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Transdiagnostic neural correlates of affective face processing in anxiety and depression

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Abstract

Background—It is unknown whether there are neurobiological differences between various anxiety and depressive disorders, or whether they are characterized by shared neurobiological variation that cuts across diagnostic boundaries. For instance, multiple anxiety disorders and depression may be characterized by abnormalities in blood-oxygen-level dependent (BOLD) response during the processing of affective scenes and faces. To interrogate the shared or unique nature of these aberrations, research that examines the influence of transdiagnostic, dimensional predictors across multiple diagnoses is needed.

Methods—One-hundred and ninety-nine individuals, 142 with primary diagnoses of social anxiety disorder (SAD), generalized anxiety disorder (GAD) or major depressive disorder (MDD), and 57 who were free from psychiatric diagnoses (healthy controls, HCs) performed a face-matching task involving fearful, angry and happy faces (and geometric shapes) while undergoing functional magnetic resonance imaging.

Results—Across the three primary diagnoses, anxiety symptom scores were associated with increased Angry>Shapes activation in the bilateral insula, anterior/midcingulate and dorsolateral prefrontal cortex (dlPFC), while depressive symptoms were associated with reduced dlPFC activation for Angry>Shapes. Patient>HC differences were limited to non *a priori* regions, and no differences in BOLD activation were observed between diagnostic groups.

Conclusions—1) Activation in paralimbic, cingulate and lateral prefrontal regions in response to angry faces is associated with transdiagnostic anxiety and depressive symptomatology. 2) Anxiety and depressive symptoms may exert opposing influences on lateral prefrontal activation. 3)

Abnormal threat processing in GAD, SAD and MDD may reflect shared neural dysfunction that varies with symptom load.

Keywords

anxiety; depression; fMRI; BOLD; RDoC; faces; threat; SAD; GAD; MDD

In recent years, psychiatry has increasingly sought to reconcile discrete diagnostic categories with growing evidence of shared phenotypic (Krueger, 1999; Krueger & Eaton, 2015; Krueger & Markon, 2006), genetic (Hettema, Neale, & Kendler, 2001; Otowa et al., 2016), and neurobiological (Goodkind et al., 2015; Jenkins et al., 2016; Oathes, Patenaude, Schatzberg, & Etkin, 2014) continuity evident across mental disorders. Some work suggests that various anxiety disorders and depression may be characterized by heightened attention toward and processing of negative emotional information in the environment (Cisler & Koster, 2010; Mathews & MacLeod, 2005). However, other work suggests that differences in the extent and timing of attention toward negative stimuli might distinguish the disorders (Bradley, Mogg, Millar, & White, 1995; Mogg & Bradley, 2005). Functional magnetic resonance imaging (fMRI) studies of neural activation elicited in response to emotional stimuli can be useful in assessing these abnormalities, yet the majority of these studies have focused on discrete comparisons between and within single diagnoses (Crane et al., 2016; Engels et al., 2010). A more contemporary approach advocates for including multiple diagnostic categories and examining neurobiological correlates of emotion processing in a continuous manner, across diagnoses (Cuthbert, 2015).

Meta-analytic results suggest that both anxiety and depression may be characterized by aberrant activation in neural networks implicated in the generation and regulation of emotion. Key nodes in these networks include the amygdala, which has been described as the body's "alarm" system (Amaral, 2002), and the insula, which is involved in the subjective experience of negative affect, interoception and physiological arousal (Craig, 2002; Phan, Wager, Taylor, & Liberzon, 2004). Etkin and Wager (2007) found that compared to healthy controls (HCs), social anxiety disorder (SAD), post-traumatic stress disorder (PTSD) and panic disorder (PD) were associated with increased activation in the amygdala and the insula. This meta-analysis incorporated studies that used a variety of different types of affective stimuli (e.g., emotional scenes, faces, trauma scripts). Still other work has focused exclusively on affective faces, which may be relevant to both anxiety and depression. For example, increased amygdala activation (Blair et al., 2008; for a meta-analysis, see Gentili et al., 2016) and insula activation (Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013; Stein, Simmons, Feinstein, & Paulus, 2007) have been observed in response to negative faces in SAD, and positive correlations involving trait anxiety and anxiety symptomatology have also been observed (Carré et al., 2014; Fonzo et al., 2015; Stein et al., 2007). On the other hand, some work suggests that generalized anxiety disorder (GAD) may be associated with *reduced* amygdala activation for fearful faces, compared to controls (Blair et al., 2008). Meta-analytic work in individuals with major depressive disorder (MDD) has found evidence of increased activation in the amygdala and the insula during the processing of negative stimuli more generally (J. P. Hamilton et al., 2012) and during face processing (for a review, see Stuhrmann, Suslow, & Dannlowski, 2011).

