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Cortico-Limbic Responses to Masked Affective Faces Across PTSD, Panic Disorder, and Specific phobia

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Abstract

Background—Exaggerated amygdala and reduced ventromedial prefrontal cortex (vmPFC) responsiveness during emotional processing have been reported in studies examining individual anxiety disorders. Studies are needed, however, that directly compare activation of amygdalo-cortical circuitry across multiple anxiety disorders within the same study. Here we compared cortico-limbic neurocircuitry across three different anxiety disorders using a well-validated emotional probe task.

Methods—Sixty-five adult volunteers, including 22 healthy controls (HC) and participants meeting DSM-IV criteria for either post-traumatic stress disorder (14 PTSD), panic disorder (14 PD), specific animal phobia (15 SP) underwent functional magnetic resonance imaging (fMRI) at 3T while passively viewing backward-masked images of faces expressing fear, happy, and neutral emotions.

Results—A group comprising all three anxiety disorders showed greater activation within the left amygdala and reduced activation within the vmPFC compared to the HC group during the masked fear versus neutral condition. Pairwise group comparisons showed that amygdala activation only reached significance for the PTSD versus HCs, while decreased vmPFC was only evident for SP and PD groups versus the HC group. Furthermore, activation did not differ among

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Dr. Killgore had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

the anxiety groups when contrasted directly with one another. A similar pattern was observed for masked happy versus neutral faces.

Conclusions—Exclusive of specific diagnostic category, anxiety disorders were generally associated with increased activation of the amygdala and reduced activation within vmPFC. Categorical distinctions were generally weak or not observed and suggest that functional differences may reflect the magnitude of responses within a common neurocircuitry across disorders rather than activation of distinct systems.

Keywords

FMRI; Anxiety; Specific phobia; PTSD; Panic Disorder; Amygdala

Nearly one in three individuals will develop an anxiety disorder at some point during their lifetime ¹. Some of the most prevalent anxiety disorders are specific phobia (SP), post-traumatic stress disorder (PTSD), and panic disorder (PD), which share in common several features, including anticipatory anxiety, exaggerated and disproportionate fear responses, and attempts to avoid situations or cues that might trigger an anxious response. The symptom presentation and phenomenology of most major anxiety disorders are actually quite heterogeneous, making it difficult to formulate a coherent neurocircuitry model of these conditions that accounts for the diversity in phenotypic expression.

Prevailing neurocircuitry models of anxiety disorders have generally focused on hyperactivation of the amygdala and potentially deficient regulation of the limbic system by cortical regions including the ventromedial prefrontal cortex and anterior cingulate gyrus ^{2,3}. These prefrontal-limbic regulation models suggest that without sufficient top-down modulation by the prefrontal cortex, amygdala responses may become exaggerated, leading to increased negative emotion processing, abnormal allocation of attentional resources, and enhanced salience attributed to objectively innocuous stimuli that are erroneously perceived to be harmful. Recent models have also emphasized the role of other limbic and paralimbic structures such as the hippocampus and insula, which are involved in contextual memory and processing of visceral bodily sensations respectively, and also more dorsal regions of the medial prefrontal cortex that may play a role in fear conditioning ⁴. The commonalities among anxiety disorders suggest that there is likely a core neurocircuitry that is affected across the various conditions, whereas the heterogeneity of symptom presentation suggests that specific nodes of this circuitry may be differentially affected in each diagnostic group.

A recent meta-analysis by Etkin and Wager suggested that elevated amygdala activation appears to be a common finding across several anxiety disorders, including general emotional fear processing in simple phobia (SP), post-traumatic stress disorder (PTSD), and social phobia, as well as normal fear conditioning, when compared to healthy controls ⁵. Interestingly, insula activation was also observed across all three anxiety disorders examined in that meta-analysis, a finding that has recently been replicated in other reviews ⁶, and raises the possibility that it too may be a core node of the anxiety disorder neurocircuitry. In contrast, the only anxiety disorder to show consistently reduced regional brain activation across studies was PTSD, with the greatest deactivations observed among the ventromedial and dorsomedial prefrontal cortex ⁵. Altogether, the emerging evidence suggests that anxiety

disorders may share a core feature of exaggerated activation within the amygdala and insula, while each diagnostic entity may be further distinguished by patterns of activation or deactivation within the dorsal and ventral medial prefrontal cortex/anterior cingulate cortex and hippocampus.

