

Neural correlates of preparatory and regulatory control over positive and negative emotion

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This study used functional magnetic resonance imaging to investigate brain activation during preparatory and regulatory control while participants ($N = 24$) were instructed either to simply view or decrease their emotional response to, pleasant, neutral or unpleasant pictures. A main effect of emotional valence on brain activity was found in the right precentral gyrus, with greater activation during positive than negative emotion regulation. A main effect of regulation phase was evident in the bilateral anterior prefrontal cortex (PFC), precuneus, posterior cingulate cortex, right putamen and temporal and occipital lobes, with greater activity in these regions during preparatory than regulatory control. A valence X regulation interaction was evident in regions of ventromedial PFC and anterior cingulate cortex, reflecting greater activation while regulating negative than positive emotion, but only during active emotion regulation (not preparation). Conjunction analyses revealed common brain regions involved in differing types of emotion regulation including selected areas of left lateral PFC, inferior parietal lobe, temporal lobe, right cerebellum and bilateral dorsomedial PFC. The right lateral PFC was additionally activated during the modulation of both positive and negative valence. Findings demonstrate significant modulation of brain activity during both preparation for, and active regulation of positive and negative emotional states.

Keywords: cognitive control; positive emotion; negative emotion; fMRI; brain

INTRODUCTION

Cognitive control of emotion refers to the process by which individuals voluntarily regulate their emotional states (Gross, 1998). The inability to regulate emotional responses has been identified as a critical contributor to inappropriate social behaviors (Karrass *et al.*, 2006) as well as various mental disorders, including impulsive aggression (Davidson *et al.*, 2000) and depression (Johnstone *et al.*, 2007). Previous research has demonstrated that efforts to consciously control emotional states such as erotic arousal (Beauregard *et al.*, 2001), sadness (Levesque *et al.*, 2003), fear (Hariri *et al.*, 2003) and negative affect more broadly (Ochsner *et al.*, 2002, 2004; Phan *et al.*, 2005) produce significant effects on neural systems. In general, such studies have reported increased activity in the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) as well as reduced activity in the amygdala during cognitive control. For example, increased activity in the lateral and medial PFC was found during the downregulation of negative emotion in conjunction with attenuated report of negative affect (Ochsner *et al.*, 2002). Another study examining the voluntary suppression of sadness found that the right orbitofrontal cortex (OFC) and lateral PFC were activated (Levesque *et al.*, 2003). Additionally, increased prefrontal and ACC activation as well as reduced amygdala activity were observed in a study examining the regulation of responses to fearful stimuli (Hariri *et al.*, 2003) and in other studies during the downregulation of negative affect (Phan *et al.*, 2005; Urry *et al.*, 2006). In sum, studies to date have demonstrated consistent effects of emotion regulation on activity in underlying neural systems.

Although prior work has been successful in identifying changes in brain activity associated with emotion regulation, it has not fully

addressed the regulatory process, being limited in two major aspects. First, studies to date have not examined brain activation effects associated with preparatory control for emotion regulation. Preparation prior to upcoming emotional events can be viewed as an adaptive coping mechanism that facilitates planned action, and some available data provide evidence of distinct neural systems associated with preparatory control (MacDonald *et al.*, 2000; Braver *et al.*, 2009). Thus, a need exists for further investigation of preparatory effects in the context of emotional regulation.

Second, previous studies have generally included only a single category of affective stimuli (most typically negative), so that direct comparisons of neuronal activity associated with the regulation of positive versus negative emotion are limited. Thus far, only one study has compared positive and negative emotions within a task, detecting bilateral PFC activation during regulation of both positive and negative emotion, while showing selective activation in ventromedial PFC (VmPFC) and ACC regions during the downregulation of negative as compared with positive emotion (Kim and Hamann, 2007). These findings highlight the need for further research directed at elucidating the brain systems underlying regulation of positive and negative emotion. In particular, the control of positive emotion is crucial in understanding problem behaviors, as difficulty regulating positive affect or appetitive reactivity is often associated with pathological conditions such as mania (Elliott *et al.*, 2004) or addictive disorders (Koob and Le Moal, 2001). There is also evidence that distinct but interacting neural systems are involved in processing of positive as compared with negative emotional stimuli (Ahern and Schwartz, 1985; Davidson and Irwin, 1999; Carver, 2001) and in affect-related individual differences (Davidson, 1998). Thus, further studies using both positive and negative affective stimuli within the same processing task are needed to advance understanding of brain systems underlying emotion regulation.

With these considerations in mind, this study was designed to investigate brain systems involved in the regulation of positive and negative emotion using functional magnetic resonance imaging (fMRI). The study extended prior work by examining activity in

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differing brain regions during preparatory and regulatory phases of an emotion regulation task in which participants were instructed either to simply view, or to decrease emotional reactions to, positive and negative affective stimuli. As our emotion regulation procedure, we utilized cognitive reappraisal as documented in previous studies (Ochsner *et al.*, 2002, 2004), and for preparatory control, we utilized a variant of a naturalistic prospective-memory procedure entailing active remembering and preparing to implement an intended action in an upcoming event (Simons *et al.*, 2006).

Based on prior research findings (MacDonald *et al.*, 2000), we hypothesized that the left lateral PFC, especially dorsolateral PFC (DLPFC), would be selectively activated during the preparatory phase in which attentional control would be expected to predominate. In addition, during the emotion regulation phase, we expected to find bilateral activations in subdivisions of PFC (ventromedial, orbito-frontal and dorsolateral) and in ACC, regions known to be involved in on-line emotion regulation (Ochsner *et al.*, 2002, 2004; Kim and Hamann, 2007) and response conflict monitoring (Botvinick *et al.*, 1999). We also hypothesized that distinct brain regions, such as the VmPFC and ACC (Kim and Hamann, 2007), would be differentially involved in the regulation of positive versus negative emotion. Regarding modulatory effects of regulation on subcortical regions, we expected, on the basis of prior research (Beauregard *et al.*, 2001; Ochsner *et al.*, 2002, 2004; Levesque *et al.*, 2003), to observe reduced activity in the amygdala. In addition, we examined the ventral striatum (VS) in view of evidence for its involvement in positive emotion (Everitt *et al.*, 2000; Knutson *et al.*, 2001), although previous studies have generally not reported changes in this region (for an exception, see Phan *et al.*, 2005).

MATERIALS AND METHODS

Participants

Participants were 24 right-handed females (age: $M = 19.58$ years, $s.d. = 1.21$ years) recruited from undergraduate psychology classes and from an advertisement in the student newspaper. Female subjects were recruited exclusively for this study to circumvent moderating effects of gender on responses to emotional stimuli (Cahill *et al.*, 2001; Seo *et al.*, 2011). All individuals included in the study had normal or corrected-to-normal vision, and were free of hearing impairments or major psychiatric disorders. The study procedures were approved by the Institutional Review Board at the University of Minnesota, and participants provided informed written consent prior to initiation of testing. Compensation for participation consisted either of course credit or a cash payment of \$52.

