Differential roles of dorsal and ventral anterior cingulate and medial prefrontal cortex in cognitive emotion regulation

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Abstract

A rapidly growing neuroimaging literature has provided extensive data on the neural systems implicated in cognitive emotion regulation. Functional imaging studies significantly contribute to the identification of the cognitive processes that underlie different types of emotion regulation such as attentional distraction and cognitive reappraisal. In this article, I review imaging studies of emotion regulation and aim to identify common and differential neural mechanisms supporting down-regulation of negative emotions through self-distraction and cognitive reappraisal. Quantitative meta-analysis of neuroimaging findings revealed overlapping activation in dorsal anterior cingulate (ACC) and dorsal medial prefrontal cortex (mPFC) for reappraisal and self-distraction as well as distraction-specific engagement of ventral ACC and mPFC. These results are discussed on the basis of recent findings that implicate dorsal ACC/mPFC in detection of emotional conflict and appraisal of emotional stimuli and ventral ACC/mPFC in inhibition of processing of emotional distracters. The influence of three other factors on regulation-related brain activation is explored. Finally, limitations of this meta-analysis and hypotheses for future research are presented.

Introduction

The human capacity to modify and control emotions is essential for our mental and physical well-being. Clinical research has also emphasized the role of emotion regulation in cognitive psychotherapy and identified a relationship between impaired emotion regulation and affective disorders. The important role that emotion regulation plays in our lives is reflected by the increasing number of studies that investigate the psychological, behavioral and neural bases of emotion regulation.

Emotion regulation refers to a heterogeneous set of processes by which physiological, behavioral, and experiential components of our affective responses are regulated (Gross and Thompson, 2007). There are automatic forms of emotion regulation in which emotional responses adapt to the change of stimulus-outcome contingencies (i.e. fear extinction or reversal) as well as voluntary emotion regulation which may involve reappraisal of an emotional situation or shift of attention away from an emotional stimulus.

According to Gross and Thompson (2007), voluntary emotion regulation processes can be divided into five basic categories based on the type of emotion generation process at which they have their primary impact (see figure 1). The first two types of emotion regulation (i.e. situation selection and situation modification) aim at either actively avoiding or modifying an unpleasant situation. However, if the given situation cannot be avoided or shaped, then directing attention to certain aspects of the situation can also influence someone's emotions (i.e. attentional distraction). The process of evaluating the meaning of the emotional stimulus follows the allocation of attention to the stimulus. Thus, even after an emotional stimulus has been attended to, it is still possible to regulate the emotional response by altering the emotional significance of the stimulus (i.e. cognitive reappraisal). Finally, after appraisal of the emotional situation, emotional responses can be modified at the physiological, experiential and behavioral level (i.e. response modulation). This process involves different ways to suppress physiological responses such as muscle tension and sympathetic hyper-reactivity as well as suppression of expressive behavior such as hiding one's true feelings.

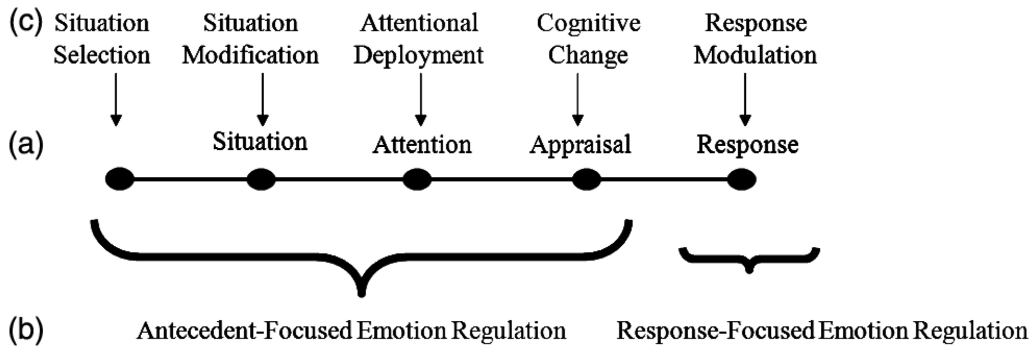

Figure 1. *The process model of emotion regulation (adapted from Gross & Thompson, 2007) (a) Components of emotion generation. (b) Antecedent-focused emotion regulation strategies: Regulation occurs before appraisals give rise to full-blown emotional response tendencies; Response-focused emotion regulation strategies: Regulation occurs after the emotional responses are generated (c) Five emotion regulation families mentioned above.*

Similarities and differences between cognitive reappraisal and self-distraction

People have to deal with emotional situations that cannot be avoided or modified on a daily basis. In these cases, cognitive forms of emotion regulation such as attentional distraction and cognitive change are crucial for regulating emotions. The importance of these two types of emotion regulation is reflected in the rapidly increasing number of neuroimaging studies on cognitive reappraisal and attentional self-distraction. Cognitive reappraisal is a form of cognitive change in which the emotional stimulus is re-interpreted in a way that changes its emotional impact. A common application of this strategy is the comparison of someone's situation with that of a less fortunate person (Gross and Thompson 2007). On the other hand, attentional distraction refers to the allocation of attention to non-emotional aspects of the situation or to the shift of attention away from the emotional situation. A typical example of this strategy is when someone brings into conscious awareness thoughts or memories irrelevant to the ongoing emotional situation (Gross and Thompson 2007).

In a typical reappraisal study, negative emotions are induced usually by aversive pictures from the International Affective Picture System (IAPS; Lang et al. 1997) but also by short films with emotional content, or anticipation of electric shocks. Subjects are instructed to reappraise the presented emotional stimulus in a more positive fashion by either "distancing" themselves from the emotional situation (i.e. view the situation as not self-relevant; distancing strategy) or by trying to change the meaning of the emotional situation in a more positive way (i.e.

reinterpretation strategy). Obviously, implementation of a reappraisal strategy is a deliberate process and requires a certain amount of cognitive effort.

In a typical self-distraction study, a distracting secondary task is used to direct attention away from emotional stimuli. This task can either be an explicit cognitive task (e.g. Stroop task, working memory task or arithmetic task) (i.e. "externally-paced self distraction" studies), or a self-generated emotionally-irrelevant thought (i.e. "internally-paced self-distraction" studies). The attentional distraction studies used various emotional stimuli. Externally-paced distraction studies usually used pictures from the International Affective Picture System (IAPS; Lang et al. 1997), or thermal painful stimuli. Internally-paced distraction studies used electric shocks, sad film excerpts or personally relevant thoughts. Both types of self-distraction have in common that the subject is actively and intentionally engaged in goal-related behaviour, drawing a distinction between this type of distraction tasks and passive distraction tasks. For this reason, we use the term "self-distraction" and apply this term to both externally (i) and internally (ii) paced distraction.

According to the process model of emotion regulation (Gross and Thompson 2007) each emotion regulation strategy targets different points in the emotion generative process. In this respect, reappraisal involves an initial appraisal of the emotional situation, whereas successful self-distraction implies that the emotional stimulus is not processed enough to generate an appraisal of the stimulus (Ochsner and Gross, 2005; Gross et al. 2007). In support of this assumption, memory encoding of the emotional situation is impaired during distraction but not during reappraisal (Van Dillen & Koole, 2007; Kross et al. 2008; Sheppes et al. 2007). Consistent with the impaired memory encoding of the emotional situation during distraction, re-exposure to images with a distraction history but not to images with a reappraisal history elicited a larger emotional response compared to images that were attended to during the regulation task (Thiruchselvam et al. 2011). In light of this evidence, it can be assumed that limited evaluation of the emotional stimulus takes place during self-distraction relative to reappraisal (Thiruchselvam et al. 2011).

One theoretical key difference between the cognitive control processes involved in reappraisal and self-distraction is related to the types of conflict that emerge during the implementation of the two emotion regulation strategies. During reappraisal, a conflict is created between two opposing appraisals: an initial stimulus-driven negative appraisal and a goal-directed neutral or positive reappraisal. The reappraised contents are linked to and depend on the contents of the initial appraisal (Sheppes et al. 2008). Therefore, resolution of the conflict between appraisals probably requires high-level semantic processing of emotional information (Ochsner et al. 2005 and 2008).

On the other hand, during self-distraction, a different type of conflict emerges when the prepotent tendency to attend to a salient emotional stimulus has to be overruled via allocation of attention to a goal-related (i.e either self-generated or externally imposed) neutral stimulus. Therefore, during resolution of this conflict, attention-related regulatory processes are probably recruited in order to inhibit processing of the emotional stimulus (Etkin et al. 2006; Egner et al. 2008; Ochsner et al. 2009).

Although inhibition of emotional processing is not a core process of reappraisal, it can be speculated that reappraisal requires the recruitment of attention-related regulatory processes to some extent, in order to inhibit emotional processing or responding especially in situations where emotional stimulation is too strong and pertinent to allow the implementation of a reappraisal strategy in the first place (Urry et al. 2006; Johnstone et al. 2007). This speculative distraction-like auxiliatory function should take place early and transiently during a reappraisal episode.

Role of dorsal and ventral ACC/mPFC in processing emotional information

Neuroimaging data are well-suited to address questions about the cognitive mechanisms that each emotion regulation strategy depends upon. In this case, different cognitive processes that take place during reappraisal and self-distraction should be reflected in the neural systems that are uniquely engaged during each type of emotion regulation (McRae et al. 2010; Kanske et al 2010; Ochsner et al. 2005 and 2008). Furthermore, both cognitive reappraisal and self-distraction recruit processes related to the basic “cold” cognitive control of attention and memory (Botvinick et al. 2004; D’Esposito et al. 2000) and thus it is very likely that both strategies engage some prefrontal areas important for cognitive control (Ochsner et al. 2005 and 2008).

Based on human neuroimaging, animal electrophysiology, and human and animal lesion studies, Etkin et al. (2011) argued that dorsal parts of ACC and mPFC are implicated in appraisal and expression of negative emotions as well as emotional conflict detection, whereas ventral parts of anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC) are implicated in emotion regulation by inhibiting negative emotional processing.

Emotional conflict tasks including the emotional Stroop task provide behavioral and neuroimaging evidence in favor of this functional differentiation between ventral and dorsal ACC/mPFC (Etkin et al. 2006; Egner et al. 2008; Ochsner et al. 2009). In these tasks, a target (i.e. facial expression or an emotional word) can either be congruent or incongruent (i.e. in terms of emotional valence) with a simultaneously presented task-irrelevant emotional word. Behaviorally, when the word was incongruent to the target, reaction times were slower compared to congruent trials (i.e. congruency effect; Etkin et al. 2006; Egner et al. 2008; Ochsner et al. 2009). This congruency effect has been suggested to reflect cognitive processes related to detection of conflict (Botvinick et al. 2001).

However, when incongruent trials were preceded by an incongruent trial, reaction times were faster than if incongruent trials were preceded by a congruent trial (Etkin et al. 2006; Egner et al. 2008). The faster responses in this type of trials probably reflect more efficient resolution of conflict (conflict adaptation; Botvinick et al. 2001). An influential model proposes that conflict in an incongruent trial is detected by a ''conflict monitor system'' that engages a "conflict resolution system" resulting in superior conflict resolution on the subsequent incongruent trial (Botvinick et al. 2001).

Dorsal ACC/mPFC areas were engaged during post-congruent incongruent trials in the emotional conflict task (Etkin et al. 2006; Egner et al. 2008). In line with this evidence, imaging, electrophysiological, and lesion studies have shown that dorsal regions of the ACC and mPFC are essential for general conflict detection between competing perceptual or semantic inputs and their associated responses (Ullsperger et al. 2004; Botvinick et al. 2001; Milham et al. 2001; Miller & Cohen, 2001; van Veen et al. 2001; Ochsner et al. 2009).

On the other hand, post-incongruent incongruent trials activated the ventral ACC (Etkin et al. 2006; Egner et al. 2008). Interestingly, three recent imaging studies provided evidence that ventral ACC is implicated in the resolution of emotional conflict (but not cognitive conflict; Egner et al. 2008). In addition, activity in ventral ACC negatively covaried with amygdala activity during emotional conflict (Egner et al. 2007; Etkin et al. 2006).

These findings suggest that ventral ACC activation during these tasks reflects resolution of emotional interference by inhibition of amygdalar responsiveness to task-irrelevant emotional stimuli (Egner et al. 2007; Etkin et al. 2006).

The field of fear conditioning has also provided substantial evidence in favor of the functional differentiation between dorsal and ventral ACC/mPFC. More specifically, fear conditioning studies consistently report activation in dorsal ACC/mPFC during the acquisition phase (Mechias et al. 2010; Klucken et al.