From the research described, a preliminary model of the neurocircuitry of anxiety is beginning to coalesce. As pointed out by Etkin and Wager⁵, however, synthesizing the available data can present only a partial picture, due in part to limitations inherent within any meta-analytic approach. It will therefore be necessary to compare across various anxiety disorders within the same study, using the same tasks, and with the same analysis methods. Here, we address this gap by comparing activation within the hypothesized neurocircuitry among four groups, including SP, PTSD, PD and healthy controls (HC) using a well-validated masked facial affect paradigm^{7–11}. These three disorders were selected based on prior research suggesting both common and different neural systems affecting each. In particular, PD and PTSD show commonalities including increased responsiveness of the “fear network”¹², including enhanced amygdala responses and deficient recruitment of the rostral anterior cingulate cortex⁶, while SP appears to be less likely to show differential amygdala response to universal threat-related stimuli¹³. The masked facial affect task was selected for its purported effectiveness at bypassing top-down cortical regulation of the amygdala^{7,11}, which might elucidate differences between groups in primary responsiveness of this region. We hypothesized that the anxiety disorders, as a group, would show greater responsiveness of the amygdala than HC subjects to masked fear versus neutral faces, while differences in vmPFC, anterior cingulate, and hippocampal activation would discriminate among the groups.

Methods

Participants

Sixty-five right-handed adults ranging in age from 19 to 58 years participated (see Table 1 for demographics). Participants were recruited within the Boston Metropolitan area via flyers and internet advertisements. Upon intake, participants were administered the Structured Clinical Interview for DSM-IV-TR (SCID-I/P)¹⁴ by a trained psychologist or psychiatrist. Volunteers were all required to have normal vision or corrected-normal vision with contact lenses, and were required to be free from known medical or neurological conditions that could potentially influence brain function, including any history of seizures, significant head trauma, or known structural lesions. Participants were also excluded if they had any history of Axis I diagnoses beyond the group-designated target diagnosis, with the exception that up to 50% of each anxiety disorder group was permitted to have a comorbid major depressive disorder. Pregnant women or individuals with metallic implants or other contraindications for MRI scanning were excluded.

According to standard diagnostic criteria from the SCID, eligible participants were assigned to one of 4 groups: Healthy Controls (HC; $n = 22$), Specific Phobia, Small Animal subtype (SP; $n = 15$), Post-Traumatic Stress Disorder (PTSD; $n = 14$), or Panic Disorder (PD; $n = 14$). As shown in Table 1, the groups did not differ significantly with respect to age, education, or gender composition. Clinician Administered PTSD Scale (CAPS) scores for

the PTSD sample ranged from 23 to 80, while the Panic Disorder Severity Scale ranged from 6 to 18 for the PD sample. According to the SCID, all participants, except one with PD, were free of current comorbid depressive disorders. Past history of depression was documented for 2 SP, 3 PTSD, and 2 other PD participants. None of the participants met current criteria for alcohol or substance abuse or dependence. A small subset of these data (9 HCs, 6 SPs) were presented in a previous manuscript on a different topic¹⁰, but the group contrasts shown here are novel and have never before been reported. HC participants were required to be free of psychotropic medications for at least 4 weeks prior to their scanning visit, while those among the anxiety disorder groups taking antidepressant medications were required to be stabilized on such medication for at least 4 weeks prior to their study visit. Medication status for each group is listed in Table 1. Written informed consent was obtained prior to participation, and a nominal financial compensation was provided. The protocol for this study was reviewed and approved by the institutional review boards of Partners Healthcare and McLean Hospital.

Functional MRI Data Acquisition

Masked Facial Affect Paradigm—While undergoing fMRI, participants passively viewed a series of masked affective faces in two counterbalanced runs. This paradigm has been described in detail elsewhere^{7,11}. Briefly, subjects were exposed to a series of photographs depicting faces expressing either the emotion of fear, happiness, or a neutral expression from the Ekman standard set of images¹⁵. To minimize or prevent conscious awareness of the target emotional expression, each target photograph was presented for only 16 msec and was then immediately replaced (i.e., masked) by a photograph of a different individual showing a neutral expression for 184 msec. Images were presented using E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA) via an LCD projector mounted at the rear of the scanner. Prior research has generally shown that this procedure effectively prevents or minimizes explicit awareness of the content of the affective face stimulus while still engaging emotion perception and its associated neural structures such as the amygdala^{7,11,16}.

Stimuli were presented in a blocked design, with each task run lasting 5 minutes and 36 seconds. Each run consisted of 12 alternating 28-second blocks of masked neutral (2 blocks), masked happy (3 blocks), and masked fearful (3 blocks) facial expressions, and 4 blocks of a fixation baseline. Target/mask stimulus pairs were presented at a rate of 2 per second, resulting in 56 target/mask pairs per block. Participants viewed the images on a translucent screen that was visible from a mirror mounted to the head coil.