Experimental stimuli

The task stimuli consisted of 150 positive (60), neutral (30), negative (60) pictures selected from the International Affective Picture System (IAPS; Lang *et al.*, 1999). Positive and negative picture sets were matched

for arousal ($M_s = 5.70$ and 5.86 , respectively, versus 3.09 for neutral pictures; $s.d. = 0.75, 0.90$ and 0.68) based on IAPS rating norms (Lang *et al.*, 1999), as a whole and across instructional conditions (view, decrease). Mean normative ratings of valence (pleasantness) for positive, negative and neutral picture categories were $7.52, 2.47$ and 4.91 , respectively ($s.d. = 0.66, 0.74$ and 0.33). The pictures of the same valence type were also counterbalanced across instruction conditions (decrease, view). Picture stimuli were presented in 6 blocks of 25 trials. To more effectively isolate brain activity associated with preparation for regulation of positive versus negative emotion, positive and negative picture stimuli were presented in separate blocks (3 positive blocks and 3 negative blocks). Neutral pictures were also included in blocks of each type, but only within the view condition. The order of positive blocks and negative blocks was counterbalanced across participants, such that half started with a positive block and the other half started with a negative block. Participants were not cued at the beginning of each block and thus were unaware of the valence of upcoming blocks. For each of five conditions (positive–decrease, positive–view, negative–decrease, negative–view and neutral–view), 30 pictures were presented. Each picture was presented only once and the order of picture presentation was randomized within blocks and across participants.

Task

Each task trial consisted of four stimulus events (Figure 1). An event-related design was used that included a “time-jitter” technique to effectively differentiate blood-oxygen-level dependent (BOLD) activity and to separate events of interest within a trial (Dale, 1999). First, an instructional cue (V for view, or D for decrease) appeared for 500 ms, followed by a jittered inter-stimulus interval that varied from 2.5 to 4.5 s (mean = 3.5 s). Participants were instructed to actively prepare to regulate emotion when a “D” cue was presented and to simply view the picture without making an effort when a “V” cue was presented. Specifically, participants were asked to prepare to reappraise their emotional responses to pictures during an upcoming presentation period, by rehearsing the preparatory cue (signaling the downregulation by reappraisal) during decrease trials. Second, a picture appeared for 7.5 s, at which point participants implemented the prior instructional cue, followed by a variable interval ranging from 1.5 to 3.5 s (mean = 2.5 s). In “decrease” trials, participants were instructed to decrease their emotional states using a reappraisal strategy, which was rehearsed before the scanning session. The reappraisal strategy entailed reinterpreting the actions, feelings and outcomes of the people or scenarios depicted in the emotional pictures to attenuate emotional reactions evoked by the pictures (Gross, 1998; Ochsner *et al.*, 2002, 2004). Following this, an affective valence rating scale (self-assessment manikin; Lang, 1980) appeared, consisting of numbered options ranging from 1 (very negative) through 9 (very positive). The participant pressed buttons to register a rating of valence (2–4 secs, depending on individual speed). At the end of the trial, a fixation cross appeared for the duration of a jittered

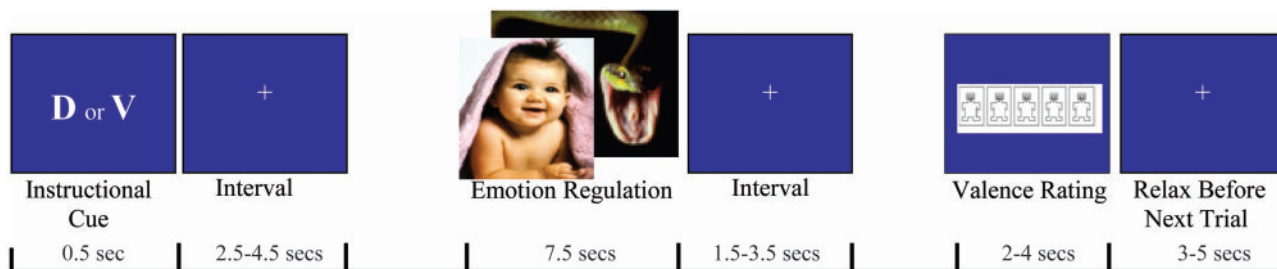


Fig. 1 Schematic time course of a single trial. Participants were instructed to view or to decrease their emotional states in response to a series of pictures using a reappraisal strategy. D, decrease; V, view.

inter-trial interval (mean 4 s, range 3–5 s), during which participants relaxed until the onset of the next trial.

Procedure

Three to four days prior to scanning, participants received a 1.5 h training session on reappraisal strategies and preparatory control for the emotion regulation task. The training procedure was standardized across participants. Participants completed a block of 25 practice trials using stimuli different from those employed in the main experiment. The MRI session took place at the University of Minnesota's Center for Magnetic Resonance Research, using a 3.0 Tesla Siemens Trio scanner. The scan session lasted approximately 1.5 h, with 1 h devoted to the fMRI task and 30 min for set-up and structural MRI scanning. While in the scanner, participants used a mirror mounted above the head coil apparatus to view images projected onto a screen.

Data acquisition

Standard T_1 -weighted anatomical image volumes were first acquired using a 3D Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence (1 mm isotropic voxels). Functional images were then collected using an 8-channel phased array coil. The functional data were acquired using an Echo-Planar Imaging pulse sequence (36 slices, slice thickness = 2 mm with a 1.5-mm gap; field of view = 22.4×22.4 cm, matrix size = 64×64 for a nominal resolution of 3.5 mm; TE = 28 ms; TR = 2 s; flip angle = 80 degrees). Slice orientation was oblique, roughly aligned with a line connecting the base of the cerebellum with the base of the frontal lobe. This orientation was used to obtain optimal signal-to-noise ratio in the OFC (Deichmann et al., 2003) and amygdala (Chen et al., 2003).

Data analysis

Affective ratings were analyzed using a two-way repeated measures analysis of variance (ANOVA), in which picture valence (positive, negative) and instructional condition (decrease, view) were included as within-subject factors. Follow-up *t*-tests were used to clarify the basis of significant effects. A one-way repeated measure ANOVA was used to evaluate effects for picture valence (positive, neutral and negative) within the view condition.

