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Differential role of fusiform gyrus coupling in depressive and anxiety symptoms during emotion perception

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Abstract

Anxiety and depression co-occur; the neural substrates of shared and unique components of these symptoms are not understood. Given emotional alterations in internalizing disorders, we hypothesized that function of regions associated with emotion processing/regulation, including the anterior cingulate cortex (ACC), amygdala and fusiform gyrus (FG), would differentiate these symptoms. Forty-three adults with depression completed an emotional functional magnetic resonance imaging task and the Hamilton Depression and Anxiety Scales. We transformed these scales to examine two orthogonal components, one representing internalizing symptom severity and the other the type of internalizing symptoms (anxiety vs depression). We extracted blood oxygen level dependent signal from FG subregions, ACC, and amygdala and performed generalized psychophysiological interaction analyses to assess relationships between symptoms and brain function. Type of internalizing symptoms was associated with FG3-FG1 coupling ($F = 8.14$, $P = 0.007$). More coupling was associated with a higher concentration of depression, demonstrating that intra-fusiform coupling is differentially associated with internalizing symptom type (anxiety *vs* depression). We found an interaction between task condition and internalizing symptoms and dorsal ($F = 4.51$, $P = 0.014$) and rostral ACC activity ($F = 4.27$, $P = 0.012$). *Post hoc* comparisons revealed that less activity was associated with greater symptom severity during emotional regulation. Functional coupling differences during emotional processing are associated with depressive relative to anxiety symptoms and internalizing symptom severity. These findings could inform future treatments for depression.

Keywords: depression; anxiety; comorbidity; fusiform gyrus; emotion perception

Introduction

Depression and anxiety are highly comorbid, with important consequences both for illness course and treatment response (Kessler *et al.*, 2003; Moffitt *et al.*, 2007; Fava *et al.*, 2008; Brown and Barlow, 2009). Individuals with depression and co-occurring anxiety are more likely to experience illness recurrence and are less likely to experience remission with treatment than those with depression alone (Vittengl *et al.*, 2019; Choi *et al.*, 2020). A substantial body of work has examined the structural relationship between the two conditions. Although there are nuanced differences between proposed theoretical models, they typically suggest that depression and anxiety are composed of both a shared general component that can help to explain the high level of co-occurrence among the disorders and unique components that distinguish separable features between them (Clark and Watson, 1991; Mineka *et al.*, 1998; Krueger, 1999; Naragon-Gainey *et al.*, 2016). Despite the growing consensus regarding the improved validity of this conceptualization over standard diagnostic nosology, surprisingly little work has directly examined the neural mechanisms that underlie the shared and unique elements of depression and anxiety. This gap in the literature limits the field's ability to (i) track the efficacy of treatments for altering the mechanisms associated both with the common (i.e. general internalizing distress) and unique (i.e. disorder specific) components of depression and anxiety and (ii) develop more effective treatments to address the mechanisms underlying each of these aspects.

Neuroimaging research regarding internalizing disorders has typically adopted either a categorical approach guided by the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic boundaries or a dimensional approach wherein depression and anxiety symptom scores are entered as competing variables in regression models of brain function (Kircanski *et al.*, 2017). Both approaches have advanced knowledge, but each has limitations. Several concerns have been raised regarding the validity of the categorical approach to psychiatric diagnoses codified in DSM (Kotov *et al.*, 2017). Most concerning for the use of diagnostic categories to identify possible neural mechanisms is the substantial

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heterogeneity that exists within DSM diagnostic categories, coupled with the arbitrary thresholds used to determine whether a condition is present (Cuthbert and Insel, 2013). Although the dimensional approach for examining the neural mechanisms underlying depressive- and anxiety-related psychopathology addresses these issues, the typical method for testing associations between symptoms and brain function renders it difficult to determine which patterns of neural function may underlie the common elements of internalizing psychopathology and which are associated with depression and anxiety uniquely. Most often, dimensional approaches utilize a multivariable regression framework in which symptom scores for depression and anxiety are entered into a model simultaneously. Doing so accounts for the common component shared by both sets of scores, in that this common element is partialed out of the resulting parameter estimates for each symptom score, but the effect of the common component is not itself typically evaluated, as there is no term in the model that represents it. Relatedly, including correlated symptom scores as two independent terms can adversely affect power to detect the unique contribution of each.