2009). In addition, neuroimaging studies showed that activity in this area is implicated in interoceptive awareness of heart beats and correlates with trait anxiety levels (Critchley et al. 2004). Dorsal ACC/mPFC are also associated with high-level appraisals of emotional stimuli (Lane & McRae, 2004; Kalisch et al., 2006b Neuroimage; Gilbert et al. 2006; Etkin et al. 2011; Rushworth et al. 2007; Lee and Siegle 2009) and with direct experience of pain, or empathy for others experiencing pain (Lamm et al. 2010). All these findings support the role of dorsal ACC/mPFC in the appraisal and expression of negative emotions.

Animal and human studies in fear conditioning have also shown that activation within the ventral ACC/mPFC is associated with fear reduction that occurs during extinction (Garcia et al. 1999; Morgan and LeDoux, 1995; Quirk, 2002; Kalisch et al. 2006; Milad et al. 2002; Phelps et al. 2004) or reversal (Schiller et al. 2008). Moreover, exposure to distant threat is associated with ventral ACC/mPFC activation (Mobbs et al. 2009), probably reflecting a shift from an acute fear response mode to a threat assessment mode which facilitates planning of adaptive responses (Etkin et al. 2011). In line with a role of this area in emotion regulation, other studies have reported negative connectivity between ventral ACC and mPFC areas and amygdala during fear perception (Das et al. 2005; Williams et al. 2006).

Detection of emotional conflict during reappraisal and self-distraction is therefore expected to recruit dorsal ACC/mPFC areas. However, during reappraisal two types of conflict may emerge. First, there is the main conflict between the two opposing appraisals of the emotional stimulus. Second, there may be a distraction-like conflict that involves the transient redirection of attention away from a task-irrelevant emotional stimulus (especially during strong emotional stimulation). The potential presence of two different conflicts may result in increased need for conflict monitoring which in turn may result in increased activation in dorsal ACC/mPFC areas during reappraisal compared to self-distraction.

In theory, appraisal of negative stimuli occurs to a greater extent during reappraisal than during self-distraction. Combining this idea with the proposed role of dorsal ACC/mPFC in appraisal of negative emotions (Mechias et al. 2010; Klucken et al. 2009; Lane & McRae, 2004; Kalisch et al., 2006b Neuroimage; Gilbert et al. 2006; Etkin et al. 2011; Rushworth et al. 2007) suggests that reappraisal is more likely to activate dorsal ACC/mPFC areas compared to self-distraction.

By contrast, the recruitment of ventral ACC/mPFC in different types of emotion regulation (i.e. fear extinction, reversal and emotional conflict tasks) combined with the reported reduction in amygdalar activity in these three paradigms (Etkin et al 2006; Egner et al. 2008; Schiller et al. 2010) are suggestive of an inhibitory role of ventral ACC/mPFC on emotional processing which is probably mediated by inhibition of amygdalar responsiveness to emotional stimuli. In theory, inhibition of emotional processing occurs to a greater extent during self-distraction than reappraisal. Therefore, it can be assumed that ventral ACC/mPFC will be activated more frequently during self-distraction than reappraisal.

Variability between neuroimaging studies of emotion regulation

There is variability in the precise neural systems recruited across emotion regulation studies. Sometimes, the variability in brain activity is even larger within a certain type of emotion regulation rather than between different types of emotion regulation (Ochsner et al. 2005). For this reason, it is important to consider the study heterogeneity in a meta-analysis of emotion regulation studies. Emotion regulation studies may differ in terms of the type of emotional stimuli (i.e. pictures, films or painful stimuli), duration of regulation, onset of regulation in relation to the onset of the emotional stimulus and many other aspects. This leaves open the possibility that any difference in the pattern of brain activation between reappraisal and self-distraction may be confounded by other factors. Despite the importance of identifying such factors, only few studies have investigated the effects of experimental factors on emotion regulation and specifically on regulation-related brain activation.

The **type of emotional stimulus** presented in an emotion regulation study may influence the difficulty of implementing an emotion regulation strategy as well as the success of emotion regulation. More importantly, it may also affect the pattern of regulation-related brain activation (Ochsner et al. 2005). For instance, it is assumed that pictures that depict aversive scenes are less salient and less imminent stimuli than painful electric shocks or thermal pain stimuli (Lissek et al. 2007). More importantly, brain responses to negative pictures and threat of shocks have been linked to dissociable neural substrates (Funayama et al. 2001). Therefore, it is plausible that regulation of emotional responses to unpleasant pictures versus threat of shock or other painful stimuli involves separable processes and the ability to suppress emotion from the former may not necessarily indicate the ability to suppress emotion from the latter. For instance, emotion regulation studies that used painful stimuli, usually instruct participants to either regulate the negative thoughts of anticipating a potential painful stimuli or regulate pain itself. On the other hand, pictures and films may induce various different emotions depending on their content but are probably less likely to induce fear and anxiety due to their symbolic nature (Lissek et al. 2007). The type of sensory stimulation may also be an important factor during regulating emotions. For instance, continuous visual (i.e. pictures and films) as opposed to nociceptive stimulation might differentially affect one's ability to recruit cognitive control in order to down-regulate negative emotions.

The **duration** of the reappraisal episode might also be a crucial factor that can explain some of the variance of the imaging data between emotion regulation studies. Recent evidence from a neuroimaging study (Paret et al 2011) supported the Implementation-Maintenance model of reappraisal (Kalisch, 2009) which distinguishes between "early" reappraisal, mainly characterized by choosing and implementing an initial reappraisal strategy, and "late" reappraisal, characterized by maintaining the strategy in working memory and monitoring its success during the course of an emotional situation. Based on the IMMO model (Kalisch, 2009), the ability to maintain a strategy and monitor its success is more important in reappraisal studies that use a long reappraisal duration, whereas cognitive processes related to the initial implementation of a reappraisal strategy are more important in studies with a short reappraisal duration (Kalisch, 2009). This functional distinction is reflected in the pattern of brain activation. Left-sided posterior frontal activity characterizes early reappraisal processes and right-sided anterior frontal activity characterizes late reappraisal processes (Kalisch, 2009; Paret et al. 2011). Although the IMMO model may be applicable to attentional distraction, no study has investigated this hypothesis. Therefore, it is possible that the duration of regulation can explain some of the variance in reappraisal-related activation but not in distraction-related activation.

In an emotion regulation study, the cue to begin implementation of a regulation strategy can either follow or precede the **onset** of the emotional stimulus. When the regulation cue follows the emotional stimulus, then the emotional response unfolds before regulation starts. This experimental manipulation directly affects the intensity of the emotional state that needs to be regulated (Sheppes et al. 2007). As a consequence, more cognitive effort may be required to regulate a fully developed emotional response than an emotional response in its initial phase (Sheppes et al. 2011). Sheppes et al. (2008 and 2011) showed that reappraisal, but not self-distraction was affected by this manipulation. In particular, they measured Stroop performance after the emotion regulation task and modulation of an event related potential component (i.e. LPP) that is enhanced during viewing of emotionally arousing compared to neutral stimuli (Hajcak et al. 2010). They found that when the onset of the regulation cue followed the onset of the emotional stimulus reappraisal resulted in weaker LPP modulation and important cognitive costs (i.e impaired Stroop performance) compared to distraction. On the other hand, when the onset of regulation preceded the onset of the emotional stimulus (i.e. low emotional intensity) both distraction and reappraisal effectively modulated LPP without important cognitive costs. In light of this evidence, Sheppes and Gross (2011) suggested that reappraisal, but not distraction, should be affected by the intensity of the emotional response. Based on these findings, it can be assumed that the increased cognitive effort and decreased success of regulation during late-onset reappraisal but not late-onset distraction may be reflected in the neural correlates of reappraisal. In this respect, only late-onset reappraisal may require a transient inhibition of emotional processing in order to initiate the implementation of this strategy, which suggests activation of ventral ACC/mPFC areas specifically during late-onset reappraisal.

In this article, I review recent fMRI studies in which subjects were instructed to down-regulate negative emotions by employing a cognitive reappraisal or a self-distraction strategy. Up to date, two imaging studies have tried to compare the neural correlates of reappraisal and attentional distraction. Both studies reported overlapping as well as differential regulation-related activation (McRae et al. 2010; Kanske et al. 2010).

Based on Etkin's and colleagues (2011) functional distinction between dorsal mPFC/ACC and ventral mPFC/ACC, I formulate the specific hypothesis that dorsal mPFC/ACC areas are commonly engaged during both reappraisal and distraction, but reappraisal is more likely to recruit these areas. I further hypothesize that ventral mPFC/ACC areas are engaged more frequently during self-distraction than reappraisal.

An additional aim of this review is to provide further insights into the role of other frontal areas (previously implicated in emotion regulation) in reappraisal and self-distraction. To this end, I also report regulation-related activation throughout the entire frontal cortex. The inclusion of the entire frontal cortex helps detect and factor out a potential confound of global activation difference between the two emotion regulation strategies. In this respect, the frequency of activation in the two main regions of interest (i.e. dorsal and ventral ACC/mPFC) can be compared with the averaged activation frequency across the entire frontal cortex.

Finally, we explore the influence of experimental factors (i.e. type of emotional stimulus, duration of regulation, onset of regulation) on frontal activation during reappraisal and distraction. Based on the assumption that ventral ACC/mPFC activity is more likely during reappraisal studies that are characterized by strong emotional stimulation (i.e. when emotional stimulation precedes onset of regulation), I also test whether the onset of regulation is a relevant factor for reappraisal-specific ventral ACC/mPFC activation.

For these purposes, I employ a quantitative meta-analytic approach in which I statistically test whether the activation/no activation ratio of reappraisal and distraction studies for a certain brain area deviates significantly from the expected activation/no activation ratio for each type of emotion regulation.

Methods

Reappraisal and distraction studies included in the meta-analysis had to fulfil the following criteria: they had to be published in a peer-reviewed scientific journal in English language; they had to be performed in healthy normal adult subjects; they had to employ functional magnetic resonance imaging (fMRI); the fMRI data had to be analyzed within a general linear model (GLM) framework to assure comparability of activation across studies. Using an approach similar to Kober, (2008), identification of reappraisal studies was achieved by searching Pubmed using keywords "reappraisal AND fMRI". Attentional distraction studies were identified in Pubmed using the following keywords: "attentional distraction AND emotion regulation AND fMRI" or "attentional control AND emotion regulation AND fMRI". Further, the reference sections of existing review papers and meta-analyses were parsed and reappraisal and distraction studies otherwise known were also included. The t values of the activation peaks were transformed into z scores. Peaks were included irrespective of whether they represented cluster maxima or local maxima within an activation cluster. Only activation peaks with a *z* score > 3.0 were included (Mechias et al. 2010; Kalisch, 2009). In total, twenty reappraisal studies and thirteen distraction studies were included in this review. The reappraisal studies recruited 466 subjects and reported 145 activation peaks (table 1) and the distraction studies recruited 230 participants and reported 48 activation peaks (table 2). All the activation peaks were reported in MNI coordinates. Talairach coordinates were converted to MNI coordinates by using the WFU pick Atlas tool in SPM 8 toolbox (www.fil.ion.ucl.ac.uk/ spm/ext/#WFU_PickAtlas). Activation peaks were located in frontal cortex or cingulate cortex (i.e. maximum posterior position allowed was y = -20).

