

# Research Article

## TRANSDIAGNOSTIC DIMENSIONS OF ANXIETY AND DEPRESSION MODERATE MOTIVATION-RELATED BRAIN NETWORKS DURING GOAL MAINTENANCE

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**Background:** *Advancing research on the etiology, prevention, and treatment of psychopathology requires the field to move beyond modular conceptualizations of neural dysfunction toward understanding disturbance in key brain networks. Although some studies of anxiety and depression have begun doing so, they typically suffer from several drawbacks, including: (1) a categorical approach ignoring transdiagnostic processes, (2) failure to account for substantial anxiety and depression comorbidity, (3) examination of networks at rest, which overlooks disruption manifesting only when networks are challenged. Accordingly, the present study examined relationships between transdiagnostic dimensions of anxiety/depression and patterns of functional connectivity while goal maintenance was challenged. Methods: Participants (n = 179, unselected community members and undergraduates selected to be high/low on anxiety/depression) performed a task in which goal maintenance was challenged (color-word Stroop) while fMRI data were collected. Analyses examined moderation by anxiety/depression of condition-dependent coupling between regions of dorsolateral prefrontal cortex (dlPFC) previously associated with approach and avoidance motivation and amygdala/orbitofrontal cortex (OFC). Results: Anxious arousal was positively associated with amygdala↔right dlPFC coupling. Depression was positively associated with OFC↔right dlPFC coupling and negatively associated with OFC↔left dlPFC coupling. Conclusions: Findings advance the field toward an integrative model of the neural instantiation of anxiety/depression by identifying specific, distinct dysfunctions associated with anxiety and depression in networks important for maintaining approach and avoidance goals. Specifically, findings shed light on potential neural mechanisms involved in attentional biases in anxiety and valuation biases in depression and underscore the importance of examining transdiagnostic dimensions of anxiety/depression while networks are challenged. Depression and Anxiety 31:805–813, 2014. © 2014 Wiley Periodicals, Inc.*

**Key words:** *amygdala; anxiety; depression; dorsolateral prefrontal cortex; orbitofrontal cortex, network; transdiagnostic*

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Given that the human brain is comprised of interconnected and interdependent circuits,<sup>[1]</sup> advancing research on the etiology, prevention, and treatment of psychiatric symptoms requires the field to move beyond modular conceptualizations of neural dysfunction (i.e., examining function in individual regions)<sup>[2,3]</sup> toward characterizing pathology-related disturbance in key brain networks.<sup>[4]</sup> Doing so fosters a richer representation of the neural instantiation of pathology,<sup>[3]</sup> increasing diagnostic reliability/validity, and introducing potential novel treatment targets.

Anxiety and depression are extremely prevalent and costly, both for society and for those personally affected.<sup>[5–8]</sup> Although research has identified some areas of anxiety/depression-related disruption in functional brain circuits,<sup>[9–14]</sup> these studies have almost uniformly taken a categorical approach (i.e., DSM-IV diagnoses) that ignores processes shared across disorders. This is at odds with recent recognition that dimensional, transdiagnostic approaches will likely have more utility when translating basic neuroscience into clinical treatments.<sup>[15–17]</sup> Furthermore, relevant studies have rarely examined anxiety and depression simultaneously, despite high comorbidity,<sup>[18]</sup> leaving unclear whether findings are related to either or both. Finally, the majority of research on functional brain networks in anxiety and depression has employed data collected while participants were at rest, which may overlook disrupted network activity that manifests only when systems are challenged.<sup>[19]</sup> Accordingly, the present study examined the relationship between dimensions of anxiety/depression and patterns of functional connectivity while goal maintenance was challenged. Given that approach and avoidance goals appear to be differentially disrupted in anxiety and depression (avoidance increased in both, approach decreased only in depression),<sup>[20–23]</sup> the present study examined one brain network related to approach and another to avoidance,<sup>[24,25]</sup> allowing for the identification of anxiety/depression-specific dysfunction.

