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Review

Emotion regulation: Quantitative meta-analysis of functional activation and deactivation

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ABSTRACT

Emotion regulation is hypothesized to be a multifaceted process by which individuals willfully modulate the intensity and direction of emotional response via prefrontally mediated inhibition of subcortical response-related regions of the brain. Here we employ activation likelihood estimation (ALE) meta-analysis of functional magnetic resonance imaging studies to (1) reveal a consistent network of structures active during emotion regulation, (2) identify the target regions inactivated by the willful regulation process, and (3) investigate the consistency of activated structures associated with downregulation and upregulation. Results reveal signal change in bilateral amygdala/parahippocampal gyrus that decreased in downregulated states and increased in upregulated states, while cortical regions including superior frontal gyrus, cingulate, and premotor areas exhibited enhanced activity across all regulation conditions. These results provide consistent evidence for the role of amygdala activity in experienced emotional intensity, where intentional dampening and exaggeration are clearly expressed. However, the execution of emotional upregulation and downregulation may involve distinct subsets of frontocortical structures.

Contents

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1. Introduction

The willful modulation of responses to emotionally evocative stimuli is thought to involve interactions among the lateral prefrontal cortex (LPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and amygdala (Banks et al., 2007; Kim and Hamann, 2007; Ochsner et al., 2002, 2004). Among other functions, the LPFC and ACC are critical in the performance of cognitive control tasks such as conflict monitoring (van Veen and Carter, 2002), working memory (Rypma et al., 1999), and the guidance of attention (Banich et al., 2000), whereas the amygdala is heavily involved in emotional processing (Garavan et al., 2001; Lane et al., 1999). Thus, the association of these brain structures identified with emotion regulation tasks is consistent with their ascribed roles in human behavior. The initial goal of the current work is to identify a consistent set of activated brain regions reported in functional magnetic resonance imaging (fMRI) investigations of emotional regulation processes using quantitative meta-analysis, taking advantage of enhanced statistical power and dampening the contributions of idiosyncratic experimental designs to reveal a consistent and reliable activated network (Eickhoff et al., 2012). Our second goal exploits the distinctive nature of the proposed emotion regulation network, in which an intentional process is associated with both the activation of regulating structures and inhibition (or in some cases enhancement) of regulated structures, which is particularly amenable to the fMRI measure that provides estimates of signal *decreases* as well as increases.

Investigations of the brain mechanisms of emotional regulation often include conditions in which participants are instructed to modulate their affective state in a single direction (e.g., to decrease felt emotion). Distinct brain regions have been identified in the comparatively few paradigms that have included both increase and decrease tasks, suggesting direction-dependent regulation networks (Kim and Hamann, 2007; Urry et al., 2006). This creates somewhat of an interpretational challenge in assessing the specificity of an emotional regulation network, in that different control structures or relative activity levels of nodes in a consistent control network may exist across downregulation and upregulation demands. Meta-analysis may therefore be useful to compare results from emotional enhancement and suppression conditions across a number of studies to detect the presence of direction-specific mechanisms involved in emotion regulation.

Three meta-analytic investigations of emotion regulation have been published recently (Buhle et al., 2013; Diekhof et al., 2011; Kohn et al., 2014), however the present effort will differ from these works in multiple ways. One significant distinction is that ours will include a contrast in which enhanced emotional reactivity is assessed, thus providing an opportunity to test how the direction of regulation alters the composition of brain structures involved. A second novel feature of our meta-analysis is the addition of a contrast depicting activation decreases during regulation states. This inclusion combines the advantages of the distinctive psychological task in which a dampening of response may conceivably result in the measurable decrease of regional brain activity. Finally, we hope to include a larger number of studies than has been possible in prior reports.

To address these research questions, the current work employed the latest iteration of the Activity Likelihood Estimation (ALE) fMRI meta-analysis method (Eickhoff et al., 2009) to combine the results of emotional regulation studies published over a 10 year period, including studies in which increased and decreased blood oxygen level dependent (BOLD) signal were reported during experimental conditions in which individuals downregulated or upregulated their affective state.

2. Methods

2.1. Article selection

Articles from 1994 through 2014 were identified using a specific search string in the PubMed database:

("1994/01/01"[Publication Date]: "2014/12/31"[Publication Date]) AND ((emotion* OR affective OR fear OR valence) AND (regulat* OR suppress* OR reappraisal) AND (fMRI OR neuroimag* OR "functional MRI" OR "functional magnetic resonance imaging")).

Studies were included if the authors reported whole-brain coordinates in Talairach or MNI space and sampled at least five subjects over 18 years of age. Contrasts that compared regulation conditions (e.g., instructed reappraisal or suppression) to non-regulation or baseline conditions (e.g. passive viewing) were included. In studies for which coordinate tables resulting from more than one contrast were reported (e.g., downregulation and upregulation contrasts), both were included. Only the results from within-subject contrasts were included, which accounted for the great majority of studies. Studies of clinical populations were excluded, however results from healthy control groups reported in clinical studies were included if listed separately.

2.2. Contrast selection

ALE contrasts reflect statistically significant whole brain clusters that were active for four contrasts:

1. Downregulation > no regulation
2. Downregulation < no regulation
3. Upregulation > no regulation
4. Upregulation < no regulation

Contrast 1 represents increases in brain activity resulting from downregulation states, in which subjects were instructed to willfully reduce their reactions to emotionally evocative material, while Contrast 2 represents decreases in brain activity associated with the same condition. Contrast 3 represents increases in brain activity resulting from upregulation states, in which subjects were instructed to willfully enhance their reactions to emotionally evocative material, while Contrast 4 represents decreases in brain activity associated with the same condition.

