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Running head: REAPPRAISAL META-ANALYSIS

Cognitive reappraisal of emotion: A meta-analysis of human neuroimaging studies

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Abstract

In recent years, an explosion of neuroimaging studies has examined cognitive reappraisal, an emotion regulation strategy that involves changing the way one thinks about a stimulus in order to change its affective impact. Existing models broadly agree that reappraisal recruits frontal and parietal control regions to modulate emotional responding in the amygdala, but they offer competing visions of how this is accomplished. One view holds that control regions engage ventromedial prefrontal cortex (vmPFC), an area associated with fear extinction, that in turn modulates amygdala responses. An alternative view is that control regions modulate semantic representations in lateral temporal cortex that indirectly influence emotion-related responses in the amygdala. Furthermore, while previous work has emphasized the amygdala, whether reappraisal influences other regions implicated in emotional responding remains unknown. To resolve these questions, we performed a meta-analysis of 48 neuroimaging studies of reappraisal, most involving downregulation of negative affect. Reappraisal consistently a) activated cognitive control regions and lateral temporal cortex, but not vmPFC, and b) modulated the bilateral amygdala, but no other brain regions. This suggests that reappraisal involves the use of cognitive control to modulate semantic representations of an emotional stimulus, and these altered representations in turn attenuate activity in the amygdala.

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We humans are nothing if not adaptive. This attribute depends, at least in part, on our ability to regulate responses to life's affective pushes and pulls. Emotion regulation allows us to respond adaptively to these affective events – to keep cool under stress, emerge resilient from tribulations, and resist harmful temptations.

In order to understand how emotions are regulated, it is useful to first consider how they are generated. Theoretically, emotion generation can be understood as a process that unfolds over time. Emotions begin with the individual perceiving a stimulus within a context and attending to its features. Next, the individual appraises a stimulus's emotional significance, and this triggers an affective, physiological and behavioral response (Scherer et al. 2001; Barrett et al. 2007). In this framework, the impact of any given emotion regulation strategy can be understood in terms of the stage of the emotion generation sequence that it impacts (Gross 1998). The best-studied strategy is cognitive reappraisal, which targets the appraisal stage and involves changing one's interpretations or appraisals of affective stimuli. One reason this strategy is so well studied is because reappraisal is highly effective at regulating affect and physiological arousal without the cognitive and physiological costs associated with response-focused strategies (e.g., expressive suppression) (Gross 1998), and with longer-lasting effects than attention-focused strategies (e.g., distraction) (Ochsner and Gross 2005; Kross and Ayduk 2008; Ochsner et al. 2012; Silvers et al. In press). But it is also well-studied because the core elements of reappraisal are central to many forms of therapy, including cognitive behavioral therapy (Beck 2005), dialectical behavioral therapy (Lynch et al. 2007), and psychodynamic therapy (Bateman and Fonagy 2006; Maroda 2010; Have-de Labije and Neborsky 2012), all of which are effective for treating a variety of mood and anxiety disorders. For this

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reason, recent work has begun applying insights from behavioral and brain imaging research on reappraisal to both characterizing and treating clinical disorders (Denny et al. 2009; Silvers *et al.* In press). As such, a clear understanding of the neural systems underlying reappraisal is important for both basic and translational research.

Psychological models of reappraisal suggest that that many of the same cognitive control processes that are used to regulate attention, memory and thoughts in non-emotional contexts are also used in the cognitive regulation of emotion (Ochsner and Gross 2008). If this is the case, we might hypothesize that reappraisal is supported by brain regions supporting domain-general cognitive control processes such as dorsomedial, dorsolateral, and ventrolateral prefrontal cortex (dmPFC, dlPFC, vlPFC) as well as posterior parietal cortex (Duncan and Owen 2000; Miller and Cohen 2001). During reappraisal, we might expect that (1) dlPFC and parietal cortex, regions generally involved in selective attention and working memory, might assist in holding reappraisals in mind, (2) vlPFC, a region strongly implicated in response selection and inhibition, may support the selection of appropriate reappraisals, and, (3) dmPFC may be recruited to assist in monitoring and reflecting on the meaning of changing emotional states (Ochsner and Gross 2005, 2008; Ochsner *et al.* 2012).

But how might these domain-general processes impact activity in regions related to emotional responding? One possibility is that cognitive control regions engage ventromedial prefrontal cortex (vmPFC), which in turn modulates activity in regions related to emotional responding, such as the amygdala (Ochsner and Gross 2005; Urry et al. 2006; Ochsner and Gross 2007; Schiller and Delgado 2010; Diekhof et al. 2011; Etkin et al. 2011). This hypothesis builds on two types of data. First, anatomical work suggests that

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direct connections between lateral PFC regions and the amygdala are relatively sparse in comparison with connections between vmPFC and the amygdala, particularly in caudal portions of vmPFC (Ghashghaei et al. 2007). Second, animal and human work show that vmPFC is critical for fear extinction and reversal learning (Milad et al. 2007; Finger et al. 2008; Schiller et al. 2008).