Face Detection Task—As a manipulation check after the scan, participants viewed a series of 24 previously seen target-mask pairs presented for identical stimulus durations as seen in the scanner. For each pair, the participant indicated the emotion they believed was displayed by the first (i.e., target) expression by pressing one of 3 response keys (neutral, fear, happy). Above chance performance was defined by the binomial distribution (24 trials, $p < .05$) for each participant. Table 1 shows that the number of participants identifying the faces above chance expectations (i.e., $> 67\%$) was negligible and did not differ significantly across groups, $\chi^2(3) = 2.52$, $p = .47$. Mean expression identification scores are reported in

Table 1 as well. The percent correct did not differ significantly across groups, $F(3,61) = 2.21$, $p = .10$.

Neuroimaging Methods—Data were acquired on a 3.0 Tesla Siemens Tim Trio whole body scanner equipped with a 12-channel head coil. High-resolution 3D MPRAGE sequences were collected for each subject (TR = 2530 msec, TE = 3.45 msec, flip angle = 7 degrees, 1.3 mm slice thickness, 1.3 mm in-plane resolution) for use in co-registration and spatial normalization and viewing of individual participant activation patterns. Blood oxygen level dependent (BOLD) fMRI data during the masked affect task were collected using a T2*-weighted sequence (TR = 2 sec, TE = 30 msec, flip angle = 90 degrees). For each scanning run, the first 3 volumes were discarded, followed by 168 echoplanar volumes collected over 25 axial slices (5 mm thick, 0 skip; 20 cm field of view; 64×64 acquisition matrix), providing an in-plane resolution of $3.125 \times 3.125 \times 5$ mm.

Image Processing—Functional data were pre-processed using standard algorithms within SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The images were motion corrected, unwrapped, and co-registered to each subjects' own anatomical scan. All images were spatially normalized to the three-dimensional Montreal Neurological Institute (MNI) template using a 12-parameter affine linear transformation followed by nonlinear warping, spatially smoothed using an isotropic Gaussian kernel (full width half maximum [FWHM] = 6 mm), and resliced to $2 \times 2 \times 2$ mm. The time series data were also corrected by convolving the data with the canonical hemodynamic response function, serial autocorrelation was corrected using AR(1), and low frequency drift was removed with a high-pass filter of 128 seconds. Data for each subject were visually inspected for artifacts using the Artifact Detection Tool (http://www.nitrc.org/projects/artifact_detect/). Individual scan volumes were regressed out of the first level analysis as a nuisance covariate if they showed mean global intensity that exceeded 3 standard deviations or scan-to-scan motion that exceeded 0.75 mm. Using these criteria, the mean number of scans excluded per run was 9.3 ($SD = 6.5$).

Statistical Analysis—A multi-stage analysis approach was used. Initially, three general linear models were estimated for each subject to identify activation differences between the 1) masked fearful versus masked neutral face conditions, 2) masked happy versus masked neutral face conditions, and 3) masked fear versus masked happy face conditions. Contrast images were then subjected to a series of second level random effects analysis of variance (ANOVA) models comparing activation patterns across the various conditions. Within the ANOVA model, several planned contrasts were undertaken, including: 1) a direct contrast between HC and all anxiety groups combined, 2) pairwise comparisons between each anxiety group and the HC group, and 3) pairwise comparisons between each anxiety disorder. All analyses were restricted to four bilateral search territories, including 1) the ventromedial/orbitofrontal cortices (i.e., superior orbitofrontal gyrus and gyrus rectus), 2) amygdala, 3) hippocampus/parahippocampal gyrus, and 4) insula. Although not part of the primary hypotheses of this study, we also included a post-hoc analysis of the anterior cingulate cortex (ACC), including subgenual, rostral, and dorsal components, as these areas have been implicated in fear conditioning studies and PTSD. Search territories were defined

based on the Automated Anatomical Labeling Atlas¹⁷ as implemented in the Wake Forest University PickAtlas Utility¹⁸. Primary comparisons were initially thresholded at $p < .001$, k (extent) = 5 contiguous voxels, small volume corrected for multiple comparisons within each search territory at $p < .05$, Family Wise Error (FWE). Data from activated clusters were extracted and plotted. Additionally, extracted data were also compared across groups using ANCOVA planned comparison models to statistically control for the influence of concurrent depressive symptoms, age, and medication use.