Number	**Study**	**Strategy**	**Stimulus**	**Subjects**	**Sex**	**Onset**	**Duration**
1	Kim et al 2007	Both strategies	Pictures	10	Females only	Regulation sign first	8
2	Mak et al 2009	Free to choose	Pictures	12	Females only	Regulation sign first	24
3	Ochsner et al 2004	Both (divided into 2 groups)	Pictures	24	Females only	Regulation sign first	10
4	Ochsner et al 2002	Reinterpretation	Pictures	15	Females only	Emotional	4

						stimulus first	
5	Kalisch et al 2005	Distancing (special place strategy)	Shock anticipation	18	Both sexes (10 females)	Regulation sign first	15
6	Walter et al 2009	Distancing	Pictures	20	Females only	Regulation sign first	8
7	Koeningsberg et al 2008	Distancing	Pictures (social stimuli)	16	Both sexes (9 females)	Regulation sign first	10
8	Levesque et al 2003	Distancing	Film (sad content)	20	Females only	Regulation sign first	48
9	Phan et al 2005	Reinterpretation	Pictures	14	Both sexes (8 females)	Regulation sign first	20
10	Goldin et al 2008	Distancing	Film (disgusting content)	17	Females only	Regulation sign first	15
11	Mc Rae et al 2008	Reinterpretation	Pictures	25	Both sexes (13 females)	Regulation sign first	8
12	Eippert et al 2007	Distancing	Pictures (threat stimuli)	24	Females only	Emotional stimulus first	6
13	Hayes et al 2010	Distancing	Pictures	25	Females only	Emotional stimulus first	8
14	Mc Rae et al 2010	Reinterpretation	Pictures	18	Females only	Regulation sign first	8
15	Kanske et al 2010	Both strategies	Pictures	30	Both sexes (17 females)	Emotional stimulus first	5
16	Johnstone et al. 2007	Reinterpretation	Pictures	21	Both sexes (13 females)	Emotional stimulus first	6
17	Opitz et al. 2010	Reinterpretation	Pictures	31	Both sexes (17 females)	Emotional stimulus first	6
18	Winecoff et al. 2010	Distancing	Pictures	42	Both sexes	Emotional stimulus first	6
19	Leiberg et al. 2011	Distancing	Pictures	24	Females only	Emotional stimulus first	6
20	Domes et al. 2010	Distancing	Pictures	33	Both sexes (17 females)	Emotional stimulus first	8

Table 1. *Design for imaging studies of cognitive reappraisal. Two main reappraisal strategies were employed: reinterpretation of the meaning of the emotional stimulus and distancing from the emotional stimulus. Stimulus: Type of stimulus employed. Subjects: Number of subjects recruited. Sex: The sex of the subjects and the number of female subjects. Onset: The onset of emotion regulation in relation to the onset of the emotional stimulus. Duration: The duration in seconds of the reappraisal process as it is defined in the analysis of the BOLD signal*

Number	Study	Strategy	Distractor	Emotional stimulus	Subjects	Onset	Duration (sec)
1	van Dillen et al. 2009	External task	Arithmetic task	pictures	17	Emotional stimulus presented first	4
2	Kanske et al 2010	External task	Arithmetic task	pictures	30	Emotional stimulus presented first	5
3	Bantick et al. 2002	External task	Stroop task	thermal stimulus	8	Regulation sign presented first	5
4	Valet et al. 2004	External task	Stroop task	thermal stimulus	7	Regulation sign presented first	40
5	Frankenstein et al. 2001	External task	Word genration task	cold stimulus	12	Emotional stimulus presented first	45
6	Erk et al. 2007	External task	Working memory task	pictures	12	Regulation sign presented first	4
7	Mc Rae et al. 2010	External task	Working memory task	pictures	18	Regulation sign presented first	8
8	Weich et al. 2005	External task	Rapid Serial Visual Processing Task	thermal stimulus	15	Emotional stimulus presented first	21
9	Wyland et al. 2003	Self-generated thought	suppress particular thought	personally-relevant thought	12	Emotional stimulus presented first	30
10	Kalisch et al. 2006	Self-generat	suppress thoughts or	anticipation of shock	15	Regulation sign	15.6

		ed thought	feelings about the shock			presented first	
11	Delgado et al. 2008	Self-generated thought	suppress thoughts or feelings about the shock	anticipation of shock	12	Regulation sign presented first	4
12	Cooney et al. 2007	Self-generated thought	recall a positive memory	sad film	14	Emotional stimulus presented first	60
13	Gillath et al. 2005	Self-generated thought	suppress negative thoughts	negative thoughts about their romantic relationship	20	Emotional stimulus presented first	120

Table 2. *Design for imaging studies of self-distraction. Strategy: Subjects either self-generate an emotionally-irrelevant thought or perform an explicit task in order to distract themselves from the emotional stimulus. Stimulus: Type of stimulus employed. Subjects: Number of subjects recruited. Onset: The onset of attentional distraction in relation to the onset of emotional stimulus. Duration: The duration in seconds of the distraction from the emotional stimulus as it is defined in the analysis of the BOLD signal.*

Usually, a reappraisal study includes two experimental conditions. A "decrease" condition in which subjects are instructed to reappraise the emotional stimulus in a more positive fashion and a "view" condition in which subjects view emotional stimuli without trying to modulate their emotions. The majority of the reappraisal studies reviewed here used both neutral and emotional stimuli. Such a design involves two experimental factors (i.e. Emotion and Reappraisal) and requires an interaction analysis (Reappraisal x Emotion; Nieuwenhuis et al. 2011) in order to identify areas active specifically when reappraising under challenging emotional conditions $[(\text{reappraisal} - \text{no-reappraisal})_{negative} - (\text{reappraisal} - \text{no-reappraisal})_{neutral}]$. Two reappraisal studies reviewed here (i.e. Koeningsberg et al 2008; Kalisch et al. 2005) performed this interaction analysis. On the contrary, nineteen reappraisal studies performed statistical tests to investigate the effect of reappraisal only for trials with emotional stimuli

There are two main experimental conditions in a typical attentional distraction study. In the "view" condition, participants do not perform the distracting secondary task and can process the emotional stimulus without interference. In the "distraction" condition, subjects either have to perform a distracting task or to suppress any thought about the emotional stimulus. In the present review, eleven distraction studies included a non-emotional experimental condition (e.g. neutral pictures, non-painful stimulus, or no shock anticipation). However, only four of these eleven studies computed the Emotion x Distraction interaction effect. On the contrary, nine distraction studies performed a test for the effect of attentional distraction on emotional trials (i.e. $[\text{distraction} - \text{no-distraction}]_{negative}$).

Despite the fact that brain activation related to down-regulation of negative emotions regulation is better reflected by the Emotion x Regulation interaction contrast), few studies performed this analysis. For this reason, both the regulation $_{negative}$ – no regulation $_{negative}$ contrast and the corresponding interaction contrast were included in the present meta-analysis.

The analysis was performed separately for eleven frontal regions of interest (ROIs). These eleven ROIs are defined a priori with strictly anatomical criteria. Left and right lateral areas are considered as separate ROIs but have the same size. All the activation peaks located more laterally than x=20 or x=-20 are grouped into lateral ROIs, whereas all the activation peaks located between -20<x<20 were grouped into medial ROIs. Two ROIs included activation peaks within the right and left dorsolateral PFC (BA 8/9/46/44) (i.e. z>20). The posterior border of these ROIs is y>10. Activation peaks in BA 6 and BA 4 were grouped into the left and right lateral premotor/motor ROIs if they were located more laterally than x>20 or x<-20. Activation peaks in BA 6/4 or the adjacent posterior dorsal anterior cingulate cortex (pdACC; BA23/24) located between -20<x<20 were grouped into the preSMA/SMA ROI. Left and right ventrolateral PFC ROIs covered BA 44, 45, 47, 48 which essentially define the inferior frontal gyrus. The two ROIs had a ventral border of z>0 (i.e. 0<z<20) and thus were demarcated from the lateral orbitofrontal cortex (OFC). The right and left lateral orbitofrontal cortex covered BA 47/11 (i.e. z<0). A bilateral ROI including the dorsomedial PFC (dmPFC), and adjacent anterior dACC (adACC) covered medial BA 8 and 9 and dorsal BA 24 and 32 (i.e. z>20). A bilateral ROI for the ventral parts of rmPFC and pgACC as well as for vmPFC and subgenual ACC (sgACC) ("vmPFC" ROI), covered the ventral BA 10 and 32 and BA 11 and 25 (i.e. z<0; see fig. 2 adapted from Etkin et al. 2011).

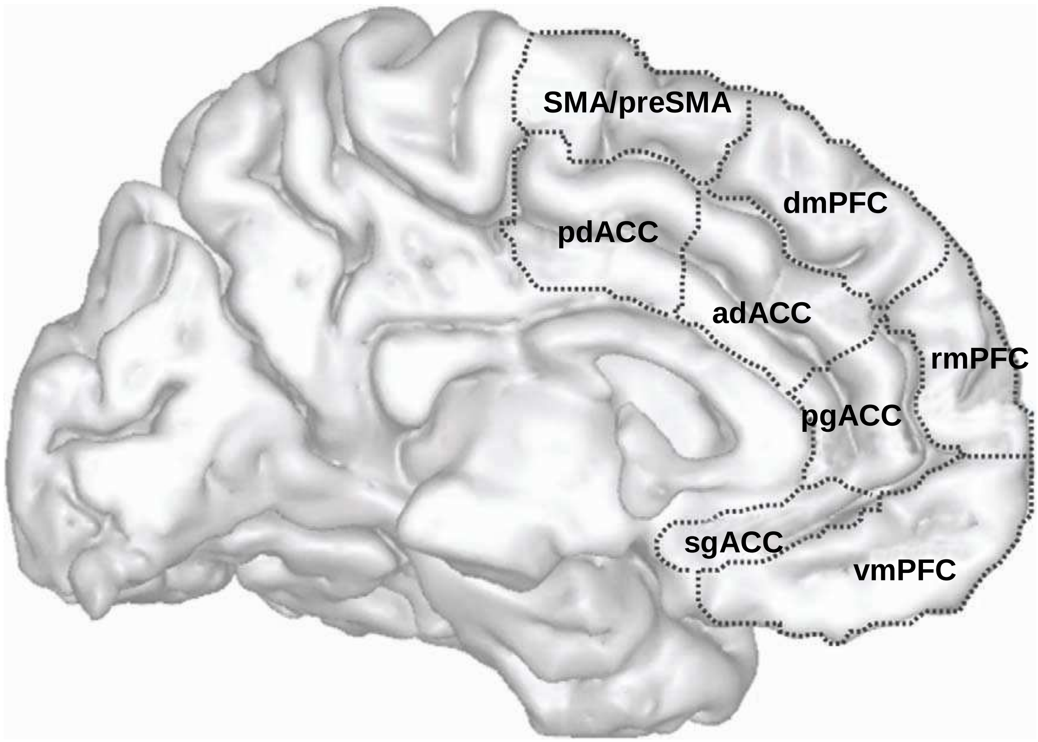

Figure 2. *Parcellation of ACC and mPFC subregions (adapted from Etkin et al. 2011). Abbreviations: sg, subgenual; pg, pregenual; vm, ventromedial; rm, rostromedial; dm, dorsomedial; ad, anterior dorsal; pd, posterior dorsal. In the present review, the dorsal ACC/mPFC ROI is comprised of the dmPFC and the adACC subregions as well as the dorsal parts of rmPFC and pgACC. The ventral ACC/mPFC ROI is comprised of the sgACC and the vmPFC.*

The presence of at least one activation peak in a region of interest signified that a certain reappraisal/self-distraction study reported activation in this ROI. Based on this scoring method, the number of reappraisal or self-distraction studies that reported activation in a certain ROI represented the frequency that this ROI is activated during reappraisal or self-distraction. The overall pattern of regulation-related activation in the eleven ROIs revealed that on average nine out of twenty reappraisal studies and only three out of thirteen distraction studies reported activation in each ROI (see average for eleven ROIs in table 3). This global effect of more frequent frontal activation in reappraisal compared to self-distraction probably reflects the increased cognitive effort required during reappraisal compared to distraction (Sheppes et al. 2011). The observed average (for the eleven ROIs) activation/no activation frequency distribution for reappraisal and distraction studies deviated significantly from an equal activation/no activation frequency distribution where the activation/no activation ratio is the same for reappraisal and self-distraction (p=.046; Pearson's chi square). As a consequence, considering the equal frequency distribution as the null hypothesis will most likely show relatively more frequent reappraisal activity in all the ROIs while at the same time will mask the variance between ROIs that is typical for either self-distraction or reappraisal. For this reason, the observed average (across ROIs) frequency distribution is used as the null hypothesis. Pearson's 2x2 chi square tests were performed in order to investigate whether the frequency of regulation-related activation in a certain ROI deviated from the average frequency of regulation-related activation from all the regions of interest (ROIs). A Bonferonni-adjusted p value was used as threshold of significance (i.e. correcting for the eleven related chi square tests; p=0.0045).

