Modulation of Amygdalar Activity by the Conscious Regulation of Negative Emotion

Stacey M. Schaefer[1], Daren C. Jackson[2], Richard J. Davidson[2], Geoffrey K. Aguirre[1], Daniel Y. Kimberg[1], and Sharon L. Thompson-Schill[1]

Abstract

■ Lesion and neuroimaging studies suggest the amygdala is important in the perception and production of negative emotion; however, the effects of emotion regulation on the amygdalar response to negative stimuli remain unknown. Using event-related fMRI, we tested the hypothesis that voluntary modulation of negative emotion is associated with changes in neural activity within the amygdala. Negative and neutral pictures were presented with instructions to either ''maintain'' the emotional response or ''passively view'' the picture without regulating the emotion. Each picture presentation was followed by a delay, after which subjects indicated how they currently felt via a response keypad. Consistent with previous reports, greater signal change was observed in the amygdala during the presentation of negative compared to neutral pictures. No significant effect of instruction was found during the picture presentation component of the trial. However, a prolonged increase in signal change was observed in the amygdala when subjects maintained the negative emotional response during the delay following negative picture offset. This increase in amygdalar signal due to the active maintenance of negative emotion was significantly correlated with subjects' self-reported dispositional levels of negative affect. These results suggest that consciously evoked cognitive mechanisms that alter the emotional response of the subject operate, at least in part, by altering the degree of neural activity within the amygdala. ■

INTRODUCTION

Emotion regulation has been defined as ''the extrinsic and intrinsic processes responsible for monitoring, evaluating, and modifying emotional reactions, especially their intensive and temporal features, to accomplish one's goals'' (Thompson, 1994). The topic of emotion regulation is receiving increasingly more attention from developmental, social, clinical, and physiological psychologists; however, the neural substrates still remain unknown. The clinical importance of emotion regulation can be seen by reviewing the diagnostic criteria for Axis I and II psychopathology in the DSM-IV (American Psychiatric Association, 1994), many of which include disturbances in regulatory processes. Examples of psychological symptoms arising from emotion dysregulation, encompassing many DSM-IV diagnostic categories, include inappropriate affect, chronic worry, avoidance or constriction of emotion, extreme emotional lability, and sustained negative affect (Cole, Michel, & Teti, 1994). Disruptions in normal emotion regulatory processes, such as a chronic inability to suppress negative affect, could result in the onset, maintenance, and reoccurrence of depression and anxiety.

Despite the interaction between emotion and cognition and the obvious importance of emotional dysfunction in psychopathology, only recently have the normal emotion regulatory processes been examined in adults. Physiological studies have generally demonstrated a pattern of increases in autonomic measures and decreases in somatic measures when healthy adults suppress positive or negative emotion (Gross & Levenson, 1993, 1997). Eyeblink startle magnitude measures have also been shown to reflect the changes in emotional state following instructions to regulate emotion (Jackson, Malmstadt, Larson, & Davidson, 2000). Conscious, voluntary suppression of negative emotion has been shown to be accompanied by smaller startle eyeblinks and enhancement of negative emotion to be accompanied by larger startle eyeblinks (Jackson et al., 2000), findings consistent with the well-demonstrated affective modulation of startle amplitude (Lang, 1995), and indicative of successful voluntary regulation of negative affect. Thus, the process of emotion regulation has been shown to have a number of physiological correlates, as the correlational studies between coping styles and physiology would suggest (see Gross, 1998, for review). However, the changes in neural activity resulting from conscious emotion regulation remain unknown.

Identifying the neural correlates of emotion regulation has the potential to both advance our understanding

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of how the brain perceives, produces, and experiences emotion as well as elucidate the neural circuitry involved in emotional dysfunction and inhibition. The amygdala seems a likely location for such regulation, given the substantive literature that implicates this region in emotional processes including the perception and production of emotion (see Davidson & Irwin, 1999, for review). For instance, previous neuroimaging studies have shown increased amygdala activation to unpleasant compared to neutral and/or positive stimuli (Lane, Fink, Chau, & Dolan, 1997; Zald & Pardo, 1997; Irwin et al., 1996; Schneider et al., 1996) as well as during induction of sad as compared to happy mood (Schneider et al., 1997). Increased amygdala activation has been found during symptom provocation in anxiety disorders including obsessive–compulsive disorder (Breiter et al., 1996), posttraumatic stress disorder (Rauch et al., 2000; Shin et al., 1997), and social phobia (Birbaumer et al., 1998). The degree of amygdala activity has also been positively correlated with trait levels of negative affect (Abercrombie et al., 1998) and severity of depression (Drevets et al., 1992) in depressed patients, suggesting that an overactive or uninhibited amygdala may be associated with unregulated negative affect.

