis 3 i 4, el PPI a l'Estudi 3, i l'anàlisi de connectivitat funcional durant el repòs als Estudis 1 i 2.

- Meta-anàlisis de neuroimatge: A més dels estudis individuals de neuroimatge estructural o funcional, també existeix software meta-analític per combinar dades de neuroimatge i determinar quins resultats són constants a través dels estudis. En concret, nosaltres hem utilitzat el software *Anisotropic Effect-Size Signed Differential Mapping* (AES-SDM) a l'Estudi 4, un software que permet combinar informació sobre coordenades reportades a articles amb dades originals de mapes estadístics (SPMs per les sigles en anglès).

4. RESULTATS

Estudi 1:

- La connectivitat funcional entre la BLA i l'àrea suplementària motora (ASM) i l'ínsula s'associa negativament amb l'ús d'estratègies de reavaluació cognitiva, de manera que a major ús d'aquestes estratègies, més connectivitat negativa (anticorrelació) entre aquestes regions.
- La connectivitat funcional entre la BLA i l'ACC dorsal (dACC) correlaciona positivament amb l'ús d'estratègies de supressió expressiva.
- Pel que fa a la CMA, una major connectivitat negativa amb l'ASM s'associa amb més ús d'estratègies de supressió.

Estudi 2:

- En pacients amb TOC, la connectivitat funcional entre la RA i el gir post-central dret es troba disminuïda en comparació amb controls sans, i a més la connectivitat entre aquestes regions correlaciona amb la severitat dels símptomes de TOC. A nivell estructural, els pacients amb TOC tenen una major difusió i un major volum en el tracte cortico-espinal dret que connecta aquestes regions.
- Pel que fa a les correlacions amb les puntuacions de l'ERQ, hi ha una interacció de grup en l'associació entre l'ús de la reavaluació cognitiva i la connectivitat funcional entre la LA i l'ínsula esquerra, deguda principalment a l'associació negativa entre l'ús de la reavaluació i la connectivitat entre aquestes regions al grup de controls sans.
- Un major ús d'estratègies de supressió s'associa negativament amb la connectivitat entre la LA i el precuneus i el gir angular bilateral, específicament al grup de pacients amb TOC.

- Tot i no haver associació entre els tractes de matèria blanca connectant aquestes regions i els valors de l'ERQ, sí s'observa una diferència de grup en els paràmetres de DTI d'aquests tractes, amb el grup de pacients mostrant una major difusió i una menor anisotropia fraccional.

Estudi 3:

- Individus amb excés de pes tenen una menor activació de l'ínsula quan estan experimentant emocions i una major activació quan han de regular-les, en comparació amb individus amb pes normal.
- Individus amb excés de pes també tenen una menor activació de l'OFC i el cerebel en els blocs d'experimentar les emocions negatives.
- Pel que fa a l'anàlisi de PPI, els subjectes amb excés de pes tenen una menor connectivitat negativa entre l'ínsula i el dlPFC dret durant la reavaluació cognitiva en comparació amb els individus amb pes normal.
- El *path analysis* indica que a més índex de massa corporal (IMC), menys activació en l'ínsula durant l'experimentació de les emocions, i aquesta disminució en activació prediu més impulsivitat, que al mateix temps prediu unes puntuacions més baixes en la valoració de l'emoció negativa experimentada durant els blocs d'Experimentar, i finalment un menor èxit alhora de disminuir les emocions. L'IMC també s'associa amb més activació de l'ínsula durant la regulació de les emocions, que al mateix temps prediu el menor èxit de regulació d'aquestes.

Estudi 4:

- El grup de pacients mostra una disminució en l'activació de regions corticals típicament reclutades pels controls sans en tasques de reavaluació cognitiva: l'escorça cingulada posterior (PCC per les sigles en anglès), el dmPFC, el gir angular i el vlPFC esquerre.
- D'altra banda, els pacients presenten una major activació en altres regions corticals com el gir precentral, el gir supramarginal, el gir inferior occipital i el lòbul parietal superior, així com en l'ínsula anterior esquerra i la vermis del cerebel.
- Trobem un patró diferent d'activacions en funció de l'estratègia de reavaluació cognitiva. Als estudis de reinterpretació, les diferències més significatives entre pacients i controls es troben al vlPFC esquerre i el gir temporal superior esquerre, mentre que als estudis de distanciament, aquestes estan localitzades en regions parietals (gir angular i PCC).

5. DISCUSSIÓ

A través dels diferents estudis hem pogut caracteritzar l'existència de patrons diferents d'activació i connectivitat cerebral en les diferents mostres de pacients comparats amb controls sans, i en els diferents tipus d'estratègies de regulació emocional. S'han vist algunes alteracions comunes així com diferències entre les diferents mostres clíniques, que es descriuen a continuació.

5.1. Alteracions comunes en les mostres estudiades

L'ínsula és la regió que hem trobat de manera consistent a través de les diferents mostres clíniques i els diferents mètodes d'anàlisi. Aquesta regió s'encarrega de processar l'experiència emocional integrant-la amb les senyals interoceptives i el context extern (Craig, 2003; Zaki, Davis and Ochsner, 2012), i també actua com una regió de regulació intermèdia encarregada de reclutar la xarxa de control prefronto-parietal quan es troba davant d'un estímul que indueix una emoció negativa (Nelson *et al.*, 2010). La menor activació d'aquesta regió durant l'experimentació d'emocions pot representar una menor habilitat per assignar recursos atencionals i generar els marcadors de retroalimentació fisiològica necessaris (Verdejo-García *et al.*, 2015), mentre que la major activació durant la regulació reflecteix el fracàs en reavaluar el contingut emocional negatiu i l'augment d'aquests marcadors fisiològics (Wiens, 2005).

Alteracions en l'ínsula també s'han vist al nivell de la connectivitat, tant funcional en repòs i en tasca, com estructural. En conclusió, aquesta regió es veu afectada a diferents mostres però també a través de les diferents modalitats d'anàlisi en neuroimatge. Pot ser seria interessant canviar el centre d'atenció dels dèficits més clàssics en regions com l'amígdala i l'escorça prefrontal i posar-lo en centres d'integració com l'ínsula.

5.2. Alteracions diferents en les mostres estudiades

També s'han trobat diferències entre les mostres estudiades. La diferència principal s'ha donat en la xarxa de control prefronto-parietal, que només hem trobat hipoactivada de manera evident al meta-anàlisi de trastorns afectius i d'ansietat. En els individus amb excés de pes, la hipoactivació durant la regulació s'ha vist limitada a l'ínsula, tot i que aquesta manca de resultats prefrontals podria deure's al fet que la mostra d'aquest estudi era considerablement més jove que a la resta, i l'escorça prefrontal continua desenvolupant-se fins l'edat adulta (Vink *et al.*, 2014). D'aquesta manera, és possible que aquesta mostra d'adults joves (tant els de pes normal com els d'excés de pes) no hagen utilitzat el control frontal sobre regions subcorticals de la mateixa manera que ho faria una mostra més gran (McRae *et al.*, 2012). Pel

que fa als pacients amb TOC, aquests sí tenien una mitjana d'edat més comparable, tot i així els resultats s'han localitzat en regions més posteriors del cervell. En aquest cas és important recordar que l'aproximació utilitzada en aquest estudi és significativament diferent als estudis basats en activacions durant una tasca que utilitzen un context experimental, i on normalment es troba l'activació en el PFC (o hipoactivació en pacients). En el nostre cas, hem utilitzat una mesura tret de regulació emocional en combinació amb la connectivitat funcional intrínseca durant el repòs, de manera que els resultats obtinguts tot i ser complementaris, no poden equiparar-se. Tot i així, és possible que els pacients amb TOC no presenten dèficits en les regions del PFC, o al menys no de manera tan evident com els pacients amb trastorns afectius i d'ansietat. En canvi, els seus dèficits estarien localitzats a regions posteriors del cervell relacionades amb el processament somatosensorial i de presa de perspectiva. Els dèficits d'aquests pacients podrien estar relacionats amb un ús predominant d'estratègies de regulació poc adaptatives com la supressió, de manera que tot i tenir els recursos prefrontals necessaris per implementar la reavaluació, pot ser tenen problemes alhora de seleccionar de manera flexible l'estratègia més adaptativa segons el context.

5.3. Implicacions generals per a la recerca

Aquesta tesi ha fet una aproximació a l'estudi de les bases neurobiològiques de la regulació emocional amb una intenció integradora, incloent tant diferents modalitats de neuroimatge com diferents grups de pacients. Els quatre estudis presentats constitueixen un avanç en la caracterització de com el cervell respon davant situacions emocionals i com les regula, i també de com canvis en aquest patró de resposta poden comprometre el comportament adaptatiu i flexible a través de diferents patologies.

A continuació es discutiran algunes línies de futur en el camp de la recerca en regulació emocional i trastorns psiquiàtrics. En primer lloc, la majoria de la bibliografia fins ara consisteix en estudis transversals, però es necessiten més estudis longitudinals per poder clarificar la direccionalitat de les relacions entre les variables de regulació emocional i els trastorns psiquiàtrics. Així, una qüestió important és si les dificultats en la regulació de les emocions són un factor de risc per a l'inici d'un trastorn o només un epifenomen d'aquests trastorns.

Pel que fa al tractament, en el futur haurien de dissenyar-se intervencions a nivell individual per ensenyar a la gent patrons de regulació emocional més sans (Gross and Muñoz, 1995), amb intervencions més específiques per aquells individus amb un diagnòstic clínic (Campbell-Sills, Ellard and Barlow, 2014; Joorman and Siemer, 2014). Cada vegada s'està posant més èmfasi en l'entrenament de la regulació emocional dintre de les intervencions psicològiques,

especialment en el context de les teràpies de tercera generació (Carvalho *et al.*, 2017). Tot i que aquestes intervencions han donat resultats prometedors per al tractament de diferents trastorns, també és possible millorar la regulació emocional mitjançant aparells tecnològics que modifiquen l'activitat de les regions cerebrals involucrades en els processos de regulació emocional. Un exemple són les tècniques d'estimulació cerebral, però aquestes solen ser tècniques invasives, el qual representa un important desavantatge. En canvi, la neurorretroalimentació (NFB per les sigles en anglès) consisteix en una tècnica no invasiva que utilitza la informació del cervell en temps real per informar al subjecte sobre l'èxit o el fracàs alhora de regular una regió i així ajudar en l'entrenament del procés psicològic que s'està aprenent. Aquesta tècnica s'ha utilitzat ja per entrenar la reavaluació cognitiva durant la RMf amb resultats prometedors, però encara s'ha d'avançar molt fins poder considerar-la com un tractament ecològic i rendible per als trastorns psiquiàtrics.

Una última consideració respecte al tractament és que, com que s'han vist correlats neurals dels dèficits de regulació emocional tant comuns com diferents als diferents grups de pacients, seria convenient adaptar el tractament de manera individualitzada en funció de la neurobiologia subjacent. En aquesta línia, es podrien tindre en compte les següents consideracions:

- En el cas del TOC, podria ser beneficiós entrenar a canviar de manera flexible entre l'ús de diferents estratègies de regulació, identificant quina és més apropiada en funció del context.
- En el cas dels individus amb excés de pes, l'entrenament podria enfocar-se principalment a millorar la consciència de les emocions, ja que si fallen ja en aquest punt (com indica la menor activació de l'ínsula durant l'experimentació d'emocions) serà encara més difícil poder regular després les emocions.
- Als trastorns afectius i d'ansietat el patró de dèficits es dona a la xarxa de control prefronto-parietal. En aquest cas seria interessant veure si l'entrenament en el control cognitiu de tipus no afectiu es transfereix després a una millora en el control sobre estímuls afectius (Schweizer, Hampshire and Dalgleish, 2011). A més, podria interessar entrenar als pacients en estratègies de regulació emocional menys demandants cognitivament com la distracció (Sheppes *et al.*, 2011), fins que aquests tinguin els recursos cognitius necessaris per implementar estratègies més complexes com la reavaluació cognitiva.
- Finalment, ja que tots els pacients han mostrat d'una manera o altra alteracions en l'ínsula, probablement tots es beneficiarien de millorar el reconeixement i la

consciència de les emocions, ja que aquest és un pas necessari abans d'implementar qualsevol estratègia de regulació.