Despite these concerns, the field has advanced knowledge of neural function associated with depression and anxiety. Depression and anxiety are both characterized by alterations in emotional processing, including perceptual biases for negative emotional stimuli (Gotlib *et al.*, 2004; Ellenbogen and Schwartzman, 2009; Sussman *et al.*, 2016). Thus, alterations in regions associated with emotional perception could be associated with the internalizing component common to both depression and anxiety (Kircanski *et al.*, 2017). The fusiform gyrus (FG) is an extrastriate cortical region associated with visual perception that has an elevated response to emotional stimuli (Müller-Bardorff *et al.*, 2018; Frank *et al.*, 2019; Sabatinelli and Frank, 2019). Within the fusiform gyrus, there are both anterior–posterior and medial–lateral functional subdivisions (Caspers *et al.*, 2014; Weiner *et al.*, 2014; Zhang *et al.*, 2016). However, psychiatric neuroimaging studies typically do not assess FG subregions. Although the FG is not typically considered a core region in the pathophysiology of depression, a 2013 meta-analysis of the major depressive disorder (MDD) functional magnetic resonance imaging (fMRI) literature identified both elevated and reduced blood oxygen level dependent (BOLD) signal in various occipital regions in MDD relative to controls. The authors speculate that reduced visual cortex BOLD is due to perceptual biases in MDD and elevated visual cortex BOLD is due to co-occurring anxiety symptoms (Graham *et al.*, 2013), but this explanation has not been directly examined.

A recent directed connectivity study of emotional scene perception in healthy adults identified bidirectional coupling of a fusiform-amygdala-prefrontal cortex circuit during emotional perception that was reliable at the individual subject level across multiple scanning sessions (Frank *et al.*, 2019). The amygdala and FG share reciprocal connections, and feedback between the FG and the amygdala likely mediates the elevated salience of emotional stimuli (Duncan and Barrett, 2007; Herrington *et al.*, 2011; Sabatinelli *et al.*, 2014). Coupling of higher-order visual cortices with the amygdala is thought to underlie the process of identifying and prioritizing emotional stimuli (LeDoux, 2000; White *et al.*, 2014; Frank *et al.*, 2019), particularly negative emotional stimuli (Miyahara *et al.*, 2013). The contributions of the amygdala to emotion processing, as well as the pathophysiology of depression and anxiety, are long-established (Price and Drevets, 2010; Kaiser *et al.*, 2015). However, improved understanding of how fusiform-amygdala coupling relates to internalizing symptoms could improve treatment approaches. For example, it is unclear whether elevated fusiform-amygdala coupling underlies the elevated salience of aversive stimuli common to both depression and anxiety.

The anterior cingulate cortex (ACC) is likewise associated with emotional regulation processes and shows alterations in internalizing disorders (Phillips *et al.*, 2003). Prefrontal cortices, including the ACC, may serve to recontextualize emotional information via coupling with extrastriate cortex (Vuilleumier and Driver, 2007). Indeed, FG resting state activity is negatively correlated with ACC activity (Zhang *et al.*, 2016). ACC activation (Andreescu *et al.*, 2009) and resting state connectivity (Kennis *et al.*, 2014; Oathes *et al.*, 2015) differentiate patients with co-occurring MDD and anxiety disorders from those with either MDD or an anxiety disorder (although see also van Tol *et al.*, 2010). Indeed, in their review of the neuroimaging literature comparing individuals with MDD with and without co-occurring anxiety disorders, Kircanski and colleagues highlight ACC functional differences during emotion processing that are consistently associated with MDD and co-occurring anxiety disorders and distinct from either disorder alone (Kircanski *et al.*, 2017). A meta-analysis of cognitive reappraisal in generalized anxiety disorder also found altered activity in the ACC and FGG (Wang *et al.*, 2018). Given established evidence for elevated threat generalization in anxiety disorders, failure to recontextualize emotional stimuli in anxiety disorders could be driven, at least in part, by altered fusiform-ACC coupling.

In this study of adults with depressive disorders, we aimed to determine the relationship between the common and unique aspects of depression and anxiety symptoms and activity and functional coupling in the fusiform gyrus, amygdala and ACC during viewing of aversive stimuli. We hypothesized that amygdala BOLD response would be associated with the common component of general internalizing symptom severity as would fusiform-amygdala coupling. We further hypothesized that FG coupling with the ACC would be associated with the specific nature of the internalizing symptom such that increased fusiform/ACC coupling would be associated with a higher relative concentration of anxiety symptoms, accounting for general internalizing symptom severity. By contrast, we hypothesized that within-FG coupling would be associated with a higher relative concentration of depressive symptoms, accounting for general internalizing symptom severity.