2.3. Activation likelihood estimation (ALE) procedure

Activation likelihood estimation (Laird et al., 2005; Turkeltaub et al., 2002) is a coordinate-based quantitative meta-analysis method that can be used to identify consistent locations of brain activation elicited across studies employing similar tasks. In ALE, activation foci reported in published studies are treated as probability distributions centered at the reported coordinates. Activation probabilities are then calculated for each standard-space voxel to construct ALE maps for contrasts of interest. To determine the reliability of the ALE map, null-distributions are generated by analyzing the distribution of ALE values across independent studies, which is conceptually similar to using permutation tests of individual voxels across experiments. The observed values in the ALE distribution are then compared to the null distribution in order to assign probability estimates to the observed (experimental) data (Eickhoff et al., 2012). Here we used GingerALE v2.1.1 (http://www.brainmap.org) with a conservative mask size and use of the Eickhoff ALE method, a variable FWHM spatial filter kernel (Eickhoff et al., 2009), a $p < 0.01$ False Discovery Rate pN threshold, and a minimum cluster size of 250 mm^3 to compute the overlapping

Table 1
Studies included in the meta-analysis.

Year	1st author	Contrast	Experimental condition	Stimuli	*N*	Age
2003	Hariri	Downregulate < control	Think about scenes < match scenes	Unpleasant scenes	11 (6F)	32
2004	Ochsner	Downregulate < control	Reappraise < view	Unpleasant scenes	24 (24F)	20.6
2005	Phan	Downregulate < control	Suppress < view	Unpleasant scenes	14 (8F)	27.6 (4.4)
2007	Blair	Downregulate < control	Suppress < view	Pleasant and unpleasant scenes	22 (12F)	28
2008	Goldin	Downregulate < control	Suppress < view	Unpleasant film clips	17 (17F)	22.7 (3.5)
2009	Mak	Downregulate < control	Reappraise < view	Pleasant and unpleasant scenes	12 (12F)	24 (1.8)
2010	Erk	Downregulate < control	Reappraise < view	Unpleasant scenes	17 (8F)	43.9 (10.1)
2010	Hayes	Downregulate < control	Reappraise < view	Unpleasant scenes	21 (11F)	21.6 (2.5)
2010	Kanske	Downregulate < control	Reappraise < view	Pleasant and unpleasant scenes	30 (17F)	21.8 (2.1)
2010	Koenigsberg	Downregulate < control	Distancing < view	Unpleasant scenes	16 (9F)	31.8 (7.7)
2010	McRae	Downregulate < control	Reappraise < view	Unpleasant scenes	18 (18F)	24.4 (3.5)
2011	Vritcka	Downregulate < control	Reappraise or suppress < view	Pleasant and unpleasant scenes	17 (17F)	24.8 (4)
2011	Winecoff	Downregulate < control	Reappraise < view	Pleasant and unpleasant scenes	42 (22F)	23 and 69
2013	Holland	Downregulate < control	Reappraise < view	Unpleasant scenes	18 (9F)	22.1 (3.7)
2013	Holland	Downregulate < control	Reappraise < view	Unpleasant scenes	22 (13F)	21.9 (3.3)
2013	Grecucci	Downregulate < control	Reappraise < natural reaction	Unpleasant outcome in ultimatum game	21 (10F)	23.5 (3.6)
2014	Otto	Downregulate < control	Reappraise < view	Unpleasant faces	26 (26F)	24.9 (5.6)
2001	Beauregard	Downregulate > control	Reduce sexual arousal > view	Erotic film clips	10 (0F)	23.5
2002	Ochsner	Downregulate > control	Reappraise > view	Unpleasant scenes	15 (15F)	21.9
2003	Hariri	Downregulate > control	Think about scenes > match scenes	Unpleasant scenes	11 (6F)	32
2003	Levesque	Downregulate > control	Suppress > natural reaction	Unpleasant film clips	20 (20F)	24.3
2004	Ochsner	Downregulate > control	Reappraise > natural reaction	Unpleasant scenes	24 (24F)	20.6
2005	Gillath	Downregulate > control	Suppress > think	Unpleasant imagery	20 (20F)	20
2005	Phan	Downregulate > control	Suppress > view	Unpleasant scenes	14 (8F)	27.6 (4.4)
2006	Beauregard	Downregulate > control	Suppress > view	Unpleasant film clips	12 (9F)	45 (10)
2006	Harenski	Downregulate > control	Suppress > view	Unpleasant scenes	10 (10F)	18–29
2006	Kalisch	Downregulate > control	Suppress > natural reaction	Fear conditioning	15 (8F)	26
2006	Urry	Downregulate > control	Suppress > view	Unpleasant scenes	19 (11F)	62–64
2007	Banks	Downregulate > control	Reappraise > view	Unpleasant scenes	14 (8F)	27.6 (4.4)
2007	Blair	Downregulate > control	Suppress > view	Pleasant and unpleasant scenes	22 (12F)	28
2007	Eippert	Downregulate > control	Reappraise > view	Unpleasant scenes	24 (24F)	23.3
2007	Herwig	Downregulate > control	Reappraise > view	Pleasant and unpleasant scenes	34 (18F)	23–36
2007	Kim	Downregulate > control	Suppress > view	Pleasant and unpleasant scenes	10 (10F)	20.7
2008	Goldin	Downregulate > control	Reappraise or suppress > view	Unpleasant film clips	17 (17F)	22.7 (3.5)
2008	Wager	Downregulate > control	Reappraise > view	Unpleasant scenes	30 (18F)	22.3
2009	Domes	Downregulate > control	Suppress > view	Unpleasant scenes	33 (17F)	25.2 (1.9)
2009	Mak	Downregulate > control	Reappraise > view	Pleasant and unpleasant scenes	12 (12F)	24 (1.8)
2010	Abler	Downregulate > control	Reappraise or suppress > view	Pleasant and unpleasant scenes	30 (14F)	23 (3.7)
2010	Amting	Downregulate > control	Suppress > view	Unpleasant faces	16 (6F)	24.9 (2.7)
2010	Butler	Downregulate > control	Suppress > experience	Unpleasant scene recall	14 (7F)	22.6 (3.9)
2010	Erk	Downregulate > control	Reappraise > view	Unpleasant scenes	17 (8F)	43.9 (10.1)
2010	Hayes	Downregulate > control	Reappraise > view	Unpleasant scenes	21 (11F)	21.6 (2.5)
2010	Herwig	Downregulate > control	Feel < think	Self-reflection	30 (17F)	23–41
2010	Hooker	Downregulate > control	Reappraise > view	Unpleasant and pleasant faces	27 (14F)	21 (2.4)
2010	Koenigsberg	Downregulate > control	Distancing > view	Unpleasant scenes	16 (9F)	31.8 (7.7)
2010	McRae	Downregulate > control	Reappraise > view	Unpleasant scenes	18 (18F)	24.4 (3.5)
2010	Modinos	Downregulate > control	Reappraise > view	Unpleasant scenes	18 (7F)	21.1 (2.8)
2011	Andreescu	Downregulate > control	Suppress > natural reaction	Unpleasantative rumination	10 (2F)	76.3 (4)
2011	Staudinger	Downregulate > control	Reappraise > natural reaction	Monetary reward task	24 (13F)	25.1 (2.8)
2011	Vritčka	Downregulate > control	Reappraise or suppress > view	Pleasant and unpleasant scenes	19 (19F)	24.8 (4)
2011	Winecoff	Downregulate > control	Reappraise > natural reaction	Pleasant and unpleasant scenes	42 (22F)	23 and 69
2012	Golkar	Downregulate > control	Reappraise > view	Unpleasant scenes	58 (32F)	24 (2.3)
2012	Veit	Downregulate > control	Suppress > view	Unpleasant scenes	11 (8F)	21–28