Results

Behavioral Data

Beck Depression Inventory (BDI) Scores—Groups differed significantly on the BDI-II, $F(3,61) = 13.00$, $p < .001$, BAI, $F(3,61) = 16.61$, $p < .001$, STAI-S, $F(3,60) = 5.87$, $p = .001$, and STAI-T, $F(3,58) = 12.14$, $p < .001$ (see Table 1). Bonferroni corrected ($p < .05$) post-hoc comparisons generally showed similarity in these ratings between PTSD and PD groups, which differed from HC and SP groups, on the whole.

Functional Neuroimaging

Masked Fear versus Masked Neutral Face Comparisons

Combined Anxiety Groups versus HC: When considered as a combined group in the ANOVA, the anxiety disorders together showed significantly greater responses within the left amygdala during the masked fear versus neutral contrast relative to the HC group (see Table 2). Data were extracted from this cluster and plotted for visualization in Figure 1A. Paired comparisons showed that this cluster was significantly more activated (or less deactivated) for the PTSD and PD groups compared to the HC group but the three anxiety disorders did not significantly differ from one another. To account for the possibility that group differences in depression, age, or medication use might have affected the results, the extracted values from the amygdala were entered into a series of ANCOVA contrasts between the anxiety disorders as a group versus the HC group, controlling for these nuisance variables. None of these variables was found to contribute to the models singly or in combination (all covariate p -values $> .66$). The anxiety groups differed significantly from the HC group even after controlling for BDI-II score ($p = .002$), BDI-II and age ($p = .002$), and BDI-II, age, and medication use ($p = .003$), suggesting that these factors had little influence on the significance of the amygdala response contrasts. In contrast to the increased activation of the amygdala, the combined group of anxiety disorders showed significantly reduced activation within the vmPFC/OFC relative to the HC group (see Table 2). Figure 1B shows that extracted data from this vmPFC/OFC cluster were lowest among the SP and PD groups, whereas the PTSD group did not differ significantly from HCs. Furthermore, the observed activation differences between the anxiety disorders group and the HC group in the vmPFC were not appreciably altered after controlling for depression, age, or medication use, whether individually or in combination (all covariate p -values $> .28$). Inclusion of BDI-II score ($p = .005$), BDI-II and age ($p = .008$), or BDI-II, age, and medication use ($p = .007$) had no appreciable effect on the significance of the vmPFC contrasts. Due to the fact that none of these nuisance covariates contributed significantly to any of the preceding models, they were not included in any of the subsequent pairwise group analyses.

Finally, a post-hoc analysis of the ACC was also undertaken, given its role in PTSD and other anxiety disorders. However, no group differences were observed, even without corrections for multiple comparisons.

Pairwise Group Comparisons

Comparisons with HCs: As shown in Figure 2, the SP group showed no regions of greater activation compared to HCs but did show significantly reduced activation within the vmPFC/orbitofrontal cortex (OFC) region (see Table 2). In contrast, the PTSD group showed significantly greater left amygdala response compared to the HC group, but no areas of significant deactivation. Finally, Figure 2 also illustrates that relative to HCs, the PD group showed significantly greater responses within the parahippocampal gyrus and fusiform gyrus, while also showing reduced activation within the vmPFC/OFC region. Post-hoc analysis of the ACC revealed no group differences.

Comparisons Between Anxiety Groups: Table 2 also presents the findings for each pairwise comparison between each of the three anxiety disorder groups. Notably, when contrasted directly, the anxiety disorder groups did not differ from one another in responses to the masked fearful faces within the search territories. Post-hoc analysis of the ACC again showed no group differences.

Masked Happy Face Comparisons—In addition to the analyses involving the Masked Fear > Neutral contrast across anxiety groups, we also conducted additional analyses to examine the possible influence of emotional valence (i.e., positive versus negative emotion) on brain responses. As evident in Table 3, and Figure 3, the Masked Happy versus Neutral contrast was similar to that found previously for the Masked Fear versus Neutral contrast, showing significantly greater activation of the left amygdala for the combined anxiety group relative to the HCs. There were no regions of reduced activation relative to the HC group for this contrast. Post-hoc analysis failed to reveal any significant group differences within the ACC for any of the contrasts, with the exception of a cluster of 5 voxels within the rostral ACC that was greater for HC versus PTSD (MNI: $x = 0$, $y = 28$, $z = 0$; $T = 3.88$), but this cluster did not survive small volume correction for the ACC.

Finally, we also examined group differences in the Masked Fear versus the Masked Happy conditions. As shown in Table 4 and Figure 3, there were no significant group differences within hypothesized regions for this contrast.

