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Brain Structure Correlates of Individual Differences in the Acquisition and Inhibition of Conditioned Fear

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Research employing aversive conditioning paradigms has elucidated the neurocircuitry involved in acquiring and diminishing fear responses. However, the factors underlying individual differences in fear acquisition and inhibition are not presently well understood. In this study, we explored whether the magnitude of individuals' acquired fear responses and the modulation of these responses via 2 fear reduction methods were correlated with structural differences in brain regions involved in affective processing. Physiological and structural magnetic resonance imaging data were obtained from experiments exploring extinction retention and intentional cognitive regulation. Our results identified 2 regions in which individual variation in brain structure correlated with subjects' fear-related arousal. Confirming previous results, increased thickness in ventromedial prefrontal cortex was correlated with the degree of extinction retention. Additionally, subjects with greater thickness in the posterior insula exhibited larger conditioned responses during acquisition. The data suggest a trend toward a negative correlation between amygdala volume and fear acquisition magnitude. There was no significant correlation between fear reduction via cognitive regulation and thickness in our prefrontal regions of interest. Acquisition and regulation measures were uncorrelated, suggesting that while certain individuals may have a propensity toward increased expression of conditioned fear, these responses can be diminished via both extinction and cognitive regulation.

Keywords: cortical thickness, emotion regulation, fear conditioning, individual differences, insula

Introduction

In order to function adaptively in a complex environment, individuals must be able to react to environmental threats and to modify their reactions as circumstances change. A large body of research employing classical fear conditioning paradigms has generated a detailed neuroscientific understanding of how fear responses are acquired (Fendt and Fanselow 1999; Davis 2000; LeDoux 2000; Maren 2001), while recent research has begun to probe the various means by which learned fear can be diminished (see Hartley and Phelps 2010 for a review). The vast majority of this research focuses on the mechanisms that underlie typical responding in an idealized "average" individual. However, a robust model of fear learning must also account for the substantial variability in fear reactivity and regulation that exists between individuals. Recent research suggests that these differences in fear expression may be stable trait-like qualities (Bush et al. 2007), suggesting corresponding variation in the underlying neurocircuitry. One possibility is that these behavioral differences may be associated with measurable differences in brain structure. In this study, we explore whether the magnitude of individuals' learned fear responses, as well as the ability to diminish those responses are related to morphological differences in brain regions involved in fear learning.

In a classical fear conditioning paradigm, a neutral stimulus such as a tone (the conditioned stimulus, or CS) is paired with an aversive stimulus such as a shock (the unconditioned stimulus, or US). After repeated pairings, an association between the CS and US is formed such that the presentation of the CS alone elicits a fear response (the conditioned response, or CR). Studies across species have shown that the amygdala is crucial for the acquisition, expression, and storage of conditioned fear (for reviews, see LeDoux 2000; Maren 2001; Phelps and LeDoux 2005). However, evidence from conditioning studies in humans and rodents suggests that the insula and dorsal anterior cingulate cortex (dACC) may also play an important role in fear acquisition (LaBar et al. 1998; Shi and Davis 1999; Critchley et al. 2002; Vidal-Gonzalez et al. 2006).

Investigations into the neural mechanisms of fear reduction have focused on 2 methods of diminishing fear that appear to recruit common inhibitory mechanisms: extinction retrieval (see Quirk and Mueller 2008 for review) and intentional cognitive regulation strategies (see Ochsner and Gross 2005 for review). In a fear extinction procedure, a CS that elicits a conditioned fear response is presented repeatedly without aversive reinforcement. After several presentations, the CR is diminished through new learning that the CS no longer predicts an aversive outcome (Bouton 2004). Extinguished fear memories often reemerge after the passage of time (Bouton 2004). Thus, the retention of extinction learning is an important index of emotion regulation capability that has been associated with resilience against anxiety disorders (Milad et al. 2008; Berry et al. 2009). While initial extinction learning, like fear learning, is amygdala dependent, the infralimbic region of the ventromedial prefrontal cortex (vmPFC) is critical for the consolidation and retention of extinction learning (see Sotres-Bayon et al. 2006, Quirk and Mueller 2008). During extinction retrieval, increased activity in the vmPFC inhibits fear expression via projections to the amygdala. Learned fear responses in humans can also be reduced via a cognitive regulation strategy in which a new mental association for a CS is intentionally generated, diminishing the conditioned fear response. Neuroimaging studies of cognitive regulation highlight the role of lateral prefrontal areas, which are thought to reflect control processes involved in the execution of the

strategy (Beauregard et al. 2001; Ochsner et al. 2004) and the emotional appraisal process itself (Wager et al. 2008). However, these prefrontal regions do not have direct projections to the amygdala (Barbas 2000), and recent studies suggest that, like extinction retention, this type of emotion regulation is also mediated by inhibitory projections from the vmPFC to the amygdala (Urry et al. 2006; Delgado et al. 2008).