Together, these data have motivated the idea that during reappraisal lateral PFC regions impact the amgygdala indirectly via the vmPFC. For example, Diekhof and colleagues suggested that vmPFC is not limited to conditioned learning contexts, but also acts as a "domain-general controller of negative affect" in more complex, cognitively-driven regulation contexts such as placebo and reappraisal, supported by structural connectivity between vmPFC and lateral PFC and amygdala (Diekhof *et al.* 2011). In a similar vein, Schiller and Delgado posited that vmPFC serves as a general mechanism for reducing learned fear by uniquely encoding a "safety signal" that can be triggered by diverse brain pathways, including high-level cognitive areas in the dlPFC (Schiller and Delgado 2010). Finally, in another influential review, Etkin and colleagues suggested that vmPFC and adjacent regions might "perform a generic negative emotion inhibitory function that can be recruited by other regions," such as the domain-general cognitive control regions described above (Etkin *et al.* 2011). If these theories are correct, then in studies of reappraisal we should see reliable activation of vmPFC alongside activation of domain-general cognitive control regions.

A second possibility is that prefrontal and parietal control regions exert their effects via changes in lateral temporal areas associated with semantic and perceptual representations. This view would be consistent with psychological models positing that

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reappraisal alters semantic and perceptual representations of stimuli in ways that change their emotional significance (Ochsner and Gross 2005, 2007; Ochsner *et al.* 2012). For example, a participant viewing an image of an accident victim may tell herself, "that's ketchup, not blood", or "those people are just actors." If similar transformations of stimulus meaning underlie reappraisal in general, then in studies of reappraisal we might expect to see consistent activity differences in the lateral temporal cortex regions that encode semantic and perceptual associations.

In contrast to this debate regarding the neural underpinnings of reappraisal, there is greater agreement concerning what brain regions are modulated by reappraisal. Extensive work in animals and humans has implicated the amygdala in the detection, encoding, and organization of responses to arousing, goal-relevant stimuli (Anderson et al. 2003; Phelps and LeDoux 2005; Cunningham and Brosch 2012; Wilson-Mendenhall et al. in press). Given that negative stimuli are commonly perceived as highly arousing, and that the majority of reappraisal studies to date utilize aversive stimuli (out of 48 studies in the present meta-analysis, 34 used aversive stimuli, 5 used positive/appetitive stimuli and 9 used both; see Table 1 for a summary), it is perhaps unsurprising that changes in amygdala activity are among the most consistent findings in the reappraisal literature. However, many other regions are involved in emotion (Kober et al. 2008; Vytal and Hamann 2010; Lindquist et al. 2012). Indeed, individual reappraisal studies sometimes show modulation of other emotion-related regions in association with particular kinds of stimuli and emotions. Such regions include, but are not limited to, the ventral striatum, a structure strongly linked to reward processing (Schultz et al. 1992), the insula, which supports integration of affective and viscerosensory information (Craig 2009; Chang et al. 2012; Zaki et al. 2012), and

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brainstem regions such as the periaqueductal gray, which is involved in the coordination of behavioral and physiological emotional responses (Buhle et al. 2012).

To resolve these questions, we performed the largest meta-analysis to date of neuroimaging studies of cognitive reappraisal. This analysis included 116 contrasts from 48 studies of healthy individuals, allowing us to identify brain regions that consistently support reappraisal (show increases in activity during reappraisal) as well as those that that are modulated by reappraisal (show decreases in activity during reappraisal when the goal is to downregulate affect).

Methods

Procedure

To identify neuroimaging studies of reappraisal, we (1) performed literature searches in PubMed and Google Scholar, (2) examined the references of relevant papers, and (3) contacted numerous researchers with a history of publishing on this topic. Inclusion was based on the following criteria: (1) participants were free from psychiatric diagnosis (nicotine dependence was not considered exclusionary); (2) peak coordinates were reported in either Talairach (Talairach and Tournoux 1988) or Montreal Neurological Institute (MNI) space; (3) analyses compared conditions using a subtraction methodology. We did not include coordinates from between-group comparisons (e.g., men vs. women), functional connectivity analyses (e.g., psychophysiological interactions), or correlations (e.g., with individual difference measures like age). Given that the primary focus of the analysis was to examine reappraisal of emotion versus naturalistic emotional responses, we did not include contrasts comparing reappraisal with different goals (e.g., using reappraisal to increase versus decrease emotional responses) or reappraisal of different

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types of stimuli (e.g., reappraisal of positive versus negative stimuli) excluded. Finally, we did not include any contrasts that sought to examine manipulations of attention (i.e., distraction) or the adoption of a general mindset (i.e., relaxation).

[INSERT TABLE 1 ABOUT HERE]

We searched the literature for studies published between 2001 and 2012, spanning the duration from when the first neuroimaging study of reappraisal was published to when the present paper was submitted. We identified 1268 peaks from 116 contrasts in 48 studies that met our criteria (see Table 1). Each contrast was coded according to the type of regulation-related neural activity we expected it to index. For example, a typical contrast may compare a condition wherein participants used reappraisal to downregulate emotional responses to negative stimuli to a condition wherein participants responded naturally (passive viewing) to negative stimuli. In such a contrast, brain regions showing greater activity would be interpreted as supporting reappraisal. However, if a brain region showed greater activation when responding naturally than during reappraisal, it would be interpreted as a region that is modulated by reappraisal. These codes were applied independently of one another, so it was possible for a given contrast to be coded as both supporting reappraisal and being modulated by reappraisal. An example would be a contrast in which reappraising a positive image as more positive (i.e., upregulating) was compared to simply viewing a positive image.