Preprocessing of fMRI data was conducted using the FSL suite from the Oxford FMRI software library. The data were motion corrected using MCFLIRT (Jenkinson et al., 2002). Functional images were spatially smoothed using a 5 mm Gaussian kernel and temporally high-pass filtered. General linear model analyses were employed to examine the imaging data, and each event was modeled using a double-gamma function. High-resolution anatomical images were spatially normalized and registered to the Montreal Neurological Institute (MNI)-152 template using FLIRT. For group analysis, a 2×2 repeated measures ANOVA was conducted on individual beta weights (decrease–view) to evaluate main effects of emotional valence (positive, negative) and regulation phase (preparation, regulation) and their interaction. As a follow-up to this, simple effect analyses (*t* tests) were conducted to clarify the sources of effects that emerged as significant. In addition, conjunction analyses were performed to identify brain regions commonly involved in levels within each main effect (valence, regulation phase), collapsing over the levels of the other factor. To correct for multiple comparisons, the Family Wise Error rate (FWE) correction was implemented such that a FWE cluster corrected, significance threshold of $Z > 2.3$ with $P < 0.05$ (Worsley et al., 1992; Friston et al., 1994) was applied across all analyses within FSL. Significant activations identified with cluster corrections are displayed in figures as a color overlay on the Colin27 Brain T_1 -weighted anatomy in MNI space (Holmes et al., 1998). To examine the effects of emotion regulation

on activity in subcortical regions, two brain regions corresponding to specific regions of interest (ROIs) were defined *a priori* based on prior research (Ochsner et al., 2002; Levesque et al., 2003; Phan et al., 2005), and we additionally examined activity in ROI regions based on small volume corrections; these regions included amygdala, and VS as defined by Harvard–Oxford atlases.

RESULTS

Affective valence ratings

For the two-way repeated-measures ANOVA, significant effects were found for both picture valence [$F(1,23) = 73.62$, $P < 0.001$] and instruction [$F(1,23) = 30.8$, $P < 0.001$] (Figure 2). Additionally a Valence \times Instruction interaction was evident [$F(1,23) = 120.35$, $P < 0.001$]. For negative picture stimuli, participants showed reduced ratings of unpleasantness for the decrease condition compared with the view condition [$t(23) = 9.82$, $P < 0.001$]. For positive picture stimuli, diminished ratings of pleasantness were evident for the decrease condition compared with the view condition [$t(23) = -11.13$, $P < 0.001$]. Additionally, the magnitude of the instructional effect (decrease–view) on affective ratings was greater for positive than for negative pictures [$t(23) = 5.55$, $P < 0.001$], suggesting more effective regulation of positive emotion than negative emotion. Additionally, a one-way repeated measures ANOVA comparing valence ratings during the viewing of positive, neutral and negative pictures yielded a significant effect [$F(1,23) = 270.55$, $P < 0.001$], with follow-up tests indicating enhanced and diminished ratings of valence, respectively, for positive and negative pictures in relation to neutral [$t(23) = 12.85$ and -16.6 , $P < 0.001$].

Brain imaging results

Repeated measures ANOVA

The results of the 2×2 repeated measures ANOVA conducted on decrease–view (Figure 3 and Table 1) indicated meaningful modulatory effects in the form of significant main effects of valence (positive, negative) and regulation phase (preparation, regulation), along with an interaction effect ($P < 0.05$, whole-brain FWE corrected). The main effect of valence was significant in the right precentral gyrus, with

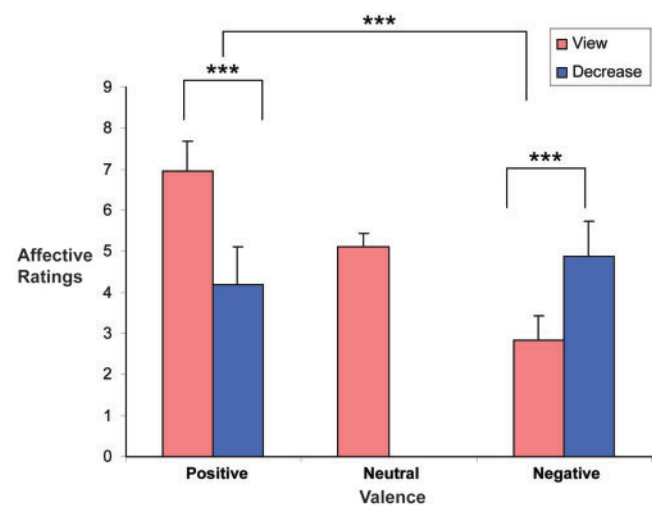


Fig. 2 Mean self-reports of affect ratings for positive, neutral and negative emotion. On the affective rating scale, 9 was the most positive and 1 the most negative. Relative to the view condition, pleasantness during the decrease condition was significantly reduced for positive emotion and unpleasantness was diminished for negative emotion, suggesting successful modulation of both positive and negative emotion. The magnitude of positive valence modulation (decrease–view) was significantly greater than negative valence modulation (decrease–view). *** $P < 0.001$.