Table 1 (*Continued*)

Year	1st author	Contrast	Experimental condition	Stimuli	*N*	Age
2013	Hessner	Downregulate > control	Reappraise > natural reaction	Gambling task	40 (24F)	20.1 (1.7)
2013	Ziv	Downregulate > control	Reappraise > natural reaction	Unpleasant faces, criticism, and beliefs	27 (13F)	32.6 (9.5)
2013	Grecucci	Downregulate > control	Reappraise > natural reaction	Unpleasant outcome in ultimatum game	21 (10F)	23.5 (3.6)
2013	Seo	Downregulate > control	Reappraisal > view	Pleasant and unpleasant scenes	24 (24F)	19.6 (1.2)
2013	Vanderhasselt	Downregulate > control	Reappraise or suppress > view	Unpleasant scenes	42 (42F)	21.3 (2.3)
2014	Otto	Downregulate > control	Reappraise > view	Unpleasant faces	26 (26F)	24.9 (5.6)
2014	Morris	Downregulate > control	Reappraise > view	Pleasant and unpleasant scenes	16 (9F)	22.7
2014	Silvers	Downregulate > control	Reappraise > view	Unpleasant scenes	30 (13F)	22
2004	Ochsner	Upregulate > control	Increase > view	Unpleasant scenes	24 (24F)	20.6
2006	Urry	Upregulate > control	Increase > view	Unpleasant scenes	19 (11F)	62–64
2007	Eippert	Upregulate > control	Increase > view	Unpleasant scenes	24 (24F)	23.3
2007	Kim	Upregulate > control	Increase > view	Pleasant and unpleasant scenes	10 (10F)	20.7
2007	van Reekum	Upregulate > control	Increase > view	Unpleasant scenes	29 (18F)	61–65
2010	Domes	Upregulate > control	Increase > view	Unpleasant scenes	33 (17F)	25.2 (1.9)
2010	Herwig	Upregulate > control	Feel > think	Self-reflection	30 (17F)	23–41
2010	Johnston	Upregulate > control	Reappraise last run > reappraise first run	Pleasant and unpleasant scenes	13 (9F)	21–52
2012	Veit	Upregulate > control	Increase > view	Unpleasant scenes	11 (8F)	21–28
2013	Holland	Upregulate > control	Increase > view	Unpleasant scenes	18 (9F)	22.1 (3.7)
2013	Holland	Upregulate > control	Increase > view	Unpleasant scenes	22 (13F)	21.9 (3.3)
2013	Grecucci	Upregulate > control	Increase > natural reaction	Unpleasant outcome in ultimatum game	21 (10F)	23.5 (3.6)

Table 2
ALE clusters resulting from downregulate < control contrasts, FDR $p < .01$.