The meta-analysis technique we used nests peaks within contrasts rather than within studies (for more details, see below). As a result, if a study reported multiple contrasts, each of which isolated quite similar processes (for example by comparing reappraising a picture as less negative to both simply viewing a negative picture and to

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performing a simple cognitive task (e.g., Harenski and Hamann, 2006)), then including both of these contrasts would oversample highly dependent data. In these rare situations, we included only the contrast deemed most methodologically canonical, which was defined as the one that was closest to a comparison between reappraising a stimulus and responding naturally to it.

Analyses

First, coordinates reported in Talaraich space were converted to MNI space using the Tal2MNI algorithm (Matthew Brett; http://www.imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/tal2mni.m). Next, we assessed the spatial density of reported peak coordinates using the Multilevel Kernel Density Analysis (MDKA) approach developed by Wager and colleagues (Wager et al. 2007; Kober *et al.* 2008; Kober and Wager 2010). This approach nests peaks within contrasts, and thus controls for the total number of peaks a given contrast reports. This is important to prevent a single contrast from unduly influencing the overall results, and it overcomes artefactual differences in peak counts that might result from analysis choices such as voxel size or smoothing kernel.

Next, an 8-mm Gaussian smoothing kernel was created around each peak such that voxels closest to the peak were given a value of 1 with those further away receiving values closer to 0. This allowed us to create graded contrast-indicator maps (CIMs) for each peak reported. These CIMs were then combined to form a single nested map for each contrast, thus ensuring each contrast could contribute no more than a value of 1 for a given voxel when overall proportion statistics were calculated. These combined CIMs were then weighted by the square root of the sample size of the contrast, so that data based on many

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participants would exert greater influence on the meta-analyses than data based on just a few participants. The 8-mm kernel used in the present analyses is slightly smaller than what has been used in other MKDA meta-analyses (typically 10-15mm), making this approach somewhat more conservative. When identical analyses were performed using a 10-mm kernel, all peaks identified using the 8-mm kernel were found to be included within the clusters identified using the 10-mm kernel. Yet, the clusters identified using the 10-mm kernel contained more voxels. One additional cluster was identified in the 10-mm kernel results that was located in left middle frontal gyrus (-27 51 30). This cluster did not meet FWE correction for the 8-mm kernel analysis (k=38) and thus was not reported in the present results.

Statistical inferences were made by comparing the proportion of contrasts showing activation in a given voxel to an empirical null distribution derived by Monte Carlo random sampling of spatially-scrambled peaks. The data were resampled to a voxel size of 3 mm, and 5000 simulations were conducted for each analysis. Results were masked using a gray matter mask created through segmentation of the MNI-T1 template (the "Colin" brain) supplied in SPM5 (49653 3mm isotropic voxels). All maps were thresholded using a Family Wise Error correction rate of p<.05, as implemented in NeuroElf (http://neuroelf.net/). All analyses and visualizations were implemented in NeuroElf

Results

To address our first question regarding what brain regions support reappraisal, we performed an analysis of contrasts comparing reappraisal to a baseline condition (e.g., "responding naturally" to an emotional stimulus). As expected, this revealed extensive

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recruitment of regions commonly observed in cognitive control tasks including posterior dmPFC and bilateral dlPFC, vlPFC, and posterior parietal cortex (Table 2; Figure 1).

With regards to our second question of whether implementation of reappraisal involves recruitment of vmPFC or recruitment of temporal regions known to support semantic and perceptual representations, two observations were made. First, we failed to observe any clusters in vmPFC. Second, a sizeable cluster was observed in left posterior temporal cortex. In this initial analysis, we included all contrasts aimed at identifying brain regions that support reappraisal. As described in the *Methods* section, this included both contrasts in which participants decreased their affective responses, and those in which they increased their affective responses. However, increasing one's affective response may upregulate activity in both regions that support reappraisal and in regions that are modulated by reappraisal and therefore may complicate interpretation of results. Therefore, we conducted a second meta-analysis that included only contrasts that compared downregulation of affect to a baseline condition, excluding any contrasts that examined neural responses supporting upregulation of affect. The results of this analysis were nearly identical, suggesting consistent prefrontal, parietal and temporal regions are consistently recruited by reappraisal, regardless of whether one is reappraising to increase or decrease affective responses. Interested readers can examine these results at http://www.scan.psych.columbia.edu/supplementary/Buhle_Silvers_FigS1_SourceOnly.html. Finally, to directly test whether any subset of studies reported peaks in vmPFC, we conducted an ROI analysis using a 15-mm radius sphere centered on a peak in vmPFC reported by Diekhof and colleagues in their meta-analysis of reappraisal studies (2011; 6,

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40, -22). We found that only one out of the 838 coordinates included in this analysis fell within this sphere (Krendl et al., 2011).