5.4. Limitacions

Els resultats obtinguts en els estudis d'aquesta tesi s'han de considerar en el context d'algunes limitacions metodològiques. En primer lloc, en el cas de l'Estudi 2 i part dels estudis inclosos en el meta-anàlisi de l'Estudi 4, els pacients estaven sotmesos a tractament farmacològic, el qual s'ha suggerit que pot actuar com a un possible factor de confusió especialment en estudis de connectivitat funcional (Posner *et al.*, 2014). Tot i així, els pacients amb TOC estaven prenent medicació de manera estable durant els tres mesos previs a la RMf, i no es van trobar relacions entre els nostres resultats i el tractament farmacològic.

En segon lloc, tots els estudis són transversals, el qual no permet parlar de relacions causals entre les variables estudiades i els seus correlats neurals. Seria interessant per futurs estudis avaluar si les alteracions neurals descrites als nostres estudis persisteixen després de la recuperació simptomàtica, i també si aquestes precedeixen, i per tant anticipen, l'inici del trastorn.

Finalment, la reavaluació cognitiva i la supressió expressiva no representen totes les estratègies possibles de regulació emocional, de manera que la generalització dels nostres resultats està limitada a un tipus específic d'estratègies. En aquesta línia, recentment s'està posant més èmfasi en l'estudi de la flexibilitat en el canvi entre estratègies més que en la divisió simplificada entre estratègies adaptatives i no adaptatives, el qual probablement reflecteix més fidelment els dèficits dels pacients psiquiàtrics. Tot i així, els grups avaluats en aquesta tesi tenen problemes alhora d'implementar la reavaluació cognitiva i fan un major ús de la supressió quan s'enfronten a estímuls emocionals negatius, per tant continua sent d'interès investigar l'ús d'aquestes estratègies. Un altra limitació similar respecte a la generalització dels nostres resultats té a veure amb que en aquesta tesi ens hem centrat exclusivament en la regulació d'emocions negatives. Tot i així, l'estudi de la regulació d'emocions positives, com per exemple la regulació en el processament del reforç, és igual d'important. Açò és molt rellevant en grups de subjectes amb problemes d'impulsivitat, com per exemple els subjectes amb excés de pes, però també en pacients que presenten anhedonia, símptoma que es troba generalment en pacients amb depressió. Seria molt interessant comprovar si es donen els mateixos o diferents correlats neurals dels dèficits en la regulació d'emocions negatives i positives, el qual aportaria nova informació sobre com personalitzar els tractaments per aquests grups de pacients.

6. CONCLUSIONS

D'aquesta tesi podem extreure les següents conclusions:

- L'ús habitual d'estratègies de reavaluació cognitiva i supressió expressiva en controls sans presenta diferents correlats neurals, amb l'ús de la reavaluació vinculat a la connectivitat funcional intrínseca entre la BLA i l'ASM i l'ínsula, i l'ús de la supressió associat a la connectivitat funcional entre la BLA i el dACC, i la CMA i l'ASM.
- Els resultats dels diferents estudis donen suport a la idea de que hi ha una alteració en el funcionament de l'ínsula als trastorns afectius i d'ansietat, el TOC, i als individus amb excés de pes, regió que es troba críticament involucrada en el reconeixement i l'avaluació de les emocions.
- Els pacients amb TOC mostren una connectivitat funcional i estructural disminuïda entre la RA i el gir post-central dret. A més, l'associació entre la connectivitat funcional intrínseca de l'amígdala i l'ús habitual d'estratègies de reavaluació i de supressió està alterada en comparació amb controls sans, amb alteracions microestructurals de matèria blanca en els tractes connectant aquestes regions.
- Els individus amb excés de pes mostren una menor implicació atencional durant l'experimentació de les emocions, junt amb una major reactivitat emocional durant la regulació emocional, segons indica la menor activació de l'ínsula, l'OFC i el cerebel durant el contrast d'Experimentar>Observar, i la major activació de l'ínsula durant el contrast de Regular>Experimentar.
- Altres alteracions en els trastorns afectius i d'ansietat consisteixen en una menor activació en la xarxa regulatòria prefronto-parietal durant la reavaluació cognitiva, així com una major activació en regions compensatòries parietals.
- D'acord amb els nostres resultats, existeixen dèficits de regulació emocional compartits a través dels diferents trastorns, en línia amb el marc de referència del RDoC, però també hi ha dèficits específics per als diferents grups de trastorns, el qual posa encara més èmfasi en la necessitat de desenvolupar tractaments personalitzats basats en el coneixement neurobiològic i enfocats a millorar les necessitats individuals.

REFERENCES

List of References

Abbey, A., Smith, M. J. and Scott, R. O. (1993) 'The relationship between reasons for drinking alcohol and alcohol consumption: An interactional approach', *Addictive Behaviors*, 18(6), pp. 659–670. doi: 10.1016/0306-4603(93)90019-6.

Abler, B. *et al.* (2007) 'Anticipation of aversive stimuli activates extended amygdala in unipolar depression.', *Journal of psychiatric research*. Elsevier, 41(6), pp. 511–22. doi: 10.1016/j.jpsychires.2006.07.020.

Abramowitz, J. S. *et al.* (2006) 'The role of cognitive factors in the pathogenesis of obsessive–compulsive symptoms: A prospective study', *Behaviour Research and Therapy*. Pergamon, 44(9), pp. 1361–1374. doi: 10.1016/J.BRAT.2005.09.011.

Admon, R. *et al.* (2012) 'Functional and structural neural indices of risk aversion in obsessive-compulsive disorder (OCD)', *Psychiatry Research - Neuroimaging*, 203(2–3), pp. 207–213. doi: 10.1016/j.pscychresns.2012.02.002.

Aggleton, J. P. (2000) *The amygdala: a functional analysis*. Oxford University Press. Available at: https://global.oup.com/academic/product/the-amygdala-9780198505013?cc=us&lang=en& (Accessed: 15 June 2018).

Albein-Urios, N. *et al.* (2014) 'Re-appraisal of negative emotions in cocaine dependence: Dysfunctional corticolimbic activation and connectivity', *Addiction Biology*, 19(3), pp. 415–426. doi: 10.1111/j.1369-1600.2012.00497.x.

Aldao, A. (2012) 'Emotion regulation strategies as transdiagnostic processes: A closer look at the invariance of their form and function', *Revista de Psicopatología y Psicología Clínica*. AEPCP ; Universidad Nacional de Educación a Distancia (España), 17(3), p. 261. doi: 10.5944/rppc.vol.17.num.3.2012.11843.

Aldao, A., Nolen-Hoeksema, S. and Schweizer, S. (2010) 'Emotion-regulation strategies across psychopathology: A meta-analytic review', *Clinical Psychology Review*. Elsevier B.V., 30(2), pp. 217–237. doi: 10.1016/j.cpr.2009.11.004.

Aldao, A., Sheppes, G. and Gross, J. J. (2015) 'Emotion Regulation Flexibility', *Cognitive Therapy and Research*. Springer US, 39(3), pp. 263–278. doi: 10.1007/s10608-014-9662-4.

Alicata, D. *et al.* (2009) 'Higher diffusion in striatum and lower fractional anisotropy in white matter of methamphetamine users.', *Psychiatry research*. NIH Public Access, 174(1), pp. 1–8.

doi: 10.1016/j.pscychresns.2009.03.011.

American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: Author.

Arnsten, A. F. T. and Rubia, K. (2012) 'Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurodevelopmental psychiatric disorders.', *Journal of the American Academy of Child and Adolescent Psychiatry*. Elsevier, 51(4), pp. 356–67. doi: 10.1016/j.jaac.2012.01.008.

Aron, A. R., Robbins, T. W. and Poldrack, R. A. (2014) 'Inhibition and the right inferior frontal cortex: one decade on.', *Trends in cognitive sciences*, 18(4), pp. 177–85. doi: 10.1016/j.tics.2013.12.003.

Badre, D. and Wagner, A. D. (2007) 'Left ventrolateral prefrontal cortex and the cognitive control of memory.', *Neuropsychologia*, 45(13), pp. 2883–901. doi: 10.1016/j.neuropsychologia.2007.06.015.

Bagby, R. M., Parker, J. D. and Taylor, G. J. (1994) 'The twenty-item Toronto Alexithymia Scale--I. Item selection and cross-validation of the factor structure.', *Journal of psychosomatic research*. Elsevier, 38(1), pp. 23–32. doi: 10.1016/0022-3999(94)90005-1.

Bagby, R. M., Taylor, G. J. and Parker, J. D. (1994) 'The Twenty-item Toronto Alexithymia Scale--II. Convergent, discriminant, and concurrent validity.', *Journal of psychosomatic research*. Elsevier, 38(1), pp. 33–40. doi: 10.1016/0022-3999(94)90006-X.

Ball, T. M. *et al.* (2013) 'Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders.', *Psychological medicine*, 43(7), pp. 1475–86. doi: 10.1017/S0033291712002383.

Banks, S. J. *et al.* (2007) 'Amygdala-frontal connectivity during emotion regulation', *Social Cognitive and Affective Neuroscience*, 2(4), pp. 303–312. doi: 10.1093/scan/nsm029.

Barrett, L. F. *et al.* (2001) 'Knowing what you're feeling and knowing what to do about it: Mapping the relation between emotion differentiation and emotion regulation', *Cognition & Emotion*. Taylor & Francis Group , 15(6), pp. 713–724. doi: 10.1080/02699930143000239.

Beauregard, M., Paquette, V. and Lévesque, J. (2006) 'Dysfunction in the neural circuitry of emotional self-regulation in major depressive disorder.', *Neuroreport*, 17(8), pp. 843–846. doi: 10.1097/01.wnr.0000220132.32091.9f.

Benedetti, F. *et al.* (2013) 'Widespread changes of white matter microstructure in obsessive–compulsive disorder: Effect of drug status', *European Neuropsychopharmacology*. Elsevier, 23(7), pp. 581–593. doi: 10.1016/J.EURONEURO.2012.07.002.

Berking, M. and Schwarz, J. (2014) 'Affect Regulation Training', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 529–547.

Bishop, S. *et al.* (2004) 'Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli', *Nature Neuroscience*. Nature Publishing Group, 7(2), pp. 184–188. doi: 10.1038/nn1173.

Bishop, S. J. (2009) 'Trait anxiety and impoverished prefrontal control of attention', *Nature Neuroscience*. Nature Publishing Group, 12(1), pp. 92–98. doi: 10.1038/nn.2242.

Biswal, B. *et al.* (1995) 'Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.', *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, 34(4), pp. 537–41.

Blalock, D. V., Kashdan, T. B. and Farmer, A. S. (2016) 'Trait and Daily Emotion Regulation in Social Anxiety Disorder', *Cognitive Therapy and Research*. Springer US, 40(3), pp. 416–425. doi: 10.1007/s10608-015-9739-8.

Bolla, K. *et al.* (2004) 'Prefrontal cortical dysfunction in abstinent cocaine abusers.', *The Journal of neuropsychiatry and clinical neurosciences*. NIH Public Access, 16(4), pp. 456–64. doi: 10.1176/jnp.16.4.456.

Bora, E. *et al.* (2012) 'White matter microstructure in opiate addiction', *Addiction Biology*. Wiley/Blackwell (10.1111), 17(1), pp. 141–148. doi: 10.1111/j.1369-1600.2010.00266.x.

Botvinick, M. M., Cohen, J. D. and Carter, C. S. (2004) 'Conflict monitoring and anterior cingulate cortex: an update.', *Trends in cognitive sciences*, 8(12), pp. 539–46. doi: 10.1016/j.tics.2004.10.003.