Structure	Volume (mm^3)	*x*	*y*	*z*
L Amygdala/parahippocampal gyrus	1816	−20	−6	−14
R Amygdala/parahippocampal gyrus	992	20	0	−14
L Inferior parietal lobule	288	−54	−26	22

Table 3
ALE clusters resulting from downregulate > control contrasts, FDR $p < .01$.

Structure	Volume (mm^3)	*x*	*y*	*z*
L Inferior frontal gyrus	4104	−46	17	−4
L Superior frontal gyrus/supplementary motor area	3192	−6	8	60
R Inferior frontal gyrus	2576	45	22	4
L Middle temporal gyrus	2360	−56	−36	−2
L Middle frontal gyrus/FEF	1968	−40	6	46
L Superior frontal gyrus	1328	−14	42	40
R Superior frontal gyrus/cingulate cortex	1128	6	20	44
L Angular gyrus	920	−45	−61	32
R Middle frontal gyrus/FEF	872	36	18	44
L Anterior cingulate cortex	640	−8	20	32
R Inferior frontal gyrus	328	38	44	2
L Superior frontal gyrus	264	−30	48	14

activation clusters for the three regulation contrasts. All ALE coordinate clusters are reported in Talairach space. A detailed description of the ALE process and analysis procedures can be found on the Brainmap website (http://www.brainmap.org/ale/manual.pdf).

3. Results and discussion

3.1. Article inclusion

The study pool for all contrasts can be found in Table 1. Forty-seven studies contributed to the downregulation condition ($n = 1033$) with 44 studies reporting brain regions exhibiting increased activation ($n = 963$) and 17 studies reporting decreased activation during regulation ($n = 348$). Twelve studies contributed to the upregulation condition ($n = 254$), all reporting increases in activation. The gender distribution was biased toward women, who made up 65% of the participants in the downregulation studies and 67% of participants in the upregulation studies.

3.2. Emotional downregulation

An ALE cluster map of activity associated with emotional downregulation tasks is shown in Fig. 1. Blue clusters represent signal decreases during regulation, compared to control conditions, and red clusters represent enhanced activation during regulation conditions. All clusters meeting the size and statistical threshold for enhanced or diminished activation are displayed in the figure and listed in Tables 2 and 3, respectively. No overlap exists between the downregulation increase and downregulation decrease contrast maps (i.e. they are spatially discrete). Areas showing decreased activation during regulation (compared to control), such as the amygdala cluster, which includes the parahippocampal gyrus (PHG), and the left inferior parietal lobule (IPL) cluster, may reflect particular sensitivity to the subjective emotional state during emotional regulation. Additionally, increased activation in the inferior frontal gyrus (IFG), middle frontal gyrus (MFG), superior frontal gyrus (SFG), and left anterior cingulate cortex (ACC) may reflect the sustained cognitive aspects of the regulatory task (McRae et al., 2010).

The amygdala is hypothesized to modulate brain circuitry supporting cognition and behavior in reaction to emotional cues, independent of awareness (Phelps, 2006). In line with the current results, previous work has found decreases in amygdala activity during emotional regulation (Ochsner et al., 2002; Phelps, 2006). For instance, participants who are asked to reappraise a negative picture (e.g., a crying woman) are instructed to describe and interpret the scene in more positive light in order to decrease their current subjective negative state (Ochsner et al., 2002). Amygdala activity has also been shown to decrease when