This study tested the hypothesis that voluntary modulation of negative affect is associated with changes in neural activity within the amygdala. Specifically, conscious maintenance of an emotional response to a negatively valenced stimulus was predicted to be associated with increased functional magnetic resonance imaging (fMRI) signal change in the amygdala in comparison to passive viewing of the stimulus. These signal changes would indicate that consciously evoked cognitive mechanisms that alter the emotional response of the subject operate, at least in part, by altering the degree of neural activity within the amygdala. This result would support the hypothesis that the amygdala response is sensitive to conscious emotion regulation.

Healthy subjects were presented with highly unpleasant, highly arousing pictures interspersed randomly with neutral pictures during acquisition of whole-brain echo-planar fMRI (Figure 1). They were instructed prior to each picture presentation either to maintain the emotional response produced by the picture (maintain condition) or to passively view the picture (passive condition). The picture presentation was followed by a delay, after which subjects were asked to indicate how they currently felt on a four-button response keypad. Prior to scanning, subjects were specifically instructed to attend to all of the pictures the entire time they were presented and to never avert their gaze from the pictures or close their eyes. They were instructed that when given the maintain instruction, they should "maintain the initial emotional response produced by the picture throughout the picture presentation and delay until they received the query asking how they feel right now." When given the passive instruction, they should "allow the initial emotional response to rise and fall naturally without trying to regulate the emotion produced by the picture."

RESULTS

Manipulation Check

After the fMRI procedure, each subject rated all of the pictures in terms of how negative they thought they were. The subjects' postscan ratings confirmed the intended manipulation of affective response to the two picture sets was successful. Each subject rated the negative picture set more negative than the neutral

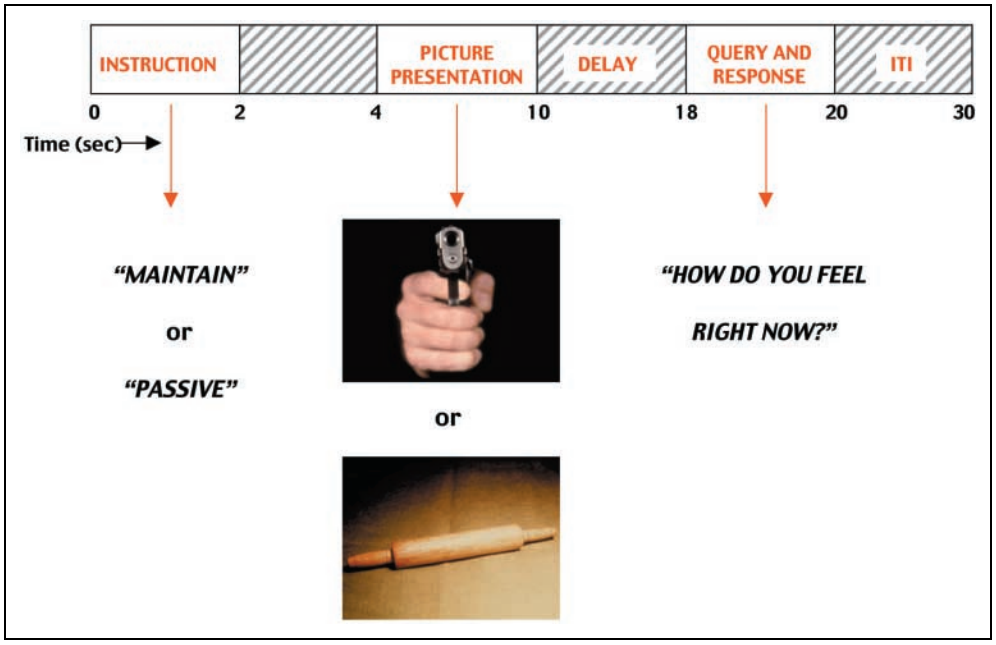

Figure 1. Trial design: The "maintain" or "passive" instruction was presented for 2 sec, after which the screen went blank for 2 sec. A negative or neutral picture was then presented for 6 sec, followed by a delay of 8 sec during which the screen was blank. At 8 sec postpicture offset, the question "How do you feel right now?" was presented for 2 sec and subjects responded via a four-button response keypad with "1" being effectively neutral and "4" being the most negative. A 10-sec intertrial interval followed.