Methods and materials

Participants

Forty-three adults aged 18 to 40 with depressive disorders (27 female) were recruited from the Pittsburgh, PA community. An additional 25 individuals (13 female) with no history or family history of psychiatric diagnoses were referenced to help characterize observed findings in the depressive disorder group relative to typical function, but we did not include them in our statistical models, given that this study was designed to assess anxiety and depression symptom severity effects on brain function (Table 1). Diagnosis of a depressive spectrum disorder was confirmed using the Structured Clinical Interview for DSM-IV (major depressive disorder, dysthymic disorder or depressive disorder not otherwise specified). No participants were receiving psychotropic medication. See Supplementary Materials for a description of inclusion/exclusion criteria.

Table 1. Demographic and clinical characteristics

	Depressive disorder	Healthy
Gender (Female/Total)	27/43	13/25
Race (Asian/Black or African American/White/Prefer Not to Disclose)	4/11*/25/3	6/7/12/0
Mean Age in Years ± SD	26.10 ± 5.86	25.93 ± 5.26
Mean HAMD Total Score ± SD (Range)	19.62 ± 4.92 (10–33)	1.08 ± 1.32 (0–4)
Mean HAMA Total Score ± SD (Range)	16.93 ± 6.33 (5–39)	0.72 ± 1.06 (0–4)
Mean Age of Illness Onset in Years ± SD**	19.03 ± 6.83	N/A
Mean Duration of Illness in Years ± SD**	4.73 ± 6.88	N/A

*One participant also reported Hispanic ethnicity.
**Six participants did not provide information on illness onset.
HAMD = Hamilton Depression Scale;
HAMA = Hamilton Anxiety Scale, SD = standard deviation.

Clinical assessments

The Hamilton Depression (HAMD) and Anxiety (HAMA) Scales were administered by a trained rater. To assess the relative contributions of the common and unique components of depression and anxiety pathology, we adopted an approach described by Kraemer and colleagues (Essex *et al.*, 2003). Using this approach, the average of the z-transformed HAMA and HAMD totals serves as the index of the common component of internalizing symptom severity, it is equivalent to the first principal component of the measures, and it captures everything that the two measures share. Both anxiety and depression symptom scores are represented positively in this measure, such that a higher score indicates higher levels of internalizing symptoms. A second index, half the difference between the two z-score transformed measures, was used to capture what is unique to depression *vs* anxiety psychopathology. This index is equivalent to the second principal component of the measures, and it captures everything that differentiates depression and anxiety, as assessed by the two measures. Kraemer and colleagues term this component a 'directionality' score, which represents the direction of symptoms towards, in this case, either depression or anxiety symptoms (Essex *et al.*, 2003). Because we subtracted the HAMA scores from the HAMD scores, a more positive score on this term reflects symptoms directed more towards depression, while a more negative score reflects symptoms directed more towards anxiety. This procedure transforms the two terms representing depression and anxiety symptoms to two terms representing the common and unique features of depression- and anxiety-related psychopathology, as measured by the HAMA and HAMD, and it has several advantages. First, the transformation preserves all the information captured in the raw symptom scores. It reorganizes that information so that the resulting parameter estimates are more easily interpreted. Second, it allows direct estimation of relationships between brain function and the common component of internalizing psychopathology while preserving the ability to examine the unique effects of depression and anxiety. Third, it resolves the collinearity inherent in including depression and anxiety measures in the same model, as the terms representing the common and unique components of depression and anxiety are correlated at $r = 0$. Fourth, it provides an explicit inferential test of whether the type of internalizing symptom (depression vs anxiety) matters in explaining variance in brain function over and above the severity of those symptoms.