Breiter, H. C. *et al.* (1993) 'Functional magnetic resonance imaging of symptom provocation in patients with obsessive compulsive disorder versus controls', *Proc. Soc. Magn. Reson. Med.*, 1(58).

Breiter, H. C. *et al.* (1996) 'Functional Magnetic Resonance Imaging of Symptom Provocation in Obsessive-compulsive Disorder', *Archives of General Psychiatry*. American Medical Association, 53(7), p. 595. doi: 10.1001/archpsyc.1996.01830070041008.

Brody, A. L. *et al.* (2004) 'Differences between smokers and nonsmokers in regional gray matter volumes and densities', *Biological Psychiatry*. Elsevier, 55(1), pp. 77–84. doi: 10.1016/S0006-3223(03)00610-3.

Buhle, J. T. *et al.* (2013) 'Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies.', *Cerebral cortex (New York, N.Y. : 1991)*, pp. 1–10. doi: 10.1093/cercor/bht154.

Butler, E. A. *et al.* (2003) 'The social consequences of expressive suppression.', *Emotion*, 3(1), pp. 48–67. doi: 10.1037/1528-3542.3.1.48.

Butler, E. A., Lee, T. L. and Gross, J. J. (2007) 'Emotion regulation and culture: Are the social consequences of emotion suppression culture-specific?', *Emotion*, 7(1), pp. 30–48. doi: 10.1037/1528-3542.7.1.30.

Byrne, B. M. (2010) *Structural equation modeling with AMOS: Basic concepts, applications, and programming, 2nd ed.*, *Structural equation modeling with AMOS: Basic concepts, applications, and programming, 2nd ed.* New York, NY, US: Routledge/Taylor & Francis Group (Multivariate applications series.).

Cabello, R. *et al.* (2013) 'A Spanish adaptation of the Emotion Regulation Questionnaire', *European Journal of Psychological Assessment*, 29(4), pp. 234–240. doi: 10.1027/1015-5759/a000150.

Campbell-Sills, L. *et al.* (2006) 'Effects of suppression and acceptance on emotional responses of individuals with anxiety and mood disorders.', *Behaviour research and therapy*, 44(9), pp. 1251–63. doi: 10.1016/j.brat.2005.10.001.

Campbell-Sills, L., Ellard, K. K. and Barlow, D. H. (2014) 'Emotion Regulation in Anxiety Disorders', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 393–412.

Canli, T., Ferri, J. and Duman, E. A. (2009) 'Genetics of emotion regulation', *Neuroscience*. Pergamon, 164(1), pp. 43–54. doi: 10.1016/J.NEUROSCIENCE.2009.06.049.

Canli, T. and Lesch, K.-P. (2007) 'Long story short: the serotonin transporter in emotion regulation and social cognition', *Nature Neuroscience*, 10(9), pp. 1103–1109. doi: 10.1038/nn1964.

Cardoner, N. *et al.* (2011) 'Enhanced brain responsiveness during active emotional face processing in obsessive compulsive disorder', *The World Journal of Biological Psychiatry*, 12(5),

pp. 349–363. doi: 10.3109/15622975.2011.559268.

Carvalho, S. *et al.* (2017) 'The evolution of cognitive behavioural therapy – The third generation and its effectiveness', *European Psychiatry*. Elsevier Masson, 41, pp. S773–S774. doi: 10.1016/J.EURPSY.2017.01.1461.

Carver, C. S. and White, T. L. (1994) 'Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS Scales.', *Journal of Personality and Social Psychology*, 67(2), pp. 319–333. doi: 10.1037/0022-3514.67.2.319.

Cato, M. A. *et al.* (2004) 'Processing Words with Emotional Connotation: An fMRI Study of Time Course and Laterality in Rostral Frontal and Retrosplenial Cortices', *Journal of Cognitive Neuroscience*. MIT Press 238 Main St., Suite 500, Cambridge, MA 02142-1046 USA journals-info@mit.edu , 16(2), pp. 167–177. doi: 10.1162/089892904322984481.

Chun, M. M., Golomb, J. D. and Turk-Browne, N. B. (2011) 'A Taxonomy of External and Internal Attention', *Annual Review of Psychology*. Annual Reviews , 62(1), pp. 73–101. doi: 10.1146/annurev.psych.093008.100427.

Cisler, J. M. and Koster, E. H. W. (2010) 'Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review.', *Clinical psychology review*. NIH Public Access, 30(2), pp. 203–16. doi: 10.1016/j.cpr.2009.11.003.

Clark, D. A. and Purdon, C. L. (1995) 'The assessment of unwanted intrusive thoughts: A review and critique of the literature', *Behaviour Research and Therapy*. Pergamon, 33(8), pp. 967–976. doi: 10.1016/0005-7967(95)00030-2.

Clark, L. (2014) 'Disordered gambling: the evolving concept of behavioral addiction.', *Annals of the New York Academy of Sciences*. Wiley-Blackwell, 1327(1), pp. 46–61. doi: 10.1111/nyas.12558.

Craig, A. D. (2003) 'Interoception: the sense of the physiological condition of the body.', *Current opinion in neurobiology*, 13(4), pp. 500–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12965300 (Accessed: 1 March 2016).

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

Cuthbert, B. N. and Insel, T. R. (2013) 'Toward the future of psychiatric diagnosis: the seven pillars of RDoC', *BMC Medicine*, 11(1), p. 126. doi: 10.1186/1741-7015-11-126.

Dan-Glauser, E. S. and Gross, J. J. (2015) 'The temporal dynamics of emotional acceptance: Experience, expression, and physiology', *Biological Psychology*. Elsevier, 108, pp. 1–12. doi: 10.1016/J.BIOPSYCHO.2015.03.005.

Daumann, J. *et al.* (2011) 'Medial prefrontal gray matter volume reductions in users of amphetamine-type stimulants revealed by combined tract-based spatial statistics and voxel-based morphometry', *NeuroImage*. Academic Press, 54(2), pp. 794–801. doi: 10.1016/J.NEUROIMAGE.2010.08.065.

Davachi, L. (2006) 'Item, context and relational episodic encoding in humans', *Current Opinion in Neurobiology*. Elsevier Current Trends, 16(6), pp. 693–700. doi: 10.1016/J.CONB.2006.10.012.

Davidson, R. J. (1994) 'On emotion, mood, and related affective constructs.', in Ekman, P. and Davidson, R. J. (eds) *The nature of emotion: fundamental questions*. New York: Oxford University Press, pp. 51–55. Available at: https://global.oup.com/ushe/product/the-nature-of-emotion-9780195089448?cc=us&lang=en& (Accessed: 2 July 2018).

Davidson, R. J. *et al.* (1999) 'The functional neuroanatomy of emotion and affective style.', *Trends in cognitive sciences*. Elsevier, 3(1), pp. 11–21. doi: 10.1016/S1364-6613(98)01265-0.

Davidson, R. J. (2000) 'Affective style, psychopathology, and resilience: Brain mechanisms and plasticity.', *American Psychologist*. US: American Psychological Association, pp. 1196–1214. doi: 10.1037/0003-066X.55.11.1196.

Davidson, R. J. *et al.* (2002) 'Depression: Perspectives from Affective Neuroscience', *Annual Review of Psychology*. Annual Reviews 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA , 53(1), pp. 545–574. doi: 10.1146/annurev.psych.53.100901.135148.

Davis, M. and Shi, C. (1999) 'The Extended Amygdala: Are the Central Nucleus of the Amygdala and the Bed Nucleus of the Stria Terminalis Differentially Involved in Fear versus Anxiety?', *Annals of the New York Academy of Sciences*. Wiley/Blackwell (10.1111), 877(1 ADVANCING FRO), pp. 281–291. doi: 10.1111/j.1749-6632.1999.tb09273.x.

Delgado, M. R. *et al.* (2009) 'Avoiding negative outcomes: tracking the mechanisms of avoidance learning in humans during fear conditioning.', *Frontiers in behavioral neuroscience*. Frontiers Media SA, 3, p. 33. doi: 10.3389/neuro.08.033.2009.

Demaree, H. A. *et al.* (2006) 'Up- and down-regulating facial disgust: Affective, vagal, sympathetic, and respiratory consequences', *Biological Psychology*. Elsevier, 71(1), pp. 90–99.

doi: 10.1016/J.BIOPSYCHO.2005.02.006.

Denny, B. T. *et al.* (2014) 'Elevated amygdala activity during reappraisal anticipation predicts anxiety in avoidant personality disorder.', *Journal of affective disorders*. Elsevier, 172C, pp. 1–7. doi: 10.1016/j.jad.2014.09.017.

Diekhof, E. K. *et al.* (2011) 'Fear is only as deep as the mind allows. A coordinate-based meta-analysis of neuroimaging studies on the regulation of negative affect', *NeuroImage*. Elsevier Inc., 58(1), pp. 275–285. doi: 10.1016/j.neuroimage.2011.05.073.

Dörfel, D. *et al.* (2014) 'Common and differential neural networks of emotion regulation by detachment, reinterpretation, distraction, and expressive suppression: A comparative fMRI investigation', *NeuroImage*. Elsevier Inc., 101, pp. 298–309. doi: 10.1016/j.neuroimage.2014.06.051.

Drevets, W. C. (2003) 'Neuroimaging Abnormalities in the Amygdala in Mood Disorders', *Annals of the New York Academy of Sciences*. Wiley/Blackwell (10.1111), 985(1), pp. 420–444. doi: 10.1111/j.1749-6632.2003.tb07098.x.

Drevets, W. C., Savitz, J. and Trimble, M. (2008) 'The Subgenual Anterior Cingulate Cortex in Mood Disorders', *CNS Spectrums*. Cambridge University Press, 13(08), pp. 663–681. doi: 10.1017/S1092852900013754.

Durazzo, T. C. *et al.* (2011) 'Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence.', *Alcoholism, clinical and experimental research*. NIH Public Access, 35(6), pp. 1187–200. doi: 10.1111/j.1530-0277.2011.01452.x.

Dvorak, R. D. *et al.* (2014) 'Alcohol use and alcohol-related consequences: associations with emotion regulation difficulties', *The American Journal of Drug and Alcohol Abuse*, 40(2), pp. 125–130. doi: 10.3109/00952990.2013.877920.

Eickhoff, S. B. *et al.* (2012) 'Activation likelihood estimation meta-analysis revisited', *NeuroImage*. Elsevier Inc., 59(3), pp. 2349–2361. doi: 10.1016/j.neuroimage.2011.09.017.

Eippert, F. *et al.* (2007) 'Regulation of emotional responses elicited by threat-related stimuli', *Human Brain Mapping*, 28(5), pp. 409–423. doi: 10.1002/hbm.20291.

Eklund, A., Nichols, T. E. and Knutsson, H. (2016) 'Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates', *Proceedings of the National Academy of Sciences*, p. 201602413. doi: 10.1073/pnas.1602413113.

Eldreth, D. A. *et al.* (2004) 'Abnormal brain activity in prefrontal brain regions in abstinent marijuana users', *NeuroImage*. Academic Press, 23(3), pp. 914–920. doi: 10.1016/J.NEUROIMAGE.2004.07.032.

Ellsworth, P. C. and Scherer, K. R. (2003) 'Appraisal processes in emotion.', in *Handbook of affective sciences.* New York, NY, US: Oxford University Press (Series in affective science.), pp. 572–595.

English, T., John, O. P. and Gross, J. J. (2013) *Emotion Regulation in Close Relationships*. Oxford University Press. doi: 10.1093/oxfordhb/9780195398694.013.0022.

Erdelyi, M. H. (1974) 'A new look at the new look: perceptual defense and vigilance.', *Psychological review*, 81(1), pp. 1–25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4812878 (Accessed: 14 June 2018).

Erk, S. *et al.* (2010) 'Acute and sustained effects of cognitive emotion regulation in major depression.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 30(47), pp. 15726–15734. doi: 10.1523/JNEUROSCI.1856-10.2010.