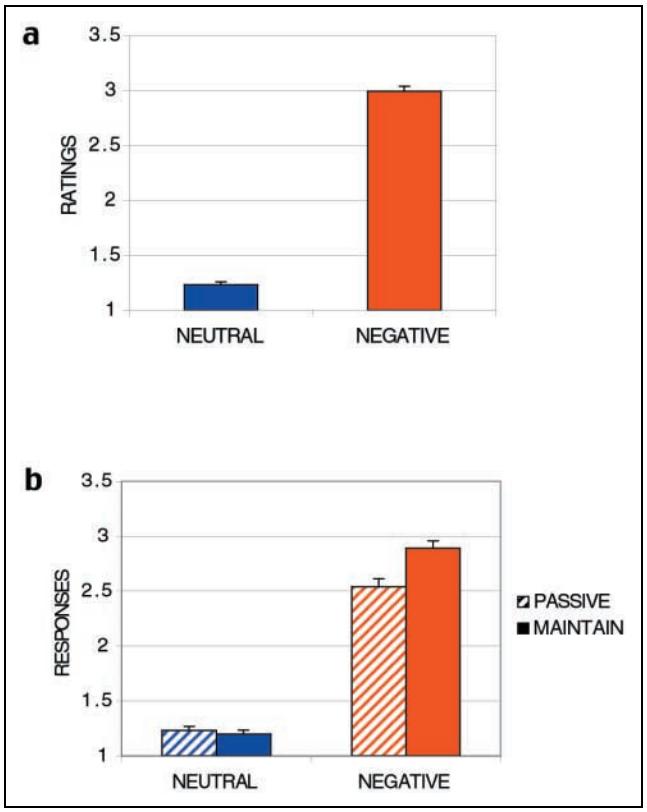

Figure 2. Behavioral results: (a) Manipulation check: Postscan ratings of the pictures confirmed the intended manipulation of affective response to the two picture sets was successful, $t(898) = 32.70$, $p < .0001$. (b) Behavioral responses during fMRI scanning: Subjects' responses to the query ''How do you feel right now?'' confirmed the intended instruction manipulation. An interaction between the instruction and picture valence conditions was found, $F(880) = 8.81$, $p < .005$. Subjects reported feeling more negative on negative picture trials than neutral trials, $F(880) = 779.43$, $p < .0001$. Subjects also reported feeling more negative on maintain than passive trials, $F(880) = 12.66$, $p < .0005$. Using Tukey's HSD test, subjects reported feeling more negative on maintain/negative than passive/negative trials but there was no difference between the maintain/neutral and passive/neutral trials.

set: all individual $t(178) > 11$, $p < .0001$, group analysis $t(898) = 32.70$, $p < .0001$ (Figure 2a).

Behavioral Results

The subjects' responses to the query ''How do you feel right now?'' were analyzed across subject with an ANOVA. Subjects' responses to the query confirmed the intended instruction manipulation. An interaction between the instruction and picture valence conditions was found, $F(880) = 8.81$, $p < .005$. Subjects reported feeling more negative on negative picture trials than neutral trials, $F(880) = 779.43$, $p < .0001$. Subjects also reported feeling more negative on maintain than passive trials, $F(880) = 12.66$, $p < .0005$. Using Tukey's HSD test, subjects reported feeling more negative on maintain/negative than passive/negative trials but there was no difference between the maintain/neutral and passive/neutral trials (Figure 2b).

fMRI Results

We used a hypothesis-driven region-of-interest (ROI) approach and performed a random effects analysis across the five subjects to confirm the reliability of the results and the generalizability of the findings to the greater population. Consistent with previous reports of increased amygdalar activation in response to unpleasant stimuli, we found greater signal in the amygdala in response to negative as compared to neutral pictures during the picture presentation component of the trial, $t(4) = 4.28$, $p < .01$, one-tailed (Figures 3 and 4a). Importantly, we found no effect of instruction on amygdalar activity during the picture presentation, $t(4) = .71$, *ns*. This suggests that receiving the regulation instructions prior to stimulus presentation does not affect the initial amygdalar response to the stimulus. The hippocampus, identified as a control region for this study, also showed greater signal in response to negative compared to neutral pictures during the picture presentation, $t(4) = 5.22$, $p < .01$, as well as no effect of instruction during the picture presentation, $t(4) = 1.85$, *ns*. No other contrasts were significant during the picture presentation component of the trial.

A significant interaction between the instruction condition (maintain, passive) and the picture valence (negative, neutral) was found in the amygdala during the delay following the picture presentation, $t(4) = 2.77$, $p < .05$, one-tailed (Figure 4b). No main effects were found. Supporting our hypotheses, within the negative picture valence condition, greater amygdalar activity was associated with maintenance of negative emotion compared to the passive viewing condition, $t(4) = 2.47$, $p < .05$, one-tailed (Figure 4c). There was no difference in amygdalar activity on neutral picture trials. The hippocampal control region did not show either the interaction [$t(4) = 1.32$, *ns*] or the negative emotion regulation effect [$t(4) = .04$, *ns*). Figure 4c provides the individual subject data to demonstrate that all five subjects showed greater amygdalar activity during the delay when they maintained the negative emotional response, whereas the mixed pattern in the hippocampus showed both increases and decreases in activity as a result of maintenance.