[INSERT FIG. 1 ABOUT HERE; INSERT TABLE 2 ABOUT HERE]

To address our third question about whether the amygdala or other regions are modulated by reappraisal, we performed an analysis of brain regions that responded more strongly during a baseline condition than during reappraisal, excluding any contrasts that indexed activity related to upregulation of affect. This analysis sought to identify regions where activation decreased in the presence of reappraisal. The analysis revealed bilateral amygdala clusters, with the left cluster extending into the ventral striatum and pallidum (Table 3; Figure 2). No clusters were observed anywhere else in the brain.

[INSERT FIG. 2 ABOUT HERE; INSERT TABLE 3 ABOUT HERE]

Discussion

In the present meta-analysis, we found that the implementation of reappraisal consistently activated cognitive control regions, including dmPFC, dlPFC, vlPFC, and posterior parietal lobe. These results are in line with the predictions of psychological models of reappraisal, which emphasize the role of domain general cognitive control processes in the cognitive regulation of emotion (Ochsner and Gross 2008). Specifically, the present results are consistent with the hypotheses that dlPFC may support manipulation of appraisals in working memory (Wager and Smith 2003), vlPFC may support selection and inhibition of appraisals (Robbins 2007; Simmonds et al. 2008), and dmPFC may support semantic and self-reflective processes relevant to elaborating the affective meaning of stimuli or perceiving one's affective state. (Crosson et al. 2002; Cato et al. 2004; Amodio and Frith 2006; Olsson and Ochsner 2008; Binder et al. 2009). These results also are

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broadly consistent with the results of earlier meta-analyses that examined smaller samples of studies (Kalisch 2009; Diekhof *et al.* 2011).

However, we found that the implementation of reappraisal in the current set of studies did not consistently recruit vmPFC. This null finding contradicts the hypothesis that vmPFC provides a necessary link by which frontal and parietal regions modulate emotion-related activity in the amygdala (Ochsner and Gross 2005, 2007; Schiller and Delgado 2010; Diekhof *et al.* 2011; Etkin *et al.* 2011). This result may appear somewhat surprising, given the rich neuroscience literature demonstrating the involvement of vmPFC in fear extinction, reversal learning and regulation of social behavior (Bechara et al. 2005; Quirk and Beer 2006; Quirk et al. 2006; Milad *et al.* 2007; Wager *et al.* 2007; Finger *et al.* 2008). One possibility is that vmPFC activation is not observable in contrasts comparing reappraisal to responding naturally to emotional stimuli because it is engaged by both. This could be because vmPFC is engaged during reappraisal as well as on baseline trials, either because it is important for relatively passive or non-goal oriented forms of emotion regulation, such as extinction (Schiller and Delgado 2010; Diekhof *et al.* 2011), that might arise spontaneously on baseline trials. Alternatively, it could be that vmPFC is involved in processes related to emotion generation, such as self-reflection (Denny et al. 2012). Indeed, whether emotion generation and regulation necessarily rely upon distinct neural mechanisms remains an open question, given that partially overlapping prefrontal regions have been shown in prior work to support emotion generation, perception, experience and regulation (Kober *et al.* 2008; Fusar-Poli et al. 2009; Ochsner et al. 2009; Vytal and Hamann 2010; Gross and Barrett 2011; Lindquist *et al.* 2012). To further investigate this issue, future work might seek to examine neural responses during reappraisal using

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experimental and analytic methods that do not rely on subtraction logic between emotion generation and regulation conditions.

That said, although an early meta-analysis of 13 reappraisal studies did not find any consistent activity in vmPFC (Kalisch 2009), a larger, more recent meta-analysis of 25 studies by Diekhof and colleagues (2011) did report consistent engagement of vmPFC. There are at least four possibilities for the differences in results between the present meta-analysis and those of Diekhof and colleagues. First, the study of Diekhof and colleagues included far fewer studies, and thus would be more prone to false positives than the present meta-analysis. A second possibility is that vmPFC recruitment is only observed in a subset of studies and such studies were more heavily sampled in the Diekhof meta-analysis than the present one. For example, it may be that vmPFC is not critical for emotion regulation per se, but is recruited in paradigms that rely more heavily on holding conceptual information in mind (Roy et al. 2012). This includes paradigms such as those utilized by Delgado and colleagues (2008) that involve imagining a calming stimulus like the ocean during exposure to affective stimuli. Indeed, Diekhof and colleagues only observed vmPFC activity in three of the twenty-five studies included. Yet, when we conducted an ROI analysis to examine this possibility, we found that only one out of the 838 coordinates included in our meta-analytic dataset fell within this sphere (Krendl et al., 2011), rendering this explanation unlikely. A third possibility is that vmPFC recruitment is not observed in main effect contrasts of reappraisal, but may relate to individual differences. Support for this comes from several studies have found that connectivity between vmPFC and subcortical structures differs between individuals as a function of psychiatric status (Johnstone et al. 2007; Erk et al. 2010), genetics (Schardt et al. 2010),