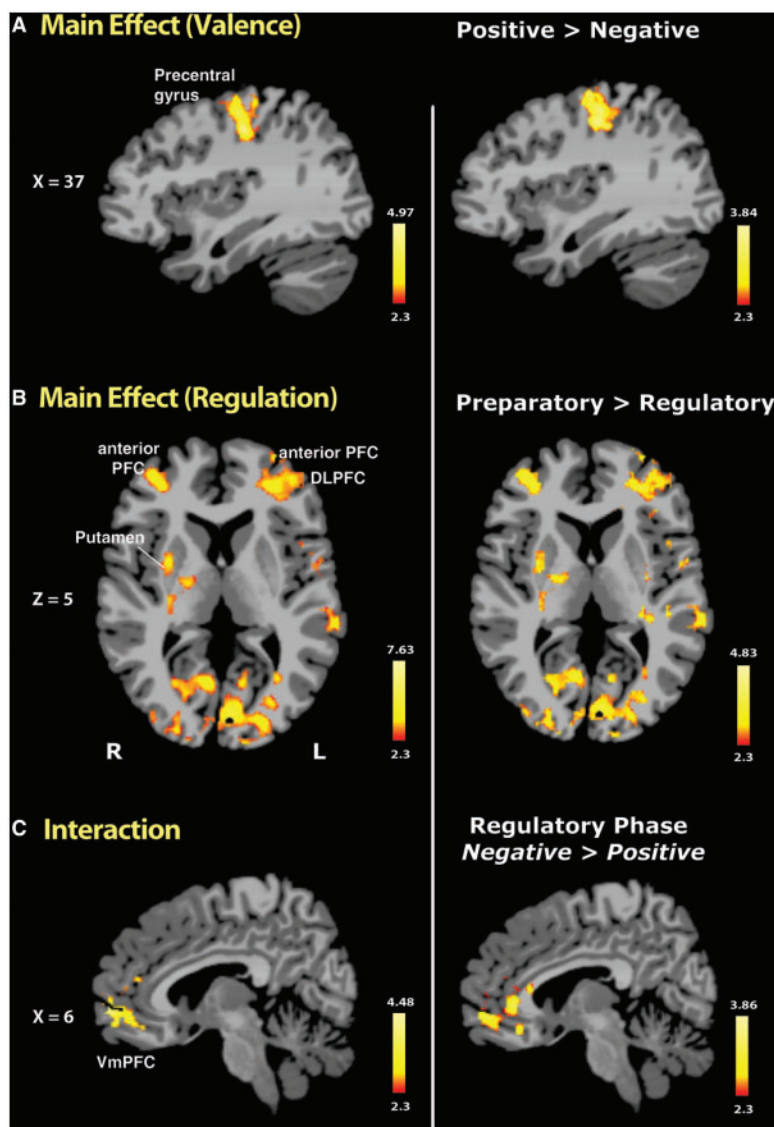


Fig. 3 Whole brain voxel-based fMRI images showing valence (positive, negative) \times regulation phase (preparation, regulation) main effects and an interaction (left panel; $P < 0.05$, whole-brain FWE corrected) and corresponding simple effects (right panel; $P < 0.05$, whole-brain FWE corrected). (A) A main effect of valence was evident in right precentral gyrus, with greater activity during positive than negative emotion regulation. (B) A main effect of regulation phase was shown in the bilateral anterior PFC, left DLPFC, right putamen and thalamus, precuneus, superior/middle temporal and occipital lobes, with greater activity in these regions during preparatory than regulatory control. (C) A valence \times regulation phase interaction was shown in the VmPFC and ACC with greater activity during negative than positive emotion regulation, but only in the regulatory phase (not preparation). L, left; R, right. Coordinates are given in MNI space.

simple effects analysis revealing greater activity in this region during positive than negative regulation ($P < 0.05$, whole-brain FWE corrected). The main effect of regulation phase was evident in the bilateral anterior PFC (BA 10), left DLPFC (BA 9/46), precuneus, posterior cingulate cortex, right putamen and selected areas of left superior/middle temporal gyrus (TG), occipital lobe and cerebellum. Simple effects analysis revealed greater activity in these regions during the preparatory phase compared with the regulatory phase, and none of these regions were found to be more active during the regulatory than the preparatory phase. The two-way interaction effect was also significant for the VmPFC and ACC regions, with simple effects analysis indicating significantly greater activity in the VmPFC/ACC during negative than positive emotion regulation, during the active regulation phase but not the preparatory phase.

Conjunction analyses

The results of conjunction analyses indicated that selected areas of the PFC, temporal and parietal lobes were commonly involved in different

types of regulation ($P < 0.05$, whole-brain FWE corrected; Figure 4 and Table 2). The analyses were conducted on the levels of each main effect (valence, regulation phase), averaging over the levels of the other factor. Brain regions that showed common activation during the regulation of both positive and negative emotion included the bilateral PFC (ventrolateral and dorsolateral), dorsomedial PFC, right cerebellum and the left side of the superior/middle temporal and inferior parietal lobes. Further, during both preparatory and regulatory controls, left-lateralized PFC (ventrolateral and dorsolateral), superior/middle temporal and inferior parietal lobes, along with bilateral dorsomedial PFC and right cerebellum, were commonly activated.

Modulation of activity in subcortical ROI

To examine activity in specific *a priori* subcortical regions (amygdala and VS) in relation to regulatory control, two-way repeated measures ANOVAs were performed in which valence (positive/negative) and instruction condition (decrease/view) as included as within subject factors (Figure 5). Laterality (left, right) was not included in this analysis, as

Table 1 Significant brain activation showing main effects and interaction (decrease-view)

Regions	Lat	BA	2 × 2 ANOVA						Simple effects					
			Z	Coordinates			Volume (mm ³)	Z	Coordinates			Volume (mm ³)		
				X	Y	Z			X	Y	Z			
Main effect (valence)												Positive > negative		
Precentral gyrus	R	4, 6	4.97	36	-22	44	4904	3	35	-23	53	3 227		
Main effect (regulation phase)												Preparatory > regulatory		
Lateral anterior PFC/DLPFC	L	10, 9, 46	3.51	-31	48	16	14 776	3	-29	45	17	14 421		
Lateral anterior PFC	R	10	3	31	50	16	5163	2.9	32	49	13	3219		
Putamen/thalamus	R	—	3.1	23	-7	8	7951	2.93	26	-10	4	7364		
Superior/middle TG	L	21, 22	3	-58	-21	-1	7769	2.85	-52	-23	5	7811		
Posterior cingulate cortex/MFG	L, R	6, 23, 24, 31	3.04	9	-23	53	29 932	2.9	9	-25	47	29 300		
Precuneus/occipital lobe/cerebellum	L, R	7, 17, 18	3.56	-2	-72	-2	94 942	3.05	-1	-72	-5	82 175		
Interaction												Negative > positive (regulation phase)		
VmPFC/ACC	L, R	10, 11, 32	3	8	54	-2	4248	2.8	-1	45	-4	6449		

$P < 0.05$, whole-brain FWE corrected. Lat, Laterality; L, left; R, right; BA, Brodmann's area. MNI coordinates were used. MFG, middle frontal gyrus.

preliminary tests revealed no significant hemispheric effects for either the amygdala or VS. For the amygdala, a significant main effect was found [$F(1,23) = 10.7$, $P < 0.01$] indicating a general decrease in amygdala activity during the regulation of emotion [$t(23) = -3.27$, $P < 0.01$] as compared with the view condition. The magnitude of this regulatory effect was similar for positive and negative picture stimuli [$t(23) = -2.98$ and -2.29 , respectively, $P < 0.05$]. No main effect of valence or two-way interaction effect (instruction × valence) was found.

For the VS region, the analysis revealed significant main effects of instruction [$F(1,23) = 10.73$, $P < 0.01$] and valence [$F(1,23) = 27.75$, $P < 0.001$], but no instruction × valence interaction. Ventral striatal activity was significantly greater during positive than negative picture trials [$t(23) = 4.5$, $P < 0.001$]. Further, ventral striatal activity was decreased significantly during the regulation of emotion [$t(23) = -3.28$, $P < 0.01$] as compared with the view condition. This regulatory effect was evident for both positive [$t(23) = -2.97$, $P < 0.01$] and negative [$t(23) = -2.0$, $P = 0.058$] pictures.

To compare activity in the amygdala and VS regions during the viewing of positive, neutral and negative pictures, one-way repeated measures ANOVAs were conducted (Figure 5). For the amygdala, significant main effects were found [$F(1,23) = 16.63$, $P < 0.001$], with greater activity observed during viewing of both positive [$t(23) = 5.74$, $P < 0.001$] and negative [$t(23) = 4.94$, $P < 0.001$] pictures relative to neutral pictures. No difference in amygdala activation was found between positive and negative pictures. A significant effect was also evident for the VS [$F(1,23) = 16.37$, $P < 0.001$], with activity in this region significantly greater during viewing of positive pictures relative to both neutral [$t(23) = 5.41$, $P < 0.001$] and negative pictures [$t(23) = 4.51$, $P < 0.001$]. Neutral and negative pictures did not differ in terms of activity in the VS.