Two previous neuroimaging studies conducted within our laboratory explored the inhibition of conditioned fear via extinction retrieval and intentional cognitive regulation (Phelps et al. 2004; Delgado et al. 2008). The magnitude of acquired fear responses and success at diminishing fear were highly variable across individuals. A recent finding that thickness of vmPFC correlated with measures of extinction retention (Milad et al. 2005) highlights the possibility that differences in fear acquisition and its reduction via cognitive regulation may be similarly related to differences in brain structure. In this study, we analyzed physiological and anatomical data to explore whether measures of fear acquisition and reduction via both successful extinction retention and cognitive regulation correlated with individual's cortical thickness or volume in regions believed to be involved in acquiring and inhibiting conditioned fear.

Materials and Methods

In this study, we assembled data from 2 previous studies investigating the neural mechanisms of fear inhibition (Phelps et al. 2004; Delgado et al. 2008) and conducted novel analyses of the physiological and structural magnetic resonance imaging (MRI) data in order to explore the relationship between individual differences in fear expression and variation in brain structure. The methods employed in each prior study are restated here to the extent that they are relevant to the present analyses.

Participants

Two separate groups of subjects participated in functional magnetic resonance imaging (fMRI) experiments from which the structural MRI and behavioral data analyzed herein were obtained. Eighteen right-handed subjects (9 males and 9 females), aged 18–30 years, participated in the intentional cognitive regulation experiment. Three of these subjects were excluded from the fMRI analysis due to failure to show acquisition or regulation of a conditioned fear response. As this study aimed to explore a potential factor underlying such variation, these subjects were included in the present analysis. Three additional subjects were excluded from the fMRI analysis due to confusion about the task instructions, but were included in this analysis as their physiological data revealed both successful acquisition and regulation despite any reported misunderstanding. Thus, all 18 subjects were included in the present analysis.

Eighteen right-handed subjects participated in the extinction experiment. One subject was excluded from the fMRI analysis due to errors in the functional image acquisition parameters but was included in the present analysis, which used only the structural MRI data. Six subjects were eliminated after the first session of the extinction study due to the absence of an initial skin conductance response (SCR) ($n = 3$) or failure to acquire a CR ($n = 3$). These subjects were not included in the present analysis as no second day extinction data were collected. The remaining 12 subjects (6 males and 6 females), aged 20–25 years, were included in this analysis. All subjects in both experiments gave their informed consent and were paid for their participation in the studies.

Conditioning Paradigm

Both experiments employed partial reinforcement fear conditioning paradigms. In both studies, the conditioned stimuli were colored squares (yellow and blue), where one of the squares (the CS+) was paired with a shock on a subset of presentations (35% in the extinction study and 17% in the cognitive regulation study) and the other was never paired with a shock (the CS–). The US was a mild shock to the wrist.

The cognitive regulation experimental paradigm consisted of a set of 66 interleaved trials in which the subject was instructed to attend to or regulate their response to the subsequent stimulus. Each trial began with a 2-s presentation of a word cue, which informed the subject of the type of trial to follow. The cue was followed by a 4-s presentation of the CS. In 6 of the CS+ trials, a mild shock to the wrist was administered during the final 200 ms of the stimulus presentation. A 12-s intertrial interval followed each trial.

Subjects received training in the cognitive regulation method prior to the scanning session. Subjects were told that a series of blue and yellow squares would appear on the screen, one of which would sometimes be paired with a shock. Subjects were shown word cues prior to the presentation of each colored square instructing them to attend to or regulate their response on a given trial. When shown the cue to attend, subjects were asked to attend to their natural feelings about the CS that followed. During an attend trial, a subject might think about the possibility of an imminent shock or their relief that a shock will not occur while attending to the CS+ or CS–, respectively. When shown the cue to regulate, subjects were asked to view the subsequent CS and to imagine something calming in nature associated with the color of that CS. During a regulate trial, a subject might think about blue skies or daffodils while attending to the blue or yellow square, respectively. Subjects were instructed to select 1 mental image for each colored square and to maintain these stimulus–image associations throughout the experiment. Subjects practiced these instructions for all 4 cue and stimulus combination trial types (attend CS+, attend CS–, regulate CS+, and regulate CS–). Following training, subjects entered the scanner, and the instructions were reiterated prior to the first functional run. Fifteen trials of each of the 4 trial types were presented during the experiment. The additional 6 CS+ trials (3 attend CS+ and 3 regulate CS+) that were paired with a shock were not included in the subsequent analyses.