Discussion

We compared functional activation within the cortico-limbic neurocircuitry among three conceptually distinct anxiety disorders as participants engaged in a well-validated affective probe task. Four primary objectives were addressed. First, we examined whether all three anxiety disorders, as a combined group, could be differentiated from HCs based by a common pattern of activation within the cortico-limbic circuitry, comprising the medial prefrontal cortex, amygdala, insula, and hippocampus, in response to a masked fear perception task. We found that these anxiety disorders, as a group, showed a convergent pattern of increased activation of the left amygdala and reduced activation within the

ventromedial prefrontal cortex (BA 11) when compared to HCs on this task, and these findings were not affected by depression, age, or medication use. Second, when each group was compared separately to HCs, there was variability in terms of the magnitude and pattern of cortico-limbic responsiveness among the diagnostic categories. Third, direct contrasts between disorder groups showed no statistically significant differences, although this null finding is difficult to interpret due to the limited power resulting from relatively small sample sizes. On the whole, these findings suggest that the anxiety disorders evaluated here do not appear to differ robustly in the pattern of responsiveness to masked stimuli and, to some extent, may share a common pattern of abnormal responsiveness of amygdalo-cortical circuitry that may differ primarily in the magnitude of responses within the amygdala and vmPFC. We initially selected these three disorders due to the phenomenological similarities shared between PTSD and PD in the manifestation of the anxiety/fear response and potential differences with SP. Instead of finding uniquely differentiated patterns, however, our data suggested that the three disorders might be better described as falling along a continuum of responsiveness of the vmPFC and amygdala. Finally, the pattern of activation observed for the masked fearful face condition was closely replicated for the masked happy face condition, suggesting that the effects within this particular neurocircuitry were primarily elicited by features of the expressions communicating affective arousal rather than emotional valence.

The most consistent finding observed was increased amygdala responsiveness across the anxiety disorders, which supports the well-established role of this structure in models of fear and anxiety^{2,3}. Animal research has led to detailed mapping of the neurocircuitry of fear processing and has established the extended amygdala as a critical node in this system¹⁹. In humans, the amygdala shows increased activation during the acquisition of conditioned fear^{20,21} and this activation is reduced following subsequent fear extinction²², suggesting that the amygdala is key to the acquisition and maintenance of fear responses. This model extends well to human anxiety disorders, as considerable research evidence confirms that the amygdala is hyperresponsive to symptom provocation and other emotional challenge tasks in studies of specific phobia^{23–25}, social anxiety disorder (SAD)^{26–28}, obsessive-compulsive disorder (OCD)^{29,30}, panic disorder³¹, and PTSD^{11,32–34}. Consistent with a recent meta-analysis of neuroimaging studies of fear and anxiety disorders⁵, our results indicate that hyperresponsiveness of the amygdala appears to be a generally common but non-specific feature that is shared across a broad range of anxiety disorders. Although other disorders such as generalized anxiety disorder (GAD), OCD, and SAD were not included in the present analysis, we speculate that a similar continuum of vmPFC-amygdala responsiveness would still be observed in some of these disorders, while additional regions, such as the striatum and insula are likely to emerge as important to differentiating among these disorders as well.

We also found a common pattern of reduced activation within the vmPFC on average for the anxiety disorder group relative to HCs. While the effect was observed for the anxiety sample as a whole, pairwise comparisons suggested that the hypoactivation of the vmPFC was driven primarily by the PD and SP groups, although the magnitude of deactivation failed to reach our threshold for statistical significance for the PTSD group. This was unexpected, as vmPFC hypoactivation has been a common finding in many neuroimaging studies of

PTSD^{33,35–37}, particularly those that have used aversive conditioning, disorder-relevant stimuli, or overt affective processing. However, this lack of significance could potentially be accounted for by the limited power of the present study, as well as the implicit nature of the masked facial affect paradigm. The masked facial expression paradigm, which by definition, bypasses explicit affect perception and modulation systems, may have been insufficiently robust to engage vmPFC responses in any of the groups. We were further surprised by the lack of insular responses in the present study, particularly given the prominence of the insula as a key region in a recent meta-analysis of anxiety disorders⁵. Although the insula has been shown to play an important role in anxiety disorders, the subliminal nature of the masked affect paradigm may limit its effectiveness for engaging this region.