Correlational analysis

To understand the relationship between functionally defined ROIs and modulation of perceived emotional experience, mean signal changes in brain regions showing task-related activations (Figures 3 and 4 and Tables 1 and 2) were independently correlated with modulated affective ratings. Results indicated that activity during preparatory control in the bilateral anterior PFC (aPFC) (Figure 3B) and left ventrolateral PFC (VLPFC) (Figure 4B) showed significant correlations with

reduced affective ratings (Figure 6). There was no significant correlation between brain activity during the regulatory phase and modulation of ratings. As the association with ratings was found for the preparatory control phase in the main effect and the conjunction map, the results of correlations focused on mean signal changes for brain regions collapsed across the levels of the valence factor.

During preparatory control, increased right aPFC (BA 10) was significant associated with reduced pleasantness in relation to positive stimuli ($r = -0.52$, $P = 0.01$) and reduced unpleasantness in relation to negative stimuli ($r = 0.50$, $P = 0.013$). Increased left aPFC/DLPFC (BA 9/10/46) and left VLPFC activity (BA 47) were also associated with reduced pleasantness ratings for positive stimuli ($r = -0.46$ and -0.42 , respectively, $P < 0.05$) and trend-level reductions in unpleasantness ratings for negative stimuli ($r = 0.40$ and 0.39 , respectively, $P = 0.056$ and 0.058). No outliers were found in these associations. To examine whether the predictive strength of brain activity in these regions differed for positive versus negative ratings, the difference in absolute r values for the two was tested using Steiger's Z test. No significant difference was found in the r for right aPFC ($Z = 0.21$, $P = \text{n.s.}$), left aPFC/DLPFC ($Z = 0.60$, $P = \text{n.s.}$) or left VLPFC ($Z = 0.3$, $P = \text{n.s.}$), indicating a comparable level of modulation for positive and negative ratings. There were also no correlations between task-related brain activity and responses of the amygdala and VS.

DISCUSSION

This study used fMRI to investigate brain systems involved in preparatory and regulatory control over positive and negative emotion. The results demonstrate differential activity in specific brain regions during preparatory as compared with active emotion regulation phases, as well as differential activity between the regulation of positive and negative emotional states. Emotion modulatory effects were also evidenced by reduced activation in the amygdala and VS along with reduced subjective ratings of pleasantness and unpleasantness for positive and negative pictures, respectively. These findings help to elucidate mechanisms underlying preparatory and regulatory control of emotion by showing common and differential brain regions associated with these processes.

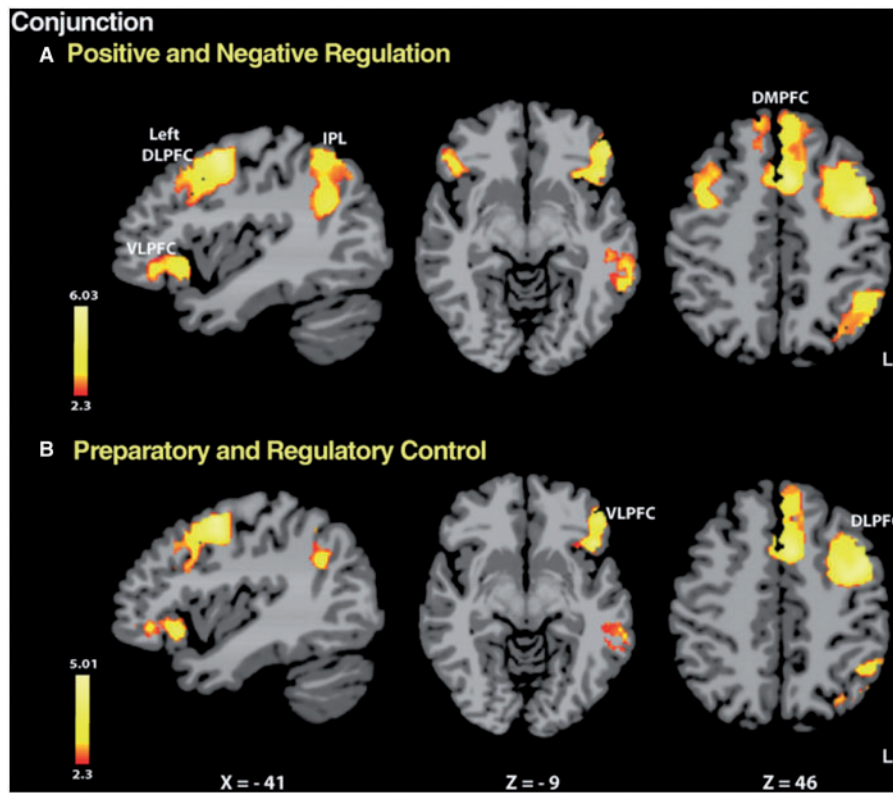


Fig. 4 Results of conjunction analyses for two main effects. (A) valence (positive and negative) and (B) regulation phase (preparation and regulation), collapsing across levels of the other factor ($P < 0.05$, whole-brain FWE corrected). During differing types of control, selected areas of the lateral PFC, dorsomedial PFC and left superior/middle temporal and inferior parietal lobes were commonly activated. Specifically, (A) during the regulation of both positive and negative emotion, bilateral PFC activity was displayed, whereas (B) during both preparatory and regulatory control, left lateral PFC activity was found. DMPFC, dorsomedial PFC; IPL, inferior parietal lobe; L, left. Coordinates are given in MNI space.

Table 2 Results of conjunction analyses (decrease-view)

Regions	Lat	BA	Positive and negative regulation				Preparatory and regulatory control					
			Z	Coordinates			Volume (mm ³)	Z	Coordinates			Volume (mm ³)
				X	Y	Z			X	Y	Z	
Lateral PFC (ventro/dorsolateral)	L	47, 44/45, 6/8/9	3.66	-41	16	27	31 209	3.36	-41	15	27	24 355
	R	47, 45, 6/8/9	3	43	17	37	4499	—	—	—	—	—
Dorsomedial PFC/middle CG	L, R	6/8/9, 32	3.6	-4	24	49	29 544	3.37	-4	22	50	21 680
Temporo-parietal regions	L	21/22, 39/40	3.38	-51	-50	20	18 185	3.17	-54	-48	15	10 898
Cerebellum	R	—	3.24	26	-72	-35	8569	3.21	26	-71	-34	5397

$P < 0.05$, whole-brain FWE corrected. MNI coordinates were used. Lat, laterality; L, left; R, right; BA, Brodmann's area; CG, cingulate gyrus. Temporo-parietal regions include superior/middle TG and inferior parietal lobe.