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and behavioral measures of reappraisal success (Wager, Davidson, et al. 2008). Importantly, one of the three vmPFC peaks observed in the meta-analysis by Diekhof and colleagues) came from a study that utilized a between-subjects correlational analysis rather than a main effect contrast (Urry *et al.* 2006), and another involved comparisons of vmPFC connectivity between healthy controls and a patient population (Johnstone *et al.* 2007). In the present analysis, we endeavored to include only analyses that best represented the main effect of reappraisal in healthy individuals, as described in detail in the *Methods* section. Therefore, unlike the Diekhof meta-analysis, we did not include (1) contrasts comparing patients and healthy controls, or (2) correlational analyses or functional connectivity. We believe this approach enhances the interpretability of our results and also effectively combats the growing multiple comparisons problem in neuroimaging, in which greater analytic flexibility increases the likelihood of finding regions compatible with one's hypotheses (Carp 2012, 2012).

The lack of involvement of vmPFC in reappraisal suggests that while reappraisal may lead to a similar outcome as extinction (i.e., cue-related emotional activity is reduced), there are likely notable differences in the psychological and neural processes that lead to this outcome. In fear extinction, activity in regions related to emotional responding is reduced as a result of contextual learning processes that may operate outside awareness. In contrast, psychological models of reappraisal posit that it is the reconstruction of semantic and perceptual representations that in turn alters a stimulus's emotional import (Ochsner and Gross 2005, 2007). In line with this interpretation, we observed recruitment of left posterior temporal regions commonly implicated in interpreting actions, reflecting on intentions and extracting semantic meaning (Vigneau et al. 2006; Van Overwalle and

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Baetens 2009; Rapp et al. 2012). This finding could be interpreted in two ways. On the one hand, reappraisal could involve constructing an alternative internally-represented version of a perceptual stimulus to which participants respond. For example, one imagines that a sick person will be well – and emotional responding is driven by that imagined stimulus. This interpretation seems plausible given prior work showing that reappraisal is effective even when individuals maintain fixation on emotionally-relevant aspects of photographic stimuli (Urry 2010). On the other hand, temporal lobe activity could reflect differential attention to emotion-relevant features that are essential for triggering one's emotions and constructing a reinterpretation of them (Bebko et al. 2011). Future work could attempt to disentangle these possibilities.

Finally, we found strong evidence that reappraisal modulates activity in bilateral amygdala, but not other regions related to emotional responding, such as anterior insula, periaqueductal gray, hypothalamus, thalamus, orbital frontal cortex, temporal pole, or rostral and subgenual anterior cingulate cortex. It is not surprising that amygdala is modulated by reappraisal, given its importance for the detection and encoding of affectively salient stimuli (Wager, Barrett, et al. 2008; Lindquist *et al.* 2012). Furthermore, prior work shows that amygdala responses track affective intensity, especially for aversive stimuli like those photos used widely in reappraisal studies (Canli et al. 2000; Williams et al. 2001; Anderson *et al.* 2003; Cunningham et al. 2004; Ochsner et al. 2004; Phan et al. 2004; Ochsner *et al.* 2009). However, it is somewhat surprising that no other regions were reliably modulated by reappraisal. Current models of emotion suggest that emotional responses are reflected in activity across a network of regions (Kober *et al.* 2008), and in

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changing one's emotional response one might expect reappraisal to impact this network as a whole.

There are several possible explanations for the amygdala-specific reductions we observed. One possibility is that this reflects the widespread use of aversive stimuli in reappraisal studies and the particular sensitivity of the amygdala in detecting threat (Phelps and LeDoux 2005). Given the role of the ventral striatum and pallidum in craving and the formation of appetitive appraisals, it could be the case that reappraisal modulates activity in the ventral striatum and pallidum for positive stimuli and activity in the amygdala for aversive stimuli. This might explain why the left amygdala cluster observed in this analysis extended somewhat into the ventral striatum and pallidum– perhaps the studies using positive stimuli contributed to one part of that cluster while studies using negative stimuli contributed to another part of that cluster. However, this may be an overly simplistic characterization of these structures' roles in emotional generation and regulation. Although the ventral striatum is involved in reward, prior research has shown that the ventral striatum responds both to positive and negative stimuli (Roitman et al. 2005) and that stimulation of this region can result in both approach and avoidance (Reynolds and Berridge 2001, 2002, 2003). Thus, it may be that the ventral striatum is involved in coordinating behavioral responses to emotion more broadly and that reappraisal is most likely to modulate activity in this region when an emotion activates a behavioral response component. In either case, a direct comparison between the neural bases of reappraisal for positive and negative stimuli in the present analysis was not possible because the relatively scant number (14) of studies using positive stimuli would have rendered such a comparison underpowered.

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A second possibility for why reappraisal modulated amygdala by, but not other brain regions, is that the overwhelming majority of the studies comprising the present meta-analysis utilized visual stimuli as a means for eliciting emotion (36 utilized photographs and 3 utilized videos). Given the dense connectivity between the amygdala and the visual system, it may be that such stimuli are more likely to elicit amygdala responses than are non-visual ones (Price 2003; Phelps and LeDoux 2005; LeDoux 2007; Pessoa and Adolphs 2010).