Outside the scanner, subjects provided self-ratings of their overall general dispositional levels of positive and negative affect (trait) and their current emotional condition (state) immediately before and after the MRI procedure. Correlations were examined between these subject-specific emotional measures and the difference in the blood oxygenation level dependent (BOLD) signal in the amygdala for the significant contrasts. Trait negative affect was significantly correlated with the increase in amygdalar activity when subjects actively maintained

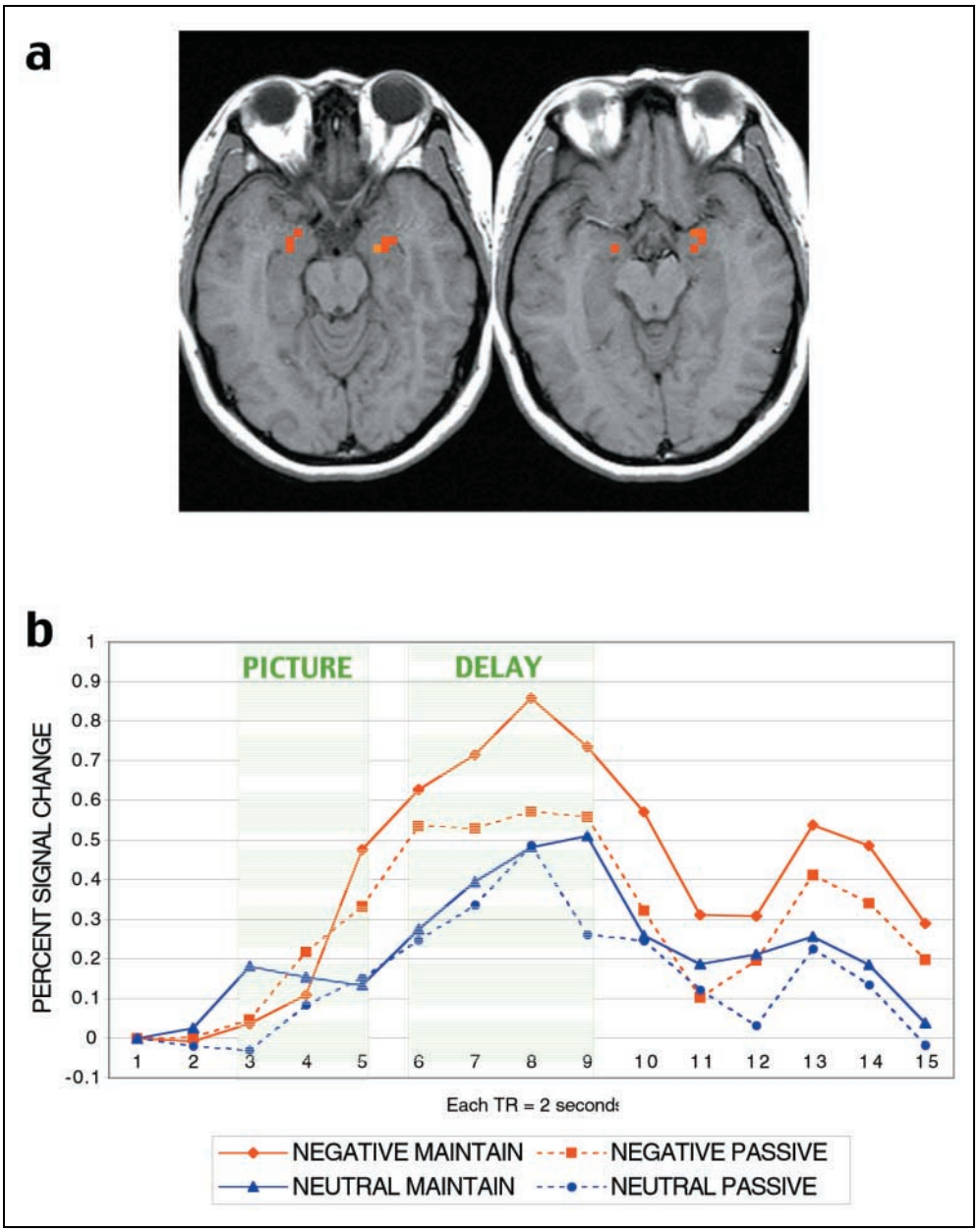

Figure 3. Amygdala ROI and time series: (a) One representative subject's voxels within the amygdala showing greater levels of activity during the picture presentation component of the trail compared to the intertrial interval ($t > 1.65$). The average time series across these voxels were obtained and t values were calculated in each ROI for both the picture presentation and delay components of the trial for the following contrasts: interaction (Instruction condition × Picture valence), negative–neutral, maintain–passive, negative: maintain–passive, and neutral: maintain–passive. (b) The time series representing percent signal change in the amygdala averaged across subjects is displayed for each trial type. Signal changes reflect the slow, prolonged hemodynamic response that peak 2–4 sec after changes in neuronal activity.