The anterior/mid cingulate cortex is involved in the generation of negative affect (Tolomeo et al., 2016) and the initiation of cognitive control (Shackman et al., 2011) and, along with the insula, is part of the “salience network” (Seeley et al., 2007). The salience network is implicated in the detection of and response to salient stimuli in the environment (Menon, 2015) and may be particularly relevant to anxiety (MacNamara, DiGangi, & Phan, 2016). For example, in one study that included disorder-specific threatening stimuli tailored to each diagnosis, transdiagnostic evidence of hyperactivation in the amygdala, insula and dorsal anterior cingulate cortex (dACC) was observed across SAD, dental phobia, PD and PTSD, with no disorder-specific differences observed (Feldker et al., 2016). However, in another study that used generic threat-related scenes, increased activation in the insula, ACC and dlPFC was observed in patients with GAD (Buff et al., 2016) but *not* SAD or PD. Fewer studies have examined nodes of the salience network in major depression; however there are isolated reports of increased (Dichter, Felder, & Smoski, 2009) and decreased ACC activation to angry faces in depression (Chan et al., 2016). In structural MRI work, reduced grey matter in the anterior cingulate and insula cortices was observed in a massive sample of more than 16,000 patients with mixed diagnoses that included anxiety, depression and psychosis (McTeague, Goodkind, & Etkin, 2016), arguing for what might be a robust, transdiagnostic role of salience network node abnormality in mental illness.

In addition to emotion-generation regions of the brain, anxiety disorders and depression have been associated with abnormalities in regions of the brain involved in emotion regulation and “top-down” cognitive control, such as the dorsolateral prefrontal cortex (dlPFC). Although reduced activation in the dlPFC has been observed for patients with anxiety who are asked to down-regulate their response to negative stimuli (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2012), simply viewing emotional stimuli seems to be associated with *increased* activation in the dlPFC for anxiety disordered patients. For example, patients with GAD and SAD have been found to exhibit increased activation in the dlPFC (Blair et al., 2008) and middle frontal gyrus (Gentili et al., 2016) during the processing of negative facial expressions, and positive correlations have also been observed with anxiety (Blair et al., 2008; Carré et al., 2014; Fonzo et al., 2015). In addition, adults with inhibited temperament (Clauss et al., 2014) have been found to exhibit increased activation in the dlPFC when viewing negative facial expressions. Although increased dlPFC activation could suggest *improved* emotion regulation, it may instead reflect worry or increased cognitive effort (at regulation) and might not necessarily infer decreased activation in emotion generation regions of the brain – at least for anxious patients (Carré et al., 2014). In comparison to the literature on anxiety, depression may be associated with *reduced* activation in the dlPFC (for a meta-analysis, see J. P. Hamilton et al., 2012; for a review of face-processing, see Stuhrmann et al., 2011).

Studies such as those described above have laid a foundation for understanding the neural correlates of face-processing in anxiety and depression. Furthermore, a literature has begun to emerge that examines multiple diagnostic categories at once and which has taken a continuous (i.e., transdiagnostic) approach to data analysis. The current study builds on this prior work by assessing the neural correlates of emotional face processing in a group of nearly 200 participants, comprised of healthy controls and patients with primary diagnoses of MDD, SAD or GAD – i.e., the three most common affective disorders, (with the

exception of specific phobia; Kessler, Chiu, Demler, & Walters, 2005). We chose to use affective faces because we wanted our results to be comparable to a large body of prior work and because we wanted to use generic stimuli that would be relevant to the majority of patients in our sample.