The extinction experiment included 3 phases: acquisition, day 1 extinction, and day 2 extinction. The acquisition phase consisted of 15 presentations each of the CS+ and CS–, as well as 8 presentations of the CS+ in which a mild shock to the wrist was administered during the final 200 ms of the stimulus presentation. Day 1 extinction began immediately after the acquisition phase and consisted of 15 unreinforced presentations each of the CS+ and CS–. The day 2 extinction phase took place approximately 24 h after the day 1 session. Prior to the day 2 session, subjects were told that the session would be similar to the first day but shorter. Day 2 extinction consisted of 17 unreinforced presentations of the CS+ and 17 presentations of the CS–. The first 2 CS+ trials from the day 2 extinction session were used as a measure of spontaneous recovery.

Physiological Measurement

The same physiological measurement procedures were used in both studies. Shocks were delivered via a stimulating bar electrode attached to the right wrist. A stimulator (Grass Instruments) generated the shock using magnetically shielded cable leads grounded through a radio frequency (RF) filter. Prior to scanning, subjects selected their own shock level via a procedure in which a mild shock (200-ms duration, 50 pulses/s) was gradually increased until subjects reported that it was "uncomfortable, but not painful" (the maximum shock level administered was 50 v). SCRs were recorded through shielded Ag–AgCl electrodes attached to the second and third fingers of the left hand using a BIOPAC skin conductance module (Biopac Systems). Electrode cables were grounded through an RF filter panel. AcqKnowledge software (Biopac Systems) was used to conduct offline analysis of the SCR waveforms. Shock trials were excluded from the analysis. The base to peak change in SCR in the 0.5- to 4.5-s window following the onset of each CS was assessed. These values were then square root transformed to normalize the distributions (Schlosberg and Stanley 1953).

For the extinction data set, the measure of acquisition was calculated by subtracting the mean CS– SCR during the acquisition phase from the

mean CS+ SCR during the acquisition phase for each subject. In order to facilitate replication, we used an index of extinction retention that was identical to that used by Milad et al. (2005) with 1 modification. In our measure, 2 CS+ responses were used from the acquisition and day 2 extinction sessions instead of a single response to increase robustness against outliers. The extinction index was calculated as follows: The mean SCR from the first 2 CS+ trials of the day 2 extinction phase were divided by the mean of the 2 largest CS+ responses during the acquisition phase, expressing fear recovery as a fraction of the maximal acquired fear response. This fractional fear recovery measure was subtracted from 1 to obtain a measure of extinction, which is then stated as a percentage.

For the cognitive regulation data set, our physiological measure of acquisition response was calculated by subtracting the mean SCR for the ATTEND CS– trials from the mean SCR for the ATTEND CS+ trials for each subject. The measure of fear inhibition via cognitive regulation was calculated by subtracting the mean SCR for the REAPPRAISE CS+ trials from the mean SCR for the ATTEND CS+ trials for each subject.

Image Acquisition and Analysis

Both sets of structural MRI data were obtained at the New York University Center for Brain Imaging using a 3-T Siemens Allegra scanner and a Siemens head coil. Anatomical images were acquired using a T_1-weighted 3D MPRAGE (Mugler and Brookeman 1990) protocol (repetition time, 2500 ms; echo time, 4.38 ms; inversion time, 900 ms; flip angle, 8°; 256 × 256 matrix; one hundred seventy-six 1-mm sagittal slices, 1 mm in-plane resolution). Only 1 anatomical scan was performed for each subject in the cognitive regulation experiment. Two anatomical scans were obtained for each subject in the extinction study.

Cortical thickness measurement for each subject and automated vertex-based group analysis were conducted using the FreeSurfer surface-based analysis software tools. Measurements obtained using this automated estimation method have been validated for accuracy against manual thickness measures on both MRI scans (Kuperberg et al. 2003) and postmortem brains (Rosas et al. 2002) and have been shown to be reliable across multiple scanning sessions and platforms (Dickerson et al. 2008). The methods used in this processing stream have been previously described in detail (Dale and Sereno 1993; Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999, 2001) and are described here in brief.

The 2 sets of structural images obtained for each subject are averaged in order to generate a single volume with a high signal-to-noise ratio. This step was omitted from the processing stream for the cognitive regulation data set as only 1 structural scan was run for each subject. White matter voxels within this volume are classified based on intensity values and neighbor constraints. The resulting boundary between the white and gray matter, referred to as the white surface, is then expanded outward to locate the intensity gradient between the gray matter and the cerebrospinal fluid, referred to as the pial surface. The shortest distance between the white and pial surfaces is then estimated (Fischl and Dale 2000) at each location on both surfaces to obtain the final cortical thickness measurements. The cortical surfaces were overlaid on the intensity volumes from which they were derived and visually inspected. Any inaccuracies apparent in any of our a priori regions of interest were manually corrected.

