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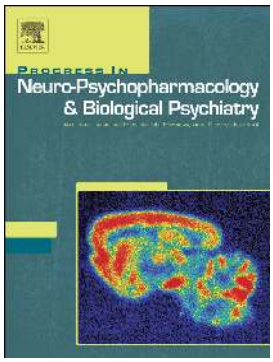

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Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies

Maria Picó-Pérez[a,b], Joaquim Radua[c,d,e,f], Trevor Steward[a,b,g], José M. Menchón[a,b,f], Carles Soriano-Mas[a,f,h,*]

[a]*Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Barcelona, Spain*

[b]*Department of Clinical Sciences, School of Medicine, University of Barcelona, Barcelona, Spain*

[c]*FIDMAG Germanes Hospitalàries, Barcelona, Spain*

[d]*Centre for Psychiatric Research and Education, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden*

[e]*Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, UK*

[f]*CIBER Salud Mental (CIBERSam), Instituto Salud Carlos III (ISCIII), Barcelona, Spain*

[g]*CIBER Fisiopatología de la Obesidad y Nutrición (CIBERObn), Instituto Salud Carlos III (ISCIII), Barcelona, Spain*

[h]*Department of Psychobiology and Methodology in Health Sciences, Universitat Autònoma de Barcelona, Barcelona, Spain*

*Corresponding author: Carles Soriano-Mas, PhD
Department of Psychiatry, Bellvitge University Hospital, Bellvitge Biomedical Research Institute-IDIBELL, Feixa Llarga s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain.
Tel: (+34) 93 2607500 (ext. 2864) Fax: (+34) 932607658
E-mail address: csoriano@idibell.cat

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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.

Keywords: Emotion regulation; Mood and anxiety disorders; Fronto-parietal network; fMRI; Meta-analysis

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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, 1998). 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 primary effect appears during the emotion-generative process (Gross, 1998). 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, 1998). 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, 1998; Gross & John, 2003; Webb *et al.*, 2012; Gross, 2014; Hu *et al.*, 2014). Importantly, several studies have shown that many

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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

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subjects are characteristically instructed to not down-regulate the evoked emotion, similarly to what was reported in Oschner 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 & 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 & Gross, 2014). Likewise, downregulated 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

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integration of information about body states, respectively (Craig, 2003; Haber & Knutson, 2010; Morrison & 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 downregulation 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

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

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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 (Figure 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 to 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-

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effects meta-analysis (weighing the studies for sample size, intra-study variance and between-study heterogeneity) (Radua & 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 & 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 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

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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

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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 (Figure 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 (Figure 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).

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 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

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and the right fusiform gyrus were associated with studies instructing the use of distancing (see Figure 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 Figure 1), while some differences were found for the patients' group when excluding studies with disorder-specific stimuli (see Supplementary Table 4 and Supplementary Figure 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

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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 & 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 & 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

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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.,

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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 & 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 & 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

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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

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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 & Walter, 2014; Joorman & 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

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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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Tables

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*
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. *In the study by Goldin et al., contrasts from both types of stimuli were combined.

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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

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	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.

Figure legends

Figure 1. PRISMA flow diagram.

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

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Figure 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).

Figure 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).