Several regions central to goal pursuit consistently differentiate individuals with and without anxiety/depression, including orbitofrontal cortex (OFC) and amygdala. With regard to anxiety, studies of OFC show consistent hyperactivation to aversive stimuli.<sup>[26,27]</sup> Both hyper- and hypoactivation have been detected in individuals with Major Depressive Disorder (MDD), depending on stimulus valence. For instance, a meta-analysis of emotional challenge studies and MDD found hyper- and hypoactivation in OFC for sad and happy stimuli, respectively.<sup>[28]</sup> Given research linking OFC to maintaining the average motivational value of stimuli,<sup>[29]</sup> hyperactivation in OFC may lead to the cost overestimation seen in anxiety<sup>[30]</sup> and depression,<sup>[31]</sup> and hypoactivation may lead to the reward underestimation seen in depression.<sup>[32]</sup> Both anxiety and depression consistently show hyperactivation in amygdala,<sup>[33–38]</sup> a subcortical structure central to identifying salient stimuli and enhancing motivationally relevant stimulus features.<sup>[39]</sup>

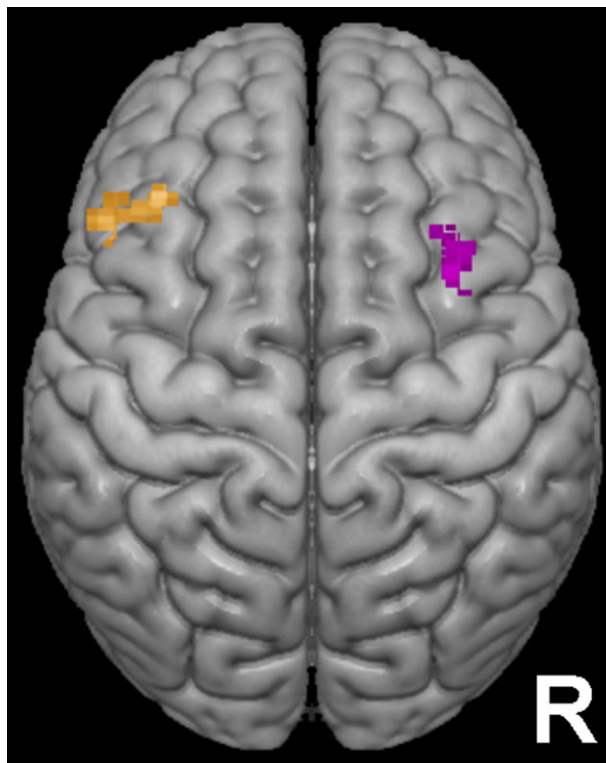


Figure 1. Regions of dorsolateral prefrontal cortex used as seed clusters. The orange cluster above left was previously associated with approach motivation.<sup>[43]</sup> The purple cluster above right was previously associated with avoidance motivation.<sup>[43]</sup>

Consequently, amygdala hyperactivation may play a role in the heightened salience for potential threat observed in anxiety in particular.<sup>[40]</sup>

Importantly for the focus of the present study on networks, emerging evidence suggests that both OFC and amygdala (anatomically mediated via OFC) interact with dorsolateral prefrontal cortex (dlPFC) as part of a circuit instantiating the maintenance of approach/avoidance goals.<sup>[25]</sup> Research consistently implicates dlPFC in top-down biasing of processing (e.g., in OFC/amygdala) to be consistent with goals,<sup>[41]</sup> and regions of dlPFC have been implicated in the integration of motivational and executive function processes.<sup>[24,42]</sup> Specifically, a region of left dlPFC has been selectively related to approach motivation and a region of right dlPFC to avoidance (see Fig. 1).<sup>[43,44]</sup> Thus, examining interactions between dlPFC and OFC/amygdala as a function of anxiety/depression may be particularly informative, because these connections appear to be important for effectively maintaining approach/avoidance goals.<sup>[25]</sup>