The primary aim was to measure the effects of current symptoms on neural activation. Data were analyzed with respect to patient versus control; continuous symptom correlations within the patient group; and primary diagnosis. We hypothesized that compared to controls, patients would show increased activation in the amygdala and insula for negative faces, and that continuous symptoms of anxiety and depression would be associated with heightened amygdala and insula activation for negative facial expressions (Blair et al., 2008; Gentili et al., 2016; Stuhmann et al., 2011). We also hypothesized that symptoms of anxiety would be associated with greater activation in the ACC (Feldker et al., 2016; Graham & Milad, 2011) and increased dlPFC activation (Blair et al., 2008; Carré et al., 2014; Gentili et al., 2016) for negative faces; we expected reduced dlPFC activation for symptoms of depression (Stuhmann et al., 2011). Prior findings using happy faces have been mixed (Stuhmann et al., 2011); therefore, we did not have specific predictions in this regard. Given symptom overlap and frequent comorbidity between GAD, SAD, and MDD (Kessler et al., 2005), we did not expect to observe substantial differences between diagnoses. As these were patients in the active phase of illness (generally higher symptom loads), we expected that current symptom dimensions would dominate differences in activation.

Materials and Methods

Participants

Participant demographics and clinical data are presented in Table 1. Diagnoses were made according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (SCID-NP; First, Spitzer, Gibbon, & Williams, 2002); continuous symptoms were assessed using the Hamilton Anxiety Scale (HAM-A; Maier, Buller, Philipp, & Heuser, 1988) and Hamilton Depression Scale (HAM-D; M. Hamilton, 1960); the SCID, HAM-A and HAM-D were administered by experienced clinicians. Mean HAM-A and HAM-D values in the patient group were in the moderate range, with the distribution of values for both scales extending from no/minimal to severe symptoms; HC scores for both scales were in the no/minimal symptom range (HAM-A; Matza, Morlock, Sexton, Malley, & Feltner, 2010; HAM-D; Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013). Participants with a primary diagnosis of MDD had greater HAM-D ($M=17.0$; $SD=5.0$) scores compared to the GAD group [$t(60)=6.2$, $p<.001$; $M=9.2$; $SD=3.6$], who had greater scores than the SAD group [$t(97)=2.8$, $p=.006$; $M=6.1$; $SD=4.4$]. Participants with a primary diagnosis of GAD did not differ on the HAM-A from those with MDD [$t(60)=1.8$, $p=.07$; GAD: $M=15.4$; $SD=6.4$; MDD: $M=18.6$; $SD=6.5$], however both GAD [$t(97)=2.8$, $p=.006$] and MDD [$t(119)=6.1$, $p<.001$] had higher HAM-A scores than those with SAD ($M=10.4$; $SD=7.3$).

Exclusionary criteria included a history of a major medical or neurological illness or traumatic brain injury, bipolar disorder, psychotic disorder, mental retardation, or a developmental disorder. Participants were free from psychotropic medications (2 weeks; 4

weeks for fluoxetine), with negative urine toxicology screens. Informed consent was obtained from all participants; procedures were in compliance with the Helsinki Declaration of 1975 (as revised in 1983), and were approved by relevant institutional review boards from the University of Michigan (UM), University of Chicago (UC) and University of Illinois at Chicago (UIC).

Task

Participants completed a version of the Emotional Face-Matching Task (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002), previously validated for use with fMRI BOLD (Gorka et al., 2015; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Phan et al., 2013). Angry, fearful and happy faces were selected from the Gur emotional faces set (Gur et al., 2002). There were 3 angry, 3 fearful and 3 happy blocks of trials, interspersed with shape-matching blocks. Each block lasted 20 s and consisted of 4 back-to-back 5-s trials. Shapes were used as control stimuli instead of neutral faces, because they may provide a more truly neutral baseline for comparison, particularly when patients are involved (Filkowski & Haas, 2016).

Functional MRI Data Acquisition and Analysis

Functional MRI based on BOLD contrast was performed on three 3T GE scanners (General Electric Healthcare; Waukesha, WI): GE Signa Systems at UM and UC and a GE MR750 scanner at UIC. Scanning was performed using an 8-channel phased-array radio frequency head coil, using either a gradient-echo echo reverse spiral sequence (UM and UC) or a gradient-echo echo planar imaging (EPI) sequence (UIC), with the following parameters: repetition time (TR) 2 s, echo time (TE) 22.2–30 ms; flip angle 77–90°; field of view 22–24 cm; acquisition matrix 64×64; 3–5 mm slices with no gap; 30–44 axial slices per volume. Results reported below (i.e., patient versus control differences and correlations with continuous symptoms of anxiety and depression) did not differ by site.