The surface dividing the white and gray matter was then inflated to expand the sulcal and gyral folds and registered to an average spherical surface using sulcal and gyral features to guide the alignment. Via this spherical transform, every vertex on each subject's cortical surface was mapped to a common coordinate system, allowing thickness measurements at each vertex to be compared across subjects. Each subject's data were smoothed with a surface-based Gaussian kernel with a 5-mm full-width at half-maximum. For each SCR covariate of interest (acquisition, extinction retention, and cognitive regulation), a general linear model was fit at each surface vertex to explain the data from all subjects in each study.

Several subjects' structural scans had hyperintensity artifacts due to the presence of blood vessels on the orbital surface of the vmPFC that made accurate gray–white segmentation and manual correction impossible in these areas. For this reason, we visually verified the validity of the segmentation in this area for every subject. Two subjects were excluded from the extinction retention covariate group analysis due to inaccuracies in the segmentation in the vmPFC region of correlation that could not be manually corrected.

The segmentation and volumetric measurement of subcortical brain structures were performed using an automated procedure described in detail by Fischl et al. (2002). Briefly, each voxel within the MRI volume is assigned a neuroanatomical label using both a subject-independent probabilistic atlas constructed from a manually labeled MRI volumes, as well as subject-specific image intensity values. The final subcortical segmentation is the one that maximizes the likelihood of the intensity value of each voxel given the prior probabilities derived from the atlas. This procedure produces subcortical labeling that is statistically indistinguishable from those generated manually (Fischl et al. 2002). For each subcortical structure, this procedure yields a volume measurement in units of 1-mm cubic voxels. We then obtained the correlation between these volume measurements for the left and right amygdala and our acquisition covariate for each subject.

Regions of Interest

Based on the findings from previous fear conditioning studies (Shi and Davis 1999; Milad et al. 2005, 2007), as well as the fMRI results of the studies from which these data were obtained (Phelps et al. 2004; Delgado et al. 2008), we had a priori hypotheses about regions in which cortical thickness might correlate with our measures of fear acquisition and inhibition. We hypothesized that amygdala volume as well as the thickness of regions within dACC and insular cortex might be correlated with our 2 measures of acquisition and that thickness within vmPFC might be correlated with our 2 measures of fear inhibition. Additionally, we hypothesized that the intentional cognitive regulation strategies might be correlated with thickness in dorsolateral and ventrolateral prefrontal cortical areas. Regions of interest were defined using automatic anatomical labeling within FreeSurfer (Fischl et al. 2004; Desikan et al. 2006) so that effects found within the region could be corrected for multiple comparisons.

Statistical Thresholding

Our cluster significance threshold for the vertex-based general linear model analysis was set at $P < 0.001$ (2-tailed, uncorrected) for the peak voxel within a cluster, a minimum cluster inclusion threshold of $P < 0.01$ (2-tailed, uncorrected) for each vertex, and a cluster size threshold of 30 mm^2 or larger (a surface area roughly corresponding to three 3-mm functional voxels). Correction for multiple comparisons for any clusters within our a priori regions of interest that exceeded this threshold was performed using the random field theory (RFT) methods implemented in SurfStat (Worsley et al. 2009), using a $P < 0.05$ (2-tailed) cluster significance threshold.

Results

Vertex-based correlation maps depicting regions of significant correlation between cortical thickness and our 2 measures of acquisition are shown in Figure 1*A*,*B*. The analysis revealed adjacent regions of right posterior insula that correlated positively with our measures of acquisition derived from both the cognitive regulation data set (Fig. 1*A*, peak vertex: $x = 40$, $y = -15$, $z = -6$; Talairach and Tournoux 1988) and the extinction data set (Fig. 1*B*, peak vertex: $x = 54$, $y = -6$, $z = 0$). Across both data sets, individuals with greater cortical thickness in the posterior insula/temporal operculum region exhibited larger conditioned SCRs. Scatter plots depicting the relationship between mean cortical thickness of the regions of significant correlation and each fear acquisition measure across subjects are shown in Figure 1*C* for the cognitive regulation data set ($r(16) = 0.701$ $P = 0.001$) and Figure 1*D* for the extinction data set ($r(10) = 0.840$ $P = 0.0006$). The region of correlation in the posterior insula/temporal operculum region in the cognitive