Etkin, A. *et al.* (2004) 'Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces.', *Neuron*. Elsevier, 44(6), pp. 1043–55. doi: 10.1016/j.neuron.2004.12.006.

Etkin, A. *et al.* (2009) 'Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder.', *Archives of general psychiatry*, 66(12), pp. 1361–72. doi: 10.1001/archgenpsychiatry.2009.104.

Etkin, A. *et al.* (2010) 'Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder.', *The American journal of psychiatry*. NIH Public Access, 167(5), pp. 545–54. doi: 10.1176/appi.ajp.2009.09070931.

Etkin, A., Büchel, C. and Gross, J. J. (2015) 'The neural bases of emotion regulation', *Nature Reviews Neuroscience*. Nature Publishing Group, 16, pp. 693–700. doi: 10.1038/nrn4044.

Etkin, A., Egner, T. and Kalisch, R. (2011) 'Emotional processing in anterior cingulate and medial prefrontal cortex.', *Trends in cognitive sciences*. NIH Public Access, 15(2), pp. 85–93. doi: 10.1016/j.tics.2010.11.004.

Etkin, A. and Wager, T. D. (2007) 'Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia', *Am J Psychiatry*,

164(10), pp. 1476–1488. doi: 10.1176/appi.ajp.2007.07030504.Functional.

Farb, N. A. S. *et al.* (2014) 'Mindfulness Interventions and Emotion Regulaion', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 548–569.

Fein, G. *et al.* (2002) 'Cortical gray matter loss in treatment-naïve alcohol dependent individuals.', *Alcoholism, clinical and experimental research*. NIH Public Access, 26(4), pp. 558–64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11981133 (Accessed: 1 July 2018).

Feinberg, M. *et al.* (2012) 'Liberating Reason From the Passions', *Psychological Science*. SAGE PublicationsSage CA: Los Angeles, CA, 23(7), pp. 788–795. doi: 10.1177/0956797611434747.

Fernandez, K. C., Jazaieri, H. and Gross, J. J. (2016) 'Emotion Regulation: A Transdiagnostic Perspective on a New RDoC Domain', *Cognitive Therapy and Research*, 40(3), pp. 426–440. doi: 10.1007/s10608-016-9772-2.

Fontenelle, L. F. *et al.* (2011) 'White Matter Changes in OCD Revealed by Diffusion Tensor Imaging.', *CNS spectrums*, 16(May), pp. 101–109. doi: 10.1017/S1092852912000.

Franklin, T. R. *et al.* (2002) 'Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients', *Biological Psychiatry*. Elsevier, 51(2), pp. 134–142. doi: 10.1016/S0006-3223(01)01269-0.

Friston, K. J. *et al.* (1997) 'Psychophysiological and modulatory interactions in neuroimaging.', *NeuroImage*, 6(3), pp. 218–29. doi: 10.1006/nimg.1997.0291.

Friston, K. J. *et al.* (2007) *Statistical parametric mapping: the analysis of funtional brain images*. Elsevier/Academic Press.

Fu, L. *et al.* (2008) 'Impaired response inhibition function in abstinent heroin dependents: An fMRI study', *Neuroscience Letters*. Elsevier, 438(3), pp. 322–326. doi: 10.1016/J.NEULET.2008.04.033.

Garibotto, V. *et al.* (2010) 'Disorganization of anatomical connectivity in obsessive compulsive disorder: A multi-parameter diffusion tensor imaging study in a subpopulation of patients', *Neurobiology of Disease*. Academic Press, 37(2), pp. 468–476. doi: 10.1016/J.NBD.2009.11.003.

Garnefski, N. and Kraaij, V. (2007) 'The cognitive emotion regulation questionnaire: Psychometric features and prospective relationships with depression and anxiety in adults', *European Journal of Psychological Assessment*, 23(3), pp. 141–149. doi: 10.1027/1015-5759.23.3.141.

Gazzaniga, M. S., Ivry, R. B. and Mangun, G. R. (George R. (2008) *Cognitive neuroscience: the biology of the mind*. Available at: http://books.wwnorton.com/books/webad.aspx?id=4294978503 (Accessed: 17 June 2018).

Gearhardt, A. N., Corbin, W. R. and Brownell, K. D. (2009) 'Preliminary validation of the Yale Food Addiction Scale', *Appetite*. Academic Press, 52(2), pp. 430–436. doi: 10.1016/J.APPET.2008.12.003.

Gilman, T. L. *et al.* (2015) 'Variation of 5-HTTLPR and deficits in emotion regulation: A pathway to risk?', *Psychology & Neuroscience*, 8(3), pp. 397–413. doi: 10.1037/pne0000017.

Giuliani, N. R., McRae, K. and Gross, J. J. (2008) 'The up- and down-regulation of amusement: Experiential, behavioral, and autonomic consequences.', *Emotion*, 8(5), pp. 714–719. doi: 10.1037/a0013236.

Gobbini, M. I. *et al.* (2007) 'Two Takes on the Social Brain: A Comparison of Theory of Mind Tasks', *Journal of Cognitive Neuroscience*. MIT Press 238 Main St., Suite 500, Cambridge, MA 02142-1046USA journals-info@mit.edu , 19(11), pp. 1803–1814. doi: 10.1162/jocn.2007.19.11.1803.

Goldberg, X. *et al.* (2016) 'Inter-individual variability in emotion regulation: Pathways to obsessive-compulsive symptoms', *Journal of Obsessive-Compulsive and Related Disorders*. Elsevier, 11(October), pp. 105–112. doi: 10.1016/j.jocrd.2016.10.002.

Goldin, P., Manber, T., *et al.* (2009) 'Neural Bases of Social Anxiety Disorder: Emotional Reactivity and Cognitive Regulation During Social and Physical Threat', *Arch Gen Psychiatry*, 66(2), pp. 170–180. doi: 10.1001/archgenpsychiatry.2008.525.

Goldin, P., Ball, T. M., *et al.* (2009) 'Neural Mechanisms of Cognitive Reappraisal of Negative Self- Beliefs in Social Anxiety Disorder', *Biological Psychiatry*, 66(12), pp. 1091–1099. doi: 10.1016/j.biopsych.2009.07.014.Neural.

Goldin, P., McRae, K., *et al.* (2009) 'The Neural Bases of Emotion Regulation: Reappraisal and Suppression of Negative Emotion', *Biological Psychiatry*, 63(6), pp. 577–586.

Goodman, W. K. *et al.* (1989) 'The Yale-Brown Obsessive Compulsive Scale', *Archives of General Psychiatry*. American Medical Association, 46(11), p. 1006. doi: 10.1001/archpsyc.1989.01810110048007.

Gotlib, I. H. and Joormann, J. (2010) 'Cognition and depression: current status and future directions.', *Annual review of clinical psychology*. NIH Public Access, 6, pp. 285–312. doi:

10.1146/annurev.clinpsy.121208.131305.

Gratz, K. L. and Roemer, L. (2004) 'Multidimensional Assessment of Emotion Regulation and Dysregulation: Development, Factor Structure, and Initial Validation of the Difficulties in Emotion Regulation Scale', *Journal of Psychopathology and Behavioral Assessment*, 26(1), pp. 41–54. doi: 10.1023/B:JOBA.0000007455.08539.94.

Gross, J. J. (1998a) 'Antecedent- and response-focused emotion regulation: Divergent consequences for experience, expression, and physiology.', *Journal of personality and social psychology*, 74(1), pp. 224–237. doi: 10.1037/0022-3514.74.1.224.

Gross, J. J. (1998b) 'The emerging field of emotion regulation: An integrative review.', *Review of General Psychology*, 2(3), pp. 271–299. doi: 10.1037/1089-2680.2.3.271.

Gross, J. J. (2013) 'Emotion regulation: Taking stock and moving forward.', *Emotion*, 13(3), pp. 359–365. doi: 10.1037/a0032135.

Gross, J. J. (2014) 'Emotion Regulation: Conceptual and Empirical Foundations', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 3–20.

Gross, J. J. (2015) 'The Extended Process Model of Emotion Regulation: Elaborations, Applications, and Future Directions', *Psychological Inquiry*. Routledge, 26(1), pp. 130–137. doi: 10.1080/1047840X.2015.989751.

Gross, J. J. and John, O. P. (2003) 'Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being.', *Journal of personality and social psychology*, 85(2), pp. 348–362. doi: 10.1037/0022-3514.85.2.348.

Gross, J. J. and Levenson, R. W. (1993) 'Emotional suppression: Physiology, self-report, and expressive behavior.', *Journal of Personality and Social Psychology*, 64(6), pp. 970–986. doi: 10.1037/0022-3514.64.6.970.

Gross, J. J. and Levenson, R. W. (1997) 'Hiding feelings: The acute effects of inhibiting negative and positive emotion.', *Journal of Abnormal Psychology*, 106(1), pp. 95–103. doi: 10.1037/0021-843X.106.1.95.

Gross, J. J. and Muñoz, R. F. (1995) 'Emotion Regulation and Mental Health', *Clinical Psychology: Science and Practice*. Wiley/Blackwell (10.1111), 2(2), pp. 151–164. doi: 10.1111/j.1468-2850.1995.tb00036.x.

Gyurak, A. and Etkin, A. (2014) 'A Neurobiological Model of Implicit and Explicit Emotion

Regulation', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press.

Hamilton, M. (1959) 'The assessment of anxiety states by rating.', *The British journal of medical psychology*, 32(1), pp. 50–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13638508 (Accessed: 13 February 2018).

Hamilton, M. (1960) 'A rating scale for depression.', *Journal of neurology, neurosurgery, and psychiatry*. BMJ Publishing Group, 23(1), pp. 56–62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14399272 (Accessed: 13 February 2018).

Hariri, A. R. and Holmes, A. (2006) 'Genetics of emotional regulation: the role of the serotonin transporter in neural function.', *Trends in cognitive sciences*. Elsevier, 10(4), pp. 182–91. doi: 10.1016/j.tics.2006.02.011.

Harris, C. R. (2001) 'Cardiovascular responses of embarrassment and effects of emotional suppression in a social setting.', *Journal of Personality and Social Psychology*, 81(5), pp. 886–897. doi: 10.1037/0022-3514.81.5.886.

Harrison, B. J. *et al.* (2009) 'Altered Corticostriatal Functional Connectivity in Obsessive-compulsive Disorder', *Archives of General Psychiatry*. American Medical Association, 66(11), p. 1189. doi: 10.1001/archgenpsychiatry.2009.152.

Harrison, N. A. *et al.* (2010) 'The embodiment of emotional feelings in the brain.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Europe PMC Funders, 30(38), pp. 12878–84. doi: 10.1523/JNEUROSCI.1725-10.2010.

Hayes, J. P. *et al.* (2010) 'Staying cool when things get hot: emotion regulation modulates neural mechanisms of memory encoding.', *Frontiers in human neuroscience*, 4, p. 230. doi: 10.3389/fnhum.2010.00230.

Hayes, S. C., Strosahl, K. D. and Wilson, K. G. (2012) *Acceptance and commitment therapy: The process and practice of mindful change, 2nd ed.*, *Acceptance and commitment therapy: The process and practice of mindful change, 2nd ed.* New York, NY, US: Guilford Press.

Hemmingsson, E. (2014) 'A new model of the role of psychological and emotional distress in promoting obesity: conceptual review with implications for treatment and prevention', *Obesity Reviews*. Wiley/Blackwell (10.1111), 15(9), pp. 769–779. doi: 10.1111/obr.12197.

Hester, R. and Garavan, H. (2004) 'Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Society for Neuroscience, 24(49), pp. 11017–22. doi:

10.1523/JNEUROSCI.3321-04.2004.

Hinwood, M. *et al.* (2012) 'Evidence that Microglia Mediate the Neurobiological Effects of Chronic Psychological Stress on the Medial Prefrontal Cortex', *Cerebral Cortex*. Oxford University Press, 22(6), pp. 1442–1454. doi: 10.1093/cercor/bhr229.

