

# Specificity of regional brain activity in anxiety types during emotion processing

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## Abstract

The present study tested the hypothesis that anxious apprehension involves more left- than right-hemisphere activity and that anxious arousal is associated with the opposite pattern. Behavioral and fMRI responses to threat stimuli in an emotional Stroop task were examined in nonpatient groups reporting anxious apprehension, anxious arousal, or neither. Reaction times were longer for negative than for neutral words. As predicted, brain activation distinguished anxious groups in a left inferior frontal region associated with speech production and in a right-hemisphere inferior temporal area. Addressing a second hypothesis about left-frontal involvement in emotion, distinct left frontal regions were associated with anxious apprehension versus processing of positive information. Results support the proposed distinction between the two types of anxiety and resolve an inconsistency about the role of left-frontal activation in emotion and psychopathology.

**Descriptors:** fMRI, Anxiety, Anxious apprehension, Anxious arousal, Emotion, Stroop

According to lifetime prevalence estimates from a recent large survey of mental illness and its treatment in the United States, anxiety disorders are the most commonly reported psychiatric disorders, closely followed by mood disorders (Kessler et al., 2005). Research, treatment, and public policy efforts regarding anxiety and depression have typically focused on emotional

symptoms. However, these emotional states have significant effects on cognitive function as well, resulting in an unmeasured but considerable toll on productivity and efficiency (for reviews, see Levin, Heller, Mohanty, Herrington, & Miller, in press; Mohanty & Heller 2002; Nitschke & Heller, 2002, 2005; Nitschke, Heller, & Miller, 2000). Anxiety has specific effects on cognition. In particular, it has been strongly associated with an attentional bias toward threatening stimuli (Compton, Heller, Banich, Palmieri, & Miller, 2000; McNally, 1998; Nitschke & Heller, 2002). In various paradigms, attention is captured by ambiguous, emotional, or threatening information. Anxiety also impairs performance on tasks that are difficult or stressful, because worrisome thoughts interfere with attention to task-relevant information (e.g., McNally, 1998). These attentional effects have been documented in trait and state anxiety (e.g., Egloff & Hock, 2001) and in every *DSM-IV-TR* (American Psychiatric Association, 2000) anxiety disorder (for reviews, see Heller, Koven, & Miller, 2003; Nitschke & Heller, 2002, 2005). An implication is that, if someone is anxious, their attention is at constant risk for diversion from the task at hand, slowing or impairing performance.

Anxiety is not a monolithic construct. We have distinguished two types of anxiety, anxious apprehension and anxious arousal, associated with different patterns of brain activity. Anxious apprehension is primarily characterized by worry and verbal rumination (Barlow, 1991; Heller, Nitschke, Etienne, & Miller,

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1997). The timescale for perceived threat in anxious apprehension can range from immediate to distant future (Nitschke et al., 2000). For example, the content of persistent worrisome thoughts may include personal and emotional threats to self, physical health, competence at work, or general world problems. These worries are mentally rehearsed repeatedly without resolution and are difficult to dismiss (Mathews, 1990). In addition to worry, physical symptoms often accompany anxious apprehension, including restlessness, fatigue, and muscle tension (Nitschke, Heller, Palmieri, & Miller, 1999).

Anxious arousal, in contrast, is characterized by somatic tension and physiological hyperarousal. Symptoms associated with anxious arousal include pounding heartbeat, sweating, dizziness, feeling of choking, and shortness of breath (Nitschke et al., 1999). Threats that trigger anxious arousal are more likely to reflect perceived immediate danger rather than events in the distant future (Nitschke et al., 2000). Although these two types of anxiety are not mutually exclusive and may be present in varying degrees in different disorders, anxious apprehension is prominent in generalized anxiety disorder and obsessive compulsive disorder, whereas anxious arousal is characteristic of panic attacks and high-stress situations (Nitschke et al., 2000).

We have argued that an understanding of the patterns of brain activity that characterize anxiety and depression directly informs understanding of their cognitive consequences. Numerous studies employing electroencephalographic (EEG), event-related brain potential (ERP), and hemodynamic (PET, fMRI) methods have shown that activity in regions of cortex specialized for particular modes of information processing covaries with performance on tasks that benefit from that type of computation. In the vast majority of studies, increased activity is associated with better performance (Heller, Nitschke, & Lindsay, 1997), whereas decreased activity is associated with impaired performance. In the few studies not showing such a relationship, the effects have been attributed to decreases in use of nonessential brain areas with practice, changes in cognitive strategies, or changes in task demands (e.g., Haier et al., 1992). Because different emotions are associated with changes in regional brain activity that may either enhance or impair performance, depending on the role that a particular brain region plays in the implementation of a task (for reviews, see Compton et al., 2003; Heller et al., 2003; Levin et al., in press), it follows that the cognitive consequences of anxiety and depression might drive or reflect changes in the levels of activity in critical regions of cortex.

We have hypothesized that patterns of brain activity are different for anxious apprehension, anxious arousal, and depression and that it is therefore critical to distinguish them in experimental paradigms. In particular, anxious apprehension should be characterized by increased left-hemisphere activity and anxious arousal by increased right-hemisphere activity (Heller, Etienne, & Miller, 1995; Heller & Nitschke, 1998; Heller, Nitschke, Etienne, et al., 1997; Nitschke et al., 2000). This hypothesis is consistent with established specializations of the two hemispheres as well as research on brain activity associated with various anxiety disorders and by EEG research directly comparing psychometrically distinct anxiety groups (Nitschke et al., 1999).

The left hemisphere has been implicated in studies of obsessive-compulsive disorder (e.g., Baxter et al., 1987; Swedo et al., 1989), generalized anxiety disorder (e.g., Wu et al., 1991; for a review, see Nitschke & Heller, 2002), and trait anxiety (Tucker, Antes, Stenslie, & Barnhardt, 1978). Compared to control participants, psychometrically defined anxious apprehension

participants exhibited an EEG asymmetry in favor of the left hemisphere during a resting condition (Heller, Nitschke, Etienne, et al., 1997). Similarly, worrying about an impromptu speech task was associated with greater left frontal EEG activity than fearing a more imminent stressor (Hofmann et al., 2005). These findings linking the left hemisphere to anxiety disorders that feature worry and anxious apprehension are consistent with its specialization for language. Thus, anxiety-related impairments in various tasks could reflect ruminative activity in left-hemisphere verbal processing circuits.