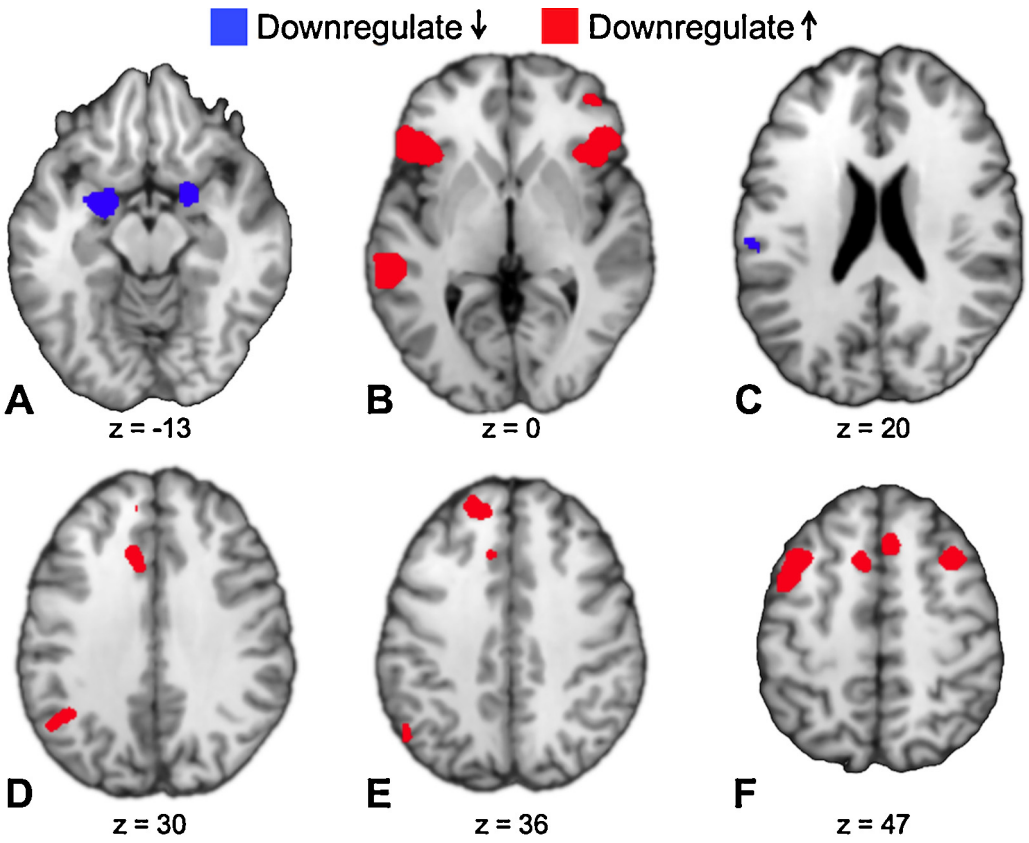

Fig. 1. Downregulation results in diminished activity (blue clusters) in amygdala and IPL, and enhanced activity in frontal regions and MTL (red clusters). Clusters were derived from ALE analyses of 47 studies, at a FDR threshold of $p < .01$, and cluster minimum of 250 μl. Talairach coordinates are listed for each image. Regional BOLD change depicted by image: (A) amygdala/PHG; (B) IFG and MTL; (C) IPL; (D) ACC; (E) SFG; (F) MFG and SFG. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

emotional downregulation strategies are employed in response to conditioned fear and when participants view non-fearful facial expressions, or expressions that are cued to be fearful (Phelps, 2006). The diminished activation found here is in line with previous literature, illustrating the covariation between amygdala activity and the intensity of emotional experience (Sabatinelli et al., 2005, 2007).

The parahippocampal gyrus, part of the amygdala cluster identified here, has been proposed to play a key role in episodic memory, receiving input from the cortex, amygdala, and hippocampus (Köhler et al., 1998; McDonald et al., 2000; Murty et al., 2010; Owen et al., 1996). The PHG, encompassing the perirhinal and entorhinal cortices, may be essential in maintaining and retrieving the relationship between stimuli and spatial location (Owen et al., 1996). Decreased activity in this area, as found in the present analysis, suggests that downregulation processes may involve preventing the continued maintenance of the emotional stimuli in working memory.

Emotional downregulation also resulted in an increase in BOLD activation across the midFG and SFG. One possible mechanism may involve the interaction of these regulatory regions within the frontal lobes, in which the midFG influences the amygdala via the orbitofrontal cortex (Davidson et al., 2000; Eippert et al., 2007; Ochsner et al., 2004). More specifically, activation of the SFG may reduce amygdala activity indirectly by activating regions in the midFG during affective regulation (Blair et al., 2007). This midFG activation may therefore reflect a cognitive control process involved during down-regulation, influencing regions including the amygdala to modulate the appraisal of affective stimuli (Ochsner et al., 2004). The enhanced activity of these regions combined with decrease in amygdala activation across studies used in the current meta-analysis is consistent with this perspective.

The IFG was also identified as reliably active across downregulation experiments. This structure has been suggested to act as a "coarse brake" to serve as an inhibitory mechanism across motor, cognitive, and affective domains (Berkman et al., 2009). In line with this idea, recruitment of the IFG has been observed during the volitional suppression of affective responses (Beauregard et al., 2001). This regions includes the pars opercularis, an area involved in imitation and considered part of the mirror neuron system, which has been suggested to suppress automatic mimicry responses (such as those elicited by an emotional stimulus) generated by this mirroring system (Lee et al., 2008). In the context of the current analysis it is possible that activity in this area may reflect the inhibition of motor responses associated with emotional reactivity.

The anterior cingulate cortex (ACC) is implicated in a number of functions including error recognition (Allman et al., 2001), conflict processing (Botvinick, 2007; van Veen and Carter, 2002), attention (Devinsky et al., 1995), pain (Zhang et al., 2005), self-regulation (Posner et al., 2007), and is involved in the recognition and vocalization of emotions (Devinsky et al., 1995). In line with the present analysis, this region shows enhanced activity during affective regulation tasks, and particularly for the downregulation of negative stimuli (Mak et al., 2009; Phan et al., 2005).

The IPL has been associated with a number of different tasks, including processing self-related information such as personality traits (Kircher et al., 2000), attention (Culham and Kanwisher, 2001), and working memory processes (Rama et al., 2001). The decreased activity in the left IPL identified here during downregulation could be explained by a reduction in any or all of these