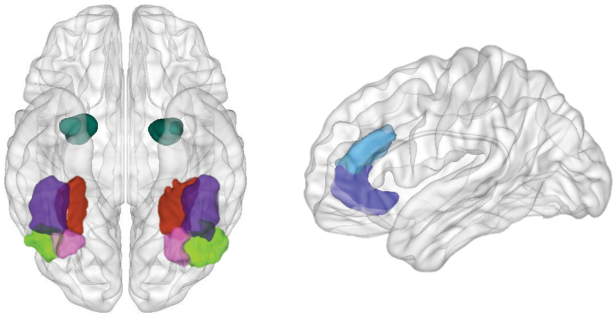

Fig. 1. ROIs for all analyses mapped on glass brains. Bilateral amygdala is shown in dark green, FG1 is shown in pink, FG2 in lime green, FG4 in purple. FG3 seed for gPPI analyses is shown in orange. rACC is shown in dark blue, and dACC is shown in light blue. FG = fusiform gyrus.

fMRI task

We used an fMRI task which examines the neural circuitry associated both with viewing and regulating response to emotionally salient stimuli (Ochsner *et al.*, 2002). Each trial begins with an instruction cue (2 s) to either 'attend' or 'reappraise' the image that will follow. Next, a negative or neutral socially relevant International Affective Picture System (IAPS) picture is presented (8 s) and participants follow the instructions for that trial. There are three trial types: attend neutral, attend negative and reappraise negative, presented in pseudorandom order. During attend trials, participants view the scene and experience any natural response without attempting to change it. During the reappraise trials, participants are instructed to reframe the meaning or outcome of the scene to diminish the emotional impact. Each image is followed by an emotional rating probe (4 s) and a fixation cross (4 s). Twenty trials of each type were presented across two 10 min, 20 s runs. For detailed task instructions, scan parameters, preprocessing and first level modeling details, see Supplementary Materials.

BOLD and gPPI region of interest (ROI) Analyses

The FG was subdivided into four regions, for a total of four bilateral ROIs (Figure 1). These subregions are based on postmortem cytoarchitecture as well as functional mapping studies (Caspers *et al.*, 2013; Lorenz *et al.*, 2017). Generalized psychophysiological interaction (gPPI) analyses were performed in SPM12 with the gPPI toolbox (McLaren *et al.*, 2012) using the medial anterior FG subregion (FG3) as a seed, given previous findings (Frank *et al.*, 2019). GPPI models were constructed using separate regressors for each task condition as described in the first level model section earlier. The target ROI for the bilateral amygdala was created using the aal atlas (Tzourio-Mazoyer *et al.*, 2002). The dorsal and rostral ACC ROIs, which correspond to Brodmann Area 32, were created using the Brainnetome Atlas (Fan *et al.*, 2016). The BOLD signal was also extracted from each of these ROIs (FG1-4, bilateral amygdala, dorsal and rostral ACC) to test for regional BOLD effects (Figure 1).

econd level modeling

We performed seven parallel linear mixed models with regional extracted beta estimates from first level models, representing BOLD signal as the dependent variable (FG1-4, bilateral amygdala, dorsal ACC (dACC) and rostral ACC (rACC)). We also performed six parallel linear-mixed models with extracted gPPI weights as the dependent variable for the bilateral FG3 subregion to each target ROI (i.e. FG3 seed to the following target ROIs: dACC, rACC, bilateral amygdala and bilateral FG1, FG2 and FG4). For all models, task