In contrast, the right hemisphere is involved in vigilance and autonomic arousal (Compton et al., 2003; Heller, Nitschke, Etienne, et al., 1997), and right-hemisphere regions such as temporoparietal cortex and inferior frontal cortex are involved in detecting salient stimuli that are behaviorally relevant (for a review, see Corbetta & Shulman, 2002). The right hemisphere has been implicated in studies of patients with panic disorder or panic symptoms (Reiman, Raichle, Butler, Herscovitch, & Robins, 1984; Swedo et al., 1989) and nonpatients in high-stress situations (Tucker, Roth, Arneson, & Buckingham, 1977). In nonpatients, exposure to threatening words enhanced left visual field (right-hemisphere) processing in subsequent letter identification tasks (Van Strien & Heijt, 1995; Van Strien & Morpurgo, 1992), the threat of electric shock decreased the left hemisphere advantage on a dichotic listening task of syllable identification (Asbjornsen, Hugdahl, & Bryden, 1992), and performance under exam stress indicated a decreased left-hemisphere advantage on a letter discrimination task (Gruzeliel & Phelan, 1991). To examine whether presenting threatening information to one hemisphere or the other would affect performance for each type of anxiety, Compton et al. (2000) used a variation of the emotional Stroop task. Positive, neutral, and threat words were presented in either the left or right visual field, a colored square was presented in either the same or opposite visual field, and participants were instructed to identify the color of the square. Consistent with other behavioral studies, an overall advantage of the left hemisphere for color naming was reduced when emotional distracters were present, due to an increase in performance of the right hemisphere, in effect a better division of labor between hemispheres. This finding was carried by the anxious apprehension group; the anxious arousal group did not make such a strategic adjustment. Thus, threat-related stimuli are likely to engage the right hemisphere and to do so differentially as a function of type of anxiety (for reviews, see Compton et al., 2000; Corbetta & Shulman, 2002; Nitschke et al., 2000).

In the Heller, Nitschke, Etienne, et al. (1997) EEG study mentioned above, participants were recruited on the basis of high or low self-reported trait anxiety scores as a means of assessing anxious apprehension, with both groups low in self-reported depression. Anxious arousal was experimentally induced using emotional narratives modeled on those of Miller et al. (1987). During the emotional narratives, the anxious apprehension group showed an increase in right but not left parietal activity, whereas the control group displayed no hemispheric difference. Thus, trait anxious apprehension served essentially as a risk factor for state anxious arousal. Nitschke et al. (1999) found different resting levels of EEG brain activity for groups characterized by anxious apprehension and anxious arousal, with the anxious arousal group showing more right- than left-hemisphere activity. Increased frontal and posterior right-hemisphere activity as measured by fMRI has also been demonstrated in normal individuals in response to high-arousal

negative words during an emotional Stroop task (Compton et al., 2003). These and other findings (e.g., for a review of the literature on brain damage, see Heller, Nitschke, Lindsay, 1997) point to the importance of the right hemisphere in anxious arousal. Overall, research supports the laterality pattern of greater left- than right-hemisphere activity for anxious apprehension and greater right- than left-hemisphere activity for anxious arousal. Although this differential laterality pattern is established in the EEG/ERP literature, it has not been examined with electromagnetic or hemodynamic methods having the spatial resolution to foster localization of the laterality effect(s).

The available picture for anxious apprehension versus anxious arousal is difficult to reconcile with another literature, that on regional brain activity associated with emotion. Because anxious apprehension is presumably unpleasant, findings of increased left prefrontal cortical activity in anxious apprehension are seemingly at odds with findings of increased left prefrontal cortical activity for positively valenced emotion or appetitive or approach motivation (e.g., Davidson, 1992, 2004; Harmon-Jones, 2004; Heller, Nitschke, & Miller, 1998; Tomarken, Davidson, Wheeler, & Doss, 1992). Dorsolateral prefrontal cortex (DLPFC), in particular, has been implicated in processing positively valenced emotional information and in the experience of positive affect (Herrington et al., 2005). Enhanced DLPFC activity has been posited to account for the improved performance that has been observed on a variety of executive function tasks during positive affect (Ashby, Isen, & Turken, 1999). An analysis of the cognitive demands of anxious apprehension suggests that it should involve brain areas associated with verbal rehearsal, such as Broca's area (Nitschke et al., 2000).

One possibility is that different prefrontal cortical regions are involved in anxious apprehension and positive emotion processing (Heller & Nitschke, 1998; Heller, Nitschke, Lindsay, 1997). Many distinctions have been offered regarding functional specialization of subregions of the PFC (e.g., dorsolateral PFC involved in manipulation of representations in working memory vs. ventrolateral PFC involved in maintenance of representations; Petrides, 2000). It is thus possible that regions of PFC are differentially involved in modulating anxious apprehension versus processing emotional information. It is also possible that there could be overlap among regions involved, depending on the cognitive demands of a particular task.

The present study examined whether patterns of brain activity during processing of negative information distinguish groups characterized by anxious apprehension, anxious arousal, or low anxiety and whether regions involved in anxious apprehension differ from those involved in processing positively valenced emotional information. fMRI was used to provide better anatomical resolution of relevant circuits than available low-density EEG studies. In addition, by using groups of psychometrically defined anxious apprehension and anxious arousal participants, it was possible to avoid comorbidity and other problems frequently associated with clinical samples and to isolate the dimensions of anxiety that are the target of this investigation. As noted above, in individuals with clinical diagnoses the degree of comorbidity among anxiety types and depression is typically high, and we have argued that it is imperative to separate their effects (e.g., Heller & Nitschke, 1998; Heller et al., 2003; Herrington, Koven, Heller, Miller, & Nitschke, in press; Keller et al., 2000; Nitschke et al., 1999). Selection procedures that minimize the presence of other types of anxiety and depression produce purer groups of participants characterized predomi-

nantly by only one type of anxiety. This experimental strategy maximizes the likelihood that the brain areas that are specifically active in anxious apprehension or anxious arousal can be identified and functionally distinguished.

The data reported here were part of a larger project that collected EEG and fMRI data in separate sessions for both emotional and color-word Stroop tasks. This report focuses on behavioral and fMRI data for the emotional Stroop task. The primary hypothesis was that the anxiety groups would show distinct patterns of brain activity. A substantial effect on overt performance was not anticipated. In nonclinical samples the impairment is typically attenuated, and even with a very large sample statistical significance may depend on careful selection of anxiety measures (e.g.,  $N = 138$  in Koven, Heller, Banich, & Miller, 2003, in which anxiety sensitivity but not anxious apprehension or anxious arousal uniquely and significantly predicted negative-word Stroop interference). The present focus was on brain mechanisms. Specifically, in response to threatening words, more left frontal activity in Broca's area was expected for anxious apprehension and more right PFC and posterior activity for anxious arousal.

Secondarily, the present study included a replication and extension of the study by Herrington et al. (2005) to identify potential differences between left-hemisphere brain regions involved in anxious apprehension versus the processing of positive information. Specifically, Herrington et al. found greater activity for left DLPFC for pleasant than for unpleasant words during an emotional Stroop task. Region-of-interest (ROI) analyses of valence and hemisphere involving this region and its homologue in the right hemisphere found greater left than right DLPFC activity for pleasant words superimposed on greater bilateral activation for pleasant compared to unpleasant words. The present study investigated whether a similar left dorsolateral prefrontal region would emerge for positive compared to negative words as well as potential differences from areas active for anxious apprehension.