Region of interest	**Strategy**	**No activation**	**Activation**	**p value**
Average for eleven ROIs (null hypothesis)	Distraction	10	3	0.046 *
	Reappraisal	11	9	
Equal frequency distribution	Distraction	6.5	6.5	
	Reappraisal	10	10	

Table 3. *Average activation/no activation frequency distributions for reappraisal and distraction studies for the eleven ROIs and the level of significance of the chi square tests. * represents significant deviation from the equal frequency distribution*

Apart from the reappraisal-distraction comparison, we explored the influence of other experimental factors that may explain some of the variance in frontal regulation-related activation within emotion regulation studies. Twenty one studies of this review used pictures with aversive scenes as emotional stimuli and twelve studies used other emotional stimuli such as film excerpts, electric shocks and other painful stimuli. Interestingly, pictures were used more frequently in reappraisal (17 out of 21 studies) than distraction studies (4 out of 13 studies) (*X2* (*N* = 33) = 10.013, *p* =.002), suggesting that the factor "emotional stimulus" cannot be statistically dissociated from the reappraisal-distraction factor.

Twelve out of twenty one "picture" studies and two out of twelve "other stimuli" studies showed activation in an ROI on average (see average for eleven ROIs in table 4). Similar to the reappraisal-distraction comparison, the observed average (i.e. from the eleven ROIs) activation/no activation frequency distribution for "picture" and "other stimuli" studies significantly deviated from an equal frequency distribution (p=.016; table 4). For the same reasons as in the reappraisal-distraction comparison, I used the observed average activation/no activation frequency distribution for "picture" and "other stimuli" studies as the null hypothesis.

Region of interest	**Strategy**	**No activation**	**Activation**	**p value**
Average for eleven ROIs (null hypothesis)	other	10	2	0.016*
	picture	12	9	
Equal frequency distribution	other	6	6	
	picture	10.5	10.5	

Table 4. *Average activation/no activation frequency distributions for "picture" and "other" studies for the eleven ROIs and the level of significance of the chi square tests. * represents significant deviation from the equal frequency distribution*

Furthermore, a distinction was drawn based on the duration of active regulation. In a previous meta-analysis that focused on the effect of the reappraisal duration on frontal activation, Kalisch (2009) performed a correlational analysis using the reappraisal duration as a weighting factor. I grouped the studies into "short duration" and "long duration" studies. There is no a priori definition of short and long regulation duration and thus the cut-off criterion was determined in such a way that the difference between the longest duration of a "short" study and the shortest duration of a "long" study is the biggest possible. Based on this criterion, "short duration" studies (twenty two studies) allowed subjects to regulate their emotions for ten seconds or less, whereas "long duration" studies (eleven studies) allowed subjects to regulate their emotions for fifteen seconds or more. Sixteen out of twenty reappraisal and six out of thirteen distraction studies were classified as "short" studies indicating that reappraisal studies more frequently were classified as "short" studies ($X2$ (N = 33) = 4.064, p =.044) suggesting that the factor "regulation duration" cannot be statistically dissociated from the reappraisal-distraction factor.

The observed average (i.e. from the eleven ROIs) activation/no activation frequency distribution showed a tendency to deviate from an equal frequency distribution (p=0.082) (see average for eleven ROIs in table 5). Therefore, the observed average activation/no activation frequency distribution for "short" and "long" studies was used as the null hypothesis in this comparison.

Region of interest	Strategy	No activation	Activation	p value
Average for eleven ROIs (null hypothesis)	short	13	9	0.082
	long	8	3	
Equal frequency distribution	short	11	11	
	long	5.5	5.5	

Table 5. *Average activation/no activation frequency distributions for "short" and "long" studies for the eleven ROIs and the level of significance of the chi square tests.*

The influence of the onset of regulation in relation to the onset of the emotional stimulus was also explored in this meta-analysis. Ten studies included a pre-regulation period of at least three seconds in which emotional stimuli can be processed without an effort to regulate emotions (i.e. "emotion first studies"). Eighteen studies presented the cue that instructed participants to regulate emotions before the presentation of the emotional stimulus (i.e. "regulation first" studies). Studies where the time to process the emotional stimuli before regulation onset was relatively short (i.e. less than 3 seconds; arbitrary cut-off) were not classified as "emotion first" or "regulation first" studies.

Twelve out of sixteen reappraisal studies and six out of twelve distraction studies were "regulation first" studies (*X2* (*N* = 28) = 1.867, *p* =.172). Hence, in contrast to the factors "emotional stimulus" and "regulation duration" the factor "order" was dissociable from the reappraisal-distraction factor. On average, six out of eighteen "regulation first" studies and three out of ten "emotion first" studies reported activation in the eleven ROIs. This ratio deviated from the equal frequency distribution (p=0.014; table 6). For this reason, the observed average activation/no activation frequency distribution was used as the null hypothesis in the comparison between "regulation first" and "emotion first" studies.

Region of interest	Strategy	No activation	Activation	p value
Average for eleven ROIs (null hypothesis)	regulation first	12	6	0.014*
	emotion first	7	3	
Equal frequency distribution				
	regulation	9	9	

	first			
	emotion first	5	5	

Table 6. *Average activation/no activation frequency distributions for "regulation first" and "emotion first" studies for the eleven ROIs and the level of significance of the chi square tests. * represents significant deviation from the equal frequency distribution*

Results

Success of emotion regulation

The subjective reports of how participants felt during reappraisal indicated that this type of emotion regulation is successful in attenuating negative emotions in eighteen out of nineteen reappraisal studies that reported subjective ratings. On the other hand, the extent to which self-distraction successfully attenuated negative emotions was dependent on the type of the distraction strategy. All externally-paced self-distraction studies reported a significant reduction of self-report ratings of pain intensity or negative affect. However, only one internally-paced self-distraction study (Cooney et al. 2007) reported decreased subjective ratings of negative emotions and another one (Kalisch et al. 2006) reported a reduction in the time that subjects spent thinking of the painful shock.

On the other hand, only three out of twenty reappraisal studies and two out of thirteen distraction studies used physiological measures (i.e skin conductance responses and heart rate level) as an indirect index of regulation-related reduction of negative emotions. As a result, no conclusion can be drawn about the influence of the two emotion regulation strategies on physiological indices of emotional arousal.

Reappraisal-specific attenuation of amygdala responses is identified in the "view > decrease" contrast (Ochsner and Gross, 2005; Phillips et al., 2008; Quirk and Beer, 2006). Fifteen out of twenty one reappraisal studies reported reduction in amygdala activity due to reappraisal. Similarly, three of the four externally-paced self-distraction studies that used emotional pictures reported reduced amygdala activity during the distraction condition and three of the four externally-paced self-distraction studies that used painful stimuli showed distraction-related reduction of pain-related activation in brain areas that are considered part of the pain system (e.g. ACC and mPFC). Interestingly, only one internally-paced self-distraction study reported decreased amygdala activation due to attentional distraction.

Imaging data

All the ROIs defined here except from the ventral ACC/mPFC (BA 10/11/25/32) (2 studies) and the right lateral premotor/motor cortex (BA 6/4) (2 studies) were reported active in at least six of the twenty reappraisal studies (see table 7).

Brain area	Studies
Right dlPFC (BA 8/9/46/44)	**1 3 6 8 9 11 14 15 17 18 20**
Left dlPFC (BA 8/9/46/44)	**1 2 3 4 10 11 12 13 14 15 16 18 20**
Right lateral OFC (BA 47/11)	**1 3 8 9 11 14 15 18 20**
Left lateral OFC (BA 47/11)	**1 2 3 9 10 12 13 15 16 17 18 19 20**
Right inferior frontal gyrus (BA 44/45/47/48)	**1 3 5 9 15 18 19 20**
Left inferior frontal gyrus (BA 44/45/47/48)	**1 3 4 7 10 11 12 16 18 20**
Dorsal ACC/mPFC (BA 8/9/24/32)	**1 3 4 6 7 9 11 12 13 14 15 17 18 19 20**
Ventral ACC/mPFC (BA 10/11/25/32)	**2 11**
Pre-SMA/SMA (BA 4/6/23/24)	**1 7 15 18 19 20**
Right lateral premotor/motor area (BA 4/6)	**3 14**
Left lateral premotor/motor area (BA 4/6)	**4 10 11 12 18 20**

Table 7. *Brain areas activated by reappraisal studies*

Only the ventral ACC/mPFC (BA 10/11/32/25) (5 studies) and the dorsal ACC/mPFC (BA 8/9/24/32) (6 studies) were reported active in more than three self-distraction studies (see table 8).

Brain area	Studies
Right dlPFC (BA 8/9/46/44)	**2 7 8**
Left dlPFC (BA 8/9/46/44)	**5 8 10**
Right lateral OFC (BA 47/11)	**12**
Left lateral OFC (BA 47/11)	**12**
Right inferior frontal gyrus (BA 44/45/47/48)	**-**
Left inferior frontal gyrus (BA 44/45/47/48)	**9**
Dorsal ACC/mPFC (BA 8/9/24/32)	**2 5 7 8 9 13**
Ventral ACC/mPFC (BA 10/11/25/32)	**3 4 10 11 12**
Pre-SMA/SMA (BA 4/6/23/24)	**2 8 9**
Right lateral premotor/motor area (BA 4/6)	**1 2 8**
Leftt lateral premotor/motor area (BA 4/6)	**2 7 8**

Table 8. *Brain areas activated by self-distraction studies*

Activation in dorsal ACC/mPFC was reported more frequently than expected in both distraction and reappraisal studies and it seems that reappraisal studies (15 out of 20 studies) activated this area relatively more frequently than distraction studies (6 out of 13 studies) (p=.0008; survived the Bonferroni correction; table 9 and figure 3). On the other hand, ventral ACC/mPFC activity was reported more frequently than expected during self-distraction and less frequently than expected during reappraisal indicating that reappraisal studies activated this area relatively less frequently than distraction studies (*p*=.0006 survived Bonferroni correction; table 9, figure 3 and figure 4).

Similar to ventral ACC/mPFC, the right lateral premotor/motor area (BA 6/4) was reported active more frequently during distraction (3 studies) than reappraisal (2 studies). No deviation from the expected activation frequency was reported for all the other ROIs (table 9 and figure 3).

Region of interest	Strategy	No activation	Activation	p value
Left inferior frontal gyrus (BA 44/45/47/48)	Distraction	12	1	0.1642
	Reappraisal	10	10	
Right inferior frontal gyrus (BA 44/45/47/48)	Distraction	13	0	0.0428
	Reappraisal	12	8	
Ventral mPFC/ACC (BA 10/11/32/25)	Distraction	**8**	**5**	**0.0006***
	Reappraisal	**18**	**2**	
Dorsal mPFC/ACC (BA 8/9/24/32)	Distraction	**7**	**6**	**0.0008***
	Reappraisal	**5**	**15**	
Left dlPFC (BA 8/9/46/44)	Distraction	10	3	0.0722
	Reappraisal	7	13	
Right dlPFC (BA 8/9/46/44)	Distraction	10	3	0.3687
	Reappraisal	9	11	
Left lateral OFC (BA 47/11)	Distraction	12	1	0.0258
	Reappraisal	7	13	
Right lateral OFC (BA 47/11)	Distraction	12	1	0.1879
	Reappraisal	11	9	
Pre-SMA/SMA (BA 4/6/23/24)	Distraction	10	3	0.1775
	Reappraisal	14	6	
Left lateral premotor/motor cortex (BA 4/6)	Distraction	10	3	0.1775
	Reappraisal	14	6	
Right lateral premotor/motor cortex (BA 4/6)	Distraction	10	3	0.0016*
	Reappraisal	18	2	
Average for eleven ROIs (null hypothesis)	Distraction	10	3	
	Reappraisal	11	9	

Table 9. *Activation/no activation frequency distributions for reappraisal and distraction studies for each ROI and the level of significance of the chi square tests. * represents significant deviation from the expected average frequencies after Bonferonni correction for multiple tests (threshold of significance is p = .0045)*