First, brain regions commonly involved in different types of control (preparatory and regulatory; positive and negative) were found, including the left-lateralized PFC, inferior parietal and superior/middle temporal lobes, dorsomedial PFC and right cerebellum. The concomitant involvement of these regions suggests potentially shared neural networks during different types of cognitive control entailing reappraisal. Specifically, increased activity in the left lateral PFC (ventro- and dorsolateral) was evident for different types of regulation. Emotion regulation requires implementation of regulatory instructions to modulate emotional response, which may primarily involve modulatory activity exerted in the left DLPFC and VLPFC, as indicated by prior neuroimaging studies of cognitive reappraisal (Ochsner *et al.*, 2002, 2004; Kim and Hamann, 2007). Specifically, the DLPFC is known to mediate cognitive control via goal representation and

guidance of planned behavioral actions (Miller and Cohen, 2001). In particular, previous studies have reported that the left DLPFC plays a crucial role in cognitive control during both preparation (MacDonald *et al.* 2000; Braver *et al.*, 2009) and online emotion regulation (Ochsner *et al.*, 2002), suggesting a central role of this region in differing phases of cognitive control.

The VLPFC is involved in the implementation of intended goals and interacts with the medial PFC/OFC to modulate emotional responses in limbic regions (Sakagami and Pan, 2007). Moreover, in the current data, increased left VLPFC activity during preparatory control was associated with reduced affective ratings, suggesting a relationship between the left VLPFC and perceived experience of emotional modulation. This observed association may reflect the contribution of the VLPFC to implementation of controlled behaviors, by serving as a

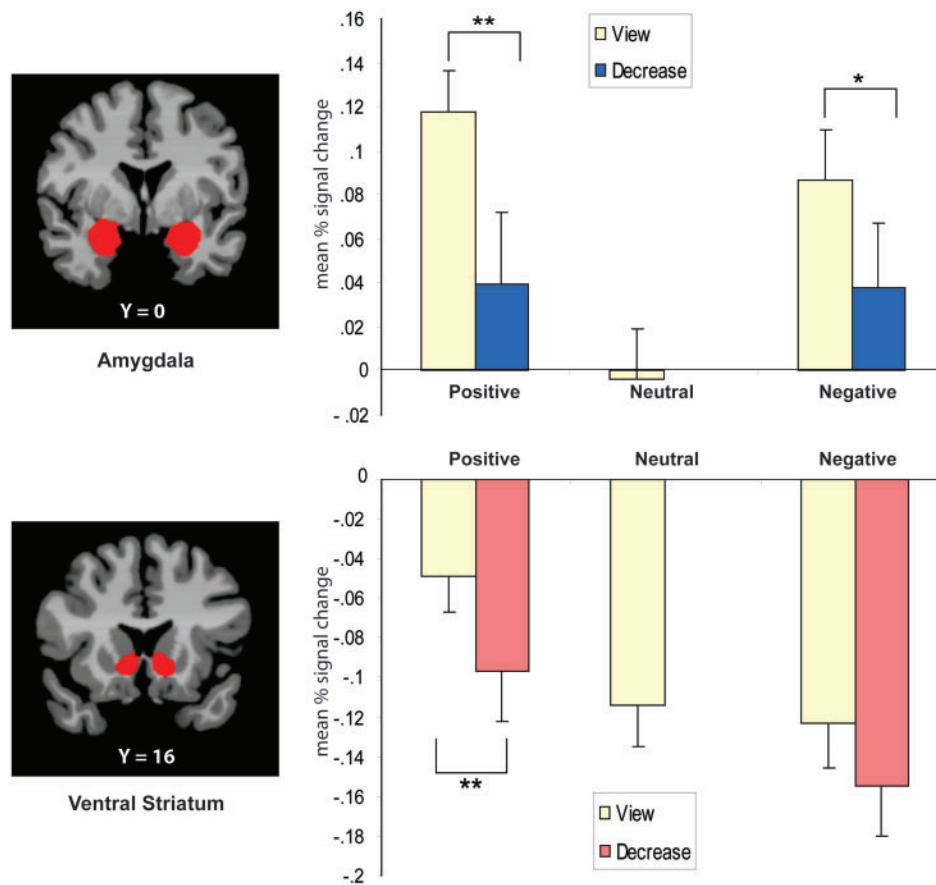


Fig. 5 Means and standard errors of mean for signal changes of the amygdala and VS during view and decrease conditions for positive, neutral and negative trials. During positive emotion regulation, the activity in the amygdala and VS was diminished compared with the view condition. During negative emotion regulation, amygdala activity was reduced relative to the view condition. Brain images show the amygdala and VS of the Harvard–Oxford structural atlas from which mean signal changes were obtained. MNI coordinates were used. * $P < 0.05$, ** $P < 0.01$.

bridge between cognition and emotion (Gray *et al.*, 2002; Sakagami and Pan, 2007). Notably, the left VLPFC demonstrates a specific association with cognitive control through language-based, semantic processing (Badre and Wagner, 2007), providing a plausible explanation for the left-specific VLPFC activation during preparatory and regulatory control phases in our task.

In addition, enhanced left-lateralized activity was noted in the inferior parietal lobe and superior/middle TG. The left inferior parietal lobe is known to play a role in inhibitory control (Bellgrove *et al.*, 2004) and mood regulation (Koven *et al.*, 2010). The TG and Broca's area—regions involved in language and semantic processing as well as storytelling (Bartha *et al.*, 2003; Steinworth *et al.*, 2005)—were also activated. During the preparatory phase, participants were instructed to rehearse the instructional cue to maintain focused control, an activity expected to recruit language-processing regions. During the active emotion regulation phase, participants were instructed to utilize reappraisal strategies, which may also entail semantic-linguistic processing involving the TG and Broca's area. These findings are in turn consistent with those of previous studies utilizing reappraisal strategies (Ochsner *et al.*, 2002, 2004; Kim and Hamann, 2007). More specifically, left-lateralized TG activation has been demonstrated during the processing of verbalizable materials, whereas the right side is implicated more in the processing of visual-spatial information (Golby *et al.*, 2001; Weintrob *et al.*, 2002).

The dorsomedial PFC has been associated with higher cognitive function related to mental operations during verbal processing (Hanakawa *et al.*, 2002), impression formation (Mitchell *et al.*, 2004), monitoring and adjustment of action plans (Nachev *et al.*,

2005), and the generation of response strategies (Matsuzaka *et al.*, 2012). Accordingly, increased dorsomedial PFC activity can be interpreted as reflecting higher cognitive operations while exerting regulatory efforts. The role of the cerebellum in cognitive and emotional processing has also been noted. For example, Krienen and Buckner (2009) concluded that cerebellar activity typically occurs contralaterally to affiliated cortical activity during emotion and cognition processing (Krienen and Buckner, 2009). This pattern could account for the occurrence of right cerebellar activity in our task. This result also coincides with work showing left PFC activity accompanied by right cerebellar activity during a cognitive task involving semantic processing (Roskies *et al.*, 2001). In sum, our finding of concurrent activity in left-lateralized PFC, temporal and inferior parietal lobes, and right cerebellum under different types of regulatory demands indicates that these regions may operate together to orchestrate higher order executive function and implement regulation of emotional processes.