the negative emotion during the delay compared with passive viewing, Pearson $r = .90$, $p < .05$ (Figure 5). Importantly, this maintain–passive difference for negative picture trials was completely unrelated to their trait levels of positive affect, Pearson $r = .02$, *ns*. In addition, there were no significant correlations with the state measures.

DISCUSSION

Consistent with previous reports of greater amygdalar activation in response to presentations of unpleasant stimuli compared to affectively neutral stimuli, we found greater levels of BOLD signal in the amygdala during the picture presentation component of the trials in response to negative compared to neutral pictures. We also found a significant interaction between the instruction condition (maintain, passive) and the picture valence (negative, neutral) during the delay following the picture presentation. When we looked within each picture valence set individually, we found a difference for the negative pictures only. Specifically, there was greater amygdalar activation during the delay when subjects were maintaining the emotional response to negative pictures than when they had simply viewed the negative pictures and did not try to regulate their emotion in any way. This suggests that the degree of neural activity within the amygdala is under some conscious control. These results both replicate previous studies in suggesting that the amygdala is a central component of emotion perception, and in addition, support the hypothesis that any consciously evoked

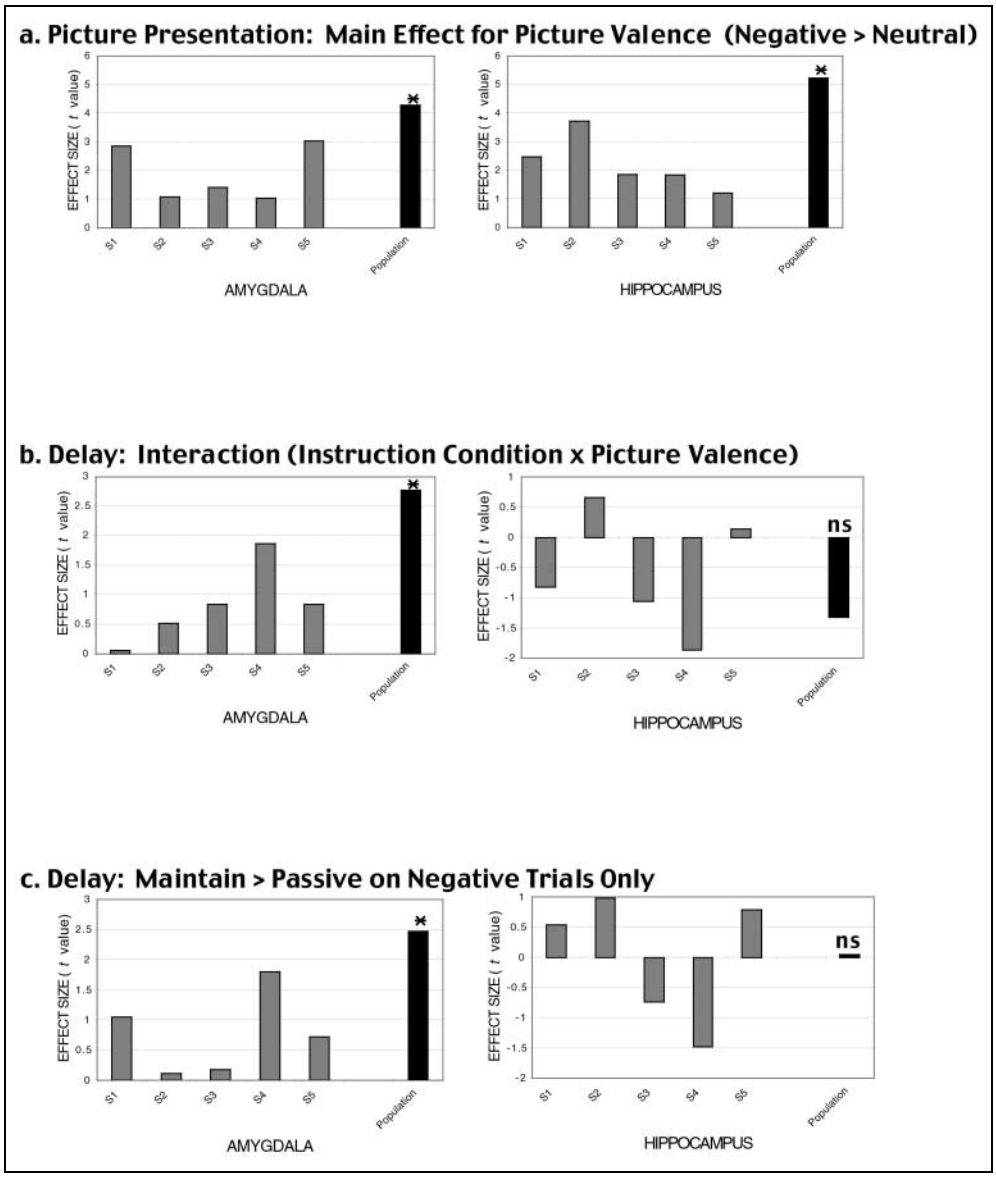

Figure 4. Significant fMRI contrasts: The effect size in each subject (S1–S5) and results of the group random effects analysis (population) are displayed for those contrasts of interest found significant in the amygdala. Hippocampal results are displayed for comparison. (a) Greater activity to negative compared to neutral pictures during the picture presentation in the amygdala, group random effects analysis, $t(4) = 4.28$, $p < .01$, and in the hippocampus, group random effects analysis, $t(4) = 5.22$, $p < .01$. (b) An interaction (Instruction condition × Picture valence) was found during the delay in the amygdala, $t(4) = 2.77$, $p < .05$, one-tailed, but not in the hippocampus, $t(4) = 1.32$, *ns*. (c) Greater activity in the amygdala during the delay on negative picture trials after ''maintain'' compared to ''passive'' instructions, $t(4) = 2.47$, $p < .05$, one-tailed, but not the hippocampus, $t(4) = 0.04$, *ns*. No other contrasts were significant in the amygdala.

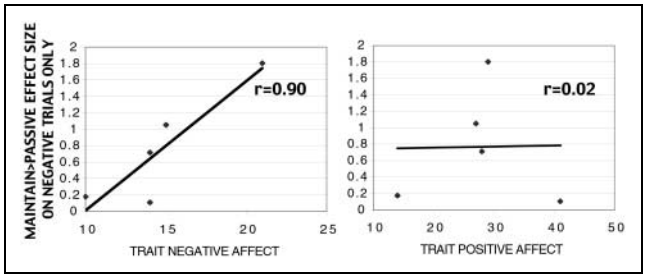

Figure 5. Relations between fMRI data and self-reported affect: State and trait positive and negative affect were correlated with the effect size in the amygdala for the significant fMRI contrasts of interest. Trait negative affect was positively correlated with the effect size for the difference in BOLD signal in the amygdala after maintain compared to passive instructions on negative picture trials. No other correlations were significant.