A third possibility is that other emotion-related regions are at least sometimes modulated by reappraisal, but these reductions have not been identified because of a lack of sensitivity of most commonly used analysis techniques. Indeed, the robust results observed in the amygdala reflect in part the selective targeting of this region with region of interest (ROI) analyses. Out of the 33 studies that contributed to the analysis of brain regions modulated by reappraisal, only 9 used an ROI analysis. However, a higher percentage of studies with ROI methods yielded peaks in the left amygdala (7/9 ROI studies versus 8/24 whole brain studies) than did those relying exclusively on whole brain analyses, $\chi^2(1, N=33)=5.215$, $p<.05$, and a similar trend was observed for the right amygdala (7/9 ROI studies versus 10/24 whole brain studies), $\chi^2(1, N=33)=3.417$, $p=.07$. Thus, we encourage more widespread use of ROI analyses in other brain regions thought to support emotion generation (e.g., ventral striatum, insula, vmPFC) in future reappraisal research.

Limitations

While the present analysis represents the largest and most complete meta-analysis of reappraisal studies to date, it is not without limitations. First, in order to clearly

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characterize the neural bases of reappraisal in healthy individuals, our meta-analysis relied solely on main effect contrasts comparing reappraisal to a baseline condition in healthy individuals. This is the most commonly reported type of contrast in reappraisal manuscripts, and it offers the most straightforward way to identify the neural regions that support reappraisal. Yet, by relying heavily on the subtraction approach for identifying brain regions related to reappraisal, we may sometimes overlook brain regions that are commonly involved in both reappraisal and in either emotion generation or spontaneous (i.e., not driven by an external goal) emotion regulation. Future work will need to employ novel paradigms in order to address this possibility.

A second limitation of the present meta-analysis is that it is largely comprised of contrasts examining downregulation of negative affect induced by viewing aversive photographic images (As seen in Table 1, 34 out of the 48 studies included this type of contrast). This homogeneity in research practices makes it difficult to formally test what brain regions support reappraisal regardless of methodological practices and which vary as a function of variables such as stimulus valence (positive or negative), stimulus type (pictures, videos, memories, etc.), tactic (reinterpretation or distancing), and reappraisal goal (increase or decrease affective response). For example, one might hypothesize that reappraisal of negative pictures would elicit different patterns of cognitive control than reappraisal in the domain of decision making. Yet, testing this hypothesis is virtually impossible at present given that only four studies have examined reappraisal in the domain of decision making and within those four studies, two examined reappraisal at the time of decision making (Grecucci, Giorgetta, Van't Wout, et al. 2012; Sokol-Hessner et al. 2012), another examined reappraisal during anticipation of monetary reward (Staudinger et al.

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2011), and another examined reappraisal during both anticipation and receipt of monetary reward (Staudinger et al. 2009). In order to use meta-analysis to compare reappraisal across different types of emotional situations, we must adopt a more diverse approach to studying reappraisal. The use of more diverse stimuli is also needed to enhance connections between basic research on reappraisal and therapeutic practices that involve elements of reappraisal (Grecucci, Giorgetta, Bonini, et al. 2012; Grecucci et al. 2013). For example, in order to better characterize clinical disorders and customize treatment, it may prove particularly useful to ask patients to reappraise stimuli specific to their symptomology. More studies have attempted to do this recently with work examining reappraisal of phobogenic stimuli in phobic populations (Hermann et al. 2009) or social stimuli in populations characterized by unstable social relationships, such as borderline personality disorder (Koenigsberg et al. 2009).

Conclusion

In line with existing models, the implementation of reappraisal consistently activated domain-general cognitive control regions, including dmPFC, dlPFC, vlPFC, and posterior parietal lobe (Ochsner and Gross 2005, 2008; Kalisch 2009; Schiller and Delgado 2010; Diekhof *et al.* 2011; Ochsner *et al.* 2012). However, in contrast to several prominent theories, the present results indicate that reappraisal does not rely on vmPFC-mediated emotional control (Ochsner and Gross 2005, 2007; Schiller and Delgado 2010; Diekhof *et al.* 2011; Etkin *et al.* 2011), but instead may act though the lateral temporal cortex, an area associated with semantic and perceptual representation. Lastly, reappraisal was consistently associated with bilateral amygdala modulation, but no change was observed in other regions related to emotional responding, or anywhere else in the brain. While these

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results affirm that the amygdala is modulated by reappraisal of aversive stimuli, more sensitive analyses and the use of a wider range of affective stimuli may be necessary to assess whether additional regions involved in emotional responding regions are similarly impacted by reappraisal.