The importance of examining connectivity with dlPFC is underscored by evidence of anxiety/depression-related dysfunction in this region. For example, hyperactivation in right dlPFC has been consistently reported when individuals encounter anxiety-relevant stimuli.<sup>[45–48]</sup> Several studies have also found

an association between depression and rightward dlPFC lateralization.<sup>[49,50]</sup> Furthermore, intervention research indicates that rightward dlPFC lateralization is functionally significant. For example, successful psychotherapy normalizes right dlPFC hyperactivation in individuals with Posttraumatic Stress Disorder (PTSD) viewing trauma-related imagery,<sup>[45]</sup> and disruption of right dlPFC via repetitive transcranial magnetic stimulation leads to reduced anxiety in individuals with Generalized Anxiety Disorder (GAD).<sup>[48]</sup> Additionally, research in our lab indicates that depression is associated with decreased left dlPFC↔dorsal anterior cingulate coupling<sup>[51]</sup> (although, a different dlPFC region was examined and coupling was based on source-localized electroencephalography).

Although dlPFC↔amygdala/OFC coupling in anxiety/depression has received little attention, several studies provide initial evidence of dysfunction in this circuit. For example, individuals with GAD<sup>[10]</sup> and MDD<sup>[52]</sup> exhibit greater right dlPFC↔amygdala connectivity at rest, and greater right dlPFC↔OFC coupling is evident in individuals with MDD performing a face-matching task.<sup>[53]</sup> Thus, emerging evidence supports the hypothesis that anxiety and depression involve dysfunction in this circuit, although these studies suffered from the flaws mentioned above.

## PRESENT STUDY

The present study tested the hypothesis that anxiety and depression moderate dlPFC↔OFC/amygdala functional connectivity during goal maintenance and evaluated whether they do so differentially. Rather than taking a unitary approach, analyses examined two dimensions of anxiety whose importance appears to cross disorder boundaries. Specifically, the present study examined anxious apprehension (characterized by worry/verbal rumination and particularly evident in GAD<sup>[54-56]</sup>) and anxious arousal (characterized by somatic tension/sympathetic hyperarousal and particularly evident in Panic Disorder<sup>[57]</sup>). In addition, the present study examined anhedonic depression, a distinct depression facet that is distinguishable from the general negative affect shared with anxiety.<sup>[57,58]</sup>

Although anxious apprehension and arousal are separable dimensions, it is not the case that there is no conceptual or empirical overlap between these constructs. For example, both dimensions show strong relationships with avoidance motivation and weaker relationships with approach.<sup>[23]</sup> Indeed, this overlap is a key reason to examine these dimensions simultaneously (to ascertain unique effects). Despite overlap, there is a growing body of research showing differential effects when unique variance is examined.<sup>[51,59,60]</sup> Thus, it appears conceptually important and methodologically acceptable to examine both dimensions of anxiety.

To elicit goal-maintenance processing, the present task involved a goal that was challenged by irrelevant but distracting information, the color-word Stroop

task.<sup>[61]</sup> Connectivity with two regions of dlPFC was assessed: a left dlPFC cluster associated with approach motivation and a right dlPFC cluster associated with avoidance.<sup>[43,44]</sup> In a previous study, we showed that connections between these clusters and OFC/amygdala were strengthened when goal maintenance was challenged.<sup>[25]</sup> Connections between dlPFC and OFC also varied as a function of trait motivation, supporting the relevance of these pathways in particular. Present hypotheses were that (1) both anxiety dimensions and anhedonic depression would be associated with increased *right* dlPFC↔OFC coupling, (2) anhedonic depression would also be linked to decreased *left* dlPFC↔OFC coupling, and (3) both anxiety dimensions and anhedonic depression would exhibit increased *right* dlPFC↔amygdala coupling.

## METHODS

### PARTICIPANTS

The sample consisted of undergraduates ( $n = 81$ ) and community members ( $n = 98$ ) and was the same as used in.<sup>[25]</sup> Undergraduates were recruited from a larger pool ( $n = 2,723$ ) based on their scores on three scales: the Penn State Worry Questionnaire (PSWQ<sup>[62]</sup>), and the Anxious Arousal (MASQ-AA) and Loss of Interest Anhedonic Depression (MASQ-AD) scales of the Mood and Anxiety Symptom Questionnaire.<sup>[57]</sup> Participants were contacted if (1) they scored  $\geq 80$ th percentile (PSWQ  $\geq 63$ , MASQ-AA  $\geq 33$ , MASQ-AD  $\geq 22$ ) on one dimension and  $\leq 50$ th percentile (PSWQ  $\leq 49$ , MASQ-AA  $\leq 25$ , MASQ-AD  $\leq 17$ ) on the others, (2)  $\geq 80$ th percentile on all three, or (3)  $\leq 50$ th percentile on all three. Unselected community members were recruited using advertisements placed in newspapers/electronic list-serves and from a local clinic. Study procedures were identical across undergraduates and community members.