cognitive mechanisms that seek to alter the emotional state of the subject operate, at least in part, by altering the degree of neural activity within the amygdala. This is consistent with Phelps et al.'s (2001) finding of amygdalar activation to a cognitive representation of fear produced by a threat of shock, but extends it by demonstrating the ability of a subject to modulate their amygdalar activity at will through cognitive regulatory strategies. However, as can be seen in Figure 4c, subjects' ability to do so may be variable.

This increase in amygdalar activity when subjects maintained the emotion produced by the negative pictures was positively correlated with their trait levels of negative affect. This finding, that subjects who showed a greater response in the amygdala when maintaining a negative emotion also reported significantly higher

levels of dispositional negative affect, is in accord with a study by Jackson et al. (2000). Using eyeblink startle measures, they obtained evidence for individual differences in ability to enhance versus suppress negative emotion. Our current findings indicate that signal changes in the amygdala in response to voluntary emotion regulation instructions predict reports that subjects provide of their trait levels of negative affect, thus suggesting that the laboratory measures relate to other trait features of affective style.

One possible interpretation of these results is that it is merely an attentional effect resulting from attentional differences between the ''maintain'' and ''passive'' conditions. However, we specifically instructed the subjects to always attend to the pictures the entire time they were presented, to never avert their gaze or close their eyes, but instead to watch the pictures the entire time they were shown regardless of regulation condition. In addition, it is hard to explain why a general attentional effect would correlate with a trait measure of negative emotion such as was found with the Positive Affect Negative Affect Schedule (PANAS). However, future studies would benefit from inclusion of additional emotion regulation instructions to more rigorously control for potential differences resulting from attentional processes.

Besides, the neural correlates of different regulatory strategies bear investigation. In this study, we examined the changes in neural activity resulting from ''maintenance'' of negative emotion. The neural changes associated with ''suppression'' and ''enhancement'' of negative emotion are of extreme interest given the clinical implications of functional deficits in emotion regulation. Because increased amygdalar activity is associated with symptom provocation in anxiety disorders (Rauch et al., 2000; Birbaumer et al., 1998; Shin et al., 1997; Breiter et al., 1996), and amygdalar activity is positively correlated with negative affect (Abercrombie et al., 1998) and depression severity (Drevets et al., 1992) in depressed patients, it has been theorized that an overactive or uninhibited amygdala may be the cause of the unregulated negative affect observed in these disorders.