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Figure 1

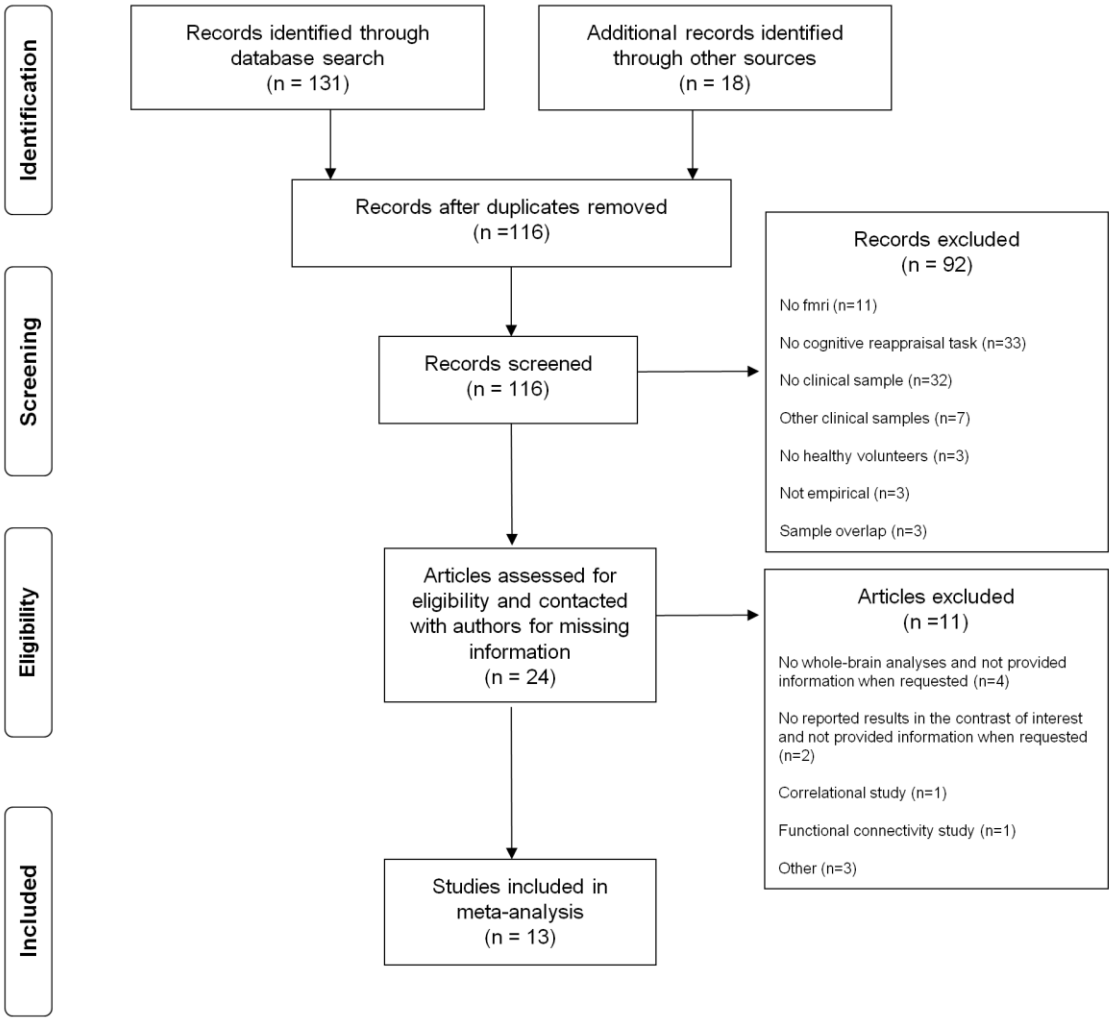

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Figure 2

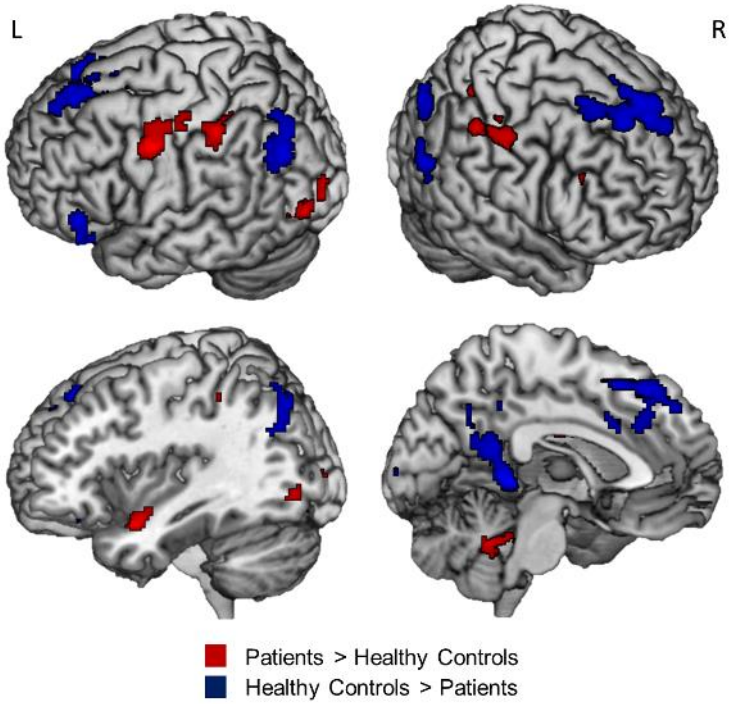

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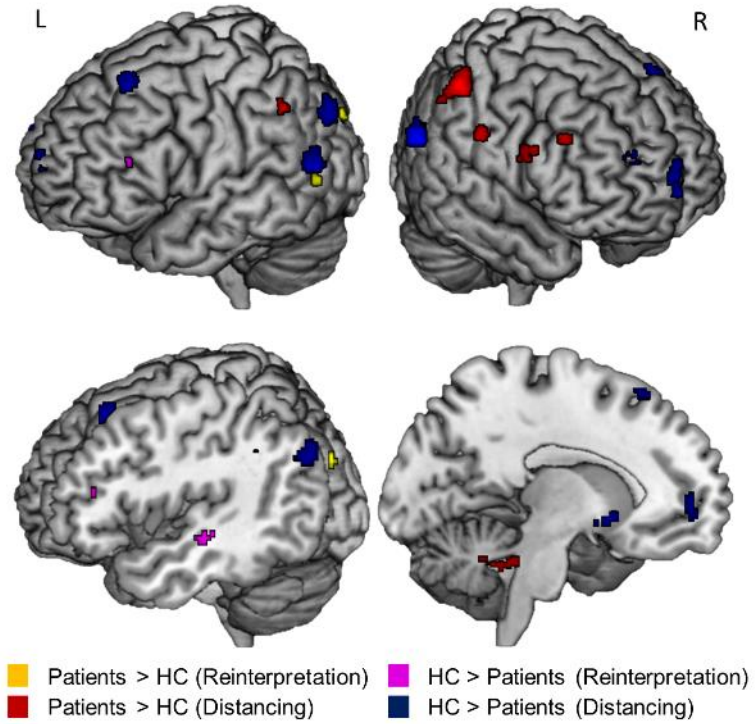
Figure 3



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Highlights

- Patient groups exhibit both abnormal decreases and increases of brain activity.
- The fronto-parietal network is hypoactivated during reappraisal in patient groups.
- Hyperactivations may relate to both emotion experience and compensatory mechanisms.
- Hypoactivations are observed both with disorder-specific and unspecific stimuli.
- The cognitive reappraisal strategy employed has a significant effect on findings.

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