Of interest, PD was uniquely associated with increased activation within the right parahippocampal and fusiform gyri during the masked fearful face task. A recent meta-analysis of voxel-based morphometry studies of patients with PD showed a common pattern of reduced gray matter volume in the right parahippocampal gyrus and other regions of the basal ganglia³⁸. Although functional neuroimaging findings from masked affect paradigms have not been previously described for PD, there have been some reports of elevated resting glucose metabolism^{39,40} as well as reduced benzodiazepine receptor binding⁴¹ and reduced n-acetylaspartate (NAA)/creatine (Cr) ratios⁴² in the hippocampus among these patients, and greater responsiveness of the right parahippocampal gyrus to threat related words⁴³, bolstering the possibility that PD may also be characterized by abnormalities of this system.

A novel component to the present study was an attempt to clarify the aspects of the masked stimuli that yielded the observed cortico-limbic responses. The affective quality of emotional stimuli such as facial expressions can be quantified along two primary dimensions of valence (positive to negative) and arousal (neutral to highly aroused)⁴⁴. Recent evidence suggests that the interaction between valence and arousal may be represented effectively by a U-shaped curve within this two-dimensional space (see Figure 4)⁴⁵. Emerging neuroimaging data suggest that the arousal dimension may be reflected in activation of the amygdala and other subcortical structures^{46,47}. Therefore, in addition to the masked fear expression condition, we also included a masked happy expression condition to examine the effect of affective valence on the pattern of brain responses. We found that the masked happy versus neutral condition elicited a pattern of amygdala hyperresponsiveness similar to what was observed for the masked fear versus neutral condition. However, when the fear and happy conditions were contrasted directly, group differences generally disappeared, suggesting that the primary effects were not being driven by the negative valence of fear expressions, but rather, were likely elicited by the emotional arousal depicted on the faces. We speculate that the masked nature of the stimuli likely prevented full assessment of the valence of the expressions (i.e., whether the face was happy or afraid) by higher cortical regions, whereas the amygdala was able to provide a crude assessment of features of the expression communicating affective arousal (e.g., bared teeth, widening of the eyes, stretched face muscles) versus the neutral expressions. These findings are consistent with recent suggestions that components of the neurocircuitry evaluated here, particularly the amygdala, may reflect a more generalized “affective salience” system rather than a specific “fear system” per se⁴⁸. From this perspective, the amygdala may respond primarily to the arousal dimension when stimuli are presented briefly (see Figure 4), thus increasing neural

processing toward emotionally relevant stimuli regardless of their valence. Based on the present findings, anxiety disorders would appear to be associated with a heightened responsiveness of this salience detection system even in the presence of objectively positive facial expression stimuli. It is not difficult to envision how such an exaggerated response system among individuals with anxiety disorders could lead to behavioral responses that might be maladaptive or inappropriate to the objective situation (e.g., heightening of an anxious response to an enthusiastic yet non-threatening social encounter). Further exploration of the role of amygdala responses to the arousal dimension of stimuli—exclusive of their positive or negative valence—may contribute important insights into the understanding of the mechanisms whereby anxiety may be elicited by objectively non-threatening stimuli.

Several caveats should be considered when evaluating these data. First, despite the relatively large overall sample size, the number of participants comprising each group remains modest, potentially limiting statistical power and generalizability. Consequently, failure to find some expected effects within groups is likely to reflect insufficient power. Given the promising findings reported here, similar work with larger samples is clearly warranted. Second, our study focused on three common anxiety disorders including SP, PD, and PTSD, but it will be necessary to compare additional groups such as GAD, SAD, and OCD to more comprehensively understand the neurocircuitry shared among these disorders. Third, the modest symptom severity of our participants may have minimized differences between groups. Future work should examine patients with more severe levels of pathology to clarify this issue. Additionally, our use of a masked face presentation may limit the systems of the brain activated by the sub-threshold presentations, and it is possible that differences in perceptual sensitivity among individuals may have added error to the data⁴⁹, further reducing significant effects of the current study. However, we evaluated this during the masked face detection task and found no significant differences between the groups, suggesting that this was unlikely to have affected the current findings.

Conclusion

Exclusive of specific diagnostic category, anxiety disorders were generally associated with increased activation of the amygdala and reduced activation within vmPFC during masked affect perception, while categorical distinctions based on DSM diagnosis were generally weak or not observed. Although power limitations warrant caution in interpretation, the present findings suggest that these anxiety disorders demonstrate abnormal responsiveness within a shared cortico-limbic neurocircuitry to masked affect presentations, with little evidence of clear differentiation among the disorders.

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All Anxiety Groups versus HC

Figure 1.