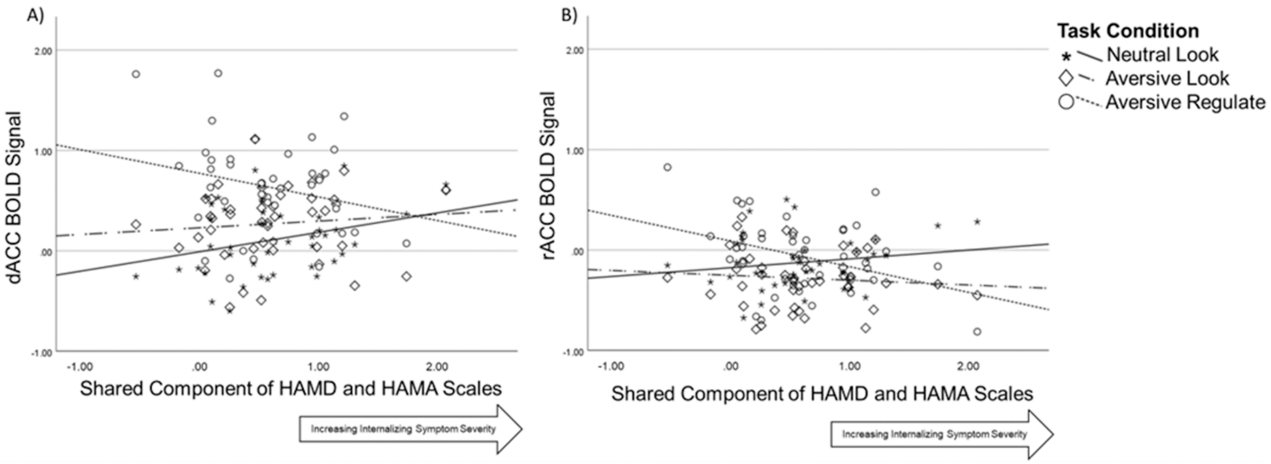

Fig. 2. Interaction effect of task condition on the relationship between summed HAMA total scores and HAMD total scores and BOLD signal in the (A) dACC and (B) rACC. BOLD = blood oxygen level dependent, HAMD = Hamilton Depression Scale, HAMA = Hamilton Anxiety Scale.

condition was included in the model as a repeated effect, assuming an unstructured variance/covariance matrix, and the terms representing common internalizing psychopathology and unique depression/anxiety pathology were included as between-subject effects. Terms representing the interactions of task condition with the two components of internalizing psychopathology were included in the model, as were age and gender as covariates. We planned *post hoc* tests for condition effects on regional BOLD or FG3 coupling. False discovery rate correction was used to correct for number of models for each model type (gPPI and BOLD).

Results

We report primary findings related to the common component representing general internalizing symptom severity and to the unique component representing the direction of the internalizing symptoms (depression *vs* anxiety). For task condition and gender findings, see Supplemental Materials.

Associations with general internalizing symptom severity (common component)

Regional BOLD findings

We observed significant interaction effects between task condition and the common component representing internalizing severity for both dACC ($F = 6.17$, $P = 0.005$) and rACC ($F = 5.23$, $P = 0.010$) BOLD activity. An influential outlier was identified in both models, but both findings remained significant when the models were repeated using a robust regression technique with sandwich estimators ($F = 4.51$, $P = 0.014$ for dACC; $F = 4.27$, $P = 0.012$ for rACC). *Post hoc* pairwise comparisons revealed that, for the dACC model, the aversive regulate condition differed from both the neutral attend ($t = 2.82$, $P = 0.006$) and the aversive attend conditions ($t = 2.78$, $P = 0.007$). There was no difference between the neutral and aversive attend conditions ($t = 1.16$, $P = 0.25$). The pattern was similar for the rACC model; the aversive regulate condition differed from the neutral attend ($t = 2.92$, $P = 0.005$) and the aversive attend conditions ($t = 2.04$, $P = 0.04$), but there was no difference between the two attend conditions ($t = 1.63$, $P = 0.11$). In both ACC models, the relationship between symptoms and BOLD during the aversive regulate condition was more negative than the other conditions, such that greater symptom severity was associated with less activity (Figure 2).

Functional coupling findings

There were no significant effects of the common component representing internalizing severity for any gPPI model (all $Ps > 0.20$).

Associations with the direction of the internalizing symptoms (the unique component)

Regional BOLD findings

There was a main effect of the unique component (representing the relative concentration of anxiety and depressive symptoms) on dACC BOLD activity ($F = 5.21$, $P = 0.028$). The results remained significant using a robust regression with a sandwich estimator to address an outlier ($F = 6.51$, $P = 0.015$). Individuals with a greater concentration of depressive relative to anxiety symptoms showed lower BOLD signal (Figure 3A).

Functional coupling findings

We observed no significant interaction effects between task condition and the unique component for any gPPI models. Therefore, the interaction term was removed from these models.

There was a significant main effect of the unique component on FG3-FG1 coupling, ($F = 8.14$, $P = 0.007$). There was also a main effect of the unique component on coupling between FG3 and FG4 that did not survive multiple comparison correction ($F = 5.00$, $P = 0.031$). In both instances, the relationship was such that individuals with a higher concentration of depression relative to anxiety symptoms showed greater intra-fusiform coupling (Figure 3B–C).

We observed no other effects of the unique component for any other models (all $Ps > 0.10$).

Twenty-three of the 43 participants met criteria for a co-occurring anxiety disorder. As a *post hoc* test, we repeated all models using the presence or absence of an anxiety disorder as a categorical, between-subjects factor, instead of the transformed HAMA and HAMD scores. There were no significant main effects of the presence of an anxiety disorder on BOLD or functional coupling in our ROIs (all $Ps > 0.10$).