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Figures and Tables

Table 1. Reappraisal studies included in meta-analysis. "Control" contrasts indexed activity supporting reappraisal; for example, downregulation of emotional responses to negative stimuli > respond naturally. "Emotion" contrasts indexed only activity that was impacted by regulation; for example, respond naturally to positive stimuli > downregulate. "Both" contrasts indexed both "control" and "emotion" activity; for example, upregulate positive stimuli > respond naturally. Stimulus valence indicates whether positive (pos), negative (neg), or both positive and negative stimuli (both) were used and stimulus type indicates the type of stimulus utilized. Goal indicates whether reappraisal was used to increase (inc), decrease (dec) or increase and decrease (both) affective responses. Tactic indicates whether participants were instructed to reinterpret (reint), distance (distance), use some combination of strategies or their own choice (both) or whether it was unclear what participants were instructed to do (unclear).* Indicates that coordinates were obtained via personal communication with authors.

Study	Contrast type(s)	N	Valence	Stimulus type	Goal	Tactic
Beauregard et al., 2001	Control	10	Pos	Videos	Dec	Dist
Domes et al., 2010	Control, Both	33	Neg	Photos	Both	Both
Eippert et al., 2007	Control, Both, Emotion	24	Neg	Photos	Both	Both
Erk et al., 2010	Control, Emotion	17	Neg	Photos	Dec	Dist
Goldin et al., 2008	Control	17	Neg	Videos	Dec	Reint
Grecucci et al., 2012	Both	21	Neg	Ultimatum offers	Both	Reint
Harenski et al., 2006	Control	10	Neg	Photos	Dec	Both
Hayes et al., 2010	Control, Emotion	25	Neg	Photos	Dec	Reint
Herwig et al., 2007	Control (2)	14	Both	Anticipation of photos	Dec	Reint
Hollmann et al., 2011	Control	17	Pos	Photos	Dec	Reint
Ichikawa et al., 2011	Both, Emotion	17	Neg	Task errors	Both	Reint
Kanske et al., 2011	Control, Emotion	30	Both	Photos	Dec	Both
Kanske et al., 2012	Control (2), Emotion (2)	26	Both	Photos	Dec	Reint

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Kim et al., 2007	Both (2), Control (2)	10	Both	Photos	Both	Reint
Kober et al., 2010	Control, Emotion	21	Pos	Photos	Dec	Reint
Koenigsberg et al., 2010	Control, Emotion	16	Neg	Photos	Dec	Dist
Krendl et al., 2011	Control, Emotion	16	Neg	Photos	Dec	Unclear
Kross et al., 2009	Emotion (2)	16	Neg	Memories	Dec	Reint
Lang et al., 2012	Both (2), Control (4)	15	Neg	Scripts	Both	Dist
Leiberg et al., 2012	Both (2), Control, Emotion	24	Neg	Photos	Both	Dist
Levesque et al., 2003	Control	20	Neg	Videos	Dec	Dist
Mak et al., 2009	Control (2), Emotion (2)	12	Both	Photos	Dec	Unclear
McRae et al., 2008	Control, Emotion	25	Neg	Photos	Dec	Reint
McRae et al., 2010*	Control, Emotion	18	Neg	Photos	Dec	Reint
McRae et al., 2012a	Control, Emotion	38	Neg	Photos	Dec	Reint
McRae et al., 2012b*	Control, Emotion	26	Neg	Photos	Dec	Reint
Modinos et al., 2010	Control, Emotion	18	Neg	Photos	Dec	Reint
New et al., 2009	Both (2), Control (3)	14	Neg	Photos	Both	Reint
Ochsner et al., 2002	Control, Emotion	15	Neg	Photos	Dec	Reint
Ochsner et al., 2004	Both, Control, Emotion	24	Neg	Photos	Both	Both
Ochsner et al., 2009	Both, Emotion	20	Neg	Photos	Inc	Both
Ohira et al., 2006	Control, Emotion	10	Both	Photos	Dec	Unclear
Opitz et al., 2012	Control	31	Neg	Photos	Both	Reint
Perlman et al., 2012	Control, Emotion	14	Neg	Photos	Dec	Reint
Phan et al., 2005	Control, Emotion	14	Neg	Photos	Dec	Reint
Pitskel et al.,	Both, Control,	15	Neg	Photos	Both	Reint

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2011	Emotion					
Schardt et al., 2010	Control, Emotion	37	Neg	Photos	Dec	Dist
Schulze et al., 2011	Both, Control, Emotion (2)	16	Neg	Photos	Both	Both
Sokol-Hessner, 2012	Control (2), Emotion	16	Both	Economic decision making	Both	Dist
Staudinger et al., 2009	Control	16	Pos	Anticipation and receipt of monetary reward	Dec	Dist
Staudinger et al., 2011	Control, Emotion	24	Pos	Anticipation of monetary reward	Dec	Dist
Urry et al., 2006	Both, Control	17	Neg	Photos	Both	Reint
Urry et al., 2009	Both, Control	26	Neg	Photos	Both	Reint
Van Reekum et al., 2007	Both, Control, Emotion	29	Neg	Photos	Both	Reint
Vrticka et al., 2011*	Control, Emotion (4)	19	Both	Photos	Dec	Reint
Wager et al., 2008*	Control, Emotion	30	Neg	Photos	Dec	Reint
Walter et al., 2009	Control, Emotion	18	Neg	Photos	Dec	Dist
Winecoff et al., 2011	Control (2), Emotion (2)	42	Both	Photos	Dec	Dist

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Table 2. Peak voxel and corresponding maximum z values for brain regions supporting reappraisal (reappraise > emotional baseline). Local maxima are denoted with "-".