Activation during the All Anxiety vs. HC group comparison. A) Left figure shows a cluster of activation within the left amygdala that is greater for the mean of all three anxiety disorders relative to the HC group ($p < .001$ for visualization). The right graph shows the mean parameter estimates for each group individually for the pairwise comparisons. B) Left figure shows a cluster of activation that is significantly decreased for all three anxiety groups relative to the HC group ($p < .001$ for visualization). Right graph shows the mean parameter estimates for each group individually. Data are overlaid on the SPM standard high-resolution template brain (colin27). * $p < .01$, ** $p < .001$.

Figure 2.

Activation differences observed for the pairwise comparisons between each anxiety group and HCs ($p < .001$ for visualization). Graphs show extracted parameter estimates from the cluster. A) The SP group showed significantly reduced activation within the vmPFC compared to the HC group. B) The PTSD group showed significantly greater activation within the left amygdala relative to the HC group. C) Compared to the HC group, the PD group showed significantly greater activation within the parahippocampal/fusiform gyrus compared to the HC group, and D) significantly reduced activation within the vmPFC. Data are overlaid on the SPM standard high-resolution template brain (colin27).

Figure 3.

Comparison of the amygdala responses from the All Anxiety vs HC group comparisons across the three task condition contrasts. A) The Masked Fear > Neutral contrast yielded significant activation within the left amygdala. B) The Masked Happy > Neutral contrast yielded significant activation within the left amygdala. C) The Masked Fear > Masked Happy contrast resulted in no significant activation differences.

Figure 4.

Hypothesized U-shaped relationship between affective valence and arousal based on Lewis et al. (2007). Neutral faces are both neutral in affective valence and low in arousal. As facial affect becomes more positive or negative along the valence dimension, there is also an increase in the level of affective arousal in the expression.

Table 1

Participant Demographics.

	HC (n = 22)	SP (n = 15)	PTSD (n = 14)	PD (n = 14)	Comparisons ^d
Age, mean (SD), y	30.7 (9.2)	35.6 (8.7)	33.1 (12.8)	28.3 (8.1)	ns
Education, y	16.2 (1.5)	16.3 (1.5)	15.1 (2.0)	14.9 (2.3)	ns
Female No., %	14 (64)	11 (73)	10 (71)	10 (71)	ns
BDI-II, mean (SD)	0.7 (1.5)	2.3 (3.9)	9.0 (7.6)	13.1 (10.9)	HC=SP<PTSD=PD
BAI, mean (SD)	2.0 (2.9)	1.7 (2.1)	12.6 (11.6)	23.4 (17.9)	HC=SP<PTSD<PD
STAI-S, mean (SD)	26.9 (5.2)	29.3 (10.4)	33.2 (9.8)	39.2 (11.0)	HC=SP<PTSD=PD
STAI-T, mean (SD)	32.0 (5.9)	34.5 (7.2)	42.5 (11.6)	48.0 (9.0)	HC=SP<PTSD=PD
Psych Medications No., %					
Fluoxetine	0 (0)	0 (0)	0 (0)	2 (14)	ns
Bupropion	0 (0)	0 (0)	0 (0)	1 (7)	ns
Lorazepam p.r.n.	0 (0)	0 (0)	0 (0)	1 (7)	ns
CAPS	--	--	44.7 (15.4)	--	--
PDSS	--	--	--	11.8 (3.9)	--
FD No. Above Chance	2	0	0	1	ns
FD Correct %	43.8 (11.3)	39.7 (8.2)	34.8 (13.1)	43.2 (10.4)	ns

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; HC, healthy controls; PD, panic disorder; PTSD, post-traumatic stress disorder; STAI-S, State-Trait Anxiety Inventory State Scale; STAI-T, State-Trait Anxiety Inventory Trait Scale, CAPS, Clinician Administered PTSD Scale; PDSS, Panic Disorder Severity Scale; FD, Face Detection task.

^d $p < .05$, Bonferroni corrected.

Table 2

Local Maxima for Fear versus Neutral Contrasts Among Anxiety Groups.

Comparison Region	Cluster Size (Voxels)			x	y	z	SPM {t}
All Anxiety Groups > HC							
L Amygdala	7	-22	2	-24	3.58*		
HC > All Anxiety Groups							
L Superior Orbitofrontal Gyrus	5	-12	48	-20	4.11*		
SP > HC							
No active voxels	--	--	--	--	--	--	--
HC > SP							
L Superior Orbitofrontal Gyrus	7	-12	48	-20	3.94*		
PTSD > HC							
L Amygdala	13	-22	0	-24	4.05*		
HC > PTSD							
No active voxels	--	--	--	--	--	--	--
PD > HC							
R Parahippocampal Gyrus/Fusiform Gyrus	8	20	-36	-14	4.04*		
HC > PD							
L Superior Orbitofrontal Gyrus	5	-12	48	-20	3.72*		
SP > PTSD							
No active voxels	--	--	--	--	--	--	--
PTSD > SP							
No active voxels	--	--	--	--	--	--	--
SP > PD							
No active voxels	--	--	--	--	--	--	--
PD > SP							
No active voxels	--	--	--	--	--	--	--
PTSD > PD							
No active voxels	--	--	--	--	--	--	--
PD > PTSD							