Discussion

In this study, we sought to differentiate associations between brain function and the common elements underlying internalizing pathology from associations with the elements specific to the type of symptoms experienced (anxiety or depression). We

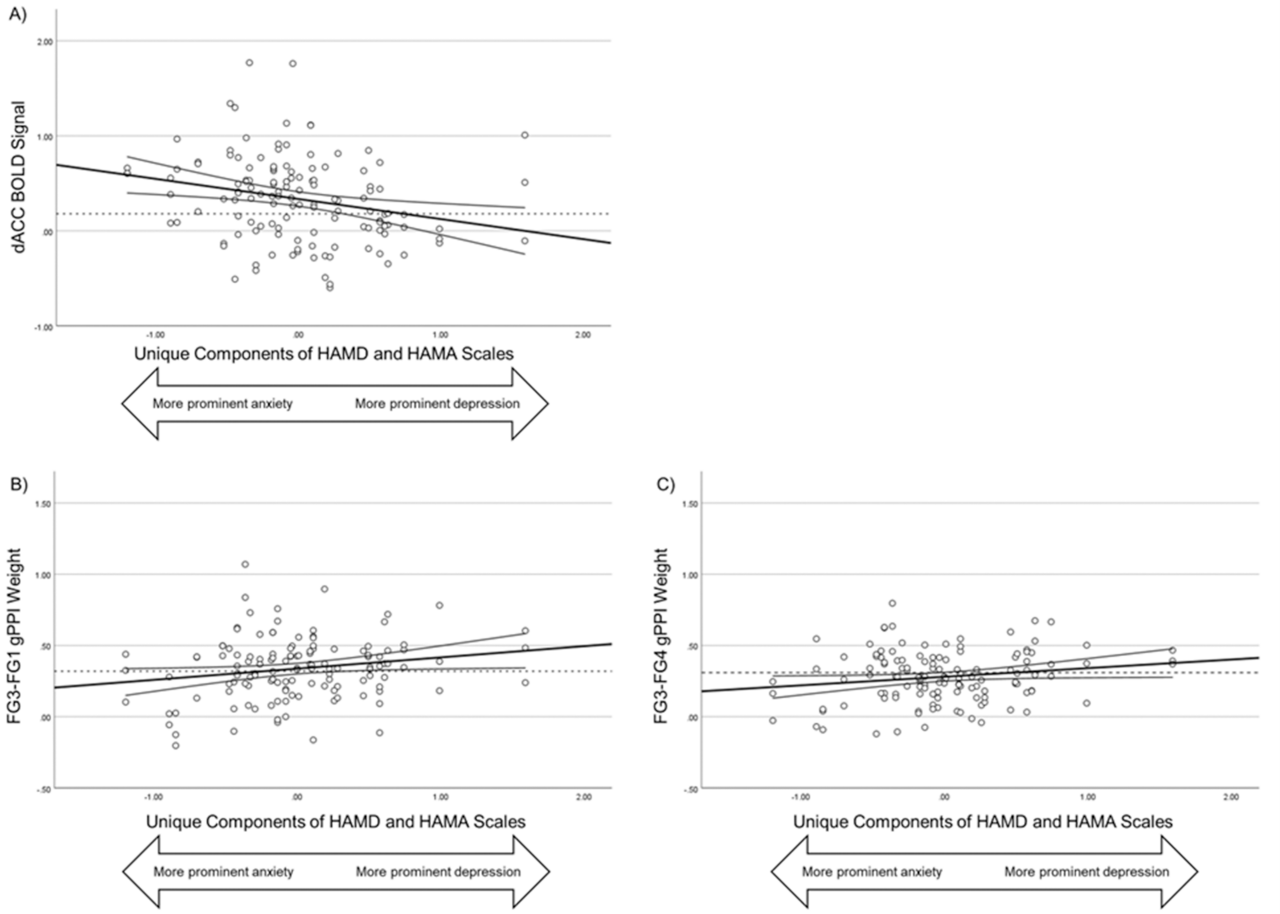

Fig. 3. HAMD total scores minus HAMA total scores as a function of (A) dACC BOLD signal, (B) anterior medial Fusiform Gyrus (FG3) coupling with posterior medial fusiform gyrus (FG1), and (C) FG3 coupling with anterior lateral fusiform gyrus (FG4) in individuals with depressive disorders. Dashed lines indicate mean values for healthy participants as a reference. FG = fusiform gyrus, gPPI = generalized psychophysiological interaction.

observed alterations in BOLD signal and functional coupling of the FG and ACC in individuals with depressive disorders. As hypothesized, we detected functional alterations associated with a common component representing the severity of internalizing psychopathology, as well as alterations that were associated with the directional component representing the relative concentration of depression and anxiety symptoms.