In addition to the brain regions discussed above, right lateral PFC activity was also evident during the regulation of both positive and negative emotional valence, displaying bilateral activation. Bilateral PFC activation has also been reported in previous studies investigating the downregulation of positive and negative emotion (Kim and Hamann, 2007), as well as in a study that focused on negative emotion only (Ochsner *et al.*, 2004). Other work has shown that emotion (both positive and negative) plays a role in orienting attention through elicitation of arousal (Lang, 2010), suggesting that the right PFC may be related to modulation of the arousal component of emotion. In support of this, Dichter and Belger (2008) found the right lateral

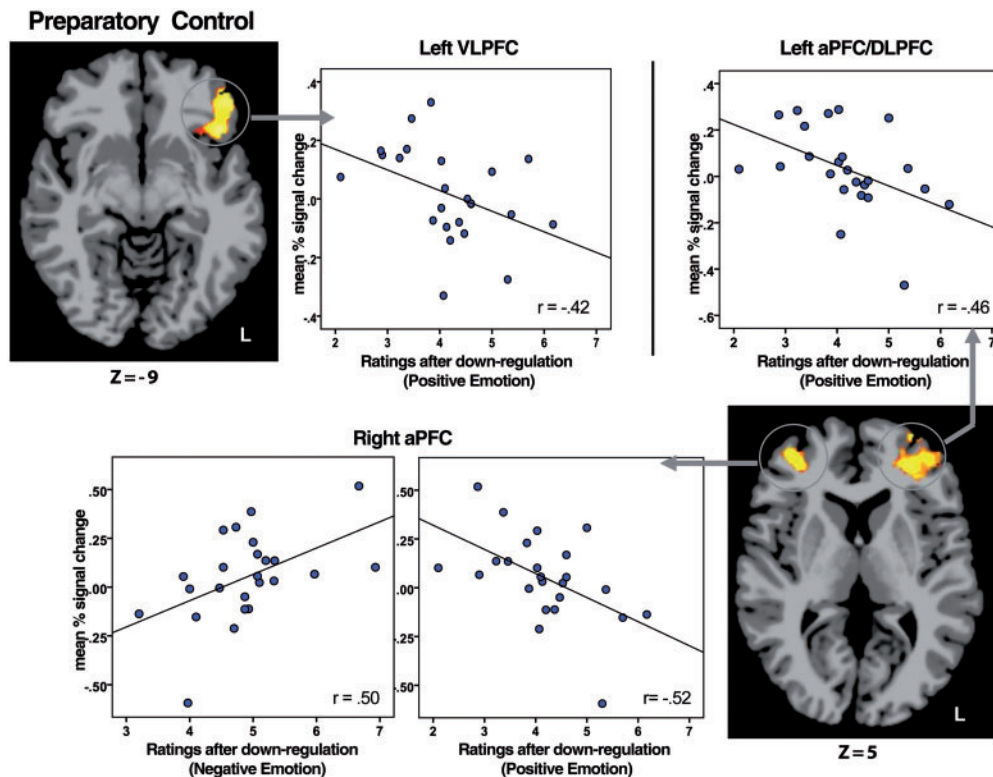


Fig. 6 Associations between brain activity during preparatory control and modulation of affective ratings (1 = most negative; 9 = most positive). During preparatory control, increased activity in the left VLPFC ($r = -0.42$, $P < 0.05$) and left anterior PFC/DLPFC ($r = -0.46$, $P < 0.05$) was associated with reduced ratings of pleasantness following downregulation of positive emotion. Increased right anterior PFC activity was also significantly associated with reduced pleasantness of positive pictures ($r = -0.52$, $P = 0.01$) and with reduced unpleasantness of negative pictures ($r = 0.50$, $P = 0.013$) following downregulation. No outliers were found in these associations. L, left. Coordinates are given in MNI space.

PFC to be selectively activated during the regulation of highly arousing emotional pictures regardless of valence. Previous studies have also demonstrated increased right PFC activation during the inhibition of affective response to both pleasant and unpleasant stimuli including erotic images (Beauregard *et al.*, 2001), sadness inductions (Levesque *et al.*, 2003) and fearful stimuli (Hariri *et al.*, 2003), indicating a role of the right lateral PFC in modulation of both positive and negative emotion.

This study also indicated valence-specific brain regions of emotion regulation. When trials involving regulation of positive emotion were compared with those involving negative emotion, the right precentral gyrus was preferentially activated. Positive or reward stimuli are known to elicit appetitive motivation and action (Lang, 2010) and activate limbic and motor regions (Roesch and Olson, 2003). The premotor cortex is involved in the modulation of motivation and reward (Roesch and Olson, 2003; Roesch and Olson, 2004) and goal-directed action control (Christensen *et al.*, 2007; Pastor-Bernier *et al.*, 2012). In particular, the right precentral gyrus has been associated with modulation of sustained attention (Cabeza and Nyberg, 2000), self-related awareness (Theoret *et al.*, 2004) and greater use of cognitive reappraisal (Leung and Lee, 2012). Based on this, it can be inferred that participants in the current study were more engaged in modulating affect-driven attention through reappraisal during positive stimulus blocks.

In addition, distinct brain regions (VmpFC/ACC) differentiating the regulation of negative from positive emotion were found, but only during the active emotion regulation phase, suggesting that online processing of emotional stimuli is necessary to differentially activate these regions. This result is consistent with previous work demonstrating greater involvement of the medial division of anterior PFC;

BA 10) in processing of externally presented stimuli (Burgess *et al.*, 2005; Gilbert *et al.*, 2005). The VmpFC also has dense anatomical connections with the amygdala and exerts inhibitory influence on this region (Cavada *et al.*, 2000; Fisher *et al.*, 2009). It follows that the observed modulation in the VmpFC/ACC may be associated with regulation of limbic activation triggered by external stimuli, especially with negative content. The role of the VmpFC/ACC in regulating negative emotion is also consistent with previous work (Kim and Hamann, 2007) reporting greater VmpFC/ACC activation during the downregulation of negative than positive emotion. This finding is also consistent with other data indicating a role of the VmpFC in the regulation of negative emotion (Urry *et al.*, 2006; Goldin *et al.*, 2008). The ACC has also been associated with negative feedback (Ruchow *et al.*, 2002) and negative reinforcement learning (Brown and Braver, 2005). In addition, individuals who exhibit difficulty in regulating negative emotion evidence impairments in VmpFC/ACC function (Davidson *et al.*, 2000). These results collectively indicate that the VmpFC/ACC activation specific to active attenuation of negative emotion may reflect online inhibitory control over stimuli with negative content.

When preparatory control was compared with regulatory control, selective areas of prefrontal and parietal cortices were found to be differentially active, including in the bilateral aPFC (BA 10), precuneus, PCC, right putamen and superior/middle temporal and occipital lobes. Given that the task in the preparatory control phase entailed actively preparing to reappraise while rehearsing the cue signaling this intended action, several processes governed by differing neural networks were likely invoked, including top-down modulation of attention, self-conscious recall of an intended action, and sensory processing of the attended cue (Carlsson *et al.*, 2000; Simons *et al.*, 2006).