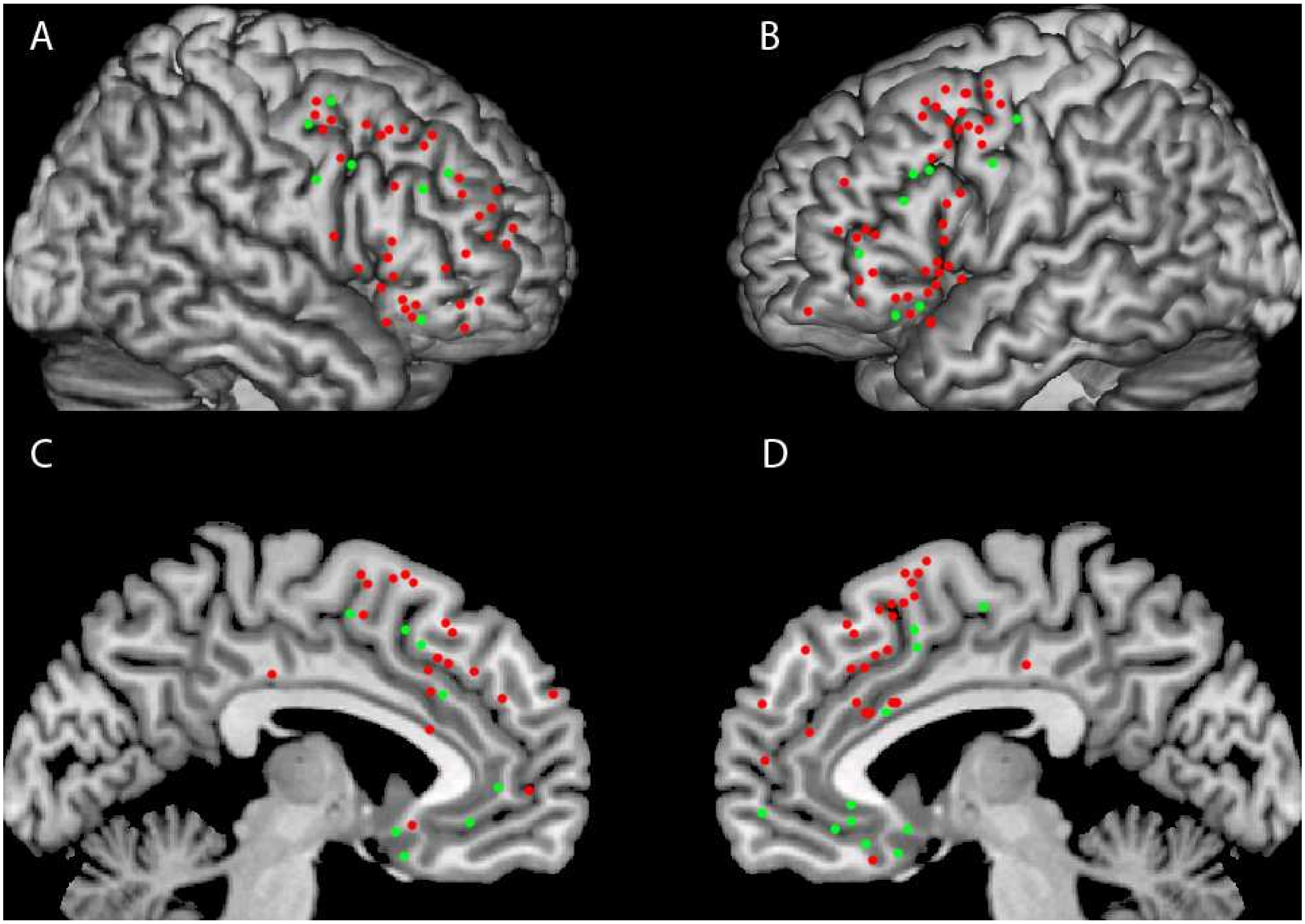

***Figure 3**. Activation in right lateral PFC (**A**), left lateral PFC (**B**), right medial PFC (**C**), and left medial PFC (**D**) associated with reappraisal (red dots) or self-distraction (green dots). Each dot corresponds to an activation peak that represents regulation-related activation as it is defined in the two contrasts studied in this review (see methods). Activation peaks located more laterally than x=20 or x=-20 are projected onto the brain templates for right lateral PFC (**A**) and left lateral PFC (**B**) respectively. Activation peaks located within 0<x<20 or within -20<x<0 are projected onto the brain templates for right medial PFC (C) and left medial PFC (D) respectively.*

It is worth noting that the activation peaks from the five self-distraction studies that reported activation in ventral ACC/mPFC were located medially between -10<x<10, whereas the activation peak from the one of the two reappraisal studies that reported activation in this area was located more laterally (i.e. -20<x<-10 or 10<x<20; figure 4) in a location that could also be classified as orbitofrontal cortex. Moreover, these five self-distraction studies reported significant reduction in self-reported negative affect or time spent engaging in negative thoughts during distraction. Three out of these five self-distraction studies also reported modulation of activity in amygdala or pain-related areas (Bantick et al. 2002; Valet et al. 2004; Delgado et al. 2008) and one study reported negative connectivity between vmPFC and amygdala (Delgado et al. 2008). On the other hand, the two reappraisal studies reported down-regulation of self-reported negative affect and one of them also showed reduced amygdala response due to reappraisal.

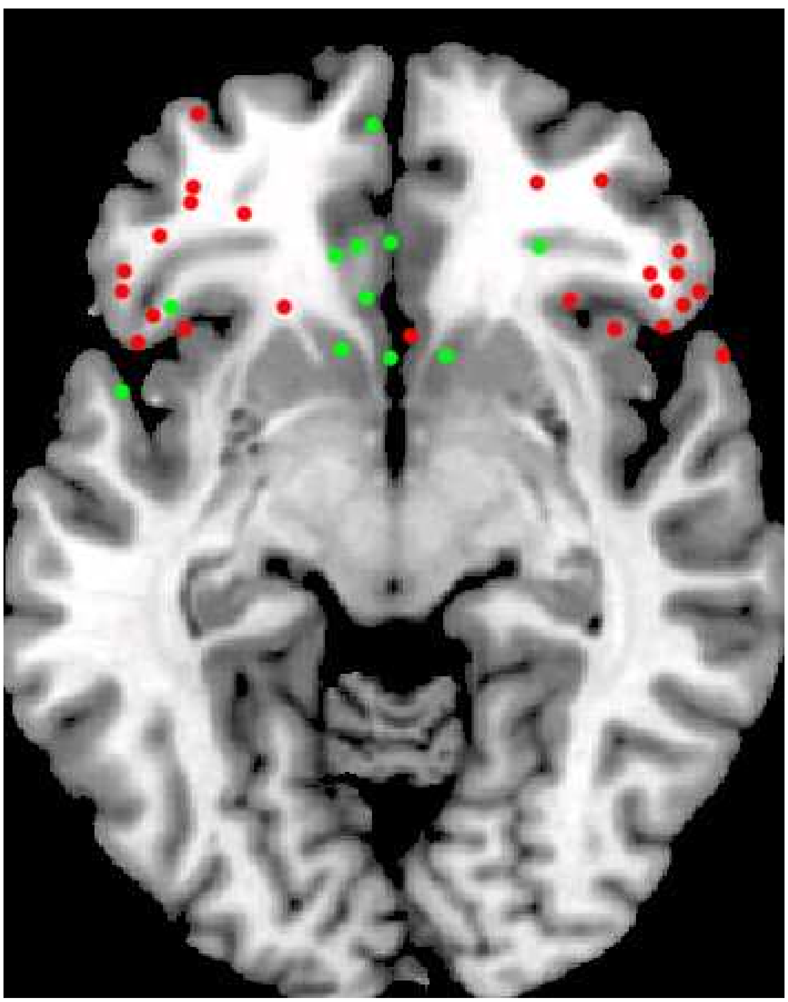

Figure 4. *Activation in the lateral and medial parts of ventral PFC (i.e. z<0; lateral OFC and ventral ACC/mPFC) associated with reappraisal (red dots) or self-distraction (green dots).*

Apart from the reappraisal-distraction comparison, studies were classified based on the type of emotional stimulus, the duration of regulation, and the onset of regulation in relation to the onset of emotional stimulation.

Seventeen out of twenty one studies that reported regulation-related activation in dorsal ACC/mPFC used pictures as emotional stimuli. This activation frequency deviates significantly from the expected average frequency ratio (i.e. p = .0001; survived Bonferonni correction; table 6 and figure 5) suggesting that dorsal ACC/mPFC activation during regulation may also be a function of emotional stimulus material and perhaps not of the strategy per se (i.e. reappraisal). Interestingly though, four out of six distraction studies that reported activation in this area used painful stimuli or sad films. Therefore, the argument about picture-specific activation of dorsal ACC/mPFC is, if at all applicable, specific for reappraisal studies.

By contrast, activation in ventral ACC/mPFC regions is reported more frequently in "other stimuli" than "picture" studies (p=.0001; survived Bonferonni correction; table 10 and figure 5). All the self-distraction studies that reported activation in ventral ACC/mPFC used painful stimuli or sad films to induce emotions suggesting that the combination of a self-distraction strategy with the use of painful stimuli or sad films might be a factor leading to activation of ventral ACC/mPFC. No deviation from the expected activation frequency was reported for all the other ROIs (table 10 and figure 5).

Region of interest	**Strategy**	**No activation**	**Activation**	**P value**
Left inferior frontal gyrus (BA 44/45/47/48)	other	10	2	1
	picture	12	9	
Right inferior frontal gyrus (BA 44/45/47/48)	other	11	1	0.2404
	picture	14	7	
Ventral mPFC/dACC (BA 10/11/32/25)	other	**7**	**5**	**0.0001***
	picture	**19**	**2**	
Dorsal mPFC/dACC (BA 8/9/32/25)	other	**8**	**4**	**0.0001***
	picture	**4**	**17**	
Left dlPFC (BA 8/9/46/44)	other	8	4	0.0416
	picture	9	12	

Right dlPFC (BA 8/9/46/44)	other	10	2	0.1858
	picture	9	12	
Left lateral OFC (BA 47/11)	other	10	2	0.1858
	picture	9	12	
Right lateral OFC (BA 47/11)	other	10	2	0.6592
	picture	13	8	
Pre-SMA/SMA (BA 4/6/23/24)	other	10	2	0.3778
	picture	14	7	
Left lateral premotor/motor cortex (BA 4/6)	other	10	2	0.3778
	picture	14	7	
Right lateral premotor/motor cortex (BA 4/6)	other	11	1	0.0194
	picture	17	4	
Average for eleven ROIs (null hypothesis)	other	10	2	
	picture	12	9	

Table 10*. Activation/no activation frequency distributions for "picture" and "other stimuli" studies for each ROI and the level of significance of the chi square tests. * represents significant deviation from the expected average frequencies after Bonferonni correction for multiple tests (threshold of significance is p = .0045)*

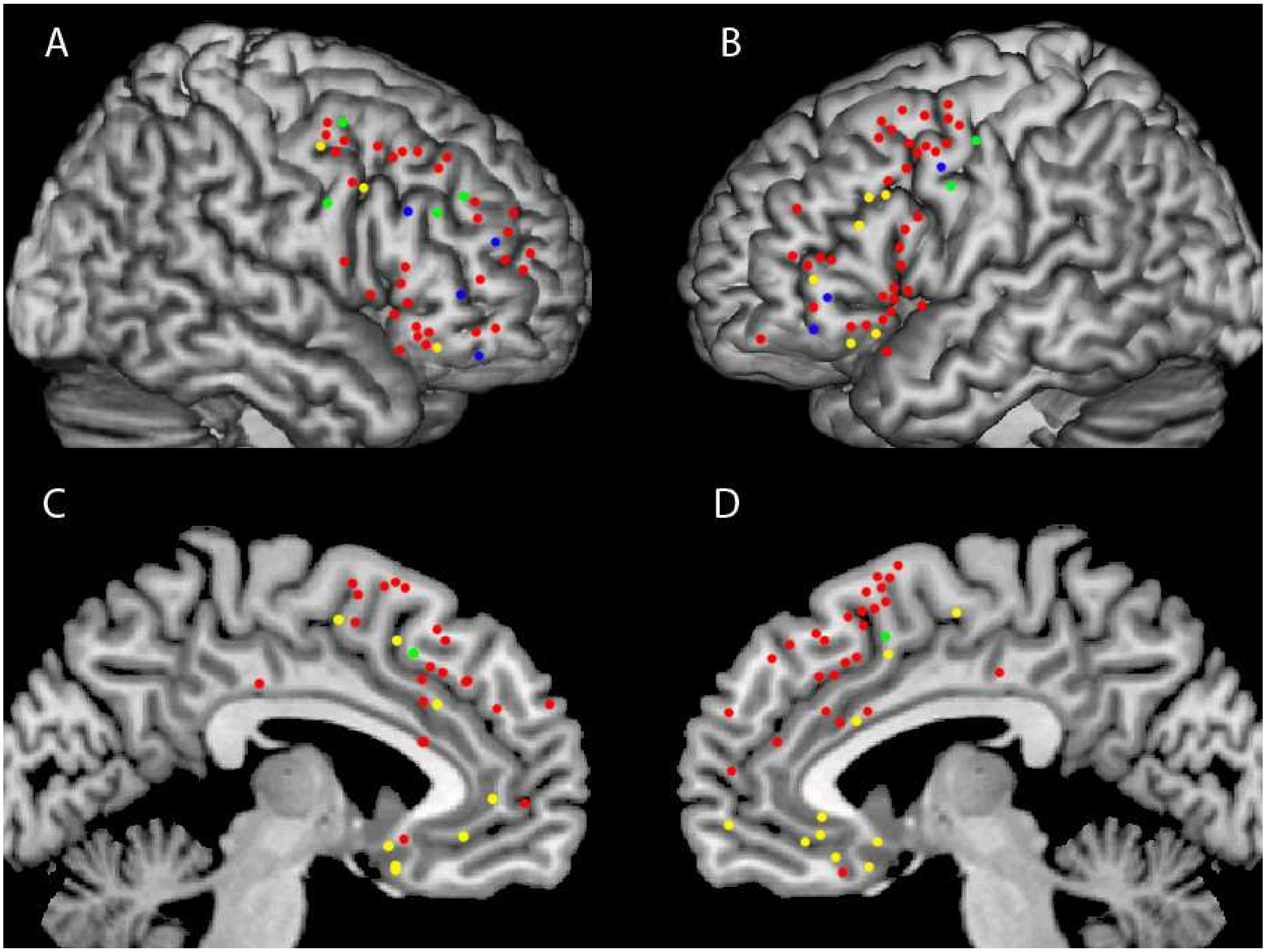

Figure 5. *Activation in right lateral PFC (**A**), left lateral PFC (**B**), right medial PFC (**C**), and left medial PFC (**D**) associated with reappraisal (red and blue dots) or self-distraction (green and yellow dots). Red and blue dots represent activation peaks from reappraisal studies that used aversive pictures or other emotional stimuli respectively. Green and yellow dots represent activation peaks from self-distraction studies that used aversive pictures or other emotional stimuli respectively.*