This study examined only pictures with a negative or neutral valence, so we cannot be certain whether our results generalize to all highly arousing stimuli. Future studies that include positively valenced stimuli that have been controlled for arousal levels are needed in order to ascertain whether increases in amygdalar activity during active maintenance of an emotion are specific to negative emotion. In addition, our sample size was limited to five female participants. Although this sample size was sufficiently large for our hypothesis-driven ROI approach to have adequate power to detect a reliable change in the amygdala (as indexed by the random effects analysis), larger sample sizes would provide enough power to allow the multiple corrections needed in order to perform more exploratory analyses using whole-brain parametric tests. Such analyses may reveal other brain regions involved in emotion regulational processes. In addition, including data from male participants would be interesting given recent findings of sex differences in the laterality of amygdalar activity associated with enhanced memory for emotional material (Cahill et al., 2001).

Finally, because of its role in aversive conditioning (Garcia, Vouimba, Baudry, & Thompson, 1999; Morgan, Romanski, & LeDoux, 1993) and depression (Abercrombie et al., 1996), the amygdala–prefrontal circuit (Amaral, 1992; McDonald, 1987) plays an integral role in current theories of emotion regulation (Davidson, Putnam, & Larson, 2000). Unfortunately, due to imaging artifacts in the vicinity of the sinuses, we were not able to obtain functional data from the ventral prefrontal cortex in the present study. Imaging all of the prefrontal cortex, in particular, the orbito-frontal cortex, will likely be necessary to fully understand the central processes mediating the conscious regulation of the amygdalar response to unpleasant, arousing stimuli that we have demonstrated in the present study. Future studies examining the relations between changes in amygdalar and prefrontal activity resulting from different emotion regulatory strategies may provide a genuine breakthrough in understanding the pathophysiology of mood disorders.

METHODS

Subjects

Seven healthy, right-handed women, aged 19–37 years (mean age = 24.6 years) were studied, however, two subjects' data were excluded from analyses because their fMRI data were found to have head movement exceeding our exclusionary criteria of 2.5 mm. Subjects were recruited via advertisements posted on University of Pennsylvania electronic newsgroups and library bulletin boards and were paid for participation. After the subjects were given a detailed description of the study and the nature of the procedures was explained, informed consent was obtained. Subjects were screened prior to acceptance into the study for any history of psychopathology and reported no history of any Axis I disorders or substance abuse. Subjects were also screened for neurological disorders and had no history of brain injury or disease. All participants were right-handed as assessed by the Chapman Handedness Inventory (Chapman & Chapman, 1987). All experiments were approved and were performed in compliance with the University of Pennsylvania Office of Regulatory Affairs.

Stimuli

Stimuli were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1999) based

on the combined female and male valence and arousal ratings to produce two distinct sets: 90 negative (standardized valence $M = -1.36$, $SD = .40$; standardized arousal $M = 1.21$, $SD = .43$) and 90 neutral (standardized valence $M = -.00$, $SD = .15$; standardized arousal $M = -1.05$, $SD = .75$), providing 45 pictures in each of the four instruction/picture valence conditions. Two quasi-random orders were created so that no more than two pictures from a particular picture set appeared consecutively and no more than three identical instruction types occurred consecutively. Pictures were counterbalanced across subjects for order of presentation and instruction type. After scanning, each subjects rated the valence of each of the pictures using a 1–4 Likert scale with ''4'' being the most negative and ''1'' being effectively neutral.

Experimental Paradigm

At the MRI Center before beginning the fMRI procedure, subjects were again given a detailed description of the study as well as practice trials to ensure full comprehension of the task. They were reminded that when given the maintain instruction, they should ''maintain the initial emotional response produced by the picture throughout the picture presentation and delay until they received the query asking how they feel right now.'' When given the passive instruction, they should ''allow the initial emotional response to rise and fall naturally without trying to regulate the emotion produced by the picture.'' Subjects were also explicitly told to never close their eyes or avert their gaze from the stimuli, but to watch the stimuli at all times. Subjects completed the state and trait version of the PANAS (Watson, Clark, & Tellegen, 1988) immediately before and after the fMRI study. The fMRI experiment consisted of 15 runs of 12 trials each (implemented using PsyScope software; Cohen, Mac Whinney, Flatt, & Provost, 1993) (see Figure 1 for a breakdown of the trial).