## Methods

### Participants

Of 1099 college undergraduates screened for the study, participants were 42 (24 female) paid volunteers (mean age = 18.71 years,  $SD = 0.80$ ) recruited via group questionnaire screening sessions. Participants were classified as high anxious apprehension ( $N = 11$ ), high anxious arousal ( $N = 13$ ), or control ( $N = 18$ ) on the basis of responses on the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990; Molina & Borkovec, 1994) and the Mood and Anxiety Symptom Questionnaire (MASQ; Watson, Clark, et al., 1995; Watson, Weber, et al., 1995). The anxious apprehension group scored above the 80th percentile on the PSWQ and below the 50th percentile on the MASQ Anxious Arousal scale. The anxious arousal group scored above the 80th percentile on the MASQ Anxious Arousal scale and below the 50th percentile on the PSWQ. The control group scored below the 50th percentile on both scales. (Data from a subset of the control group were analyzed for a portion of a report by Mohanty et al., 2007.) All subjects also scored below the 50th percentile on a depressed-mood subscale (Nitschke, Heller, Imig, McDonald, & Miller, 2001) of the MASQ Anhedonic Depression scale. The PSWQ, MASQ-AA, and full

**Table 1.** Questionnaire Scores Used in Group Selection

Group	PSWQ		MASQ-AA		MASQ-AD	
	Time 1	Time 2	Time 1	Time 2	Time 1	Time 2
Anxious apprehension	69.00 (3.52)	62.91 (8.57)	20.18 (1.99)	20.91 (2.77)	13.09 (2.43)	14.00 (3.26)
Anxious arousal	39.31 (7.33)	36.31 (10.18)	38.08 (4.33)	32.46 (9.89)	14.85 (1.82)	13.92 (1.44)
Control	37.22 (8.68)	34.39 (8.42)	20.33 (1.85)	20.17 (2.20)	12.00 (2.30)	12.67 (2.68)

*Note.* Questionnaire scores (mean (*SD*)) for each group at mass testing (Time 1) and laboratory session (Time 2). The anxious apprehension group scored higher than the other two groups on the Penn State Worry Questionnaire (PSWQ) ( $p < .001$ ), and the anxious arousal group and control group did not differ significantly from each other. The anxious arousal group scored higher than the other two groups on the Mood and Anxiety Symptom Questionnaire Anxious Arousal scale (MASQ-AA) ( $p < .001$ ), and the anxious apprehension group and control group did not differ significantly from each other. On the MASQ Anhedonic Depression scales (MASQ-AD), the anxious arousal group scored higher than the control group at Time 1 ( $p = .003$ ), but the three groups did not significantly differ at Time 2.

MASQ-AD were administered again when participants came to the laboratory session. As expected, the three groups differed significantly on the two anxiety scales and did not differ on MASQ-AD (see Table 1 for means and standard deviations). The groups did not differ in age,  $F(2,39) = 0.248$ ,  $p = .782$ , or gender balance,  $\chi^2(2, N = 42) = 2.379$ ,  $p = .304$ . All participants were right-handed, native speakers of English with self-reported normal color vision. Participants were given a laboratory tour, informed of the procedures of the study, and screened for claustrophobia or other contraindications for MRI participation. Six participants (2 anxious apprehension, 1 anxious arousal, 3 control) were excluded from the study due to scanner artifact, yielding the total of 42 participants.

#### Stimuli and Experimental Design

The emotional Stroop task consisted of blocks of pleasant or unpleasant emotion words alternating with blocks of neutral words. Each trial consisted of one word presented in one of four ink colors (red, yellow, green, blue) on a black background, with each color occurring equally often with each word type (pleasant, neutral, unpleasant). Participants were instructed to press one of four buttons to indicate the color in which the word appeared on the screen, with word meaning irrelevant to the task. To the extent emotion stimuli attract attention, rapid and correct performance depends on attention being directed away from word meaning. Participants received 256 trials in 16 blocks (4 positive, 8 neutral, 4 negative) of 16 trials. Pilot studies for this project as well as published studies show that a blocked design is more effective in eliciting emotion-word Stroop interference than is an intermixed design (e.g., Compton et al., 2000; Dalgleish, 1995; Holle, Neely, & Heimberg, 1997).

Word presentation and reaction-time measurement were controlled by STIM software (James Long Company, Caroga Lake, NY). Stimuli were displayed using LCD goggles (Magnetic Resonance Technologies, Willoughby, OH). A trial began with the presentation of a word for 1500 ms, followed by a fixation cross for 275 to 725 ms (onset-to-onset ITI  $2000 \pm 225$  ms). Each participant received one of eight orders designed specifically to control stimulus order effects. In four of the eight presentation orders, the first and third blocks were neutral words, with pleasant and unpleasant blocks second or fourth, with valence order counterbalanced across participants. This sequence of four blocks occurred four times for a total of 16 blocks. The remaining four presentation orders complemented this pattern, with the first and third blocks being either pleasant or unpleasant emotion words and the neutral words second and fourth. Pilot work showed that in a blocked design there is an increased likelihood

that emotional words influence the reaction time for the neutral words immediately following the emotional words. Thus, these eight orders of presentation were designed to ensure that the neutral and emotional words preceded each other equally often. Stimulus familiarity was controlled by ensuring that no word was repeated throughout the experiment. Within a block, each color appeared four times, and trials were pseudorandomized such that no more than two trials featuring the same color appeared in a row. After every fourth block, there was a brief rest period. In addition to the 16 word blocks, there were four fixation blocks, one at the beginning, one at the end, and two in the middle of the experiment. Instead of a word, a brighter fixation cross was presented for 1500 ms, followed by the fixation cross that followed word stimuli.

The 256 word stimuli were selected from the Affective Norms for English Words set (ANEW: Bradley & Lang, 1998). Sixty-four pleasant (e.g., birthday, ecstasy, laughter), 64 unpleasant (e.g., suicide, war, victim), and two sets of 64 neutral (e.g., hydrant, moment, carpet) words were carefully selected on the basis of established norms for valence, arousal, and frequency of usage in the English language (Bradley & Lang, 1998; Toggia & Battig, 1978) as well as for number of letters. In the ANEW rating system, all words are considered "emotional" and located somewhere in a valence/arousal plane. Neutral words are toward the low-arousal end of the arousal dimension, and the positive and negative words selected for this study are on the high-arousal end. Words ranged from three to eight letters in length and were presented in capital letters using Tahoma 72-point font.

#### Image Acquisition

Instructions were read verbatim by experimenters to assure that participants were provided with all relevant information about the procedure before participating. The MRI technologist and experimenter assisted the participant in correct placement of earplugs, goggles, and protective headphones. During an initial low-resolution acquisition of anatomical data, the participant performed 64 practice trials. No participants failed to understand the task instructions or the mapping between colors and buttons after completing practice trials. Participants then completed the emotion-word task (and a color-word task not reported here) during functional MRI data acquisition.

MR data were collected using a research-dedicated 3T Siemens Allegra. A gradient-echo echo-planar imaging (EPI) sequence (TR = 2000 ms, TE = 25 ms, flip angle = 60°, FOV = 24 cm) provided 370 functional images (16 images per block of 16 stimuli). Twenty oblique slices were acquired parallel to the axial plane of the anterior and posterior commissures 7

mm contiguous slices, in-plane  $3.75 \times 3.75$  mm). After the EPI sequence, a 128-slice high-resolution structural image was acquired with an MPRAGE sequence (1.3 mm contiguous slices, in-plane  $1 \times 1$  mm) for registering each participant's functional data to standard space.