General internalizing symptom severity

We found a significant interaction between task condition and the severity of the common elements of depression and anxiety scores on BOLD signal in both ACC ROIs. In both instances, the relationship between BOLD and internalizing psychopathology was such that greater internalizing severity was associated with decreased BOLD signal during the emotional regulation condition. These findings are consistent with the role of the ACC in emotional regulation and reappraisal (Kohn *et al.*, 2014), as well as differences in ACC function associated with emotional regulation difficulties in people with internalizing disorders (Zilverstand *et al.*, 2017). In a study of individuals with co-occurring MDD and anxiety disorders, symptom severity was also negatively correlated with dACC BOLD during emotional reappraisal (Fitzgerald *et al.*, 2019). In another study, adults with anxiety disorders did not engage the dACC during emotional regulation, while healthy controls did (Blair *et al.*, 2012). Our observation of a negative relationship between general internalizing symptom severity and activity in ACC during emotional regulation adds to this literature and suggests that abnormal function of the ACC is associated with internalizing symptoms generally. We observed the same pattern of relationship in both ACC ROIs. Studies of the functional connectivity of subregions of the ACC have suggested that the more rostral portion may be associated with autonomic function via its connections with the insula and orbitofrontal cortices, while the more dorsal component of the ACC, via connections with lateral prefrontal regions, may be associated with cognitive control and error monitoring (Matthews *et al.*, 2004; Margulies *et al.*, 2007; Rolls *et al.*, 2019). Both cognitive control and autonomic processes are likely engaged during the emotional regulate condition of this task, and alterations in these functions are associated with poor emotional regulation in internalizing disorders.

The relative concentration of internalizing symptoms

We observed a significant relationship between the unique symptom direction component and coupling of the anterior medial FG (FG3) with both the posterior medial (FG1) and the anterior lateral FG (FG4). In both instances, the relationship was such that individuals with a preponderance of depressive symptoms relative to anxiety symptoms showed more coupling than those with a preponderance of anxiety symptoms relative to depressive symptoms. Although there are few functional connectivity studies of

coupling within the FG in depression, there is literature indicating altered FG structure and function in MDD (Arnone *et al.*, 2016; Stuhrmann *et al.*, 2011; Le *et al.*, 2017; Li *et al.*, 2020; Wang *et al.*, 2022). In a study of visual motion perception in MDD, elevated visual cortex activity mediated the association between reduced GABAergic function in higher order visual cortex and aberrant visual perception (Liu *et al.*, 2022). Interestingly, that study was not conducted with emotional stimuli, but instead simple moving gratings, suggesting that visual perceptual and cortical function alterations in depression may not be specific to emotional stimuli. Although we hesitate to over-interpret the lack of a significant interaction effect between the unique directional component and task condition in the present study, the pattern we observed is consistent with the findings from that study suggesting a difference in a more basic, stimulus-independent mechanism. Furthermore, it highlights the importance of statistically modeling neutral or 'control' task conditions separately from emotional conditions (for further discussion of task condition effects, see Supplementary Materials). Future studies with a variety of stimuli are needed to determine if differences in visual cortex are associated with basic perceptual features of stimuli that are not related to emotion *per se*.

To date, there has been a single study examining within FG connectivity in anxiety disorders, which found that local connectivity in the FG was lower in individuals with anxiety disorders relative to healthy individuals (Cui *et al.*, 2020). Broadly consistent with these results, we observed that individuals with depression who had more dominant anxiety symptoms tended to have lower intra-fusiform coupling across task conditions. Fusiform subregions share reciprocal connections, and reduced coupling between fusiform regions could indicate impaired integrative function in the fusiform gyrus. More anterior portions provide inhibitory feedback to more posterior visual cortex, perhaps to 'fine tune' cortical receptive fields. This serves to normalize any mismatches between bottom-up sensory information and top-down contextual predictions (Cardin *et al.*, 2011). Thus, we speculate that an association between reduced coupling of FG3 with FG1 could be related to inhibitory feedback differences within extrastriate cortices in individuals with anxiety symptoms, potentially resulting in overgeneralization of threat. Future studies combining measures of GABAergic function with fMRI could help to clarify these relationships.