Hofmann, S. G. *et al.* (2009) 'How to handle anxiety: The effects of reappraisal, acceptance, and suppression strategies on anxious arousal', *Behaviour Research and Therapy*. Pergamon, 47(5), pp. 389–394. doi: 10.1016/J.BRAT.2009.02.010.

Holland, P. C. and Gallagher, M. (2004) 'Amygdala–frontal interactions and reward expectancy', *Current Opinion in Neurobiology*. Elsevier Current Trends, 14(2), pp. 148–155. doi: 10.1016/J.CONB.2004.03.007.

Holmes, A. P. *et al.* (1996) 'Nonparametric Analysis of Statistic Images from Functional Mapping Experiments', *Journal of Cerebral Blood Flow & Metabolism*. SAGE PublicationsSage UK: London, England, 16(1), pp. 7–22. doi: 10.1097/00004647-199601000-00002.

Holtzheimer, P. E. and Mayberg, H. S. (2011) 'Stuck in a rut: rethinking depression and its treatment.', *Trends in neurosciences*. NIH Public Access, 34(1), pp. 1–9. doi: 10.1016/j.tins.2010.10.004.

Hu, T. *et al.* (2014) 'Relation between emotion regulation and mental health: a meta-analysis review', *Psychological Reports*, 114(2), pp. 341–362. doi: 10.2466/03.20.PR0.114k22w4.

Huettel, S. A., Song, A. W. and McCarthy, G. (2008) 'BOLD fMRI: Origins and Properties.', in *Functional Magnetic Resonance Imaging*. 2nd edn. Sinauer, pp. 193–242.

Huettel, S. A., Song, A. W. and McCarthy, G. (2008) *Functional Magnetic Resonance Imaging*. Foundation/Artists Rights Society (ARS), New York.

Ichikawa, N. *et al.* (2011) 'Feeling bad about screwing up: emotion regulation and action monitoring in the anterior cingulate cortex.', *Cognitive, affective & behavioral neuroscience*. NIH Public Access, 11(3), pp. 354–71. doi: 10.3758/s13415-011-0028-z.

Jahromi, L. B., Meek, S. E. and Ober-Reynolds, S. (2012) 'Emotion regulation in the context of frustration in children with high functioning autism and their typical peers', *Journal of Child Psychology and Psychiatry*. Wiley/Blackwell (10.1111), 53(12), pp. 1250–1258. doi: 10.1111/j.1469-7610.2012.02560.x.

Jamieson, J. P. *et al.* (2010) 'Turning the knots in your stomach into bows: Reappraising arousal

improves performance on the GRE.', *Journal of experimental social psychology*. NIH Public Access, 46(1), pp. 208–212. doi: 10.1016/j.jesp.2009.08.015.

Jayarajan, R. N. *et al.* (2012) 'White matter abnormalities in children and adolescents with obsessive-compulsive disorder: a diffusion tensor imaging study', *Depression and Anxiety*, 29(9), pp. 780–788. doi: 10.1002/da.21890.

Johns, M., Inzlicht, M. and Schmader, T. (2008) 'Stereotype threat and executive resource depletion: examining the influence of emotion regulation.', *Journal of experimental psychology. General*. NIH Public Access, 137(4), pp. 691–705. doi: 10.1037/a0013834.

Johnstone, T. *et al.* (2007) 'Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 27(33), pp. 8877–8884. doi: 10.1523/JNEUROSCI.2063-07.2007.

Johnstone, T. and Walter, H. (2014) 'The Neural Basis of Emotion Dysregulation', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 58–75.

Jones, D. K., Knösche, T. R. and Turner, R. (2013) 'White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI', *NeuroImage*. Elsevier Inc., 73, pp. 239–254. doi: 10.1016/j.neuroimage.2012.06.081.

Joorman, J. and Siemer, M. (2014) 'Emotion Regulation in Mood Disorders', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 413–427.

Joormann, J. and Siemer, M. (2004) 'Memory Accessibility, Mood Regulation, and Dysphoria: Difficulties in Repairing Sad Mood With Happy Memories?', *Journal of Abnormal Psychology*, 113(2), pp. 179–188. doi: 10.1037/0021-843X.113.2.179.

Joormann, J., Siemer, M. and Gotlib, I. H. (2007) 'Mood regulation in depression: Differential effects of distraction and recall of happy memories on sad mood.', *Journal of Abnormal Psychology*, 116(3), pp. 484–490. doi: 10.1037/0021-843X.116.3.484.

Kalisch, R. (2009) 'The functional neuroanatomy of reappraisal: Time matters', *Neuroscience and Biobehavioral Reviews*, 33(8), pp. 1215–1226. doi: 10.1016/j.neubiorev.2009.06.003.

Kanske, P. *et al.* (2011) 'How to regulate emotion? Neural networks for reappraisal and distraction', *Cerebral Cortex*, 21(6), pp. 1379–1388. doi: 10.1093/cercor/bhq216.

Keay, K. A. and Bandler, R. (2001) 'Parallel circuits mediating distinct emotional coping

reactions to different types of stress', *Neuroscience & Biobehavioral Reviews*. Pergamon, 25(7–8), pp. 669–678. doi: 10.1016/S0149-7634(01)00049-5.

Kim, S. H. and Hamann, S. (2012) 'The effect of cognitive reappraisal on physiological reactivity and emotional memory', *International Journal of Psychophysiology*. Elsevier, 83(3), pp. 348–356. doi: 10.1016/J.IJPSYCHO.2011.12.001.

Kober, H. (2008) 'Functional grouping and cortical–subcortical interactions in emotion: A meta-analysis of neuroimaging studies', *NeuroImage*, 29(6), pp. 997–1003. doi: 10.1016/j.biotechadv.2011.08.021.Secreted.

Kober, H. (2014) 'Emotion Regulation in Substance Use Disorders', in *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 428–446.

Kohn, N. *et al.* (2014) 'Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis', *NeuroImage*. Elsevier Inc., 87, pp. 345–355. doi: 10.1016/j.neuroimage.2013.11.001.

Konishi, S. *et al.* (1999) 'Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI.', *Brain : a journal of neurology*, 122 (Pt 5), pp. 981–91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10355680 (Accessed: 15 June 2018).

Koole, S. L. (2009) 'The psychology of emotion regulation: An integrative review', *Cognition & Emotion*, 23(September), pp. 4–41. doi: 10.1080/02699930802619031.

Kozak, M. J. and Cuthbert, B. N. (2016) 'The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics', *Psychophysiology*, 53, pp. 286–297. doi: 10.1111/psyp.12518.

Kring, A. M. and Sloan, D. M. (2010) *Emotion regulation and psychopathology : a transdiagnostic approach to etiology and treatment*. Guilford Press. Available at: https://www.guilford.com/books/Emotion-Regulation-and-Psychopathology/Kring-Sloan/9781606234501/contents (Accessed: 19 June 2018).

Kurth, F. *et al.* (2010) 'A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis.', *Brain structure & function*. NIH Public Access, 214(5–6), pp. 519–34. doi: 10.1007/s00429-010-0255-z.

Lam, S. *et al.* (2009) 'Emotion regulation and cortisol reactivity to a social-evaluative speech task', *Psychoneuroendocrinology*, 34(9), pp. 1355–1362. doi: 10.1016/j.psyneuen.2009.04.006.

Lang, P., Bradley, M. and Cuthbert, B. (2005) 'International Affective Picture System (IAPS): Digitized Photographs, Instruction Manual and Affective Ratings. Technical Report A-6.', *2005*.

Larsen, J. T. *et al.* (2008) 'The psychophysiology of emotion.', in *Handbook of emotions, 3rd ed.* New York, NY, US: Guilford Press, pp. 180–195.

Larsen, R. J. (2000) 'Toward a Science of Mood Regulation', *Psychological Inquiry*. Taylor & Francis, Ltd., pp. 129–141. doi: 10.2307/1449791.

Lazarus, R. S. (1993) 'From Psychological Stress to the Emotions: A History of Changing Outlooks', *Annual Review of Psychology*. Annual Reviews 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA , 44(1), pp. 1–22. doi: 10.1146/annurev.ps.44.020193.000245.

Lazarus, R. S. and Alfert, E. (1964) 'Short-circuiting of threat by experimentally altering cognitive appraisal.', *The Journal of Abnormal and Social Psychology*, 69(2), pp. 195–205. doi: 10.1037/h0044635.

Lazarus, R. S. and Folkman, S. (1984) *Stress, Appraisal and Coping.* Springer. doi: 10.1017/S0033291700031652.

Lee, H. *et al.* (2012) 'Amygdala-prefrontal coupling underlies individual differences in emotion regulation', *NeuroImage*, 62(3), pp. 1575–1581. doi: 10.1016/j.neuroimage.2012.05.044. Amygdala-prefrontal.

Levitt, J. T. *et al.* (2004) 'The effects of acceptance versus suppression of emotion on subjective and psychophysiological response to carbon dioxide challenge in patients with panic disorder', *Behavior Therapy*, 35(4), pp. 747–766. doi: 10.1016/S0005-7894(04)80018-2.

Liberzon, I. and Sripada, C. S. (2007) 'The functional neuroanatomy of PTSD: a critical review', *Progress in Brain Research*. Elsevier, 167, pp. 151–169. doi: 10.1016/S0079-6123(07)67011-3.

Lieberman, M. D. *et al.* (2007) 'Putting Feelings Into Words', *Psychological Science*. SAGE PublicationsSage CA: Los Angeles, CA, 18(5), pp. 421–428. doi: 10.1111/j.1467-9280.2007.01916.x.

Lieberman, M. D. *et al.* (2011) 'Subjective responses to emotional stimuli during labeling, reappraisal, and distraction.', *Emotion (Washington, D.C.)*. American Psychological Association, 11(3), pp. 468–80. doi: 10.1037/a0023503.

Lindquist, K. A. *et al.* (2012) 'The brain basis of emotion: a meta-analytic review.', *The*

Behavioral and brain sciences. NIH Public Access, 35(3), pp. 121–43. doi: 10.1017/S0140525X11000446.

Lindquist, K. A. and Barrett, L. F. (2008) 'Constructing emotion: the experience of fear as a conceptual act.', *Psychological science*. NIH Public Access, 19(9), pp. 898–903. doi: 10.1111/j.1467-9280.2008.02174.x.

Liu, H. *et al.* (2008) 'Disrupted White Matter Integrity in Heroin Dependence: A Controlled Study Utilizing Diffusion Tensor Imaging', *The American Journal of Drug and Alcohol Abuse*. Taylor & Francis, 34(5), pp. 562–575. doi: 10.1080/00952990802295238.

MacLeod, C. and Grafton, B. (2014) 'Regulation of Emotion through Modification of Attention', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 508–528.

MacLeod, C., Mathews, A. and Tata, P. (1986) 'Attentional bias in emotional disorders.', *Journal of Abnormal Psychology*, 95(1), pp. 15–20. doi: 10.1037/0021-843X.95.1.15.

MacNamara, A., Kotov, R. and Hajcak, G. (2016) 'Diagnostic and Symptom-Based Predictors of Emotional Processing in Generalized Anxiety Disorder and Major Depressive Disorder: An Event-Related Potential Study', *Cognitive Therapy and Research*, 40(3), pp. 275–289. doi: 10.1007/s10608-015-9717-1.

Manser, R., Cooper, M. and Trefusis, J. (2012) 'Beliefs about Emotions as a Metacognitive Construct: Initial Development of a Self-Report Questionnaire Measure and Preliminary Investigation in Relation to Emotion Regulation', *Clinical Psychology & Psychotherapy*, 19(3), pp. 235–246. doi: 10.1002/cpp.745.

Mataix-Cols, D. *et al.* (2004) 'Distinct Neural Correlates of Washing, Checking, and Hoarding SymptomDimensions in Obsessive-compulsive Disorder', *Archives of General Psychiatry*. American Medical Association, 61(6), p. 564. doi: 10.1001/archpsyc.61.6.564.