#### *fMRI Data Reduction and Analysis*

Prior to image processing, the first three volumes of each data set were discarded to allow the MR signal to reach a steady state. Functional image processing and analyses were done via FEAT (fMRI Expert Analysis Tool, FMRIB's Software Library, <http://www.fmrib.ox.ac.uk/analysis/research/feat/>), part of the FSL analysis package (<http://www.fmrib.ox.ac.uk/fsl>). Additional ROI analyses were carried out using locally written Matlab programs (e.g., Herrington et al., 2005) and SPSS version 12.0.1 (SPSS Inc., Chicago IL).

Each fMRI time series was motion-corrected using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), temporally filtered with a nonlinear high-pass filter (to remove drift in signal intensity), mean-based intensity-normalized by the same single scaling factor, and spatially smoothed using a 3D Gaussian kernel (full-width-half-maximum 7 mm) prior to analysis. MCFLIRT effectively adjusts for motion up to one voxel (Jenkinson et al., 2002). No participants exhibited head motion of more than one voxel.

After these preprocessing steps, regression analyses were performed on each participant's time series using FILM (FMRIB's Improved Linear Model) with autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). Statistical maps were generated by applying a regression analysis to each intracerebral voxel. An explanatory variable (EV) was created for each regressor following a customized square waveform that reflected the presentation of each experimental condition. Four EVs were included in the regression model, one for each condition (fixation, positive, neutral, negative). For each EV, the vector of assigned weights corresponding to the experimental condition of interest was convolved with a gamma function to better approximate the temporal course of the blood-oxygen-dependent (BOLD) hemodynamic response (e.g., Aguirre, Zarahn, & D'Esposito, 1998; Miezin, Maccotta, Ollinger, Petersen, & Buckner, 2000). Each EV yielded a per-voxel effect-size parameter ( $\beta$ ) estimate (PE) map representing the magnitude of activity associated with that regressor. Functional activation maps, as well as their corresponding structural MRI map, were transformed into a common stereotaxic space (Talairach & Tournoux, 1988) using FMRIB's Linear Image Registration Tool (FLIRT; Jenkinson & Smith, 2001; Jenkinson et al., 2002).

Inferential statistical analyses were carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) and SPSS. To identify regions of interest for subsequent analysis, voxels with significantly more activity for the negative than the neutral condition were identified within each group via two-tailed, per-voxel  $t$  tests on contrast  $\beta$  maps and then converted to  $z$  scores. Monte Carlo simulations via AFNI's AlphaSim program were used to estimate the overall significance level (probability of a false detection) for thresholding the 3D functional  $z$ -map image (Ward, 2000). These simulations indicated that a cluster size of 206 in combination with a  $z$  value of 2.58 ( $p = .01$ ) provided an overall familywise error rate of .05. Thus, the threshold  $z$  value was set to  $\pm 2.58$  and the minimum cluster size to 206.

To test hypotheses regarding group and laterality, clusters where the response to negative words exceeded the response to

neutral words that survived this thresholding were defined as ROIs for further analysis. (No regions in which response to neutral words exceeded the response to negative words survived this thresholding.) For each ROI, for each participant, the mean  $\beta$  value of the negative-versus-neutral contrast (across voxels within the ROI) was calculated, weighting each voxel equally. Mean  $\beta$  values were also extracted from the homologous region in the opposite hemisphere for each ROI.

To test the primary hypothesis that the anxiety groups would show distinct patterns of brain activity, group variance was captured in two orthogonal contrasts reflecting the hypothesis and applied to the negative-versus-neutral  $\beta$  values. The first contrast pooled the two anxiety groups for comparison to controls, and the second contrast compared the two anxiety groups to each other. The secondary hypothesis, that left-hemisphere regions involved in anxious apprehension and in processing of positive information are distinct, did not rely on such a pattern of group differences. Thus, a three-level group factor was used. The dependent measure was activation for the positive, neutral, or negative condition minus fixation, with the three-level emotion factor evaluated with orthogonal trend components following Herrington et al. (2005). The linear trend (valence) compared positive and negative activation, and the quadratic trend (arousal) pooled positive and negative for comparison to neutral activation. Simple-effects ANOVAs explored significant interactions as appropriate. All tests were two-tailed.

## **Results**

### *Behavioral Data*

Average reaction times (RT) were computed for negative- and neutral-word trials. Every participant demonstrated greater than 80% performance accuracy on the task. A Group (anxious apprehension, anxious arousal, control)  $\times$  Emotion (negative, neutral) MANOVA was conducted. As expected, RT was greater for negative (mean = 680 ms,  $SD = 70$  ms) than for neutral (mean = 664 ms,  $SD = 70$  ms) words,  $F(1,39) = 9.343$ ,  $p = .004$ . Anxious groups exhibited slightly greater interference than the control group, although the difference did not approach significance. That overt performance was equivalent among the groups indicates comparable task engagement, avoiding some interpretive problems often faced in clinical studies with large behavioral differences.

A second Group (anxious apprehension, anxious arousal, control)  $\times$  Emotion (positive, neutral, negative) MANOVA was conducted to explore linear (valence) and quadratic (arousal) orthogonal trends on the emotion factor for reaction time. Results revealed a main effect of emotion,  $F(2,38) = 5.232$ ,  $p = .010$ . The arousal effect confirmed delayed responses for positive and negative relative to neutral stimuli,  $F(1,39) = 10.468$ ,  $p = .002$ . There was no valence effect on RT. Group differences did not approach significance.

### *Primary Hypothesis: Group Differences Processing Negative Words versus Neutral Words*

Table 2 lists regions showing more activity for negative than for neutral words in any group according to the cluster-size threshold described above. The anxious apprehension group exhibited activation in left-hemisphere inferior frontal gyrus (IFG) closely approximating Broca's area (Brodmann areas 44 and 45), middle temporal gyrus, and inferior parietal lobule. The anxious arousal group showed activation in right-hemisphere inferior temporal

**Table 2.** Brain Regions More Active for Negative Than for Neutral Words, by Group

Region	Cluster size	Mean <i>z</i>	Location			Group	Hemisphere	Group × Hemisphere
			X	Y	Z			
High anxious apprehension								
Left inferior frontal gyrus (BA 44, 45, 9, 47)	1138	2.90	-44	20	16		<i>p</i> < .001	<i>p</i> < .05
Left inferior temporal gyrus (BA 20)	312	2.97	-50	-38	0		<i>p</i> < .001	n.s.
Left inferior parietal lobule (BA 7)	432	2.92	-30	-58	44		<i>p</i> < .001	n.s.
High anxious arousal								
Right inferior temporal gyrus (BA 21, 20)	218	2.88	54	-16	-18	<i>p</i> < .05		<i>p</i> < .10
Control								
Right cerebellum	308	2.88	20	-82	-18		<i>p</i> < .01	n.s.
Left inferior frontal gyrus (BA 47)	561	3.14	-46	28	-2		<i>p</i> < .001	n.s.
Left medial frontal gyrus (BA 10)	1007	3.04	-2	54	10	<i>p</i> < .05	<i>p</i> < .001	n.s.
Left superior temporal gyrus (BA 22)	914	3.11	-54	-52	22		<i>p</i> < .05	<i>p</i> < .10

Note. For each group, brain regions showing more activity for negative words than for neutral words. BA refers to Brodmann area in standard brain anatomy. Mean *z* is the average *z* value for the cluster. Whether each region displays an effect of group, hemisphere, or Group × Hemisphere at a *p* < .10 threshold is noted. Degrees of freedom were (2,39), (1,39), and (2,39) for the group, hemisphere, and Group × Hemisphere tests.

gyrus (ITG). The control group displayed activation in left medial frontal gyrus (MFG) extending into rostral anterior cingulate (rACC), left IFG, left superior temporal gyrus, and right-hemisphere cerebellum. Activation in the amygdalae did not survive thresholding procedures.