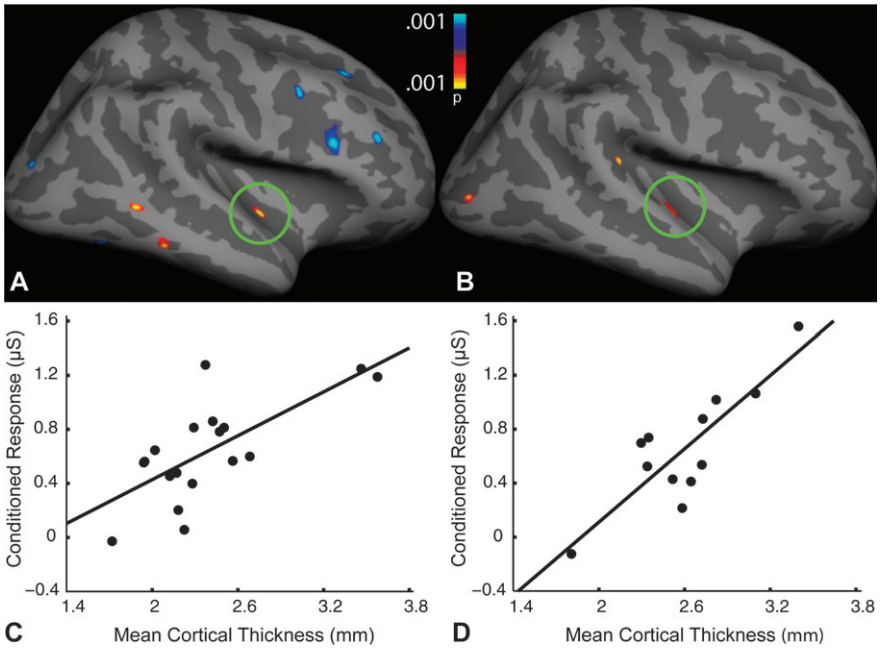

Figure 1. (*A*/*B*) Shown here on the FreeSurfer average brain surface are adjacent regions of right posterior insula/temporal operculum in which cortical thickness was correlated with conditioned fear during acquisition in the cognitive regulation (*A*) and extinction (*B*) experiments (cluster maximum of $P < 0.001$, uncorrected, minimum vertex inclusion threshold $P < 0.01$, uncorrected). (*C*) Scatter plot depicting the relationship between the mean cortical thickness of the region shown in (*A*) and the skin conductance measure of conditioned fear during acquisition in the cognitive regulation experiment. (*D*) Scatter plot depicting the relationship between the mean cortical thickness of the region shown in (*B*) and the skin conductance measure of conditioned fear during acquisition in the extinction experiment.

regulation data set remained significant after correction for multiple comparisons within the insula using RFT ($P = 0.035$); however, the corresponding region in the extinction data set (with only 12 participants) did not survive RFT correction. Amygdala volume was not significantly correlated with our acquisition measure in either data set; however, these data suggest a trend toward a negative correlation between amygdala volume and the magnitude of subjects' acquired fear responses in both the cognitive regulation data set (left amygdala: $r(16) = -0.399$, $P = 0.101$; right amygdala: $r(16) = 0.036$, $P = 0.886$) and the extinction data set (left amygdala: $r(10) = -0.549$, $P = 0.065$; right amygdala: $r(10) = -0.580$, $P = 0.048$).

We did not find a correlation that attained our significance threshold between our extinction retention measure and cortical thickness within vmPFC, our extinction region of interest. However, using a lowered peak voxel threshold of $P = 0.003$, uncorrected, we found a small region of left vmPFC that correlated positively with our measure of fear inhibition via extinction (Fig. 2*A*, peak vertex: $x = -4$, $y = 39$, $z = -20$). This correlation did not attain significance after correction for multiple comparisons within the vmPFC using RFT. A scatter plot depicting the relationship between the mean cortical thickness of the significant region and the extinction retention index across subjects is shown in Figure 2*B* ($r(8) = 0.832$ $P = 0.003$). Individuals with thicker cortex in this vmPFC region exhibit greater fear inhibition during day 2 recall of extinction retention learning. There was no significant correlation between our measure of intentional cognitive regulation and cortical thickness within vmPFC or lateral prefrontal cortex, our a priori regions of interest.

Notably, our measures of fear acquisition and inhibition were uncorrelated. Thus, the magnitude of an individual's acquired fear response was uncorrelated with the magnitude of fear reduction via cognitive regulation or extinction learning.

There was no correlation between state or trait anxiety measures from the cognitive regulation data set and our physiological measures of acquisition, suggesting that anxiety does not mediate the relationship between fear expression and thickness in the insula region. Individual shock levels were not recorded; however, previous research has found no relationship between shock intensity and CR magnitude (Kimmel et al. 1969; Silver et al. 1978). Unconditioned response magnitude was unrelated to thickness in the insula region in both data sets.

There was no significant difference in either data set between males and females in amygdala volume, mean cortical thickness of the vmPFC and insula regions, or the physiological measures of acquisition and regulation.

Our analyses also revealed areas outside of our a priori regions of interest in which there was a positive correlation between cortical thickness and our fear acquisition and inhibition covariates. Regions that exceeded our significance threshold are listed in Table 1.