Mathers, C. D., Lopez, A. D. and Murray, C. J. L. (2006) *The Burden of Disease and Mortality by Condition: Data, Methods, and Results for 2001*, *Global Burden of Disease and Risk Factors*. The International Bank for Reconstruction and Development / The World Bank. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21250373 (Accessed: 20 June 2018).

Mauss, I. B. *et al.* (2007) 'Individual differences in cognitive reappraisal: Experiential and physiological responses to an anger provocation', *International Journal of Psychophysiology*, 66(2), pp. 116–124. doi: 10.1016/j.ijpsycho.2007.03.017.

Mauss, I. B. *et al.* (2011) 'Don't hide your happiness! Positive emotion dissociation, social

connectedness, and psychological functioning.', *Journal of personality and social psychology*. NIH Public Access, 100(4), pp. 738–48. doi: 10.1037/a0022410.

Mauss, I. B., Bunge, S. A. and Gross, J. J. (2007) 'Automatic Emotion Regulation', *Social and Personality Psychology Compass*. Wiley/Blackwell (10.1111), 1(1), pp. 146–167. doi: 10.1111/j.1751-9004.2007.00005.x.

McRae, K. *et al.* (2012) 'The development of emotion regulation: An fMRI study of cognitive reappraisal in children, adolescents and young adults', *Social Cognitive and Affective Neuroscience*, 7(1), pp. 11–22. doi: 10.1093/scan/nsr093.

Mennin, D. S. and Fresco, D. M. (2014) 'Emotion Regulation Therapy', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 469–490.

Menzies, L. *et al.* (2008) 'Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited', *Neuroscience and Biobehavioral Reviews*, 32(3), pp. 525–549. doi: 10.1016/j.neubiorev.2007.09.005.

Van Meter, A. R. and Youngstrom, E. A. (2016) 'Distinct Roles of Emotion Reactivity and Regulation in Depressive and Manic Symptoms Among Euthymic Patients', *Cognitive Therapy and Research*. Springer US, 40(3), pp. 262–274. doi: 10.1007/s10608-015-9738-9.

Miller, A. H., Capuron, L. and Raison, C. L. (2005) 'Immunologic influences on emotion regulation', *Clinical Neuroscience Research*. Elsevier, 4(5–6), pp. 325–333. doi: 10.1016/J.CNR.2005.03.010.

Miller, E. K. (2000) 'The prefontral cortex and cognitive control', *Nature Reviews Neuroscience*. Nature Publishing Group, 1(1), pp. 59–65. doi: 10.1038/35036228.

Mischel, W., Shoda, Y. and Rodriguez, M. I. (1989) 'Delay of gratification in children.', *Science (New York, N.Y.)*. American Association for the Advancement of Science, 244(4907), pp. 933–8. doi: 10.1126/SCIENCE.2658056.

Mitchell, J. P. (2009) 'Inferences about mental states.', *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*. The Royal Society, 364(1521), pp. 1309–16. doi: 10.1098/rstb.2008.0318.

Miu, A. C. *et al.* (2013) 'Reappraisal as a mediator in the link between 5-HTTLPR and social anxiety symptoms.', *Emotion*, 13(6), pp. 1012–1022. doi: 10.1037/a0033383.

Moore, S. A., Zoellner, L. A. and Mollenholt, N. (2008) 'Are expressive suppression and cognitive reappraisal associated with stress-related symptoms?', *Behaviour research and therapy*. NIH Public Access, 46(9), pp. 993–1000. doi: 10.1016/j.brat.2008.05.001.

Morawetz, C. *et al.* (2017) 'The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies', *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd, 72, pp. 111–128. doi: 10.1016/j.neubiorev.2016.11.014.

Murray, E. A., O'Doherty, J. P. and Schoenbaum, G. (2007) 'What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*. NIH Public Access, 27(31), pp. 8166–9. doi: 10.1523/JNEUROSCI.1556-07.2007.

National Institute of Mental Health (NIMH) (2007) 'National Comorbidity Survey: Life-time prevalence estimates.' Available at: www.hcp.med.harvard.edu/ncs.

Naumann, E. *et al.* (2016) 'Spontaneous Emotion Regulation in Anorexia and Bulimia Nervosa', *Cognitive Therapy and Research*. Springer US, 40(3), pp. 304–313. doi: 10.1007/s10608-015-9723-3.

Navas, J. F. *et al.* (2017) 'Trait and neurobiological underpinnings of negative emotion regulation in gambling disorder', *Addiction*. Wiley/Blackwell (10.1111), 112(6), pp. 1086–1094. doi: 10.1111/add.13751.

Neacsiu, A. D., Bohus, M. and Linehan, M. M. (2014) 'Dialectical Behavior Therapy: An Intervention for Emotion Dysregulation', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 491–507.

Nelson, S. M. *et al.* (2010) 'Role of the anterior insula in task-level control and focal attention.', *Brain structure & function*. Springer, 214(5–6), pp. 669–80. doi: 10.1007/s00429-010-0260-2.

Nestor, L. J. *et al.* (2011) 'Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects.', *Psychiatry research*. NIH Public Access, 194(3), pp. 287–295. doi: 10.1016/j.pscychresns.2011.04.010.

New, A. S. *et al.* (2009) 'A Functional Magnetic Resonance Imaging Study of Deliberate Emotion Regulation in Resilience and Posttraumatic Stress Disorder', *Biological Psychiatry*. Elsevier Inc., 66(7), pp. 656–664. doi: 10.1016/j.biopsych.2009.05.020.

Nezlek, J. B. and Kuppens, P. (2008) 'Regulating Positive and Negative Emotions in Daily Life', *Journal of Personality*. Wiley/Blackwell (10.1111), 76(3), pp. 561–580. doi: 10.1111/j.1467-

6494.2008.00496.x.

Nichols, T. E. and Holmes, A. P. (2001) 'Nonparametric Permutation Tests for {PET} functional Neuroimaging Experiments: A Primer with examples', *Human Brain Mapping*, 15(1), pp. 1–25. doi: 10.1002/hbm.1058.

Nolen-Hoeksema, S. (2000) 'The role of rumination in depressive disorders and mixed anxiety/depressive symptoms.', *Journal of Abnormal Psychology*, 109(3), pp. 504–511. doi: 10.1037//0021-843X.109.3.504.

Nolen-Hoeksema, S., Morrow, J. and Fredrickson, B. L. (1993) 'Response styles and the duration of episodes of depressed mood.', *Journal of Abnormal Psychology*, 102(1), pp. 20–28. doi: 10.1037//0021-843X.102.1.20.

O'Doherty, J. P. (2004) 'Reward representations and reward-related learning in the human brain: insights from neuroimaging', *Current Opinion in Neurobiology*. Elsevier Current Trends, 14(6), pp. 769–776. doi: 10.1016/J.CONB.2004.10.016.

Ochsner, K. N. *et al.* (2002) 'Rethinking feelings: an FMRI study of the cognitive regulation of emotion.', *Journal of cognitive neuroscience*, 14(8), pp. 1215–29. doi: 10.1162/089892902760807212.

Ochsner, K. N. *et al.* (2004) 'For better or for worse: Neural systems supporting the cognitive down- and up-regulation of negative emotion', *NeuroImage*, 23(2), pp. 483–499. doi: 10.1016/j.neuroimage.2004.06.030.

Ochsner, K. N. *et al.* (2009) 'Bottom-up and top-down processes in emotion generation: common and distinct neural mechanisms.', *Psychological science*. NIH Public Access, 20(11), pp. 1322–31. doi: 10.1111/j.1467-9280.2009.02459.x.

Ochsner, K. N. and Barrett, L. F. (2001) 'A multiprocess perspective on the neuroscience of emotion.', in *Emotions: Current issues and future directions.* New York, NY, US: Guilford Press (Emotions and social behavior.), pp. 38–81.

Ochsner, K. N. and Gross, J. J. (2005) 'The cognitive control of emotion', *Trends in Cognitive Sciences*, 9(5), pp. 242–249. doi: 10.1016/j.tics.2005.03.010.

Ochsner, K. N. and Gross, J. J. (2008) 'Insights From Social Cognitive and Affective Neuroscience', *Current Directions in Psychological Science*, 17(2), pp. 153–158. doi: 10.1111/j.1467-8721.2008.00566.x.

Ochsner, K. N. and Gross, J. J. (2014) 'The Neural Bases of Emotion and Emotion Regulation: A Valuation Perspective', in Gross, J. J. (ed.) *Handbook of Emotion Regulation*. 2nd edn. The Guilford Press, pp. 23–42.

Ochsner, K., Silvers, J. and Buhle, J. (2012) 'Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion', *Ann N Y Acad Sci*, 1252, pp. 1–35. doi: 10.1111/j.1749-6632.2012.06751.x.

Ogawa, S. *et al.* (1990) 'Brain magnetic resonance imaging with contrast dependent on blood oxygenation.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 87(24), pp. 9868–72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2124706 (Accessed: 1 July 2018).

Olsson, A. and Ochsner, K. N. (2008) 'The role of social cognition in emotion.', *Trends in cognitive sciences*. Elsevier, 12(2), pp. 65–71. doi: 10.1016/j.tics.2007.11.010.

Öngür, D., Ferry, A. T. and Price, J. L. (2003) 'Architectonic subdivision of the human orbital and medial prefrontal cortex', *The Journal of Comparative Neurology*. Wiley-Blackwell, 460(3), pp. 425–449. doi: 10.1002/cne.10609.

Outhred, T. *et al.* (2015) 'Facilitation of emotion regulation with a single dose of escitalopram: A randomized fMRI study', *Psychiatry Research - Neuroimaging*. Elsevier, 233(3), pp. 451–457. doi: 10.1016/j.pscychresns.2015.07.018.

Packard, M. G. (2009) 'Anxiety, cognition, and habit: A multiple memory systems perspective', *Brain Research*. Elsevier, 1293, pp. 121–128. doi: 10.1016/J.BRAINRES.2009.03.029.

Parkinson, B. (1996) *Changing moods: the psychology of mood and mood regulation*. Addison Wesley Longman. Available at: https://ueaeprints.uea.ac.uk/14584/ (Accessed: 2 July 2018).

Paschke, L. M. *et al.* (2016) 'Individual Differences in Self-Reported Self-Control Predict Successful Emotion Regulation', *Social Cognitive and Affective Neuroscience*, (September 2015), p. nsw036. doi: 10.1093/scan/nsw036.

Patton, J. H., Stanford, M. S. and Barratt, E. S. (1995) 'Factor structure of the Barratt impulsiveness scale.', *Journal of clinical psychology*, 51(6), pp. 768–74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8778124 (Accessed: 1 July 2018).

Paulhus, D. L., Fridhandler, B. and Hayes, S. (1997) 'Psychological Defense', in *Handbook of Personality Psychology*. Elsevier, pp. 543–579. doi: 10.1016/B978-012134645-4/50023-8.

Pauls, D. L. *et al.* (2014) 'Obsessive–compulsive disorder: an integrative genetic and neurobiological perspective', *Nature Reviews Neuroscience*. Nature Publishing Group, 15(6), pp. 410–424. doi: 10.1038/nrn3746.

Pfefferbaum, A. *et al.* (2009) 'Degradation of association and projection white matter systems in alcoholism detected with quantitative fiber tracking.', *Biological psychiatry*. NIH Public Access, 65(8), pp. 680–90. doi: 10.1016/j.biopsych.2008.10.039.

Phillips, M. L. *et al.* (2003a) 'Neurobiology of emotion perception I: the neural basis of normal emotion perception', *Biological Psychiatry*, 54(5), pp. 504–514. doi: 10.1016/S0006-3223(03)00168-9.

Phillips, M. L. *et al.* (2003b) 'Neurobiology of emotion perception II: implications for major psychiatric disorders', *Biological Psychiatry*. Elsevier, 54(5), pp. 515–528. doi: 10.1016/S0006-3223(03)00171-9.

Phillips, M., Ladouceur, C. and Drevets, W. (2008) 'A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder', *Molecular Psychiatry*, 13(9), pp. 829–857. doi: 10.1038/mp.2008.65.A.