With regard to the finding of increased activity in the lateral division of the aPFC (BA 10) during preparatory than regulatory control, this region plays a key role in online maintenance of an intended action (Burgess *et al.*, 2001). Multiple studies demonstrated a role for the lateral aPFC in prospective memory, an executive function requiring attentional control during cue presentation and maintenance of an intended action during a delay period (Burgess *et al.*, 2001, 2003; West and Ross-Munroe, 2002; den Ouden *et al.*, 2005; Simons *et al.*, 2006). Thus, enhanced lateral aPFC activity during preparatory control could reflect increased attention modulation and goal-directed maintenance of an intended action (reappraisal) for an upcoming event. Consistent with this, activity in the bilateral aPFC along with left DLPFC during preparatory control was also significantly associated with reductions in affective ratings in the current study, suggesting an important executive role for lateral aPFC during preparation for modulation of emotional reactivity.

In addition, the precuneus and PCC, brain regions related to modulating consciousness and self-reflection (Kelley *et al.*, 2002; Lou *et al.*, 2004), were more active during preparatory control. The precuneus is involved in self-conscious mental processes (den Ouden *et al.*, 2005; Cavanna and Trimble, 2006) and attentive control (Luo *et al.*, 2004), suggesting greater conscious, attention-driven processing of internal goals during this phase. This is in turn consistent with previous studies showing concurrent activity in the lateral aPFC, PCC and precuneus during prospective memory process (Burgess *et al.*, 2001; den Ouden *et al.*, 2005). Further, activity in the temporal and occipital cortices was elicited, which can be interpreted as reflecting the modulation of anticipatory attention in cue-related processing (Corbetta and Shulman, 2002; Serences and Yantis, 2006). Increased activity of the putamen has likewise been demonstrated in other studies of anticipatory processing (Haruno and Kawato, 2006), with concomitant activity of the lateral aPFC and striatum specifically observed during goal-directed anticipation of emotional stimuli (Rea *et al.*, 2011). From the perspective of anticipation and preparation as processes facilitating awareness of one's intentions in relation to an upcoming event, it can be inferred that the lateral aPFC, PCC and precuneus were involved in goal-directed preparation and self-conscious awareness of intended action during the preparatory phase of the current study, in conjunction with activity in sensory processing regions reflecting cue processing and readiness to receive upcoming stimulus information.

Although preparatory control elicited enhanced activity in these differing regions, regulatory control did not elicit greater activity than the preparation phase, suggesting that participants were more easily engaged in intended regulation during the preparatory phase than in the subsequent regulation phase, where cognitive control was needed to overcome bottom-up emotional arousal. This may in turn relate to instances in everyday life where advance cognitive preparation is found to be easier than regulation during unexpected stressors or conflicts. However, this result should be interpreted with caution. Although view trials were subtracted from decrease trials during both phases, the nature of regulatory control can be considered only roughly comparable for the two phases—given that regulatory control entailed context-driven reappraisal whereas preparatory control entailed anticipation of an unknown context. Accordingly, further studies will be needed to clarify commonalities and differences in processing within these two phases.

Emotion modulatory effects were also evident in responses of the amygdala and VS. During the regulation of positive and negative emotion, activity in both these subcortical regions decreased in comparison with the view condition. Consistent with this result, prior studies have reported reductions in amygdala activity during the regulation of both positive (Beauregard *et al.*, 2001) and negative emotion (Levesque *et al.*, 2003; Ochsner *et al.*, 2002; Schaefer *et al.*, 2002). The VS, a

structure known to play a major role in pleasure and reward (Everitt *et al.*, 2000; Knutson *et al.*, 2001), evidenced greater activation during viewing of positive pictures than either negative or neutral pictures. During active regulation of positive emotion, ventral striatal activity significantly decreased in comparison with the view condition. For active regulation of negative emotion, a parallel trend-level reduction was evident. Another previous study also demonstrated a similar pattern, reporting decreased activity in the amygdala and VS during the regulation of negative emotion (Phan *et al.*, 2005).

For positive picture trials, during both viewing and regulation conditions, an overall signal decrease in structurally defined VS was observed relative to baseline. This pattern contrasts with prior findings of increased VS signal during viewing of positive stimuli (Sabatinelli *et al.*, 2007). Decreased VS response on positive picture trials relative to baseline in the current study could be attributable to our selection of a structurally defined ROI that was quite large in relation to a functionally defined area, localized more to the medial part of the VS. Within this more localized VS area, we did find increased BOLD signals relative to baseline during positive picture trials. However, the selection of structurally defined ROIs was necessary to effectively compare VS activity across different conditions. In this context, it should be noted that the pattern of structurally defined VS activity observed in the current study across positive, neutral and negative viewing trials (Positive > Neutral/Negative) coincides with findings from prior work (Sabatinelli *et al.*, 2007; Wittmann *et al.*, 2008).

In summary, this study provides neural evidence underlying the effects of emotion modulation during preparation for as well as during active implementation of emotion regulation. The findings of this study have important implications for the mechanisms underlying conscious control of evoked emotional responses. Specifically, in line with clinical studies showing that cognitive preparation enhances the performance and the effects of psychotherapy in anxiety disordered patients (Harve *et al.*, 2000; Nilsson *et al.*, 2011), our findings suggest potential benefits of mental preparation as a therapeutic strategy. In addition, the current study demonstrated differential regulatory systems specific to positive and negative emotions. Specifically, the right precentral gyrus was recruited specifically in regulating positive emotion, whereas the VmPFC and rostral ACC appear more important for regulating negative emotion during only regulatory phase. Some limitations of the current study warrant mention. First, our study included only female participants to optimize power to detect effects (i.e. in the absence of moderation by gender) and to permit comparisons with prior studies that have included only women (Ochsner *et al.*, 2002; Kim and Hamann, 2007). More specifically, sex differences in brain responses to emotional stimuli have been reported (Goldstein *et al.*, 2010; Seo *et al.*, 2011). Although studying female participants provides specific, valuable information about individuals of this gender, there are clearly limitations in generalizing these findings to the population as a whole. A further limitation is that subjective ratings were collected for the regulation phase but not the preparatory phase, which constrains direct interpretations of brain activity effects observed during the preparatory phase. In addition, an optimal design for the preparatory control (e.g. the duration of jittered intervals) and its effects on emotion regulation should be further explored in future studies to advance our understanding on the nature of the preparatory control. Despite these limitations, this study contributes to basic understanding of neural systems underlying preparatory and regulatory control of emotion. Along more practical lines, our findings may also contribute to understanding of the mechanisms by which cognitive-behavioral strategies work to alleviate emotional suffering related to situational stressors or dysfunctional reward-seeking and in facilitating recovery of prefrontal regulatory function. Future research should continue to focus on the complex relationship between cognition and emotional

control, especially in the area of understanding brain mechanisms underlying emotion regulatory deficits of individuals with mental disorders.

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