Each cluster and the homologous region in the other hemisphere served as ROIs in orthogonal Group (anxious apprehension, anxious arousal, control) × Hemisphere (left, right) ANOVAs that represented the primary hypothesis.<sup>1</sup> Negative words prompted left-lateralized activation in all ROIs except for cerebellum (right-lateralized) and ITG (no lateralization). The generally leftward lateralization presumably reflected language processing prompted by the task. Main effects for group emerged for the inferior temporal region identified in the anxious arousal group and for the medial frontal region identified in the control group. These main effects largely reflect how the ROIs were selected and are not as informative as the interactions. Of primary interest were Group × Hemisphere effects. Regions producing neither group nor Group × Hemisphere effects are not discussed further.

Figure 1 illustrates the critical Group × Hemisphere interaction for IFG. The first contrast found no difference between the pooled anxiety groups and controls. The second contrast, comparing the two anxiety groups, produced a Group × Hemisphere effect,  $F(1,22) = 7.847$ ,  $p = .010$ , with more leftward asymmetry in the anxious apprehension group,  $p < .001$ , than in the anxious arousal group,  $p = .024$ , apparent in the right panel of Figure 1.

<sup>1</sup>In the ANOVAs, the left IFG region was that identified in the anxious apprehension group. Use of an ROI across groups and hemispheres defined by activation in a single group and hemisphere potentially fosters regression to the mean and thus artifactual differences in group, hemisphere, and their interaction. Present results, however, cannot be accounted for that way, because the a priori predictions they support are not subject to that problem and because the results do not generally follow regression toward the mean. For example, the ITG region was defined in the right hemisphere of the anxious arousal group, but the anxious apprehension group showed a significant contrary lateralization in that ROI. Regression toward the mean, at worst, would produce no lateralization in that group. An analysis using a spherical ROI centered on Broca's area in IFG was done to avoid the possibility that IFG group differences were an artifact due to regression to the mean, given how the original IFG ROI was selected. This alternative analysis produced the same significant Group × Hemisphere interaction (and main effect of Hemisphere) found using the IFG region identified in the anxious apprehension group, ruling out the regression to the mean confound.

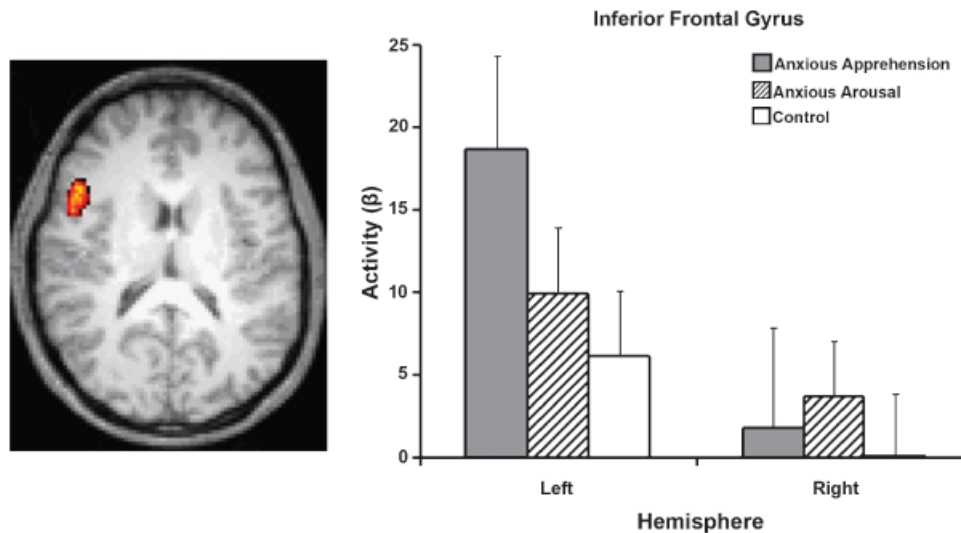
In ITG, Figure 2 shows relatively large responses and distinct laterality patterns in the anxiety groups. Orthogonal contrasts confirmed a larger response than in controls,  $F(1,40) = 9.206$ ,  $p = .004$ , with the two anxious groups not differing overall. The pooled anxiety groups versus controls did not differ by hemisphere, but Figure 2 illustrates contrasting asymmetries for the two anxiety groups, Group × Hemisphere,  $F(1,22) = 13.019$ ,  $p = .002$ , with more left-hemisphere activation in the anxious apprehension group,  $p = .009$ , and more right-hemisphere activation in the anxious arousal group,  $p = .039$ . An alternative dissection of the interaction showed that the anxious arousal group showed greater right-hemisphere activation than did the anxious apprehension group,  $p = .043$ , whereas the groups did not differ in the left hemisphere.

Figure 3 indicates that the medial frontal cluster extending into rACC was less active in the anxiety groups than in controls,  $F(1,40) = 6.578$ ,  $p = .014$ , with no difference between the anxiety groups. The Group × Hemisphere interactions did not approach significance.

Group × Hemisphere ANOVAs were repeated for each of these ROIs, examining activation for positive words relative to neutral words. These were done as omnibus (three-group) tests in the absence of an a priori hypothesis about the groups and positive emotion, in order to test the emotion specificity of the findings above for negative words. Left-hemisphere exceeded right-hemisphere activation for all ROIs in Table 2 (all  $ps < .017$ ) except for right ITG and right cerebellum. No significant group or Group × Hemisphere effects emerged, indicating that group effects were specific to negative-word activation.