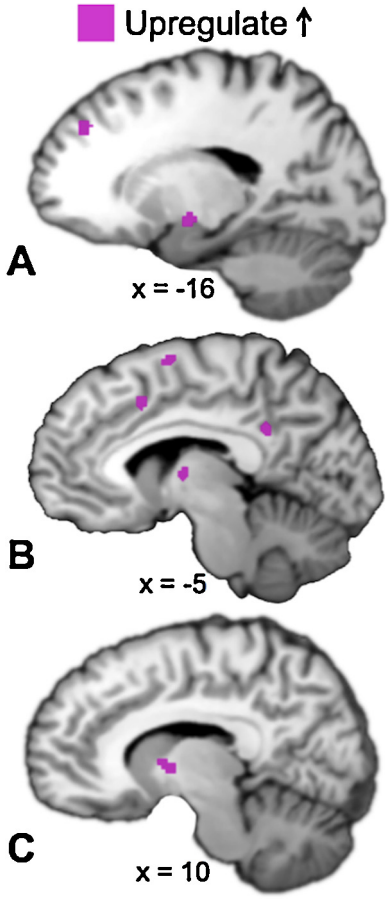

Fig. 2. Upregulation results in enhanced activation (purple clusters) of widespread cortical and subcortical regions. Clusters were derived from an ALE analysis of 12 studies, at a FDR threshold of $p < .01$, and cluster minimum of 250 μl. Talairach coordinates are listed for each image. Regional BOLD signal increase depicted by image: (A) amygdala/PHG and SFG; (B) SMA, PCC, and thalamus; (C) GP. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

processes. For instance, a person may attempt to ignore the content of an emotional stimulus in an attempt to decrease their emotional. A similar argument was made by Canli and colleagues (2004) who found that depressed patients showed significantly greater activation in the left inferior parietal lobule than did controls in response to sad words, which the authors attributed as an attempt by depressed patients to dampen oversensitivity.

The results for emotional downregulation represent a great majority of studies in which participants were instructed to suppress or reappraise an emotional response. Some work has shown that individuals who suppress often look away from the stimulus, which can increase activity in attention and motor planning regions such as cortex and supplementary motor cortex (van Reekum et al., 2007). Therefore, the pre-SMA findings in the present analysis may be, to some extent, due to ocular fixation effects.

3.3. Emotional upregulation

Eight ALE clusters associated with an increased BOLD response during affective upregulation that met our chosen reliability and volume threshold are shown in Fig. 2 and listed in Table 4. These regions were primarily left lateralized and include the left amygdala (including PHG), left SFG, left thalamus, left supplementary motor area (SMA), and right globus pallidus (GP). As this upregulation contrast was of particular relevance to our research question, and the number of studies including upregulation conditions was

Table 4
ALE clusters resulting from upregulate > control contrasts, FDR $p < .01$.

Structure	Volume (mm^3)	x	y	z
L Posterior cingulate cortex	392	−6	−48	26
L Putamen	368	−20	6	8
L Thalamus	352	−8	−8	2
L Supplementary motor area	328	−4	−2	60
L Superior frontal gyrus	312	−14	40	36
L Amygdala	288	−18	−10	−10
R Globus pallidus	272	10	0	2
L Anterior cingulate cortex	256	−4	12	40

Table 5
ALE clusters resulting from upregulate > control contrasts, FDR < .05.

Structure	Volume (mm^3)	x	y	z
L Insula/inferior frontal gyrus	1160	−50	7	13
L Putamen	1136	−20	6	8
L Posterior cingulate cortex	848	−6	−48	26
L Superior frontal gyrus	824	−13	44	38
L Thalamus	816	−8	−8	2
L Superior frontal gyrus	808	−4	−2	60
R Globus pallidus	744	10	0	2
L Anterior cingulate cortex	576	−4	12	40
L Amygdala	520	−18	−10	−10
R Insula	328	44	10	−2
R Precentral gyrus	288	52	−6	50
L Cingulate cortex	256	−8	6	26

comparatively few (12 vs. 44 for downregulation increases), we ran a second ALE analysis of this upregulation contrast using the default reliability (FDR $p < .05$) and volume thresholds (200 μl). The resulting clusters are listed in Table 5, and essentially add volume to the 8 clusters produced in the more conservative analysis, plus 4 new clusters, including bilateral insula, precentral gyrus, and midcingulate cortex.

As described above, the amygdala has been well associated with the processing of emotionally arousing stimuli. Recent human neuroimaging work has also shown that it is possible to willfully increase amygdala activity via real time neuro-feedback (Zotev et al., 2011, 2013). The present analysis confirms that the volitional increase in subjective emotional experience will also increase amygdala activity. The PHG, a conjoined region of this cluster, has been implicated in tasks involving working memory. Specifically, the PHG is recruited when novel information is maintained in working memory, and inhibition of this area results in diminished long-term memory encoding (Schon et al., 2005). The PHG is also recruited during the recall of emotional stimuli (Lanius et al., 2003; Thomaes et al., 2009). Increased activity of the PHG found in the current investigation may therefore reflect the maintenance of the emotionally laden stimuli in working memory, the recall of associated emotional memories, or a combination of the two.

The thalamus is involved in processing sensory information for emotionally arousing and behaviorally relevant information, may relay emotional information to cortical areas (LaBar and Cabeza, 2006; Vertes et al., 2007). By controlling the transfer of information, the thalamus also has a modulatory influence on cortical activity (Heilman, 2002). A positive relationship between thalamic activity and emotional arousal has also been demonstrated (Colibazzi et al., 2010; Reiman et al., 1997). This region may be modulated, at least in part, by the SFG, which also exhibited an increase in activity during upregulation, and is in a favorable position to modulate other brain regions, with connections to the thalamus, striatum, and limbic system (Lacoboni et al., 2004; Narayanan and Laubach, 2006). Indeed, its regulatory influence has been demonstrated in the case of SFG lesion subjects, who exhibit impaired behavioral inhibition (Fuchs et al., 2005; McLaughlin and See, 2003; Narayanan

and Laubach, 2006). The current results are in line with the notion that SFG activation may reflect general cognitive control.