The distinction between "short" and "long" studies reveals that dorsal ACC/mPFC activation was reported more frequently than average in both "short" and "long" studies ($p=.0008$; survived Bonferonni correction; table 11 and figure 6). This effect probably reflects the globally increased frequency of activation in this area compared to other areas irrespective of the long-short categorization and indicates that the duration of regulation per se does not seem to influence activation in dorsal ACC/mPFC areas. On the other hand, there was a trend for less frequent than expected ventral ACC/mPFC activation in "short" studies (p = .0071; did not survive Bonferonni correction; table 11 and figure 6). No deviation from the expected activation frequency was reported for all the other ROIs (table 11 and figure 6).

Region of interest	**Strategy**	**No activation**	**Activation**	**P value**
Left inferior frontal gyrus (BA 44/45/47/48)	short	12	10	0.1551
	long	10	1	
Right inferior frontal gyrus (BA 44/45/47/48)	short	16	6	0.1425
	long	9	2	
Ventral mPFC/dACC (BA 10/11/32/25)	short	**19**	**3**	**0.0071**
	long	**7**	**4**	
Dorsal mPFC/dACC (BA 8/9/32/25)	short	**6**	**16**	**0.0008***
	long	**6**	**5**	
Left dlPFC (BA 8/9/46/44)	short	10	12	0.1425
	long	7	4	
Right dlPFC (BA 8/9/46/44)	short	11	11	0.3858
	long	8	3	
Left lateral OFC (BA 47/11)	short	11	11	0.3858
	long	8	3	
Right lateral OFC (BA 47/11)	short	15	7	0.3858
	long	8	3	
Pre-SMA/SMA (BA 4/6/23/24)	short	15	7	0.2712
	long	9	2	
Left lateral premotor/motor cortex (BA 4/6)	short	14	8	0.1551
	long	10	1	
Right lateral premotor/motor cortex (BA 4/6)	short	18	4	0.0105
	long	10	1	
Average for eleven ROIs (null hypothesis)	short	13	9	
	long	8	3	

Table 11. *Activation/no activation frequency distributions for "short" and "long" studies for each ROI and the level of significance of the chi square tests. * represents significant deviation from the expected average frequencies after Bonferonni correction for multiple tests (threshold of significance is p = .0045)*

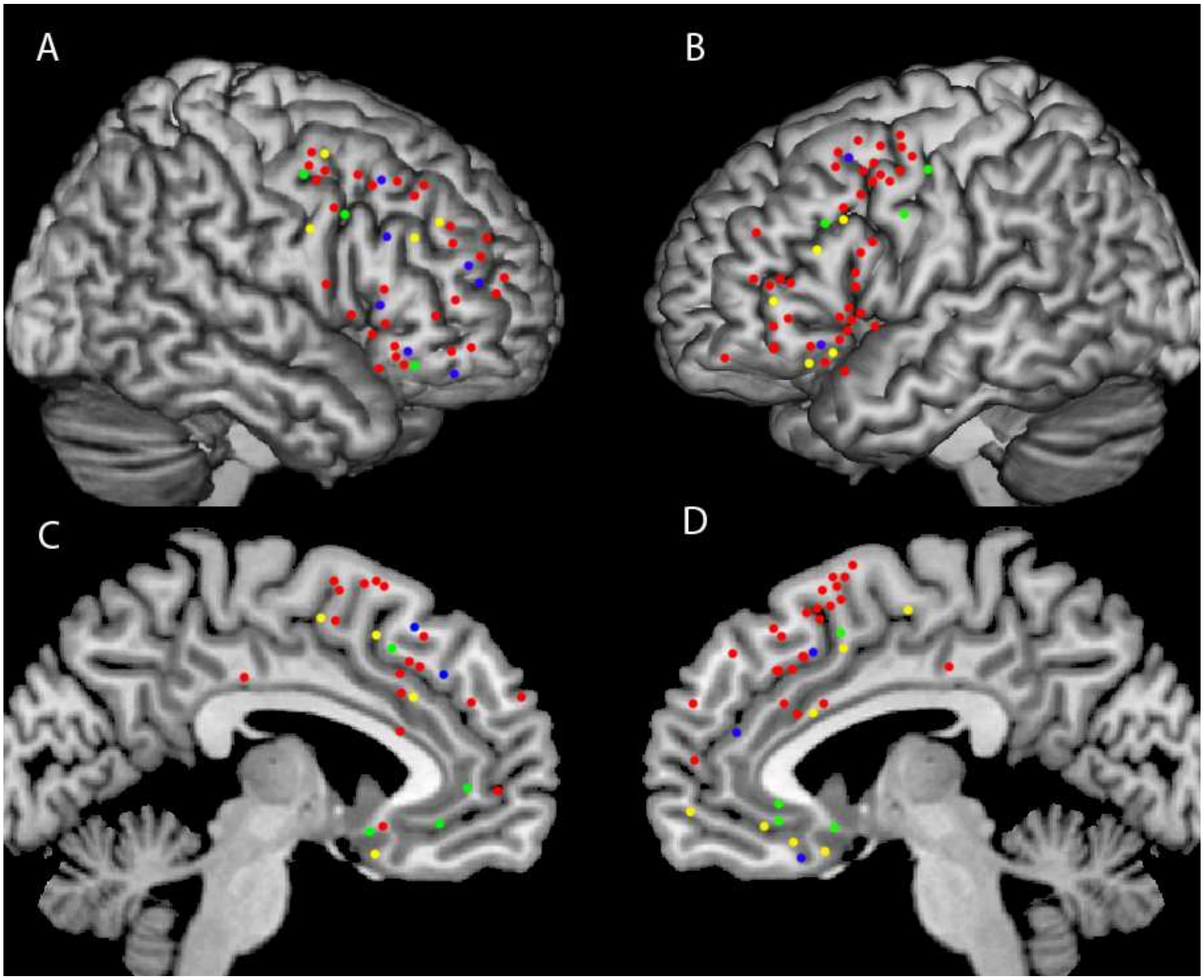

*Figure 6. Activation in right lateral PFC (**A**), left lateral PFC (**B**), right medial PFC (**C**), and left medial PFC (**D**) associated with reappraisal (red and blue dots) or self-distraction (green and yellow dots). Red and blue dots represent activation peaks from reappraisal studies with a relatively long (i.e more than 15 sec) or short (i.e less than 10 sec) reappraisal duration respectively. Green and yellow dots represent activation peaks from self-distraction studies with a long (i.e more than 15 sec) or short (i.e less than 10 sec) distraction duration respectively.*

The categorization that was based on the onset of regulation relatively to the onset of the emotional stimulus revealed more frequent than expected dorsal ACC/mPFC activation for both types of studies (i.e. "emotion first" and "regulation first" studies) (p =.0006; survived Bonferonni correction; table 12 and figure 7). This finding probably reflects the general observation that dorsal ACC/mPFC activation is reported more frequently than other frontal areas. Thus activation in this ROI was not affected by the "onset of regulation" categorization. No deviation from the expected activation frequency was reported for all the other ROIs (table 12 and figure 7).

Region of interest	**Strategy**	**No activation**	**Activation**	**P value**
Left inferior frontal gyrus (BA 44/45/47/48)	regulation first	12	6	0.2482
	emotion first	6	4	
Right inferior frontal gyrus (BA 44/45/47/48)	regulation first	13	5	0.2082
	emotion first	9	1	
Ventral mPFC/dACC (BA 10/11/32/25)	regulation first	**12**	**6**	**0.2482**
	emotion first	**9**	**1**	
Dorsal mPFC/dACC (BA 8/9/32/25)	regulation first	**9**	**9**	**0.0006***
	emotion first	**3**	**7**	
Left dlPFC (BA 8/9/46/44)	regulation first	10	8	0.0426
	emotion first	5	5	
Right dlPFC (BA 8/9/46/44)	regulation first	9	9	0.1006
	emotion first	7	3	
Left lateral OFC (BA 47/11)	regulation first	11	7	0.2082
	emotion first	6	4	
Right lateral OFC (BA 47/11)	regulation first	11	7	0.4046
	emotion first	8	2	
Pre-SMA/SMA (BA 4/6/23/24)	regulation first	15	3	0.1006
	emotion first	7	3	
Left lateral premotor/motor cortex (BA 4/6)	regulation first	14	4	0.2294
	emotion first	7	3	
Right lateral premotor/motor cortex (BA 4/6)	regulation first	16	2	0.0351
	emotion first	8	2	
Average for eleven ROIs (null hypothesis)	regulation first	12	6	
	emotion first	7	3	

Table 12. *Activation/no activation frequency distributions for "regulation first" and "emotion first" studies for each ROI and the level of significance of the chi square tests. * represents significant deviation from the expected average frequencies after Bonferonni correction for multiple tests (threshold of significance is p = .0045)*