All data met our criteria for image quality with minimal motion correction (movements ≤ 3 mm in any direction across the run). The first 4 volumes were discarded to allow for the magnetization to reach equilibrium. Statistical Parametric Mapping (SPM8) software (Wellcome Trust Centre for Neuroimaging, London, www.fil.ion.ucl.ac.uk/spm) was used to perform conventional preprocessing steps. In brief, slice-time correction was performed to account for temporal differences between slice collection order, images were spatially realigned to the first image of the run, normalized to a Montreal Neurological Institute (MNI) template using the EPI template, resampled to 2 mm³ voxels and smoothed with an 8 mm isotropic Gaussian kernel.

The time series data were subjected to a general linear model, convolved with the canonical hemodynamic response function and filtered with a 128 s high-pass filter. Conditions of interest were Angry, Fearful, Happy and Shapes trials, which were modeled separately, with effects estimated for each voxel for each participant. Individual motion parameters were entered in the model as covariates of no interest. Angry>Shapes, Fearful>Shapes and Happy>Shapes contrasts, created separately for each participant, were taken to the second level for random effects analysis.

Diagnostic and Symptom Associations with fMRI BOLD

Because different facial expressions may reveal different neural correlates in anxious (Phan et al., 2013) and depressed (Stuhrmann et al., 2011) psychopathology, as well as in healthy individuals (Fusar-Poli et al., 2009), we performed analyses separately for each contrast (Angry>Shapes, Fearful>Shapes and Happy>Shapes). We used a two-sample *t*-test to examine patient versus control differences. Within the patient group, we conducted whole-brain correlations between a) symptoms of anxiety (HAM-A scores) and BOLD activation, controlling for symptoms of depression (HAM-D scores), and b) symptoms of depression (HAM-D scores) and BOLD activation, controlling for symptoms of anxiety (HAM-A scores). We also assessed effects of primary diagnosis within the patient group. For each of these analyses, age, gender and education were entered as covariates of no interest. To threshold results we used a whole-brain mask (volume=1459.3 cm³) encompassing all grey matter regions. Clusters of activation were identified using an uncorrected voxel threshold of $p<.001$, and then subjected to correction for multiple comparisons via simulation using the 3dClustSim utility (Dec. 16, 2015 updated release; 10,000 iterations; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html; Eklund, Nichols, & Knutsson, 2016). Given smoothness estimates of the data, FWE correction at $\alpha<0.05$ was achieved using a voxel threshold of $p<.001$ with minimum cluster sizes of 88-115 voxels (volume=704-920 mm³). To clarify the direction of significant results, we extracted BOLD signal responses (β -weights in arbitrary units of activation), averaged across voxels within a 5 mm radius sphere surrounding each peak maxima.

Results

There was a significant effect of patient status in the right inferior occipital/lingual gyrus for Angry>Shapes and Fearful>Shapes. Follow-up tests (controlling for age, sex and education as in the whole brain analyses) indicated that compared to controls, patients showed greater BOLD activation in this region for both Angry>Shapes [$F(4,194)=14.16$, $p<.001$; Patients: $M=1.74$, $SD=.64$; Controls: $M=1.36$, $SD=.65$] and Fearful>Shapes [$F(4,194)=13.71$, $p<.001$; Patients: $M=1.78$, $SD=.72$; Controls: $M=1.37$, $SD=.64$].

Tables 2 and 3 present significant whole-brain correlations within the patient group that fell inside (so noted) and outside of *a priori* regions. There were significant positive associations between symptoms of anxiety and activation in the left and right insula (Table 2; Fig. 1), the anterior/midcingulate (Table 2; Fig. 2) and the right dlPFC (Table 2; Fig. 3A) for Angry>Shapes. There were also significant negative correlations between depressive symptoms and activation in the right dlPFC (Table 3; Fig. 3B) for Angry>Shapes. No effects of primary diagnosis surpassed our threshold for significance.

Discussion

Recent initiatives have stressed the importance of examining how neurobiological activity varies along dimensions that might span diagnostic boundaries (Cuthbert, 2015). Surprisingly, few studies have yet accomplished this task. In the current study, across a group of more than 140 patients, increased symptoms of anxiety were associated with greater Angry>Shapes activation in the bilateral insula, anterior/midcingulate and the right

dIPFC; continuous symptoms of depression were associated with reduced activation in the right dIPFC for Angry>Shapes.