Due to its role in preparing motor movement, the SMA's function in processing affective stimuli across studies may associated with emotional mimicry. An increased BOLD response in the SMA has been shown when individuals mimic emotions such as laughter (Iwase et al., 2002), and the SMA exhibits an even stronger response when individuals mimic incongruent emotions, such as frowning after watching a person smile (Lee et al., 2008). The SMA has also been implicated in several emotional mental imagery studies in which individuals imagine themselves involved in arousing situations (Lamm et al., 2007; Sabatinelli et al., 2006). Increased activity in the SMA during emotional upregulation tasks may reflect its role in preparatory motor movement. During an emotionally laden event the SMA could be important in preparing appropriate muscle movements not only for the engagement or disengagement of the situation, but also in mirroring the event through affective facial and bodily gesturing.

Regulatory frontal-subcortical circuitry contains frontal regions with projections to the striatum, forming connections to the globus pallidus and substantia nigra. Direct and indirect pathways project from the globus pallidus to specific thalamic nuclei, and these thalamic nuclei project back to various areas of the frontal lobe (Cummings, 1993). The GP is an output nucleus of the basal ganglia that innervates multiple cortical motor areas and is involved with the generation and control of movement (Alexander et al., 1986; Hoover and Strick, 1993). Input nuclei of the basal ganglia (the caudate and putamen) receive projections from various regions of the cerebral cortex. The output of the GP projects to specific thalamic nuclei, including the ventral lateral nucleus (VL), which is an integrative center involved in the relay and feedback of motor information (Tlamsa and Brumberg, 2010). This thalamic output projects back to several motor areas, including the SMA, premotor cortex, and the primary motor cortex (Haque et al., 2010). Inhibitory efferents from direct pathways of the GP serve to excite the thalamus (Thayer and Lane, 2000), which could explain the consistent activation of these areas due to recruitment and signaling of cognitive control strategies involved during upregulation. Previous research has found that activation of the globus pallidus and thalamic nuclei are directly related to emotionally arousing stimuli (Colibazzi et al., 2010), and this activation may reflect signaling of motor planning in regions of the cerebral cortex (Huguenard and McCormick, 2007). Furthermore, activation in the globus pallidus may be related to arousing stimuli because it plays a role in learning stimulus-response associations (Malhi et al., 2004), whereby arousing emotions activate this subcortical circuit that guides associations between the stimuli and their appropriate response (Colibazzi et al., 2010). Interestingly, research has found selective activation for positive, but not negative, stimuli (Hamann and Mao, 2002) in regions of the dorsal and ventral striatal regions (i.e. putamen and globus pallidus) which, in turn, have been associated with reward and positive affect (Elliott et al., 2000; Lane et al., 1997). In sum, because striatum has been impicated in both stimulus-response association (Colibazzi et al., 2010; Malhi et al., 2004), the processing of affective stimuli (Elliott et al., 2000; Lane et al., 1997), and projects to regions involved in action preparation (Alexander et al., 1986; Cummings, 1993), the striatal activation increase during upregulation in the current analysis may be reflective of the its potential role in affective learning and the early stages of action preparation. Since most of the studies in the current meta-analysis used unpleasant stimuli, it is still unclear if striatum is modulated by valence during emotional regulation.

Three additional clusters were identified in the ALE upregulation contrast at the standard reliability threshold (FDR < .05) and volume (200 μl), including insula, the precentral gyrus, and cingulate. The insular cortex is implicated in processing both pleasant and unpleasant emotional stimuli, and may be involved in the monitoring of internal emotional states (Damasio et al., 2000; Phan et al., 2002; Reiman et al., 1997). It is unclear if regulation strategy differentially effects insula activation. Several researchers have noted that downregulating affective stimuli using reappraisal reduces insula reactivity, while suppressing affective stimuli results in the opposite effect (Goldin et al., 2008; Ochsner and Gross, 2008). This may contribute to the lack of insula findings in the current downregulation contrast map.

The precentral gyrus cluster falls within the premotor cortex, which is associated with preparing and executing complex movements (Graziano et al., 2002; Kwan et al., 1978). Several studies have also shown this region to be involved during exposure to affective stimuli and recalling emotionally laden memories (Adolphs et al., 2000; Canli et al., 2002; Mitchell et al., 2003). While its contribution to upregulation is unclear, we speculate that premotor activity may reflect a regulation strategy involving imagery reflecting personal involvement in the affective stimuli to increase emotional salience (Sabatinelli et al., 2006).

Finally, we found an increase in activation of the midcingulate cortex during upregulation. This region is connected with the amygdala (Phan et al., 2002), associated with fear stimulus processing (Vogt et al., 2003) and appears to be a link between the limbic and motor system, potentially serving the role of emotionally driven action preparation (Dum and Strick, 1991; Morecraft and van Hoesen, 1992; Shima et al., 1991). As this region provides a link between amygdala and motor areas, the current results could be a result of imagined involvement in a affective situation in order to increase their reactivity to a given emotional cue.