Comparison Region	Cluster Size (Voxels)	x	y	z	SPM {t}
No active voxels		--	--	--	--

Note. L = left hemisphere, R = right hemisphere. Atlas coordinates are from the MNI standard atlas, such that $\bar{x}$ reflects the distance (mm) to the right or left of midline, $\bar{y}$ reflects the distance anterior or posterior to the anterior commissure, and $\bar{z}$ reflects the distance superior or inferior to the horizontal plane through the AC-PC line.

* All activated voxels are significant at $\bar{p} < .001$ (small volume corrected for family-wise error (FWE)), with a spatial extent of $k = 5$ contiguous voxels.

Table 3

Local Maxima for Happy versus Neutral Contrasts Among Anxiety Groups.

Comparison Region	Cluster Size (Voxels)	x	y	z	SPM (t)
All Anxiety Groups > HC					
L Amygdala	22	-22	2	-22	4.55*
HC > All Anxiety Groups					
No active voxels	--	--	--	--	--
SP > HC					
No active voxels	--	--	--	--	--
HC > SP					
No active voxels	--	--	--	--	--
PTSD > HC					
L Amygdala	9	-22	2	-22	3.67*
HC > PTSD					
No active voxels	--	--	--	--	--
PD > HC					
No active voxels	--	--	--	--	--
HC > PD					
No active voxels	--	--	--	--	--
SP > PTSD					
No active voxels	--	--	--	--	--
PTSD > SP					
No active voxels	--	--	--	--	--
SP > PD					
No active voxels	--	--	--	--	--
PD > SP					
R Insula	5	34	-16	14	3.96*
PTSD > PD					
No active voxels	--	--	--	--	--
PD > PTSD					

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Comparison Region	Cluster Size (Voxels)	x	y	z	SPM (t)
No active voxels					

Note. L = left hemisphere, R = right hemisphere. Atlas coordinates are from the MNI standard atlas, such that $\bar{x}$ reflects the distance (mm) to the right or left of midline, $\bar{y}$ reflects the distance anterior or posterior to the anterior commissure, and $\bar{z}$ reflects the distance superior or inferior to the horizontal plane through the AC-PC line.

* All activated voxels are significant at $p < .001$ (small volume corrected for family-wise error (FWE)), with a spatial extent of $k = 5$ contiguous voxels.

Table 4

Local Maxima for Fear versus Happy Contrasts Among Anxiety Groups.

Comparison Region	Cluster Size (Voxels)	x	y	z	SPM {t}
All Anxiety Groups > HC					
No active voxels	--	--	--	--	--
HC > All Anxiety Groups					
No active voxels	--	--	--	--	--
SP > HC					
No active voxels	--	--	--	--	--
HC > SP					
R Hippocampus/Fusiform gyrus	33	40	-20	-18	4.40*
L Amygdala	9	-22	0	-22	3.63*
PTSD > HC					
No active voxels	--	--	--	--	--
HC > PTSD					
No active voxels	--	--	--	--	--
PD > HC					
No active voxels	--	--	--	--	--
HC > PD					
No active voxels	--	--	--	--	--
SP > PTSD					
No active voxels	--	--	--	--	--
PTSD > SP					
R Hippocampus	37	38	-22	-16	4.27*
No active voxels	--	--	--	--	--
PD > SP					
R Hippocampus	40	38	-18	-16	4.35*
PTSD > PD					
No active voxels	--	--	--	--	--
PD > PTSD					

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Comparison Region	Cluster Size (Voxels)	x	y	z	SPM {t}
No active voxels		--	--	--	--

Note. L = left hemisphere, R = right hemisphere. Atlas coordinates are from the MNI standard atlas, such that $\bar{x}$ reflects the distance (mm) to the right or left of midline, $\bar{y}$ reflects the distance anterior or posterior to the anterior commissure, and $\bar{z}$ reflects the distance superior or inferior to the horizontal plane through the AC-PC line.

* All activated voxels are significant at $p < .001$ (small volume corrected for family-wise error (FWE)), with a spatial extent of $k = 5$ contiguous voxels.