Our finding of a significant positive association between anxiety symptoms and insula activation for negative faces is consistent with work suggesting anxiety symptoms drive and are perhaps reflective of excessive emotional reactivity (Carré et al., 2014; Etkin & Wager, 2007; Klumpp et al., 2013; Stein et al., 2007). Because of the insula's critical role in the prediction of unpleasant or aversive body states, it may have particular relevance to anxiety disorders, which are characterized by maladaptive attempts to predict and control future aversive events/body states (Paulus & Stein, 2006). The current findings are also in line with prior reports of increased insula activation in SAD (Feldker et al., 2016; Klumpp, Angstadt, & Phan, 2012) and GAD (Buff et al., 2016). By using a standardized paradigm across these multiple diagnostic groups, the current results confirm that increased insula activation cuts across diagnoses and indicate that insula involvement increases with anxiety symptom load. In addition, failure to find an association with depressive symptoms suggests that heightened insula activation may be distinctly associated with current anxiety symptom burden, rather than depression symptom burden – even for those whose primary diagnosis is MDD.

We also observed evidence of increased activation in the anterior/midcingulate cortex among participants reporting increased symptoms of anxiety. Along with the insula, the anterior cingulate is part of the salience network, implicated in the pathophysiology of anxiety (MacNamara et al., 2016). Prior work has found evidence of increased ACC activation in SAD, dental phobia, PD, PTSD and GAD (Buff et al., 2016; Feldker et al., 2016); here, we extend these results by showing evidence of transdiagnostic correlations, including in MDD. Using event-related potentials, researchers have similarly found evidence that anxiety is associated with increases in the error related negativity (ERN) which has been localized to the ACC (for a meta-analysis, see Moser, Moran, Schroder, Donnellan, & Yeung, 2013). On the other hand, depression has *not* typically been associated with an increased ERN, and may even attenuate error-related processing in anxiety (Weinberg, Klein, & Hajcak, 2012). Recently, the dACC has been subdivided into intrinsic cortical networks relevant to salience and emotional (SEN), cognitive control (CCN), and default mode (DMN) networks. On inspection, the region identified here was more heavily overlapping with the SEN relative to CCN and DMN, suggesting that anxiety increases the draw to salient negative stimuli (Yeo et al., 2011).

Coupled with our observation of increased insula activation among individuals with greater anxiety, it is possible that greater recruitment of the dIPFC (Blair et al., 2008; Carré et al., 2014; Fonzo et al., 2015) may reflect CCN attempts to downregulate affective responding to angry faces. However, whereas lateral PFC engagement may yield reductions in negative affect for healthy individuals (Buhle et al., 2013; Messina, Bianco, Sambin, & Viviani, 2015), this process may be disrupted among individuals with greater anxiety (Carré et al., 2014), as suggested by weaker connectivity between the right dIPFC and amygdala while at rest in those with GAD (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009). Therefore, while it is tempting to think of increased dIPFC activation as adaptive, greater engagement of this regulatory region may instead signal taxing on a system that functions inefficiently. In addition, hemispheric specialization of the dIPFC has also been suggested, such that the left

dIPFC has been associated with the processing of positive stimuli/positive mood and the right dIPFC has been associated with the processing of negative stimuli/negative mood (Canli, Desmond, Zhao, Glover, & Gabrieli, 1998). Therefore, increased right prefrontal activation observed here could alternately signal increased negative affect in anxiety.

In contrast to anxiety, symptoms of depression were associated with reduced activation of the right dIPFC for angry faces, in keeping with broader evidence of reduced dIPFC activation in depression (reviewed in Koenigs & Grafman, 2009) and with work showing that remediation of activation in this region may promote recovery (Kekic, Boysen, Campbell, & Schmidt, 2016; Ma, 2014). Results observed here could therefore be interpreted as a neural substrate for emotion dysregulation in depressed participants – i.e., reduced activation in cognitive control regions might lead to impaired emotion regulation. Interestingly, electroencephalographic (EEG) studies have associated depression with greater right than left frontal activation (e.g., Schaffer, Davidson, & Saron, 1983). However, recent work suggests that these effects may be driven by co-occurring anxiety (Engels et al., 2010), which would align with results observed here – i.e., symptoms of anxiety were associated with *increased* right lateral activation, even in those diagnosed with depression. Therefore, transdiagnostic dimensions that cut across categorical diagnoses may play a key role in predicting the direction and extent of activation in this region.