Discussion

In data from 2 separate fear conditioning experiments, the magnitude of individual's acquired fear responses was correlated with cortical thickness of a region within the posterior insula/temporal operculum, suggesting a role for this region in the expression of conditioned fear. The insula is thought to be critically involved in the representation of aversive experience. The posterior insula receives afferent viscerosensory information about the physiological state of the body via the posterior portion of the ventral medial nucleus of the thalamus (Craig

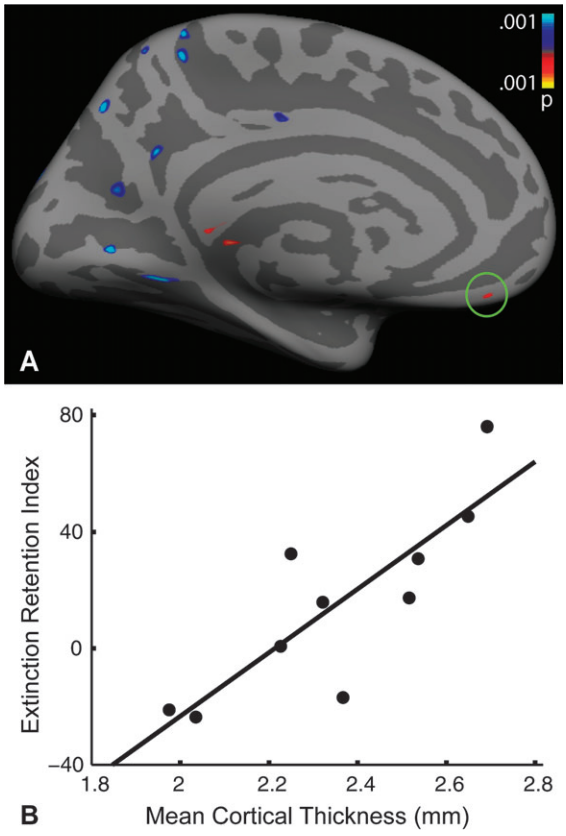

Figure 2. (*A*) Shown on the FreeSurfer average brain surface is a region of left vmPFC in which cortical thickness was correlated with conditioned fear expression during extinction recall. The peak vertex cluster significance threshold was reduced to $P = 0.003$ (uncorrected), and the cluster area threshold was removed in an attempt to replicate the previous finding by Milad et al. (2005). (*B*) Scatter plot depicting the relationship between the mean cortical thickness of the region shown in (*A*) and the extinction retention index from the extinction experiment.

Table 1

Clusters of size 30 mm^2 or greater with peak vertex of $P < 0.001$, uncorrected, showing a positive correlation with a given covariate

Region	*x,y,z* (Talairach)	Max *P*	Size (mm^2)
Cognitive regulation data set—acquisition covariate			
R, posterior insula	41, −15, −6	0.0003	34.53
R, medial temporal gyrus	62, −49, 1	0.0005	49.90
L, medial temporal gyrus	−60, −27, −9	0.0006	36.00
R, inferior temporal gyrus	57, −40, −12	0.0008	56.10
Cognitive regulation data set—regulation covariate			
L, superior parietal lobule	−27, −65, 41	0.000002	63.02
L, fusiform gyrus	−31, −66, −6	0.000005	74.97
L, superior parietal lobule	−23, −58, 54	0.0001	43.20
L, postcentral gyrus	−57, −19, 27	0.0002	45.52
L, superior temporal gyrus	−60, −20, 0	0.0002	31.58
R, precuneus	19, −52, 10	0.0003	81.95
R, medial temporal gyrus	60, −52, 9	0.0003	38.08
L, medial temporal gyrus	−60, −46, 4	0.0004	34.31
Extinction data set—acquisition covariate			
R, transverse temporal gyrus	46, −33, 15	0.000002	34.68
L, fusiform gyrus	37, −37, −17	0.00003	52.56
R, posterior cingulate sulcus	14, −37, 40	0.00006	68.16
R, medial occipital gyrus	40, −78, 4	0.0003	54.87
L, inferior frontal gyrus	48, 18, 10	0.0005	41.61
R, posterior insula/temporal operculum	54, −6, 0	0.0009	100.48
Extinction data set—regulation covariate			
L, superior temporal gyrus	−60, −25, 2	0.0002	48.22
L, medial temporal gyrus	−41, −9, −28	0.0005	65.60
R, medial temporal gyrus	50, 2, −22	0.0009	35.6
L, medial temporal gyrus	−52, −18, −12	0.0009	92.00

Note: Vertex-based cluster inclusion threshold of $P < 0.01$, uncorrected.

2002). This includes nocioceptive information about painful somatic sensations. Consistent with this anatomical connectivity, single-unit recording in monkeys has found neurons within the posterior insula that are responsive to painful stimulation (Robinson and Burton 1980). Furthermore, microstimulation of regions within the human posterior insula in epileptic patients elicited reports of painful sensation (Ostrowsky et al. 2002). Thus, evidence across species supports the interpretation that the posterior insula is involved in the representation of pain. The posterior insula, in turn, has reciprocal connections with the amygdala (Reynolds and Zahm 2005) and is thus well positioned to convey somatosensory information about an aversive US to the amygdala during fear conditioning. Lesion studies in rodents suggest that the posterior insula is part of 1 of 2 parallel pathways responsible for relaying information about the US to the amygdala during conditioning (Shi and Davis 1999).