### Secondary Hypothesis: Functional Distinctions between Left-Frontal Regions

To test the hypothesis that anxious apprehension and positive affect are associated with activity in distinct regions of left PFC, regions were evaluated for possible association with positive affect, using the procedures of Herrington et al. (2005) to identify a region in the control group with more activation for positive than negative words. A left DLPFC cluster that survived thresholding ( $-26, 18, 38$ ; see Figure 4) overlapping with Herrington et al.'s ( $-32, 24, 42$ ) emerged. This region and the homologous ROI in the right hemisphere were subjected to a Group (anxious apprehension, anxious arousal, control) × Emotion (positive, neutral, negative, each relative to fixation) × Hemisphere MANOVA

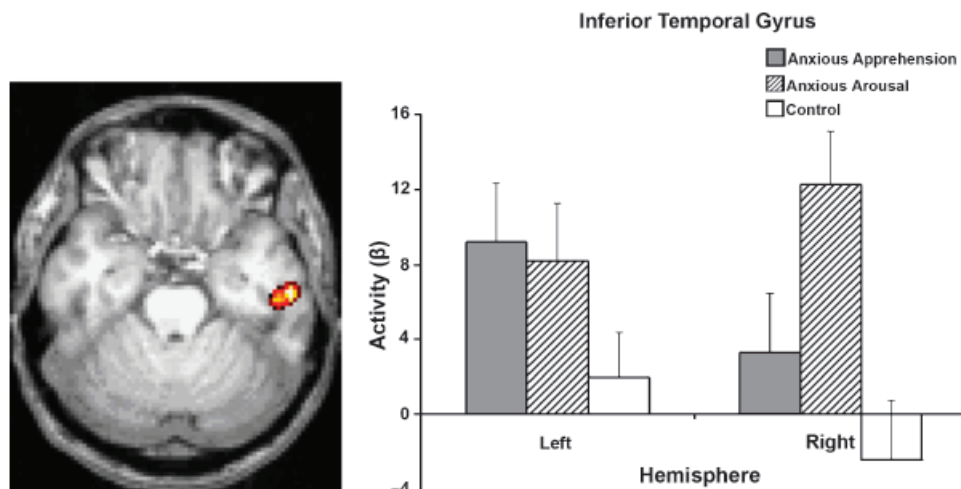


**Figure 1.** Left inferior frontal gyrus (IFG) region identified in the anxious apprehension group as more active for negative than neutral words (Talairach coordinates  $-44, 20, 16$ ; left panel) and Group  $\times$  Hemisphere mean activations (right; mean  $\beta$  values). The left side of the brain is on the left side in the axial slice, and highlighted voxels are those with  $z$  scores  $> 2.58$  meeting cluster-size threshold (see Methods).

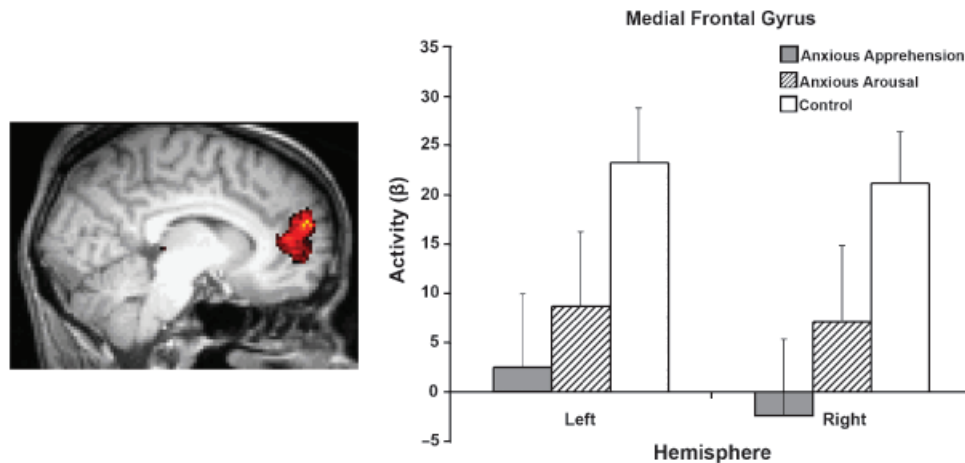
and to orthogonal contrasts described in the Methods section that distinguished emotional valence (positive vs. negative) and emotional arousal (positive and negative vs. neutral).

In contrast to the IFG and ITG regions, in this DLPFC region there were no main effects and no interactions involving group. Figure 5 illustrates an arousal effect for the DLPFC region confined to the left hemisphere, Emotion  $\times$  Hemisphere,  $F(2,38) = 6.205$ ,  $p = .005$ , quadratic Emotion  $\times$  Hemisphere,  $F(1,39) = 12.707$ ,  $p = .001$ , left-hemisphere quadratic Emotion,  $F(1,39) = 8.634$ ,  $p = .006$ . The three-factor MANOVA was repeated after removing a small subregion that overlapped with the IFG region identified in the earlier analysis, with essentially the same results. When the analysis was confined to the control

group (more comparable to the unselected sample of Herrington et al., 2005), findings were even more similar to those of Herrington et al., with more activation of positive than negative words, emotion,  $F(2,16) = 6.744$ ,  $p = .008$ , linear emotion,  $F(1,17) = 14.264$ ,  $p = .002$ , more so in the left hemisphere, Emotion  $\times$  Hemisphere,  $F(2,16) = 5.582$ ,  $p = .014$ , linear Emotion  $\times$  Hemisphere,  $F(1,17) = 3.238$ ,  $p = .090$ . This replicates the Valence and Valence  $\times$  Hemisphere effects of Herrington et al. (as a replication, the present  $p = .090$  for the interaction is adequate). In contrast with Herrington et al., who did not find any effects involving quadratic trends (arousal), the present control-group data showed an arousal effect confined to the left hemisphere, with emotion prompting more activation than



**Figure 2.** Right inferior temporal gyrus (ITG) region identified in the anxious arousal group as more active for negative than neutral words (Talairach coordinates  $54, -16, -17$ ; left panel) and Group  $\times$  Hemisphere mean activations (right; mean  $\beta$  values). The left side of the brain is on the left side in the axial slice, and highlighted voxels are those with  $z$  scores  $> 2.58$  meeting cluster-size threshold (see Methods).



**Figure 3.** Medial frontal gyrus (MFG) region (extending into rostral anterior cingulate cortex, rACC) identified in the control group as more active for negative than neutral words (Talairach coordinates  $-2, 54, 10$ ) and Group  $\times$  Hemisphere mean activations (right; mean  $\beta$  values). Highlighted voxels are those with  $z$  scores  $> 2.58$  meeting cluster-size threshold (see Methods).

neutral trials, quadratic Emotion  $\times$  Hemisphere,  $F(1,17) = 9.740, p = .006$ .

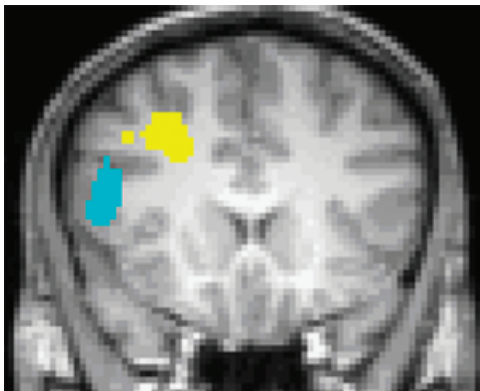
To confirm that the two left frontal clusters, the one in DLPFC and the other in IFG, behaved differently, a direct comparison was carried out with a Group (anxious apprehension, anxious arousal, and control)  $\times$  Emotion (positive, neutral, negative)  $\times$  Hemisphere (left, right)  $\times$  Region (IFG, DLPFC) MANOVA, with orthogonal trends on the Emotion factor. The numerous significant effects (see Table 3) will be briefly summarized, because they largely recapitulated those reported above for separate regions. Overall, positive and negative words prompted greater activity than did neutral words, there was more activation in the left than in the right hemisphere, and there was more in IFG than in DLPFC. The difference between IFG and DLPFC was larger for the left hemisphere. Positive and negative words prompted more activation in IFG and less in DLPFC than did neutral words, and the emotion effect was confined to the left hemisphere. An Emotion  $\times$  Hemisphere  $\times$  Region effect was qualified by a Group  $\times$  Emotion  $\times$  Hemisphere  $\times$  Region interaction, pursued with simple-effects tests. The groups differed