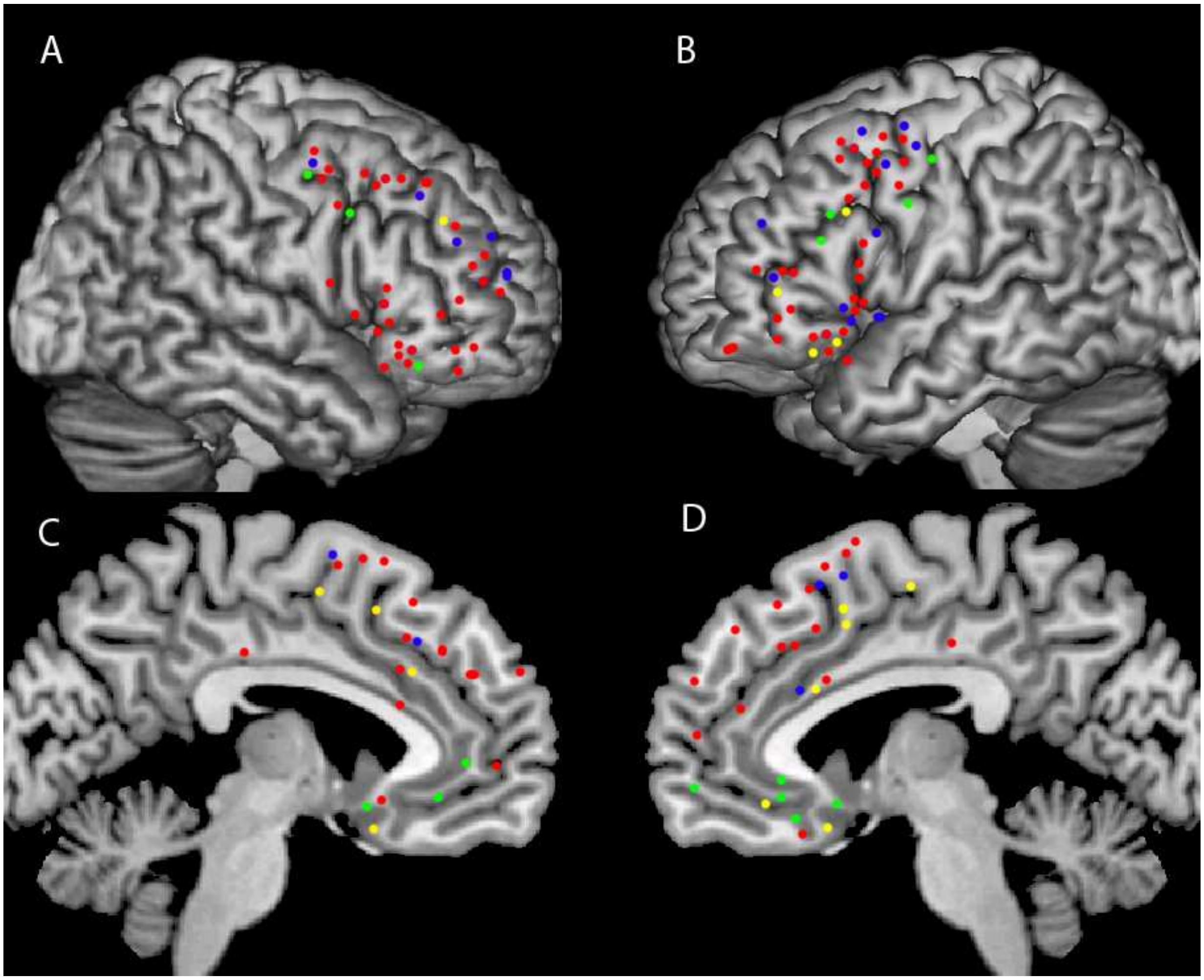

Figure 7. *Activation in right lateral PFC (**A**), left lateral PFC (**B**), right medial PFC (**C**), and left medial PFC (**D**) associated with reappraisal (red and blue dots) or self-distraction (green and yellow dots). Red and blue dots represent activation peaks from "early" and "late" reappraisal studies respectively. Green and yellow dots represent activation peaks from "early" and "late" self-distraction studies respectively.*

Based on behavioral and electrophysiological evidence that the onset of regulation" manipulation affects only reappraisal studies (Sheppes et al 2008 and 2011), the same analysis was performed only for reappraisal studies. There was no effect of the onset of regulation in reappraisal-related activation in any of the eleven ROIs (table 13).

Region of interest	Strategy	No activation	Activation	P value
Left inferior frontal gyrus (BA 44/45/47/48)	regulation first	6	5	0.2379
	emotion first	1	3	
Right inferior frontal gyrus (BA 44/45/47/48)	regulation first	7	4	0.3173
	emotion first	3	1	
Ventral mPFC/dACC (BA 10/11/32/25)	regulation first	**9**	**2**	**0.0182**
	emotion first	**4**	**0**	
Dorsal mPFC/dACC (BA 8/9/32/25)	regulation first	**4**	**7**	**0.0331**
	emotion first	**1**	**3**	
Left dlPFC (BA 8/9/46/44)	regulation first	5	6	0.1088
	emotion first	1	3	
Right dlPFC (BA 8/9/46/44)	regulation first	4	7	0.0601
	emotion first	2	2	
Left lateral OFC (BA 47/11)	regulation first	5	6	0.1088
	emotion first	1	3	
Right lateral OFC (BA 47/11)	regulation first	5	6	0.1088
	emotion first	3	1	
Pre-SMA/SMA (BA 4/6/23/24)	regulation first	9	2	0.1088
	emotion first	3	1	
Left lateral premotor/motor cortex (BA 4/6)	regulation first	9	2	0.2099
	emotion first	2	2	
Right lateral premotor/motor cortex (BA 4/6)	regulation first	9	2	0.0182
	emotion first	4	0	
Average for eleven ROIs (null hypothesis)	regulation first	7	4	
	emotion first	5	4	

***Table 13**. Activation/no activation frequency distributions for "regulation first" and "emotion first" reappraisal studies for each ROI and the level of significance of the chi square tests. * represents significant deviation from the expected average frequencies after Bonferonni correction for multiple tests (threshold of significance is p = .0045)*

Discussion

Role of dorsal and ventral ACC/mPFC in reappraisal and self-distraction

Consistent with our initial hypothesis, dorsal ACC/mPFC is prominently engaged during both reappraisal and distraction but more so during reappraisal, whereas ventral ACC/mPFC is recruited mainly during self-distraction.

The present findings are in line with human neuroimaging studies from the field of fear conditioning (Mechias et al. 2010; Klucken et al. 2009; Kalisch et al., 2006b; Gilbert et al. 2006; Rushworth et al. 2007) and emotional conflict tasks (Etkin et al. 2006; Egner et al. 2008; Ochsner et al. 2009) that have implicated dorsal ACC/mPFC in appraisal of negative stimuli and in conflict detection respectively.

More importantly, the other two imaging studies that compared reappraisal and distraction-related brain activation showed overlapping activation increases for the two regulation strategies (McRae et al. 2010; Kanske et al. 2011). Additional neuroimaging and behavioral data from emotion regulation studies have shown that reappraisal-related dorsal ACC/mPFC activity correlates negatively with self-reported negative affect (Ochsner et al. 2002; Phan et al. 2005; McRae et al. 2010), suggesting that conflict detection and recruitment of additional cognitive resources (Botvinick et al. 2001) are associated with successful down-regulation of negative affect. More convincing evidence in favor of this idea was provided by a thought suppression study (Mitchell et al. 2003). This study found that the magnitude of dorsal ACC activity accompanying an intrusive thought predicted the length of time to the next intrusion of an unwanted thought (Mitchell et al. 2003). In the face of this evidence, it has been argued that during thought suppression, dorsal ACC monitors for intrusion of unwanted thoughts and actions in working memory (Wyland et al. 2003).

Based on these findings, it can be argued that dorsal ACC/mPFC areas are recruited during reappraisal and distraction and probably reflect the detection of emotional conflict. However, due to the limitations of the present analysis, I cannot draw a conclusion about the hypothesized more important role of these areas in reappraisal than self-distraction. Nevertheless, the fact that fifteen out of twenty reappraisal and only six out of thirteen self-distraction studies activated this area provide an indication that dorsal ACC/mPFC plays a more important role during reappraisal than during self-distraction.

On the other hand, imaging data from fear conditioning studies (Kalisch et al. 2006; Milad et al. 2002; Phelps et al. 2004; Schiller et al. 2008; Mobbs et al.

2009), and emotional conflict tasks (Etkin et al. 2006; Egner et al. 2008; Ochsner et al. 2009; Chiew et al. 2011) have implicated ventral ACC/mPFC areas in suppression of emotional processing probably by inhibition of amygdala activity. In support of the idea that inhibition of negative emotional processing mainly occurs during self-distraction, I provided evidence of more frequent ventral ACC/mPFC activation during self-distraction than reappraisal.

Two reappraisal studies that did not find ventral ACC/mPFC activation in any of the contrasts permitted in this meta-analysis have however reported negative correlation between ventral ACC/mPFC and amygdala activity when down-regulating amygdala activity (Johnstone et al. 2007; Urry et al. 2006). In light of this evidence, the authors argued that ventral ACC/mPFC are mediators between activation in dorsal medial and lateral prefrontal areas, involved in reappraisal, and modulation of amygdala activity. This assumption fits well with the fact that amygdala has little or no direct connectivity with lateral prefrontal structures (Amaral et al. 1992) but has direct connectivity with ventral ACC/mPFC areas (Ghashghaei. et al. 2007; Beckmann et al. 2009; Amaral et al. 1992).

Therefore, it can be assumed that ventral ACC/mPFC performs a basic negative emotion inhibitory function that can be recruited by other regions (e.g. dorsal ACC and mPFC and lateral PFC) when there is need to suppress limbic reactivity (Schiller et al. 2010; Milad et al. 2002: Etkin, 2011). In the case of self-distraction, activity in ventral ACC/mPFC areas probably reflects the main task of inhibiting the processing of a salient, but task-irrelevant, emotional stimulus in order to better perform the cognitive task at hand (Etkin et al. 2011; Schiller et al. 2010).

On the other hand, inhibition of emotional processing is not an essential part of a reappraisal strategy and even the unusual recruitment of ventral ACC/mPFC areas during reappraisal (i.e. 2 out of 20 reappraisal studies) probably reflects an auxiliatory function related to a transient inhibition of emotional processing that facilitates the implementation of a reappraisal strategy.

Influence of other factors

The present findings regarding the comparison between reappraisal- and distraction-related brain activation may be confounded by other experimental factors.

Regulation-related activation in dorsal and ventral ACC/mPFC seems to be influenced by the interaction of the emotion regulation strategy (i.e. reappraisal vs self-distraction) with the type of emotional stimulus (i.e. aversive pictures vs painful stimuli or sad films). In particular, only reappraisal studies that used pictures activate dorsal ACC/mPFC areas and only self-distraction studies that used painful stimuli or sad films activate ventral ACC/mPFC areas.

There is no good reason to argue that reappraisal-related activation is picture-specific. Therefore, this could be a chance finding related to the fact that only three reappraisal studies of the present review did not use pictures as emotional stimuli. Nevertheless, future studies should investigate the role of the type of emotional stimulus in reappraisal-related activation.

On the other hand, distraction-related ventral ACC/mPFC activation in studies that used painful and sad stimuli is less likely to be a chance finding. Induction and elaboration of a sad mood state have been associated with increased neural responding in ventral ACC/mPFC in studies that used sad films (Cooney et al 2007; Levesque et al. 2003b; Gotlib et al. 2005). Moreover, perigenual ACC and orbitofrontal cortex have been implicated in pain processing and pain modulation in animal studies (Hutchison et al. 1996) and lesion studies (Bouckoms, 1994; Daum et al. 1995). In line with these findings, high blood flow changes in ventral ACC/mPFC were reported during opioid analgesia (Petrovic et al. 2002 and Wagner et al. 2001) and increased density of opioid receptors in ventral ACC/mPFC was shown by ligand-PET studies (Vogt, 1995; Willoch et al. 1999; Zubieta et al. 2001). A careful consideration of these findings leads to the conclusion that ventral ACC/mPFC areas are implicated in down-regulation of negative affect induced by painful and sad stimuli (i.e. analgesia or down-regulation of sadness).

Another experimental factor that has been previously shown to be relevant to reappraisal is the duration of the active regulation (Kalisch, 2009; Paret et al. 2011). This factor did not affect activation in dorsal ACC/mPFC areas but seems to influence ventral ACC/mPFC activation. There was a trend towards less frequent than expected ventral ACC/mPFC activation in “short” studies. This finding raises the question whether the infrequent reappraisal-related ventral ACC/mPFC activation is confounded by the fact that the majority of the reappraisal studies are “short” studies. However, based on the assumption that ventral ACC/mPFC mediates a transient inhibition of emotional processing, frequent ventral ACC/mPFC activation in “short” studies is expected. Therefore, an effect of the type of emotion regulation (i.e. reappraisal; $p = .0006$) rather than an effect of the reappraisal duration (short duration; $p = .0070$) seems like a more plausible explanation for the infrequent reappraisal-related ventral ACC/mPFC activation.

The “onset of regulation” categorization did not reveal any significant effect of this manipulation on the regulation-related activation in any of the ROIs. Similarly, there was no effect of this manipulation in regulation-related activation when the analysis is restricted to reappraisal studies. More importantly, the two reappraisal studies that reported ventral ACC/mPFC activation are “regulation first” studies. This finding runs against the hypothesized link between ventral ACC/mPFC activation and late-onset reappraisal studies. Nevertheless, only one of these two studies reported reappraisal-related activation in the ventromedial region that is assumed to be involved in inhibition of emotion processing. Based on findings from only one reappraisal study, no inferences can be drawn about the relationship of late-onset reappraisal and ventral ACC/mPFC activation.

Success of regulation

The cognitive effort required during regulation of negative emotions as well as the extent to which reappraisal or self-distraction successfully attenuate negative emotion can also influence the pattern of regulation-related activity in the frontal cortex (Ochsner et al. 2005). The attenuation of negative emotion is assessed directly through self-report measures, or indirectly through autonomic responses (e.g. electrodermal activity, heart rate). Another indirect way to assess the success of emotion regulation is by measuring the reappraisal-related modulation of neural responses in emotion-related brain regions such as amygdala. However, in this case, emotion regulation is assumed because of the reduction of amygdala responses without a proven correlation between these two variables.