Pitskel, N. B. *et al.* (2011) 'How grossed out are you? The neural bases of emotion regulation from childhood to adolescence.', *Developmental cognitive neuroscience*. NIH Public Access, 1(3), pp. 324–37. doi: 10.1016/j.dcn.2011.03.004.

Pizzagalli, D. A. *et al.* (2009) 'Reduced Caudate and Nucleus Accumbens Response to Rewards in Unmedicated Individuals With Major Depressive Disorder', *American Journal of Psychiatry*. American Psychiatric Association , 166(6), pp. 702–710. doi: 10.1176/appi.ajp.2008.08081201.

Pizzagalli, D. A. (2011) 'Frontocingulate Dysfunction in Depression: Toward Biomarkers of Treatment Response', *Neuropsychopharmacology*. Nature Publishing Group, 36(1), pp. 183–206. doi: 10.1038/npp.2010.166.

Poon, J. A. *et al.* (2016) 'Adolescent Substance Use & Psychopathology: Interactive Effects of Cortisol Reactivity and Emotion Regulation', *Cognitive Therapy and Research*, 40(3), pp. 368–380. doi: 10.1007/s10608-015-9729-x.

Posner, J. *et al.* (2014) 'Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder.', *Human brain mapping*. NIH Public Access, 35(6), pp. 2852–60. doi: 10.1002/hbm.22371.

Price, J. L. (1999) 'Prefrontal Cortical Networks Related to Visceral Function and Mood', *Annals of the New York Academy of Sciences*. Wiley/Blackwell (10.1111), 877(1 ADVANCING FRO), pp. 383–396. doi: 10.1111/j.1749-6632.1999.tb09278.x.

Quirin, M., Kuhl, J. and Düsing, R. (2011) 'Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities.', *Psychoneuroendocrinology*. Elsevier, 36(6), pp. 898–904. doi: 10.1016/j.psyneuen.2010.12.005.

Radua, J. *et al.* (2012) 'A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps', *European Psychiatry*. Elsevier Masson SAS, 27(8), pp. 605–611. doi: 10.1016/j.eurpsy.2011.04.001.

Radua, J. *et al.* (2014) 'Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies', *Frontiers in Psychiatry*, 5(FEB), pp. 1–8. doi: 10.3389/fpsyt.2014.00013.

Rando, K. *et al.* (2011) 'Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: a prospective study.', *The American journal of psychiatry*. NIH Public Access, 168(2), pp. 183–92. doi: 10.1176/appi.ajp.2010.10020233.

Ray, R. D. *et al.* (2010) 'Cognitive reappraisal of negative affect: converging evidence from EMG and self-report.', *Emotion (Washington, D.C.)*. NIH Public Access, 10(4), pp. 587–92. doi: 10.1037/a0019015.

Ray, R. D. and Zald, D. H. (2012) 'Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex', *Neuroscience & Biobehavioral Reviews*. Pergamon, 36(1), pp. 479–501. doi: 10.1016/J.NEUBIOREV.2011.08.005.

Van Reekum, C. M. *et al.* (2007) 'Gaze fixations predict brain activation during the voluntary regulation of picture-induced negative affect', *NeuroImage*. Elsevier Inc., 36(3), pp. 1041–1055. doi: 10.1016/j.neuroimage.2007.03.052.

Richards, J. M. and Gross, J. J. (2000) 'Emotion regulation and memory: The cognitive costs of keeping one's cool.', *Journal of Personality and Social Psychology*, 79(3), pp. 410–424. doi: 10.1037/0022-3514.79.3.410.

Richards, J. M. and Gross, J. J. (2006) 'Personality and emotional memory: How regulating emotion impairs memory for emotional events', *Journal of Research in Personality*. Academic Press, 40(5), pp. 631–651. doi: 10.1016/J.JRP.2005.07.002.

Rimes, K. A. and Watkins, E. (2005) 'The effects of self-focused rumination on global negative self-judgements in depression', *Behaviour Research and Therapy*. Pergamon, 43(12), pp. 1673–

1681. doi: 10.1016/J.BRAT.2004.12.002.

Rive, M. M. *et al.* (2013) 'Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies.', *Neuroscience and biobehavioral reviews*. Elsevier Ltd, 37(10 Pt 2), pp. 2529–53. doi: 10.1016/j.neubiorev.2013.07.018.

Roberts, N. A., Levenson, R. W. and Gross, J. J. (2008) 'Cardiovascular costs of emotion suppression cross ethnic lines.', *International journal of psychophysiology : official journal of the International Organization of Psychophysiology*. NIH Public Access, 70(1), pp. 82–7. doi: 10.1016/j.ijpsycho.2008.06.003.

Romero, M. J. *et al.* (2010) 'Cocaine addiction: diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter.', *Psychiatry research*. Elsevier, 181(1), pp. 57–63. doi: 10.1016/j.pscychresns.2009.07.004.

Rosenthal, M. Z. *et al.* (2016) 'Emotional Reactivity to Personally-Relevant and Standardized Sounds in Borderline Personality Disorder', *Cognitive Therapy and Research*. Springer US, 40(3), pp. 314–327. doi: 10.1007/s10608-015-9736-y.

Rudenga, K. J., Sinha, R. and Small, D. M. (2013) 'Acute stress potentiates brain response to milkshake as a function of body weight and chronic stress', *International Journal of Obesity*. Nature Publishing Group, 37(2), pp. 309–316. doi: 10.1038/ijo.2012.39.

Rus, O. G. *et al.* (2017) 'Functional and structural connectivity of the amygdala in obsessive-compulsive disorder.', *NeuroImage Clinical*. Elsevier, 13, pp. 246–255. doi: 10.1016/j.nicl.2016.12.007.

Ruscio, A. M. *et al.* (2010) 'The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication.', *Molecular psychiatry*. NIH Public Access, 15(1), pp. 53–63. doi: 10.1038/mp.2008.94.

Salgado-Pineda, P. *et al.* (2005) 'Dopaminergic Contribution to the Regulation of Emotional Perception', *Clinical Neuropharmacology*, 28(5), pp. 228–237. doi: 10.1097/01.wnf.0000185824.57690.f0.

Salkovskis, P. M. (1985) 'Obsessional-compulsive problems: A cognitive-behavioural analysis', *Behaviour Research and Therapy*. Pergamon, 23(5), pp. 571–583. doi: 10.1016/0005-7967(85)90105-6.

Salters-Pedneault, K. *et al.* (2006) 'Evidence of Broad Deficits in Emotion Regulation Associated

with Chronic Worry and Generalized Anxiety Disorder', *Cognitive Therapy and Research*. Kluwer Academic Publishers-Plenum Publishers, 30(4), pp. 469–480. doi: 10.1007/s10608-006-9055-4.

Sandín, B. *et al.* (1999) 'Escalas PANAS de afecto positivo y negativo: Validacion factorial y convergencia transcultural', *Psicothema*, pp. 37–51. doi: ISSN 0214-9915.

Sarkheil, P. *et al.* (2015) 'fMRI feedback enhances emotion regulation as evidenced by a reduced amygdala response', *Behavioural Brain Research*, 281, pp. 326–332. doi: 10.1016/j.bbr.2014.11.027.

Saxe, R. (2006) 'Uniquely human social cognition', *Current Opinion in Neurobiology*. Elsevier Current Trends, 16(2), pp. 235–239. doi: 10.1016/J.CONB.2006.03.001.

Saxena, S. and Rauch, S. L. (2000) 'Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder', *Psychiatric Clinics of North America*. Elsevier, 23(3), pp. 563–586. doi: 10.1016/S0193-953X(05)70181-7.

Scherer, K. R. (1984) 'On the nature and function of emotion: a component process approach', in Scherer, K. and Ekman, P. (eds) *Approaches to emotion*. Hillsdale, NJ: Erlbaum, pp. 293–317. Available at: citeulike-article-id:1223796.

Scherer, K. R., Schorr, A. and Johnstone, T. (eds) (2001) *Appraisal processes in emotion: Theory, methods, research.* New York, NY, US: Oxford University Press (Series in affective science.).

Schultz, W. (2007) 'Multiple Dopamine Functions at Different Time Courses', *Annual Review of Neuroscience*. Annual Reviews, 30(1), pp. 259–288. doi: 10.1146/annurev.neuro.28.061604.135722.

Schulze, L. *et al.* (2011) 'Neuronal correlates of cognitive reappraisal in borderline patients with affective instability', *Biological Psychiatry*. Elsevier Inc., 69(6), pp. 564–573. doi: 10.1016/j.biopsych.2010.10.025.

Schweizer, S., Hampshire, A. and Dalgleish, T. (2011) 'Extending brain-training to the affective domain: increasing cognitive and affective executive control through emotional working memory training.', *PloS one*. Public Library of Science, 6(9), p. e24372. doi: 10.1371/journal.pone.0024372.

Shackman, A. J. *et al.* (2006) 'Anxiety selectively disrupts visuospatial working memory.', *Emotion*, 6(1), pp. 40–61. doi: 10.1037/1528-3542.6.1.40.

Sheppes, G. *et al.* (2011) 'Emotion-Regulation Choice', *Psychological Science*. SAGE PublicationsSage CA: Los Angeles, CA, 22(11), pp. 1391–1396. doi: 10.1177/0956797611418350.

Sheppes, G., Catran, E. and Meiran, N. (2009) 'Reappraisal (but not distraction) is going to make you sweat: Physiological evidence for self-control effort', *International Journal of Psychophysiology*. Elsevier, 71(2), pp. 91–96. doi: 10.1016/J.IJPSYCHO.2008.06.006.

Sheppes, G., Suri, G. and Gross, J. J. (2015) 'Emotion Regulation and Psychopathology', *Annual Review of Clinical Psychology*. Annual Reviews , 11(1), pp. 379–405. doi: 10.1146/annurev-clinpsy-032814-112739.

Shin, L. M. and Liberzon, I. (2010) 'The neurocircuitry of fear, stress, and anxiety disorders.', *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. Nature Publishing Group, 35(1), pp. 169–91. doi: 10.1038/npp.2009.83.

Shiota, M. N. and Levenson, R. W. (2012) 'Turn down the volume or change the channel? Emotional effects of detached versus positive reappraisal.', *Journal of personality and social psychology*. NIH Public Access, 103(3), pp. 416–29. doi: 10.1037/a0029208.

Simon, D. *et al.* (2010) 'Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation', *Psychophysiology*. Blackwell Publishing Inc, 47(4), pp. 728–738. doi: 10.1111/j.1469-8986.2010.00980.x.

Smith, S. M. and Nichols, T. E. (2009) 'Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference', *NeuroImage*. Elsevier Inc., 44(1), pp. 83–98. doi: 10.1016/j.neuroimage.2008.03.061.

Somerville, L. H. *et al.* (2013) 'Interactions between transient and sustained neural signals support the generation and regulation of anxious emotion.', *Cerebral cortex (New York, N.Y. : 1991)*. Oxford University Press, 23(1), pp. 49–60. doi: 10.1093/cercor/bhr373.

Soto, J. A. *et al.* (2011) 'Is expressive suppression always associated with poorer psychological functioning? A cross-cultural comparison between European Americans and Hong Kong Chinese.', *Emotion*, 11(6), pp. 1450–1455. doi: 10.1037/a0023340.

Srivastava, S. *et al.* (2009) 'The social costs of emotional suppression: a prospective study of the transition to college.', *Journal of personality and social psychology*. NIH Public Access, 96(4), pp. 883–97. doi: 10.1037/a0014755.

Staudinger, M. R. *et al.* (2009) 'Cognitive reappraisal modulates expected value and prediction error encoding in the ventral striatum', *NeuroImage*. Academic Press, 47(2), pp. 713–721. doi: 10.1016/J.NEUROIMAGE.2009.04.095.

Strata, P. (2015) 'The Emotional Cerebellum', *Cerebellum*, 14(5), pp. 570–577. doi: 10.1007/s12311-015-0649-9.