in IFG, Group  $\times$  Emotion  $\times$  Hemisphere,  $F(4,74) = 2.613, p = .042$ , not in DLPFC. In IFG, all groups showed significantly greater left- than right-hemisphere activity for negative words, but this difference was most pronounced for the anxious apprehension group ( $p < .001$ ). The anxious apprehension group also produced greater left- than right-hemisphere activation for positive ( $p < .001$ ) and neutral ( $p < .05$ ) words, and within the left hemisphere both positive and negative words showed greater activation than neutral ( $p < .001$ ). Pairwise tests confirmed more lateralization in the anxious apprehension group ( $p < .001$ ) than in the anxious arousal group ( $p = .012$ ). Further dissection of the interactions yielded a consistent pattern: Positive and negative (but not neutral) words prompted leftward lateralization specific to or larger in the anxious apprehension group. An analysis comparing the two regions with overlapping voxels removed yielded essentially the same results. Consistently, then, group effects in PFC were confined to IFG, whereas valence effects were confined to DLPFC. These findings indicate that distinct regions in left PFC are involved in processing positive emotion (DLPFC) and in modulating the effects of anxiety on the processing of emotional information (IFG).

## Discussion

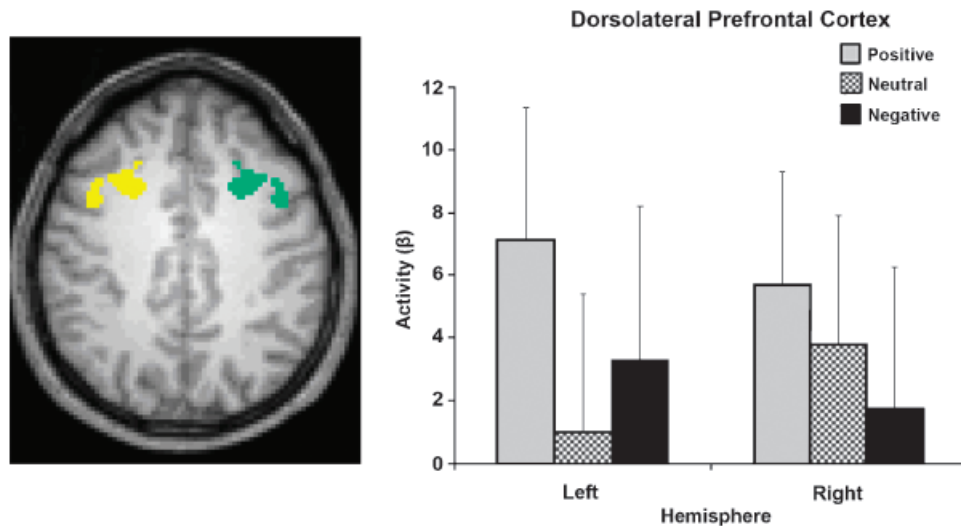
The primary hypothesis was that the anxiety groups would show distinct patterns of brain activity. The anxious groups' hyperactivation in ITG and hypoactivation in rACC suggests an exaggerated alarm response (Compton et al., 2003; Corbetta & Shulman, 2002) accompanied by compromise of attentional control mechanisms (Bush, Luu, & Posner, 2000; Mohanty et al., 2007). Moreover, as predicted, the anxious groups diverged in response to negative words: The anxious apprehension group exhibited more left-hemisphere activity in IFG and ITG, and the anxious arousal group exhibited less leftward IFG asymmetry and more right-hemisphere posterior activation. Thus, distinct patterns of lateralized brain activity characterized psychometrically distinct types of anxiety.

The secondary goal of the present study was a replication and extension of Herrington et al. (2005), in order to distinguish left frontal brain regions involved in anxious apprehension versus the processing of positive information. The valence and Valence  $\times$



**Figure 4.** Coronal view of left inferior frontal gyrus (IFG, blue) region for negative  $>$  neutral (same cluster as is displayed in Figure 1's axial view) and left dorsolateral prefrontal cortex (DLPFC, yellow) for positive  $>$  neutral, displayed at Talairach coordinate  $y = 18$ .





**Figure 5.** Left dorsolateral prefrontal cortex (DLPFC) region identified in the control group as more active for positive than negative words (as in Herrington et al., 2005) and the homologous ROI in the right hemisphere (left; Talairach coordinates  $-26, 18, 38$ ) and Emotion  $\times$  Hemisphere mean activations (right).

Hemisphere effects in DLPFC from the earlier study were confirmed (even though subject sample, scanner field strength, and much of the analysis software differed in the two studies). Analyses demonstrated that this region, most activated when attention must be directed away from positive words, is anatomically and functionally distinct from the region around Broca's area that is particularly active in individuals who exhibit high levels of anxious apprehension.

#### Group Differences in Negative Emotion

Demonstration of exaggerated left-hemisphere activity in anterior language areas when anxious apprehension participants must direct their attention away from negative words has considerable construct validity, given the strong linguistic component in worry. Broca's area is involved in speech production,

syntactic processing, phonological processing, and subvocal articulatory rehearsal (Awh et al., 1996; Zatorre, Meyer, Gjedde, & Evans, 1996). Inferior prefrontal regions have been implicated in maintenance of verbal information (Fletcher & Henson, 2001; Wagner, 1999), and enhanced activity in these regions reflects a variety of verbal processes such as accessing word meaning, holding language-related information online, and verbal rehearsal, consistent with the ruminative style of cognition that characterizes anxious apprehension. Worry may affect attention and working memory by drawing from a limited pool of resources (Eysenck & Calvo, 1992) or by interfering with performance due to competition with or distraction from attention to task-relevant information (Nitschke et al., 2000). For example, anxious apprehension participants may be doing more semantic processing of word stimuli, which interferes with selective attention to the task-relevant attribute of color. In the present study of nonpatients, there were no significant performance differences among the groups. However, with a large enough sample size, performance differences related to anxiety may emerge as noted in the Introduction (Koven et al., 2003). It might be expected, therefore, that worry would interfere with optimum performance in a variety of circumstances, particularly those that require or would benefit from high levels of selective attention.