Numerous neuroimaging studies in humans have observed increases in blood oxygen level–dependent (BOLD) activation in the posterior insula in response to painful stimulation (see Peyron et al. 2000 review). Interestingly, many of these studies report increases in insula activation not only in response to the experience of aversive stimulation but also to the anticipation of imminent aversive physical sensation as well. While such anticipatory responses are typically associated with BOLD increases in the anterior insula (Ploghaus et al. 1999; Jensen et al. 2003; Wager et al. 2004), several studies have reported increased posterior insula activation during the anticipation of aversive physical or visual stimuli (Dalton et al. 2005; Berns et al. 2006; Simmons et al. 2006). Models for the formation of associations between stimuli and future salient outcomes have proposed that the prediction of future events involves evaluating a representation of an anticipated outcome against an actual outcome to update expectancies (Rescorla and Wagner 1972; Schultz et al. 1997). Research suggests that the insular cortex may be involved in the encoding of anticipatory signals that play a role in aversive learning (Ploghaus et al. 1999). Based on the observations that the insula is highly responsive to anticipated aversive events and that anxious individuals appear to exhibit altered function in insular cortex, Paulus and Stein (2006) recently proposed that anxiety-prone individuals may invoke exaggerated representations of predicted aversive events. Our finding that increased fear reactivity in normal healthy subjects was correlated with cortical thickness in insular cortex is consistent with this proposal that differential processing in this region may underlie individual differences in responses to anticipated aversive events.

In addition to its role in representing experienced or anticipated aversive stimulation, the insula is also involved in modulating sympathetic nervous system arousal, including blood pressure, heart rate, and electrodermal activity, via descending projections to autonomic nuclei (Oppenheimer et al. 1992; Critchley 2002). Previous studies have observed a positive correlation between BOLD activation in the insula and SCRs while participants are under the threat of shock (Phelps et al. 2001), as well as in a nonfear-related task (Critchley et al. 2000). This dual role of the insula suggests a potential mechanism by which anticipatory signals during fear learning may be associated with conditioned arousal.

In conflict with a recent finding that cortical thickness of the dACC correlated with SCR during fear acquisition (Milad et al. 2007), we did not find any region of the dACC in which thickness correlated with our acquisition measures. One difference between the conditioning paradigm used in the study of Milad et al. and ours was their use of a 100% reinforcement schedule for the US, while both of our experiments used partial reinforcement. A recent study exploring differences in BOLD activation during fear conditioning as a function of reinforcement rate reported that the dACC activation to a CS increases linearly with reinforcement rate, while the insula is maximally responsive to partial reinforced cues (Dunsmoor et al. 2007). This is consistent with several studies investigating anticipatory activity to certain or uncertain predictors of reinforcement that report greater insula activity to cues indicating increased uncertainty (Huettel et al. 2005; Brown et al. 2007; Sarinopoulos et al. 2010). A recent proposal based on a computational model of fear conditioning is that the dACC computes a prediction of the UCS, while insula activity is better approximated by an attention-modulated representation of the CS, which incorporates factors such as uncertainty (Dunsmoor and Schmajuk 2009). While the precise computational roles of the regions involved in fear learning have yet to be clarified, there is strong evidence that the neural structures recruited during fear learning may vary depending on the degree of uncertainty about the relationship between the CS and UCS.

Amygdala volume across subjects was not significantly correlated with our fear acquisition measure. However, the observed correlations suggest a trend toward a negative relationship between amygdala volume and the magnitude of subjects' conditioned fear responses. The amygdala is a heterogeneous structure composed of multiple nuclei that are differentially implicated in the acquisition, storage, and expression of conditioned fear (for reviews, see LeDoux 2000; Maren 2001; Phelps and LeDoux 2005). While numerous studies have reported a significant difference in amygdala volumes in individuals with various psychiatric conditions versus normal controls (Szeszko et al. 1999; Zetzsche et al. 2006; Rosso et al. 2007), few have explored the relationship between amygdala volume and differences in affective responding in healthy individuals. A recent study found that strains of mice with smaller basolateral amygdala nucleus (BLA) volume exhibited stronger fear responses to conditioned stimuli when compared with larger BLA groups (Yang et al. 2008). Furthermore, this variation in BLA volume was unrelated to the display of anxiety or depression-like behavior in individual animals. This is consistent with recent evidence of increased stressor-evoked physiological reactivity in healthy human subjects with reduced amygdala volume (Gianaros et al. 2008). Although our present data do not provide clear evidence of an inverse relationship between total amygdala volume and subjects' CR during acquisition, future research might examine directly whether variation in BLA volume is more closely related to such individual differences in fear acquisition.