Strata, P., Scelfo, B. and Sacchetti, B. (2011) 'Involvement of cerebellum in emotional behavior', *Physiological Research*, 60(SUPPL.1).

Substance Abuse and Mental Health Services Administration (SAMHSA) (2011) 'Results from the 2010 National Survey on Drug Use and Health (NSDUH): Summary of national findings (NSDUH Series H-41)'. Rockville.

Szasz, P. L., Szentagotai, A. and Hofmann, S. G. (2011) 'The effect of emotion regulation strategies on anger', *Behaviour Research and Therapy*. Pergamon, 49(2), pp. 114–119. doi: 10.1016/J.BRAT.2010.11.011.

Tabibnia, G. *et al.* (2011) 'Different forms of self-control share a neurocognitive substrate.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*. NIH Public Access, 31(13), pp. 4805–10. doi: 10.1523/JNEUROSCI.2859-10.2011.

Taylor, S. F. and Liberzon, I. (2007) 'Neural correlates of emotion regulation in psychopathology', *Trends in Cognitive Sciences*, 11(10), pp. 413–418. doi: 10.1016/j.tics.2007.08.006.

Taylor Tavares, J. V. *et al.* (2008) 'Neural basis of abnormal response to negative feedback in unmedicated mood disorders', *NeuroImage*. Academic Press, 42(3), pp. 1118–1126. doi: 10.1016/J.NEUROIMAGE.2008.05.049.

Thompson-Schill, S. L., Bedny, M. and Goldberg, R. F. (2005) 'The frontal lobes and the regulation of mental activity.', *Current opinion in neurobiology*, 15(2), pp. 219–24. doi: 10.1016/j.conb.2005.03.006.

Torres, A. *et al.* (2013) 'Emotional and non-emotional pathways to impulsive behavior and addiction.', *Frontiers in human neuroscience*, 7(February), p. 43. doi: 10.3389/fnhum.2013.00043.

Townsend, J. D. *et al.* (2013) 'Frontal-Amygdala connectivity alterations during emotion downregulation in bipolar i disorder', *Biological Psychiatry*. Elsevier Inc., 73(2), pp. 127–135. doi: 10.1016/j.biopsych.2012.06.030.

Uchida, M. *et al.* (2014) 'Emotion regulation ability varies in relation to intrinsic functional brain architecture', *Social Cognitive and Affective Neuroscience*, 10(12), pp. 1738–1748. doi: 10.1093/scan/nsv059.

Urry, H. L. (2009) 'Using reappraisal to regulate unpleasant emotional episodes: Goals and timing matter.', *Emotion*, 9(6), pp. 782–797. doi: 10.1037/a0017109.

Vanderhasselt, M. A. *et al.* (2013) 'Inter-individual differences in the habitual use of cognitive reappraisal and expressive suppression are associated with variations in prefrontal cognitive control for emotional information: An event related fMRI study', *Biological Psychology*. Elsevier B.V., 92(3), pp. 433–439. doi: 10.1016/j.biopsycho.2012.03.005.

Vega-Dienstmaier, J. M. *et al.* (2002) 'Validation of a version in Spanish of the Yale-Brown Obsessive-Compulsive Scale', *Actas españolas de psiquiatria*, 30(1), pp. 30–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11893289 (Accessed: 1 July 2018).

Verdejo-García, A. *et al.* (2015) 'Dysfunctional involvement of emotion and reward brain regions on social decision making in excess weight adolescents', *Human Brain Mapping*, 36(1), pp. 226–237. doi: 10.1002/hbm.22625.

Verdejo-Garcia, A., Clark, L. and Dunn, B. D. (2012) 'The role of interoception in addiction: A critical review', *Neuroscience & Biobehavioral Reviews*, 36(8), pp. 1857–1869. doi: 10.1016/j.neubiorev.2012.05.007.

Via, E. *et al.* (2014) 'Amygdala activation and symptom dimensions in obsessive-compulsive disorder.', *The British journal of psychiatry : the journal of mental science*. The Royal College of Psychiatrists, 204(1), pp. 61–8. doi: 10.1192/bjp.bp.112.123364.

Vink, M. *et al.* (2014) 'Functional differences in emotion processing during adolescence and early adulthood', *NeuroImage*. Academic Press, 91, pp. 70–76. doi: 10.1016/J.NEUROIMAGE.2014.01.035.

Volkow, N. D. *et al.* (2013) 'Obesity and addiction: neurobiological overlaps', *Obesity Reviews*. Wiley/Blackwell (10.1111), 14(1), pp. 2–18. doi: 10.1111/j.1467-789X.2012.01031.x.

Volkow, N. D. *et al.* (2013) 'The Addictive Dimensionality of Obesity', *Biological Psychiatry*, 73(9), pp. 811–818. doi: 10.1016/j.biopsych.2012.12.020.

de Vries, F. E. *et al.* (2014) 'Compensatory Frontoparietal Activity During Working Memory: An Endophenotype of Obsessive-Compulsive Disorder', *Biological Psychiatry*. Elsevier, 76(11), pp. 878–887. doi: 10.1016/J.BIOPSYCH.2013.11.021.

Wager, T. D. *et al.* (2008) 'The Neuroimaging of Emotion', in Lewis, M., Haviland-Jones, J., and Barrett, L. (eds) *The handbook of emotion*. New York: Guildford, pp. 249–271.

Wager, T. D., Jonides, J. and Reading, S. (2004) 'Neuroimaging studies of shifting attention: a meta-analysis', *NeuroImage*. Academic Press, 22(4), pp. 1679–1693. doi: 10.1016/J.NEUROIMAGE.2004.03.052.

Wager, T. D. and Smith, E. E. (2003) 'Neuroimaging studies of working memory: a meta-analysis.', *Cognitive, affective & behavioral neuroscience*, 3(4), pp. 255–74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15040547 (Accessed: 13 May 2016).

Walker, D. L., Toufexis, D. J. and Davis, M. (2003) 'Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety', *European Journal of Pharmacology*. Elsevier, 463(1–3), pp. 199–216. doi: 10.1016/S0014-2999(03)01282-2.

Walker, F., Nilsson, M. and Jones, K. (2013) 'Acute and Chronic Stress-Induced Disturbances of Microglial Plasticity, Phenotype and Function', *Current Drug Targets*, 14(11), pp. 1262–1276. doi: 10.2174/13894501113149990208.

Wang, H. and Bello, P. (2006) 'Ritualized behavior as a domain-general choice of actions', *Behavioral and Brain Sciences*. Cambridge University Press, 29(06), pp. 633–634. doi: 10.1017/S0140525X06009551.

Ward, B. (2000) *Simultaneous Inference for FMRI Data. NIMH.* NIMH.

Watson, D., Clark, L. and Tellegen, A. (1988) 'Development and validation of brief measures of positive and negative affect: the PANAS scales.', *Journal of personality and social psychology*, 54(6), pp. 1063–1070. doi: 10.1037/0022-3514.54.6.1063.

Webb, T. L., Miles, E. and Sheeran, P. (2012) 'Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation.', *Psychological Bulletin*, 138(4), pp. 775–808. doi: 10.1037/a0027600.

Weidt, S. *et al.* (2016) 'Common and differential alterations of general emotion processing in obsessive-compulsive and social anxiety disorder', *Psychological Medicine*, 46(07), pp. 1427–1436. doi: 10.1017/S0033291715002998.

Weiss, J. A., Thomson, K. and Chan, L. (2014) 'A Systematic Literature Review of Emotion Regulation Measurement in Individuals With Autism Spectrum Disorder', *Autism Research*. Wiley-Blackwell, 7(6), pp. 629–648. doi: 10.1002/aur.1426.

Werner, K. H. *et al.* (2011) 'Assessing Emotion Regulation in Social Anxiety Disorder: The Emotion Regulation Interview', *Journal of Psychopathology and Behavioral Assessment*, 33(3), pp. 346–354. doi: 10.1007/s10862-011-9225-x.

Westen, D. (1994) 'Toward an Integrative Model of Affect Regulation: Applications to Social-Psychological Research', *Journal of Personality*. Wiley/Blackwell (10.1111), 62(4), pp. 641–667. doi: 10.1111/j.1467-6494.1994.tb00312.x.

Whalen, P. J. *et al.* (2004) 'Human amygdala responsivity to masked fearful eye whites.', *Science (New York, N.Y.)*. American Association for the Advancement of Science, 306(5704), p. 2061. doi: 10.1126/science.1103617.

Wiens, S. (2005) 'Interoception in emotional experience.', *Current opinion in neurology*, 18(4), pp. 442–447. doi: 10.1097/01.wco.0000168079.92106.99.

Wiggins, J. L. *et al.* (2016) 'Developmental differences in the neural mechanisms of facial emotion labeling.', *Social cognitive and affective neuroscience*, 11(1), pp. 172–81. doi: 10.1093/scan/nsv101.

Williams, A. D. *et al.* (2012) 'Deficits in emotion regulation associated with pathological gambling', *British Journal of Clinical Psychology*, 51(2), pp. 223–238. doi: 10.1111/j.2044-8260.2011.02022.x.

Williams, L. M. (2016) 'Precision psychiatry: A neural circuit taxonomy for depression and anxiety', *The Lancet Psychiatry*. Elsevier Ltd, 3(5), pp. 472–480. doi: 10.1016/S2215-0366(15)00579-9.

Willis, W. D. and Westlund, K. N. (1997) 'Neuroanatomy of the pain system and of the pathways that modulate pain.', *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*, 14(1), pp. 2–31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9013357 (Accessed: 15 June 2018).

de Wit, S. J. *et al.* (2015) 'Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder', *Psychological Medicine*, 45(14), pp. 3059–3073. doi: 10.1017/S0033291715001026.

Wohleb, E. S. *et al.* (2011) 'β-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat.', *The Journal of neuroscience : the official journal of the Society for Neuroscience*. Society for Neuroscience, 31(17), pp. 6277–88. doi: 10.1523/JNEUROSCI.0450-11.2011.

Wolgast, M., Lundh, L.-G. and Viborg, G. (2011) 'Cognitive reappraisal and acceptance: An experimental comparison of two emotion regulation strategies', *Behaviour Research and Therapy*. Pergamon, 49(12), pp. 858–866. doi: 10.1016/J.BRAT.2011.09.011.

Yokum, S. and Stice, E. (2013) 'Cognitive regulation of food craving: effects of three cognitive reappraisal strategies on neural response to palatable foods.', *International journal of obesity (2005)*, 37(12), pp. 1565–70. doi: 10.1038/ijo.2013.39.

Young, L. *et al.* (2010) 'Disruption of the right temporoparietal junction with transcranial magnetic stimulation reduces the role of beliefs in moral judgments.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 107(15), pp. 6753–8. doi: 10.1073/pnas.0914826107.

Yuan, J. *et al.* (2015) 'Unconscious emotion regulation: Nonconscious reappraisal decreases emotion-related physiological reactivity during frustration', *Cognition and Emotion*, 29(6), pp. 1042–1053. doi: 10.1080/02699931.2014.965663.

Zaki, J., Davis, J. I. and Ochsner, K. N. (2012) 'Overlapping activity in anterior insula during interoception and emotional experience.', *NeuroImage*, 62(1), pp. 493–9. doi: 10.1016/j.neuroimage.2012.05.012.

Zaki, J. and Ochsner, K. (2012) 'The neuroscience of empathy: Progress, pitfalls and promise', *Nature Neuroscience*, 15(5), pp. 675–680. doi: 10.1038/nn.3085.

Zilverstand, A. *et al.* (2015) 'fMRI neurofeedback facilitates anxiety regulation in females with spider phobia.', *Frontiers in behavioral neuroscience*. Frontiers Media SA, 9, p. 148. doi: 10.3389/fnbeh.2015.00148.

Zysset, S. *et al.* (2002) 'The Anterior Frontomedian Cortex and Evaluative Judgment: An fMRI Study', *NeuroImage*. Academic Press, 15(4), pp. 983–991. doi: 10.1006/NIMG.2001.1008.