3.4. Regulatory and emotion specific regions

Only two overlapping ALE clusters were identified (SFG & cingulate), both between downregulate and upregulate task conditions. An increase in reactivity to both regulation conditions was found in the left SFG. Since this region is non-specific to the direction of affective change, it is likely that this structure is especially involved in the cognitive control process of modulating the current emotional state. In contrast, the left amygdala and PHG exhibited diminished reactivity during affective downregulation but increased reactivity during upregulation. Thus, the amygdala and PHG appear to show a particular sensitivity to the degree of experienced emotional intensity. It should be noted that the comparison between these overlapping regions is being made between an unequal number of studies, with only 12 upregulation studies compared to 47 downregulation studies. While the ALE method is designed to control for this discrepancy, and the functional specificity of these regions is consistent with previous work, we must interpret the functional role of the SFG and amygdala/PHG with caution, especially when comparing the results of downregulate and upregulate manipulations.

3.5. Reliance on memory to regulate

Regulating one's emotional state is a complex process that relies on a mechanism to organize and modify neural activity during emotional processing (i.e. top-down processing). In the current meta-analysis, we have seen several prefrontal cortical regions involved during affective modulation. Memory retrieval might also be an important element necessary to alter the current affective state. Previous meta analyses investigating anatomical regions associated with memory encoding and retrieval have reported increased activation in all regions identified by the present analysis, including the parahippocampal gyrus (PHG), amygdala, thalamus, ACC, PCC, SFG, midFG, and IFG (Kim, 2011; Owen et al., 2005; Rottschy et al., 2012; Spreng et al., 2009; Svoboda et al., 2006). It is

conceivable that future work may identify more specific evidence working and long-term memory mechanisms in which cognitive control structures drive emotional modulation, as reflected by subcortical structures such as the amygdala and thalamus, by incorporating memory retrieval mechanisms. It would also be interesting if these mechanisms change between reappraisal and suppression conditions.

3.6. Comparisons with other meta-analyses

Several informative meta-analyses of emotional regulation studies have been conducted in recent years. Diekhof and colleagues (2011) explored studies involving emotional downregulation, finding similar results to our own. Notably, the authors found increased activation in the ventromedial prefrontal cortex (vmPFC), whereas this was not the case in the present study. This may be due to the fact that fewer studies were incorporated in their analysis compared to our own (25 vs. 50). Additionally, the authors only included studies involving reappraisal conditions, excluding emotional suppression strategies.

More recently, a meta-analysis of emotional regulation was conducted using both reappraisal and suppression strategies (Kohn et al., 2014). The results were similar to the present meta-analysis, except an increase in amygdala activation was not found. While this study incorporated relatively few studies (23), the lack of an amygdala effect may be the result of the combined upregulate and downregulate increase contrast while not providing a downregulate decrease contrast.

A larger meta-analysis (48 studies) was conducted that also included both reappraisal and suppression emotional regulation strategies (Buhle et al., 2013). The results and structure of this study is similar to our own, although the authors use a different meta-analytic technique. However, our study is novel in that it is the only meta-analysis to date, to our knowledge, that includes a contrast in which enhanced emotional reactivity is assessed. This provides the unique ability to test how the direction of regulation alters the composition of brain structures involved in emotional regulation. It demonstrates, for example, that activity of the amygdala is reduced in downregulated states, and enhanced in upregulated states. Moreover, a subset of dorsal frontal structures associated with downregulation (left SFG, dorsal ACC, and SMA) also show evidence of activity during upregulation states. While tentative, this meta-analytic result provides support for a generalized mechanism of emotion regulation.

3.7. Limitations of ALE analysis

The clusters identified in the current meta-analysis are a result of ALE; a coordinate-based method. Unlike image-based analyses in which the complete activation maps are included, the data used here were based solely on reported peak activation coordinates. Therefore, we are unable to take into account all relevant hemodynamic information, the methodology of any given experiment, or determine how these influences would affect the current results. However, our conservative FDR and cluster size threshold help aid in interpretation. It should also be noted that the clusters identified were analyzed using conservative ALE thresholds. As such, there are certainly regions that did not meet our criteria that may be deemed functionally important.

An unequal number of studies contributed to the comparisons among our three functional contrasts. To help control for the effect these differences may have on cluster size, ALE analysis uses the number of participants contributing to each study to determine the degree of Gaussian smoothing of individual foci. The result of such smoothing is a decrease of ALE value magnitude for smaller experiments, increasing the difficulty to reach the significance threshold. Additionally, certain studies may have contributed multiple foci clustered in close proximity, which would theoretically increase their respective ALE values. However, this would also increase the null distribution and thus increase the statistical significance threshold for these regions (Eickhoff et al., 2012). The comparisons between regulation contrasts should still be interpreted with caution.

In summary, the present meta-analysis indicates two distinct sets of activity modulated brain regions during the downregulation of emotional content. Those that increase in activity, residing primarily in the frontal lobes, may be implicated in the cognitive control involved in changing one's subjective emotional state. Those regions that decrease, namely amygdala and IPL, may be sensitive to internal emotional states, and perhaps specialized for assessing affective qualia. The process of emotional regulation may thus be at least partially explained as an inhibitory effect of frontal regions on amygdala and IPL. Furthermore, all regions recruited during downregulation have been implicated in working memory tasks, which are potentially incorporated in the process of affective regulation. The current results may therefore reflect a cohesive system involving the interplay of discrete affective and regulatory mechanisms. Future work may tease apart the specific regulation strategies incorporated here.

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