Replicating a previous finding by Milad et al. (2005), we observed a positive correlation between cortical thickness in a region of vmPFC and our extinction retention measure. Converging lines of research across species suggest that the vmPFC plays a critical role in the retrieval of extinction learning after consolidation (see Sotres-Bayon et al. 2006; Quirk and Mueller 2008 for a review). Lesion studies have implicated the infralimbic region of the rodent medial prefrontal cortex as a key region involved in the retention of extinction learning (Morgan and LeDoux 1995; Milad and Quirk 2002). In these studies, lesioned animals showed failure to recall extinction memory after a delay. Electrophysiological evidence suggests that the infralimbic region may play a role in inhibiting fear expression during extinction recall. Single-unit recordings from the infralimbic region revealed an inverse correlation between neuronal activity and the expression of conditioned fear, and microstimulation within this same region reduced conditioned freezing in rats that had not undergone extinction learning (Milad and Quirk 2002). Although direct homology across species is difficult to infer, the subgenual anterior cingulate cortex and medial orbitofrontal cortex have been proposed to be potential human homologues of the rodent infralimbic region (Ongur and Price 2000). Thus, consistent with the finding that increased activity in the rodent infralimbic region modulates the reduction in fear expression, the fMRI study in humans from which the data in this study were obtained found that increased BOLD signal in the subgenual cingulate region of the vmPFC correlated with the reduction of fear expression during extinction recall (Phelps et al. 2004; see also Knight et al. 2004). Our replication of the finding that cortical thickness in a region of vmPFC correlates positively with the retention of extinction learning suggests that individual differences in fear inhibition via extinction retrieval may have a structural basis. Thickness in this cortical region may be tied to one's vulnerability to or resilience against fear-related disorders. Evidence of structural and functional abnormalities in the vmPFC region of PTSD individuals supports this notion (see Rauch et al. 2006 for review).

Our analysis did not reveal a relationship between cortical thickness in our prefrontal regions of interest and the reduction of fear via cognitive regulation strategies. This suggests that individual differences in the ability to inhibit conditioned fear using intentional strategies may not have a structural basis or that the present methods used were not sufficient to reveal such a relationship. This may reflect a substantive difference between automatic and controlled processes. Fear expression during acquisition and fear inhibition during extinction retrieval are relatively automatic processes that may be critically influenced by their structural substrates. However, it seems plausible that any executive control processes recruited during the intentional cognitive regulation task may not be specific to affective control and thus might not have a structural basis that is correlated with our physiological arousal measure. Additionally, individual subjects may be using distinct cognitive processes during intentional cognitive regulation, due to the fundamentally subjective nature of the mental imagery task involved in the strategy.

An important finding revealed in this individual differences analysis of fear acquisition and inhibition was that the physiological measures indexing fear reactivity and regulation were uncorrelated within subjects. Individuals displaying larger acquired fear responses were able to reduce these fear responses via extinction learning or intentional cognitive regulation. Correspondingly, we identified distinct regions in the brain in which cortical thickness was correlated with fear acquisition and fear inhibition via extinction retention. This decoupling suggests that fear reactivity and fear reduction have distinct underlying processes and implies that individuals who are highly reactive to cues indicating potential aversive events

can adaptively modulate these responses via implicit extinction learning and intentional cognitive regulation strategies.

The mechanism by which cortical thickness might give rise to functional differences is not presently well understood; however, research on the neuroanatomy of the cortex provides a basis for speculation. Neurons within the cerebral cortex are clustered into columns that are oriented perpendicular to the pial surface (Mountcastle 1997). The radial unit hypothesis, a prominent theory of cortical development, proposes that neurons within a given column migrate from a common origin and that the thickness of cortex is primarily determined by the number of neurons within the column (Rakic 1995). These columns may function as modular processing units, involved in the transformation of incoming signals (Mountcastle 1997). Although the functional properties of cortical columns have been questioned (Horton and Adams 2005), one possibility is that increased cortical thickness, due to the presence of a greater number of neurons within a column, may influence the strength of the excitatory or inhibitory output signals from the region.

An understanding of how the brain generates and regulates emotional expression is of fundamental interest. Emotion regulation is critical for the adaptive behavior of social animals, such as humans. Basic research into how fears are acquired and diminished has important implications for the potential treatment of fear and anxiety related disorders, as well as for the understanding of the normal variation in emotional behavior. Much of the research on the acquisition and reduction of conditioned fear has focused on investigating factors that determine the mean behavior within a group. Though this approach has yielded valuable knowledge about the neural mechanisms underlying classical conditioning, it does not address the considerable variability in emotional expression across individuals. The relationship reported here between cortical thickness measurements and physiological measures of fear acquisition and extinction suggests that brain structure may be an important factor mediating individual differences in affective reactivity and control.

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