Fusiform coupling with ACC and amygdala

Contrary to our hypotheses, we did not identify effects of FG3 coupling with the ACC or amygdala and symptom measures. This is surprising given the established literature regarding these regions in the pathophysiology of mood and anxiety disorders. In their study of healthy adults, Frank and colleagues identified FG3 as an important component of emotional visual perception (Frank *et al.*, 2019). Differences in the present study could be because coupling of this specific portion of the FG with the ACC or amygdala is not relevant in adults with depressive disorders. Likewise, in a study of functional coupling of ACC subregions, more superior portions of both the dACC and rACC were negatively associated with FG activity, while more inferior portions of these subregions were not (Margulies *et al.*, 2007). Because our ACC ROIs collapsed these inferior and superior portions, we may not have been able to detect effects, although we hesitate to draw definitive conclusions from a null finding. The lack of task condition effects in the amygdala models, despite positive findings in healthy adults in other studies, could indicate that during emotional perception, individuals with depressive disorders are engaging other portions of visual cortices as a compensatory mechanism. Future studies focused on thorough characterization of visual perception in mood and anxiety disorders that are needed to better understand the role of visual cortices, and their links to limbic and prefrontal cortices, during emotional perception.

Limitations

We were underpowered to detect moderation effects of gender. However, gender representation in our sample is consistent with the demographics of adults with depressive disorders. Future studies with larger samples will be best suited to address moderating effects. Another limitation is the use of IAPS photos, which vary in their complexity and content. To mitigate this concern, we ensured that IAPS stimuli in all conditions contained social content. This was a study of the functional coupling of the FG during visual perception of complex emotional scenes. Importantly, this was not a study designed to assess the fusiform face area or face perception, and while many of the IAPS images contain face content, many do not. Additionally, we were unable to determine if the effects we observed were valence-specific, as inclusion of a positive emotional condition was outside the scope of this study. Co-occurring generalized anxiety disorder in patients with MDD has been associated with differences in limbic and prefrontal activity relative to patients with MDD alone, but only during perception of aversive stimuli, suggesting that co-occurring anxiety may be associated with valence-specific modulations of these regions (Schlund *et al.*, 2012). Meanwhile, MDD alone has been associated with elevated ACC activity relative to MDD with co-occurring anxiety, but only in response to positive stimuli, suggesting increased conflict between mood state and stimulus valence in MDD (van Tol *et al.*, 2012). Future studies should assess for valence effects in both depression and anxiety to clarify these relationships. Finally, all participants with internalizing psychopathology in this study were diagnosed with a depressive disorder, which limits the generalizability of the present findings for individuals with more pure presentations of anxiety. Future work with a broader sampling frame will be needed to confirm these findings across the full range of internalizing psychopathology.

Future directions

We identified associations between activity in the ACC and both the shared and unique components of depression and anxiety symptoms. Associations between reduced ACC activity and greater general internalizing symptom severity were driven by ACC engagement during the emotional regulation condition. This study also demonstrated the presence of alterations in higher-order visual cortex functional coupling, namely increased intra-fusiform coupling, that were associated specifically with a higher concentration of depressive, relative to anxiety, symptoms. Given the frequent co-occurrence of depression and anxiety, the present study offers a novel insight into how visual perceptual processes may be used to disaggregate depression and anxiety symptoms.

The FG is an important component of emotional processing that is often overlooked in the psychiatric neuroimaging literature. Our findings highlight the contributions of bottom-up processing as well as top-down regulation in depressive disorders and indicate differences in functional coupling during emotional processing on the basis of depressive *vs* anxiety symptom contributions to psychopathology. The FG may serve as an important target for intervention, including neuromodulation. Our novel approach to understanding the relative contributions of co-occurring anxiety and depressive symptoms could help to identify personalized treatment targets.

Supplementary data

Supplementary data is available at *SCAN* online.

Data availability

The data underlying this article will be shared upon reasonable request sent to the corresponding author.

List of contributors

Dr Edmiston contributed to hypothesis generation, testing and drafted the manuscript. Dr Chase contributed to data preprocessing and provided manuscript feedback. Dr Jones contributed to the design of the study and provided feedback on the manuscript. Ms Nhan created figures and performed demographic data analysis, as well as contributions to manuscript drafting. Dr Phillips provided feedback on approach and the drafted manuscript. Dr Fournier designed the study, contributed to hypothesis generation and testing, as well as drafting the manuscript. All authors have contributed to and approved the final manuscript.

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Conflict of interest

The authors declared that they had no conflict of interest with respect to their authorship or the publication of this article.

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