Image Acquisition

Imaging was performed using a 1.5-T GE Signa scanner (GE Medical Systems, Milwaukee, WI) with a standard head coil. High-resolution sagittal and axial T1-weighted images were obtained in each subject prior to functional scanning. Using the BOLD technique (Ogawa et al., 1993), a total of 180 gradient-echo echo-planar images (TR = 2000 msec, TE = 50 msec) were acquired in each of 15 runs. Each image consisted of 21 contiguous 5-mm slices, with an in-plane resolution of 64×64 in a 24-cm field of view, yielding voxel sizes of $3.75 \times 3.75 \times 5$ mm. The start of each trial component was triggered by the scanner to ensure that the timing of the trials was locked to image acquisition. Twenty seconds of ''dummy'' gradient and RF pulses always preceded the actual data acquisition to approach steady-state magnetization.

Image Processing

Off-line data processing was performed using VoxBo software (www.voxbo.org). After image reconstruction, the data were sinc interpolated in time to correct for the fMRI acquisition sequence. A slice-wise motion compensation method removed spatially coherent signal changes by the application of a partial correlation method to each slice in time (Zarahn, Aguirre, & D'Esposito, 1997a). Additional motion detection and correction was undertaken using a six-parameter, rigid-body transformation (Friston et al., 1995). No spatial smoothing or normalization was performed.

Image Analyses

Voxel-wise analysis was performed on data from each subject using a general linear model for serially correlated error terms (Worsley & Friston, 1995). A model for intrinsic serial autocorrelation derived from similarly treated null hypothesis data was assumed (Zarahn, Aguirre, & D'Esposito, 1997b). The two trial components of interest, the picture presentation and the delay, were modeled as boxcar functions, whereas the instruction and the query/response were modeled as brief impulses (Zarahn et al., 1997b). The picture presentation was modeled as a 6-sec boxcar starting 4 sec after the start of the trial. The delay was modeled as a 4-sec boxcar starting 12 sec after the start of the trial. These covariates were then smoothed with an empirically derived estimate of the hemodynamic response of the BOLD signal (Aguirre, Zarahn, & D'Esposito, 1998), to render them appropriate models of the fMRI signal. Additional covariates were constructed by taking the first and second derivatives of the smoothed vectors that modeled the picture presentation. These covariates modeled signal variance attributable to picture presentation not otherwise explained by the smoothed boxcar, and thereby reduced the influence of neural activity during the picture presentation upon the delay covariates (Zarahn, 2000).

ROIs of the amygdala were drawn separately for each subject. A hippocampal ROI was also drawn to provide a control region for comparison. The amygdalar ROI was bordered anteriorly, medially, and laterally by white matter on inferior slices and anteriorly and medially by CSF and laterally by white matter on superior slices. When white matter differentiating the amygdala's posterior border with the hippocampus was not clear, the temporal horn of the lateral ventricle was used to provide a border between the amygdala and the hippocampus. The amygdala was always drawn anterior to the temporal horn of the lateral ventricle, whereas the head of the hippocampus was drawn more posterior to it. Inferior slices of the hippocampus were bordered laterally, medially, and posteriorly by white matter and anteriorly and laterally by the inferior horn of the lateral

ventricle. Medial and superior slices of the hippocampus were bordered laterally by the lateral ventricle, anteriorly by the lateral ventricle and/or white matter, medially by CSF, and posteriorly by white matter. Care was taken to avoid including the entorhinal cortex in the amygdala ROI, however, voxels that included some entorhinal tissue but were judged to include >50% amygdalar tissue were included in the amygdala ROI. In addition, care was taken to avoid including the parahippocampal gyrus in the hippocampal ROI, and white matter between the hippocampus and the parahippocampal gyrus was used as a border. However, voxels including some parahippocampal tissue that were judged to include >50% hippocampal tissue were included in the hippocampal ROI.

Voxels within the ROIs were identified that showed activation (greater than $t = 1.65$) to the presentation of pictures compared to a baseline of the intertrial interval, and the average time series across these voxels were obtained. With this spatially averaged time series, t values were calculated in each ROI for both the picture presentation and the delay components of the trial for the following contrasts: interaction (Instruction condition × Picture valence), negative–neutral, maintain–passive, negative: maintain–passive, and neutral: maintain–passive. The t values across all five subjects were used as the dependent variable in a random effects analysis. The t value was used as an index of the statistical effect size because it provides information about the magnitude of the signal change relative to the variability, or noise, in the data; this is preferable over a measure such as percent signal change because of the variability between subjects in the overall scaling of the BOLD signal, which affects both the signal and noise of fMRI data (Zarahn et al., 1997a).

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The data reported in this experiment have been deposited in The fMRI Data Center (http://www.fmridc.org). The accession number is 2-2002-112PQ.

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