				MNI Coordinates		
Region	Side	Extent	z	x	y	z
Middle frontal gyrus	Right	175	3.72	60	24	3
Middle frontal gyrus	Right	-	3.72	48	24	9
Middle frontal gyrus	Right	-	3.72	48	15	6
Inferior frontal gyrus	Right	101	3.72	51	15	48
Inferior frontal gyrus	Right	-	3.72	51	6	48
Inferior frontal gyrus	Right	-	3.72	42	21	45
Inferior frontal gyrus	Right	-	3.72	42	30	39
Medial frontal gyrus	Right	309	3.72	9	30	39
Medial frontal gyrus	Midline	-	3.72	0	15	63
Medial frontal gyrus	Midline	-	3.72	0	6	63
Medial frontal gyrus	Midline	-	3.72	0	-9	63
Medial frontal gyrus	Midline	-	3.72	0	18	42
Anterior cingulate gyrus	Left	-	3.72	-3	24	30
Superior frontal gyrus	Left	-	3.72	-9	12	69
Middle frontal gyrus	Left	517	3.72	-33	3	54
Middle frontal gyrus	Left	-	3.72	-36	15	57
Anterior insula	Left	-	3.72	-36	21	-3
Anterior insula	Left	-	3.72	-42	18	9
Inferior frontal gyrus	Left	-	3.72	-42	45	-6
Inferior frontal gyrus	Left	-	3.72	-51	12	21
Inferior frontal gyrus	Left	-	3.72	-51	21	9
Superior parietal lobule	Right	77	3.72	63	-51	39
Superior parietal lobule	Right	-	3.72	60	-60	30
Superior parietal lobule	Right	-	3.72	51	-60	42
Inferior parietal lobule	Right	-	3.16	60	-45	27

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Superior parietal lobule	Left	126	3.72	-42	-66	42
Parietooccipital sulcus	Left	-	3.72	-45	-69	18
Middle temporal gyrus	Left	-	3.72	-51	-60	27
Superior occipital lobe	Left	-	3.72	-54	-72	27
Superior temporal gyrus	Left	-	3.09	-63	-51	21
Middle temporal gyrus	Left	125	3.72	-51	-39	3
Middle temporal gyrus	Left	-	3.35	-57	-24	-12

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Table 3. Peak voxel and corresponding maximum z values for brain regions modulated by reappraisal (emotional baseline > reappraise). Local maxima are denoted with "-".

				MNI Coordinates		
Region	Side	Extent	z	x	y	z
Amygdala	Right	126	3.72	30	-3	-15
Extended amygdala	Right	-	3.72	27	6	-12
Amygdala	Left	111	3.72	-18	-3	-15

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Figure Captions

Figure 1. Results of the meta-analysis of brain regions supporting reappraisal (reappraise > emotional baseline).

Figure 2. Results of the meta-analysis of brain regions modulated by reappraisal (y=-3; emotional baseline > reappraise).

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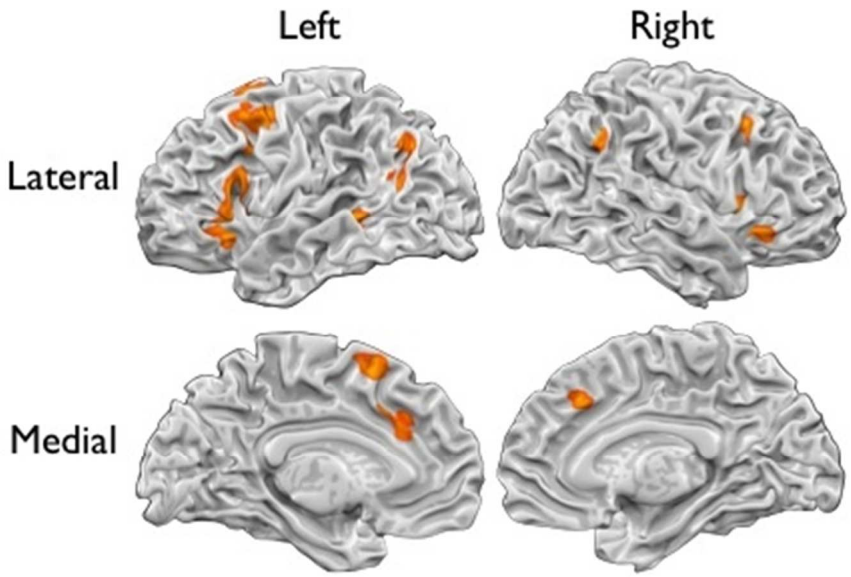

Figure 1. Results of the meta-analysis of neural sources of reappraisal (reappraise > emotional response baseline).
152x105mm (72 x 72 DPI)

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Figure 2. Results of the meta-analysis of neural targets of reappraisal (y=-3; "respond naturally">reappraise).
64x55mm (72 x 72 DPI)

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