Notably, we did not observe evidence of increased amygdala activation between patients and controls or among patients with greater symptoms of anxiety or depression. Amygdala hyperactivity has frequently been implicated in the pathophysiology of anxiety and depressive disorders (Heller, 2016; Shin & Liberzon, 2009), mostly when comparing single disorders and healthy controls. Nonetheless, fMRI evidence in support of this notion has been somewhat inconsistent (e.g., Lanius, Bluhm, Lanius, & Pain, 2006; Palm, Elliott, McKie, Deakin, & Anderson, 2011; Thomas et al., 2001; Whalen et al., 2008). Indeed, in a recent study of 135 patients with a variety of psychiatric disorders, no group differences in amygdala activation to negative pictures were observed, nor were any correlations with anxiety or depressive symptoms observed across groups (Hägele et al., 2016; see also Müller et al., 2016). Results observed here suggest that amygdala hyperactivation to negative faces may not be evident across all anxiety and depressive patients. Nonetheless, we caution against overinterpreting this null finding, which could be due to differences between the current study and previous work. Furthermore, we do note that amygdala activation in response to emotional stimuli *was* observed, but across all subjects and not specifically to any patient group (results not shown).

Whereas prior work (e.g. Etkin & Wager, 2007) included studies that used a wide variety of negative stimuli, such as those that were selected for use with a particular diagnosis (e.g., trauma scripts for PTSD, public speaking or anticipation for SAD), the current study used a standardized set of emotional faces. Despite their potential for transdiagnostic relevance, faces may be less evocative elicitors of emotion for some patients (e.g., diminished intensity, personal salience). In their review of face-processing studies in depression, Stuhrmann and colleagues (2011) report having observed evidence of amygdala hyperactivation in MDD in only 9 of 20 studies, attesting to inconsistency in findings. Moreover, for 5 of the 9 studies in

which amygdala hyperactivation was observed, results were found only for sad faces, which were not included here.

Another difference with prior work is our analytic strategy, which differed from the purely categorical and single disorder approach used in many prior studies and meta-analyses. Additionally, many of the studies included in prior meta-analytic work have taken an ROI-driven approach to threshold results, which can increase the likelihood of identifying activation in brain regions like the amygdala. Nonetheless, despite these differences, it is important to consider the possibility that – at least for more generic socio-emotional stimuli (e.g., faces) – GAD, MDD and SAD may *not* be characterized by increased amygdala activation (Hägele et al., 2016).

The current study is limited in that only certain anxiety disorders were included - missing were PD and SP (Fonzo et al., 2015; Killgore et al., 2013), among others. In addition, sad faces were not included among the stimuli, and, given the nature of the analyses, it is possible that results reflect the salience of faces more generally, rather than emotion-specific effects. Finally, the HAM-A and HAM-D may be better at measuring symptom profiles for some disorders than others (e.g., the HAM-A as a general measure of anxiety, may be more applicable to GAD than SAD). Future studies may wish to pursue transdiagnostic analyses using more sophisticated symptom measures (e.g., Watson et al., 2007). In addition, amid a growing climate of concern about the replicability of neuroimaging effects, future work may wish to employ procedures such as using one-half of the sample to identify voxels of interest, and the other half to replicate and assess effects sizes (Kriegeskorte, Lindquist, Nichols, Poldrack, & Vul, 2010).

Conclusion

Results underscore the importance of paralimbic, midline cortical and lateral prefrontal brain regions in the neurobiology of anxiety and depression. They affirm that variation in these regions covaries with symptom load and transcends diagnostic boundaries, and suggest that social signals of “direct” threat (Whalen, 1998) may be especially relevant in probing transdiagnostic neural correlates of anxious and depressive symptomatology. The results also indicate that anxiety and depression can be dissociated at the neural level, and that these symptom profiles may at times exert opposing influences on neural activation (i.e., in the lateral PFC). Continued work of this nature is needed, and may eventually help close the gap between current diagnostic systems and underlying neurobiology.

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Figure 1.

Location of the whole brain correlation between anxiety symptoms and Angry (>Shapes) BOLD activation in the insula (left), controlling for depression symptoms, age, gender and education. Scatterplots depicting these associations (as unstandardized residuals after controlling for covariates) in the left insula (middle) and right insula (right); removal of the data point in the top right corner does not affect results. Primary Dx, Primary diagnosis: SAD, social anxiety disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder. A>S, Angry>Shapes.

Figure 2.