Although, physiological indices of emotion regulation are independent of subjective biases and are considered as an objective measure of emotional arousal, limited amount of the studies reviewed here included physiological measures.

Nevertheless, the present findings indicate that reappraisal and externally-paced self-distraction can successfully attenuate self-reported negative affect and decrease the activity in limbic areas that are related with emotional processing. By contrast, implementation of an internally-paced distraction strategy is more difficult and less likely to be successful. This difference between externally- and internally-paced self-distraction studies may influence the pattern of distraction-related activation. For instance, three out of five internally-paced self-distraction studies and only two out of eight externally-paced self-distraction studies reported activation in ventral ACC/mPFC. Although not statistically tested (small sample), it can be speculated that this difference reflects the increased effort to inhibit emotional processing during internally-paced self-distraction.

The role of lateral prefrontal and orbitofrontal cortex in reappraisal and self-distraction

The right lateral premotor/motor area (BA 6/4) is reported active more frequently during distraction (3 out of X studies) than reappraisal (2 out of X studies). This finding is consistent with IMMO that suggests the recruitment of anterior parts of the right lateral frontal cortex and posterior parts of the left lateral cortex (Kalisch, 2009; Paret et al. 2011) but not posterior right lateral frontal cortex during reappraisal. More specifically, it has been argued that posterior left lateral frontal cortex (LFC) has been implicated in controlled retrieval of information from long-term memory (Badre et al. 2007; Danker et al. 2008; Martin et al. 2006; Thompson-Schill et al. 2006). These cognitive processes are probably important for implementing a reappraisal strategy (Kalisch, 2009). In addition, the anterior part of right LFC has been implicated in monitoring of working memory contents (Champod et al. 2007). The same area is involved in monitoring of retrieved information in working memory (Allan et al. 2000; Cabeza et al. 2003; Henson et al. 1999; Schacter et al. 1996; Shallice et al. 1996; Vallesi et al. 2006) This type of monitoring is well suited to evaluate how compatible the reappraisal contents are with reality (Kalisch et al. 2006a).

Although IMMO is consistent with the absence of reappraisal specific activation in the posterior right LFC, this finding might as well have emerged by the anatomical segmentation used in the present review. Namely, eleven reappraisal studies reported activation in right dlPFC which includes activation peaks as posterior as y = 10. Therefore, the absence of posterior right LFC activation is limited to posterior right premotor/motor areas (BA 6/4) and does not include posterior parts of middle frontal gyrus (BA 8/9/44).

The present comparison between reappraisal and self-distraction studies can only reveal in which regions of interest the activation/no activation frequency distribution deviates significantly from the observed average activation/no activation frequency distribution throughout the entire frontal cortex. As a consequence, regions of interest that do not deviate from the average frequency distribution but deviate significantly from an equal frequency distribution are not taken into account.

For instance, lateral prefrontal and orbitofrontal regions seem to have reappraisal-specific activation despite the fact that they do not deviate significantly from the average activation/no activation frequency distribution.

Ten reappraisal studies and only one distraction study reported activation in left inferior frontal gyrus. This finding is consistent with the reappraisal-specific activation in ventral lPFC in one of the studies that compared reappraisal and distraction-related brain activation (McRae et al. 2010). Left inferior frontal gyrus has long been implicated in language processing (Tyler et al 2011; Hirshorn et al. 2006; Poldrack et al. 1999; Thompson-Schill et al. 2002; Thompson-Schill et al. 1998). For instance, during word production, subjects usually produce semantically related items (e.g., cow, pig and sheep) and occasionally "switch" to other clusters (e.g., lion, tiger and bear). Previous studies have shown that the ability to switch between semantic categories is associated with activity in the left inferior frontal gyrus (Tyler et al. 2011; Hirshorn et al. 2006) and with deficits in patients with lesions in this area (Thompson-Schill et al. 2002; Thompson-Schill et al. 1998). The ability to initiate a switch between two semantic categories probably requires the selection of weakly activated representations over active representations from semantic memory (Tyler et al. 2011; Thompson-Schill et al. 1998). This ability may be very crucial during implementation of a reappraisal strategy when the dominant stimulus-diven appraisal of the emotional situation has to be replaced by a semantically different goal-directed second appraisal.

Left dlPFC is also reported active more frequently during reappraisal (13 studies) than distraction (3 studies). Left dlPFC has been associated with retrieval of long-term memories, maintenance of the goal of a cognitive strategy and goal-related information in working memory, and resisting interference from competing inputs (Cabeza et al 1999 and 2003; Smith et al. 1999; Courtney et al. 1998; Petit et al. 1998; Alexander et al. 1996; Ochsner & Gross, 2005; Kalisch et al. 2006; Gabrieli et al. 1998; Shallice et al. 1996; Chao and Knight, 1995). Furthermore, left dlPFC is implicated in episodic verbal memory processes (Rami et al. 2003). It can be argued that during reappraisal, more than self-distraction, subjects must construct a new story in order to change the meaning of an emotional situation. This process probably requires the ability to retain information about the story in working memory.

More importantly, bilateral lateral OFC (i.e. two ROIs together) is reported active in sixteen reappraisal and only two distraction studies. Kanske et al. (2011) also reported lateral OFC activation during reappraisal but not during distraction. Lateral OFC has been implicated in affective reversal learning tasks (Kringelbach and Rolls 2003) and generally in updating the context-sensitive motivational relevance of stimuli (Bechara et al. 2000; Ochsner et al. 2001; Rolls, 2000; Schinder et al. 2002). Through direct reciprocal connections between lateral OFC and appraisal systems representation of goal-relevant information in lateral OFC regions can be affected by appraisal systems (e.g. amygdala) (Ochsner et al. 2005). Moreover, lesions in the OFC are linked to deficits in the actualization of a current context (Schnider and Ptak 1999; Schnider 2003). Within a cognitive emotion regulation context, these processes are probably more relevant to reappraisal than distraction. Reappraisal of an emotional situation requires a self-induced update of the context-sensitive motivational relevance of the emotional stimulus during the process of changing its meaning (Kanske et al. 2011).

Summing up, dorsal ACC/mPFC areas are recruited during both reappraisal and self-distraction (more frequently during reappraisal) and ventral ACC/mPFC areas are recruited mainly during self-distraction. Common activation of dorsal ACC/mPFC areas likely reflects detection of conflict that can either be between the task-irrelevant emotional stimulus and the goal-directed neutral stimulus (i.e. mainly during self-distraction but sometimes during reappraisal as well) or between the stimulus-driven initial appraisal of the emotional situation and the goal-directed neutral re-appraisal of this situation (i.e. only for reappraisal). Self-distraction-specific activation in ventral ACC/mPFC likely reflects inhibition of emotional processing, probably by ventral ACC/mPFC-mediated inhibition of limbic emotional responses (Etkin et al. 2011; Schiller et al. 2010).
In addition, painful stimuli and sad films mainly activate ventral ACC/mPFC areas during distraction and pictures with aversive scenes mainly activate dorsal ACC/mPFC areas. This finding highlights the potential influence of the type of emotional stimulus on emotion regulation processes and on the pattern of brain activation. Finally, consistent with previous studies, the present findings provide some indications for reappraisal-specific activation in left dlPFC, left inferior frontal gyrus, and lateral OFC.

Limitations and future challenges

Several important limitations of this meta-analysis need to be acknowledged. Reappraisal-related activation was reported more frequently than distraction-related activation throughout the frontal cortex (except from the ventral ACC/mPFC). This finding did not allow us to treat reappraisal and distraction as strategies that are equally possible to engage a certain brain area. This decision probably led to false negative effects regarding reappraisal-related activity in lateral prefrontal and orbitofrontal areas. Therefore, future research should further investigate the hypothesized reappraisal-specific role of lateral OFC and left prefrontal regions as previous studies have also reported a reappraisal-specific activation of these areas (see McRae et al. 2010 for vlPFC and Kanske et al. 2011 for lateral OFC).

Another limitation is related to the anatomical segmentation used in the present meta-analysis. Despite the fact that a priori anatomical criteria were used, the eleven ROIs varied in size and therefore the probability of finding activation may not be the same for the eleven ROIs. Depending on the anatomical segmentation, different average frequency distributions emerge which in turn modify the null hypothesis. For example, in an additional exploratory analysis (not shown here), lateral ROIs were defined bilaterally. In this analysis, the dorsal ACC/mPFC effect was not significant. For this reason, future studies should address specific hypothesis-driven questions and define the regions of interest based on previous imaging data from emotion regulation studies.

The restriction of the present analysis to frontal areas is based on evidence that these areas are implicated in "cold" cognitive control processes that are probably also involved in emotion regulation (Ochsner et al. 2005 and 2008). However, the role of parietal cortex in attention-related processes (Rushworth et al. 2001; McRae et al. 2010) and the role of temporal cortex in semantic processing (Visser et al. 2010) suggest that these areas may also be important for the implementation of a reappraisal or a self-distraction strategy.

The majority of the studies reviewed here reported regulation-related activation derived from the regulation>view contrast from emotional trials. This activation might reflect the recruitment of areas that are important for the implementation of a complex cognitive strategy irrespective of whether the situation involves an emotional component (Paret et al. 2011). However, the main focus of interest in emotion regulation research involves the neural correlates of emotion down-regulation. Future research should take into account the Emotion x Regulation interaction effect rather than the simple effect of regulation in emotional trials (Nieuwenhuis et al. 2011). For the same reason, emphasis should be placed on the control "view" condition. This control condition should recruit similar cognitive processes as the "regulation" condition but without including an emotion-regulatory component. In this way, processes specifically related to down-regulation of negative emotions can be isolated.

Another limitation of the present review is related to the possibility of sub-threshold regulation-related activation. It has been argued that implementation of a reappraisal strategy probably requires more cognitive effort than distracting oneself from an emotional stimulus (Sheppes et al. 2008 and 2011). In the face of this assumption, the general pattern of less frequent distraction-related activation might be explained by sub-threshold distraction-related activation. However, this argument is not supported by the fact that in the present meta-analysis there were less than 10 out of 200 activation peaks with $z<3$.

Meta-analytic reviews are subjected to problems related to study heterogeneity. Variability in activations across studies of the same type of emotion regulation make it difficult to draw firm and highly specific inferences about the cognitive processes that are carried out by specific neural systems. We tried to predict some of this variability by taking into account three experimental factors. However, further investigation of the influence of these factors in emotion regulation processes is necessary. In addition, previous evidence suggests that there are more potential sources of variance. For instance, the precise strategy employed (i.e. distancing or reinterpretation; Ochsner et al. 2004 and task or self distraction; Ochsner et al. 2005), the gender and the age of the participants (McRae et al. 2008, Domes et al. 2010; Opitz et al. 2010; Winecoff et al. 2010), the direction of the regulatory goal (i.e. decrease or increase) (Ochsner et al. 2004; Kim et al 2007) and the valence of the stimulus (i.e. positive or negative stimuli) (Ochsner et al. 2004; Kim et al 2007) are some additional factors. Future research will need to take these factors into account.

More importantly, future studies need to include experiential, behavioral and physiological indices of emotion regulation in parallel to brain activation. The inclusion of these additional measures will help avoid the reverse inference problem when speculating about the cognitive effort required or the extent to which emotion was modulated during implementation of an emotion regulation strategy. Moreover, as the field matures and as theories of the functional architecture of emotion regulation become more refined, studies should be able to test specific hypotheses about the functional roles played by discrete brain systems. For instance, our hypothesis about a specific role of ventral ACC/mPFC in inhibition of emotional processing and a more general role of dorsal ACC/mPFC in detection of conflict within the context of emotion regulation should be tested by studies that are designed to isolate these cognitive processes.

Conclusion

The present review provides new insights into the neural bases of cognitive emotion regulation by highlighting the differential role of dorsal and ventral ACC/mPFC in cognitive reappraisal and self-distraction. We also provide preliminary evidence that experimental factors such as the type of emotional stimuli can influence regulation-related brain activity. Imaging data from this review are consistent with the idea that cognitive reappraisal and self-distraction rely on different cognitive processes. The identification of the cognitive processes underlying these two emotion regulation strategies may be relevant to clinical practice. Evidence that reappraisal increases mental health (Gross et al. 2004) and is more efficient than distraction in the long-term (Kross et al. 2008) highlight the potential role of this type of emotion regulation in improving cognitive therapies of anxiety disorders and depression.

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