In addition to the IFG finding for anxious apprehension, the opposing patterns of lateralization in ITG for the two anxious groups further support the model presented in the Introduction. Negative emotional words prompted greater right-hemisphere temporoparietal activity specific to the anxious arousal group. These results are consistent with hypotheses that the right hemisphere houses an integrated system for responding to immediate threat, promoting sympathetic nervous system activity, spatial attention, visual scanning of the environment, and sensitivity to meaningful nonverbal cues (Compton et al., 2003; Nitschke et al., 2000). ITG is also implicated as important for object identification (the "what" system; Hermann, Seidenberg, Wyler, & Haltiner, 1993), and right temporoparietal cortex is important

**Table 3.** Group  $\times$  Emotion  $\times$  Hemisphere  $\times$  Region MANOVA for Negative-Word Activation

Effect	df	F	p
Emotion	2,38	7.112	.002
Quadratic Emotion	1,39	13.514	.001
Hemisphere	1,39	7.842	.008
Region	1,39	49.971	<.001
Region $\times$ Hemisphere	1,39	40.801	<.001
Emotion $\times$ Region	2,38	20.634	<.001
Quadratic Emotion $\times$ Region	1,39	42.260	<.001
Emotion $\times$ Hemisphere	2,38	15.190	<.001
Quadratic Emotion $\times$ Hemisphere	1,39	29.366	<.001
Emotion $\times$ Hemisphere $\times$ Region	2,38	13.024	<.001
Quadratic Emotion $\times$ Hemisphere $\times$ Region	1,39	20.252	<.001
Group $\times$ Emotion $\times$ Hemisphere $\times$ Region	4,74	4.173	.004
Group $\times$ quadratic Emotion $\times$ Hemisphere $\times$ Region	2,39	8.516	.001

*Note.* Only effects exceeding  $p = .05$  are listed. For orthogonal trends on emotion, the linear trend component (none  $p < .05$  in this analysis) contrasts positive and negative words, reflecting emotional valence, and the quadratic trend component contrasts those with neutral words, reflecting emotional arousal.

for detecting salient and unexpected stimuli (Corbetta & Shulman, 2002). Differential engagement of this system for anxious arousal is consistent with the cognition that characterizes this type of anxiety. Present findings are also consistent with previous fMRI results using an emotional Stroop task with unselected subjects, showing activation as a function of emotional arousal near the present ITG area (Compton et al., 2003). This provides independent confirmation of relatively posterior activity associated with emotional arousal that we propose characterizes the anxious arousal construct.

In contrast, the anxious apprehension group showed more left-hemisphere activation in ITG, again consistent with a more verbally mediated response to threatening cues. PFC (particularly inferior frontal and middle frontal regions) is likely to play a prominent role in the synthesis of attention and emotion. According to a model of the neural network involved in attention (Banich et al., 2000a, 2000b, 2001; Compton et al., 2003; Milham & Banich, 2005; Milham et al., 2001, 2002; Milham, Banich, & Barad, 2003; Milham, Banich, Claus, & Cohen, 2003), these regions are important for imposing an attentional set or bias for the information to be attended, especially when processing of the to-be-attended information is less automatic than that of the task-irrelevant information. As attentional demands increase (e.g., the more difficult it is to direct attention to task-relevant vs. task-irrelevant information), the degree to which these prefrontal regions are called upon increases. Frontal activity can therefore provide a metric for how much attentional control is required to ignore the task-irrelevant information. In the context of the emotional Stroop task, an interpretation of the greater left frontal activation observed for the anxious apprehension group is that such individuals find it difficult to suppress task-irrelevant emotional word meaning and require more attentional control to impose an attentional set.

#### ***Apprehension versus Pleasure: Functional Distinctions between Left-Frontal Regions***

Evidence here and elsewhere of exaggerated left frontal activation in anxious apprehension appears contradictory to reports of increased left frontal activity associated with positive emotion or appetitive or approach motivation cited in the Introduction. Present data suggest a resolution, however, because at least in this emotional Stroop task different regions are involved when a stimulus contains positive emotional content versus those differentially activated in individuals who have anxious apprehension. Whereas left IFG was more active for the anxious apprehension group for negative than for neutral words and was sensitive to group differences, a replication of the analysis procedures of Herrington et al. (2005) identified an anatomically and functionally distinct region in left DLPFC that was more active when a stimulus contained positive emotional content and showed no group differentiation.

Present results encourage ongoing efforts to make functional distinctions among PFC regions. In our work and that of others, the term “dorsolateral prefrontal cortex” has often been used broadly, including coordinates in IFG. However, functional distinctions have been proposed between ventrolateral (BA 44, 45, 47), dorsolateral (BA 9, 46), and anterior (BA 8, 10) regions of the frontal cortex (Fletcher & Henson, 2001; Milham et al., 2002; Petrides, 2000). Ventrolateral areas (such as the IFG region observed here as more active for the anxious apprehension

group) have been implicated in articulatory rehearsal and maintenance of verbal information, whereas dorsolateral areas are implicated in manipulating information in working memory. Present findings suggest extending this ventral/dorsal differentiation to the notion that distinct regions of left PFC are involved in processing positive emotional content and in modulating the effects of anxious apprehension on processing related to negative emotion.

#### ***Rostral Anterior Cingulate Cortex in the Emotional Stroop Task***

Both anxiety groups showed less activation than the control group in medial PFC extending into rACC (also, activation in this region was negatively correlated with anxious apprehension ratings). Considerable evidence implicates rACC in the assessment of the salience of emotional information as well as the regulation of emotional responses (see Bush et al., 2000; Mohanty et al., 2007). Activation in this region for the control group supports results from an emotional counting Stroop task with normal controls, showing greater activity in this region for negative than neutral words (Whalen et al., 1998). Research has also demonstrated diminished activity in this region for participants with PTSD (Shin et al., 2005). In addition, medial PFC activity has been shown to correlate negatively with anxiety symptom severity (Bishop, Duncan, Brett, & Lawrence, 2004; Shin et al., 2005). Present results are consistent with these findings and suggest reduced control in the presence of threatening stimuli for participants with anxiety (Bishop et al., 2004; Whalen et al., 1998). However, present results are inconsistent with other studies that have found enhanced rACC activity for anxiety (for a review, see Hajcak, McDonald, & Simons, 2003). Results for the present task, which relies on emotional self-regulation, make sense in light of a proposal that rACC normally acts to down-regulate amygdala activity, central to some types of anxiety (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). Thus, present anxious groups showed abnormally low rACC activation. In these nonpatient individuals, a consequent amygdala hyperactivation did not emerge here.

Present results provide support for the hypothesis that two conceptually, psychometrically, and clinically distinct types of anxiety are associated with different neural mechanisms. Furthermore, a region specifically involved in anxious apprehension differs anatomically and functionally from one specifically involved in processing positive information. The consistency of distinctions, across several measurement domains, between anxious apprehension and anxious arousal indicates that they warrant separate, systematic assessment in psychopathology research and in treatment development. Present data also support an integrationist (not merely interactionist) objection (Miller, 1996) to the commonly assumed distinction between cognition, emotion, and their relationship to shared and distinct neural mechanisms. Functionally, it makes sense that anxious apprehension engages Broca’s area, because this region is involved in verbal production and rehearsal. Similarly, it is functionally appropriate that anxious arousal fosters engagement of right-hemisphere regions involved in responding to immediate threat. Differential activation of these regions for each anxiety type thus supports the contention that patterns of brain activity associated with distinct emotional states implement the distinctive computations associated with these states, rather than reflecting either cognition or emotion in some mutually exclusive sense.

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