Location of the whole brain correlation between anxiety symptoms and Angry (>Shapes) BOLD activation in the anterior/midcingulate cortex (MCC; left), controlling for depression symptoms, age, gender and education. Scatterplots depicting this association (as unstandardized residuals after controlling for covariates; right). Primary Dx, Primary diagnosis: SAD, social anxiety disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder. A>S, Angry>Shapes.

Figure 3.

A) Location of the whole brain correlation between anxiety symptoms and Angry (>Shapes) BOLD activation in the right dlPFC (left), controlling for depression symptoms, age, gender and education. Scatterplots depicting this association (as unstandardized residuals after controlling for covariates; right). B) Location of the whole brain correlation between depressive symptoms and Angry (>Shapes) BOLD activation in the right dlPFC (left), controlling for anxiety symptoms, age, gender and education. Scatterplot depicting this association (as unstandardized residuals after controlling for covariates; right). Primary Dx, Primary diagnosis: SAD, social anxiety disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder. A>S, Angry>Shapes.

Table 1

Sample characteristics

	Healthy Controls (<i>n</i> = 57)		Patients (<i>n</i> = 142)		Group Comparison
	<i>n</i>	%	<i>n</i>	%	
Gender					
Female	40	70.2	104	73.2	$\chi^2(1) = .66$
Male	17	29.8	38	26.8	
Race					
Caucasian	29	50.9	96	67.6	$\chi^2(1) = .15$
Other	22	38.6	45	31.7	
Primary Diagnosis					
SAD			79	55.6	
MDD			43	30.3	
GAD			20	14.1	
Age	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	$t(79.62) = 1.17$
	27.5	9.8	25.9	6.9	
Education					$t(197) = 1.35$
	14.9	2.8	15.4	2.3	
Hamilton Depression					$t(161.82) = 18.73^a$
	0.7	1.4	9.8	6.6	
Hamilton Anxiety					$t(152.60) = 16.70^a$
	0.4	0.9	13.7	8.0	

SAD, social anxiety disorder; MDD, major depressive disorder; GAD, generalized anxiety disorder. Percentages that do not sum to 100 result from missing data.
^a $p < .001$.

Table 2
Whole-brain correlations with anxiety symptoms (patients; n = 142)

Brain Region	Volume	MNI Coordinates			
	mm ³	t-score	x	y	z
Angry>Shapes					
Positive Correlation					
R dlPFC	4360	4.87	42	28	52
		4.63	32	34	50
Posterior cingulate cortex	5416	4.29	14	-30	28
		3.57	66	-26	6
		3.5	4	-22	34
L Insula	1976	3.98	-44	-8	12
		3.3	-32	-20	16
Anterior/midcingulate cortex	1304	3.85	2	-4	42
R Insula	1456	3.75	44	-6	12
		3.31	38	-22	20
Negative Correlation					
No significant findings					
Fearful>Shapes					
Positive Correlation					
No significant findings					
Negative Correlation					
L Inferior Frontal Gyrus	4824	4.09	-48	8	20
		3.47	-46	18	32
		3.41	-50	-2	34
Parahippocampus	720	3.54	20	-16	-14
		3.4	20	-14	-22
Happy>Shapes					
Positive Correlation					
No significant findings					
Negative Correlation					

MNI Coordinates				
z	y	x	score	Volume
Brain Region				
No significant findings				

A priori ROIs shown in bold and italics. All activations are significant at a whole-brain voxel-wise threshold of $p < 0.05$, corrected, based on 3dClustSim. L, left; R, right; MNI, Montreal Neurological Institute.

Table 3
Whole-brain correlations with depression symptoms (patients; n = 142)

Brain Region	Volume		MINI Coordinates		
	mm ³	t-score	x	y	z
<u>Angry>Shapes</u>					
<i>Positive Correlation</i>					
No significant findings					
<i>Negative Correlation</i>					
R dlPFC	3184	5.4	44	28	54
Posterior cingulate cortex	3240	4.19	8	-24	24
		4.15	4	-16	24
<u>Fearful>Shapes</u>					
<i>Positive Correlation</i>					
No significant findings					
<i>Negative Correlation</i>					
No significant findings					
<u>Happy>Shapes</u>					
<i>Positive Correlation</i>					
No significant findings					
<i>Negative Correlation</i>					
No significant findings					

A priori ROIs shown in bold and italics. All activations are significant at a whole-brain voxel-wise threshold of $p < 0.05$, corrected, based on 3dClustSim. L, left; R, right; MNI, Montreal Neurological Institute.