Two hundred and twenty-seven participants completed the protocol, and data from 179 (60% female, mean age = 27.32, SD = 10.0) passed data quality screening. Exclusion criteria were (1) moved  $> 3.3$  mm relative to the middle volume or  $> 2$  mm relative to the previous volume, (2) committed errors on  $> 15\%$  trials, (3) exhibited reaction times (RT)  $> 3$  SD, (4) had susceptibility artifact in relevant areas, or (5) exhibited activation patterns indicative of motion. Questionnaire data were not available for one participant.

### PSYCHOPATHOLOGY ASSESSMENT

The 16-item PSWQ assessed anxious apprehension, the 17-item MASQ-AA assessed anxious arousal, and an 8-item subscale of the MASQ-AD assessed anhedonic depression. PSWQ correlated 0.376 with MASQ-AA and 0.421 with MASQ-AD, and MASQ-AA correlated 0.525 with MASQ-AD ( $P_s < .001$ ).

The Structured Clinical Interview for the DSM-IV (SCID<sup>[63]</sup>) was also administered. Given our focus on transdiagnostic dimensions of anxiety/depression, SCID data are not reported beyond disorder rates. With regard to depression, 46 participants had a diagnosis of MDD, eight of Dysthymia, and two of Depressive Disorder NOS. With regard to anxiety, 44 participants had at least one diagnosis (GAD = 21, Specific Phobia = 16, Social Phobia = 13, Obsessive Compulsive Disorder = 5, PTSD = 4, Anxiety Disorder NOS = 2, Panic Disorder = 1, Agoraphobia Without Panic = 1).

### EXPERIMENTAL DESIGN

Participants completed two tasks during fMRI data collection: a color-word and an emotion-word Stroop (duration of each =

12.33 min). Only data from the color-word task are discussed. In the color-word Stroop, 256 trials were presented in 16 blocks (four congruent, four incongruent, eight neutral), with a variable ITI (2,000  $\pm$  225 ms). Each trial consisted of one word presented in one of four ink colors, each color occurring equally often with each word type. Word meaning was the same as ink color in *congruent* trials (e.g., 'RED' in red ink), whereas word meaning differed from ink color in *incongruent* trials (e.g., 'GREEN' in red ink), and the two were unrelated in *neutral* trials (e.g., 'LOT' in red ink). Task condition alternated by block, and task and condition order were counterbalanced.

## BEHAVIORAL DATA PROCESSING

Mean RT and accuracy were calculated per condition and entered into paired *t*-tests. The impact of psychopathology on behavior was evaluated by entering RT/accuracy into repeated-measures GLMs with psychopathology dimensions as between-participant predictors.

## fMRI DATA COLLECTION

fMRI data were 370 EPI images (TR 2,000 ms, TE 25 ms, flip angle 80°, FOV 220 cm), each consisting of 38 axial slices (slice thickness 3 mm, 0.3 mm gap, resolution 3.4375  $\times$  3.4375 mm). A 1 mm<sup>3</sup> structural sequence was also acquired.

## dIPFC SEED CLUSTERS

dIPFC seed areas were those identified in,<sup>[43]</sup> which used a subsample of the data used in the present analyses (i.e., undergraduate data). Analyses in<sup>[43]</sup> identified regions in which activation during incongruent was greater for those individuals who were higher on approach/avoidance temperament. One cluster, located in left dIPFC (BA 9, max *z*-coordinates = [-36,30,46]), was associated with approach temperament, and one cluster, located in right dIPFC (BA 9/8/6, max *z*-coordinates = [36,12,44]), was associated with avoidance. These dIPFC seeds were also used in<sup>[25]</sup>, which initially identified the network tested in the present study.

## fMRI DATA PROCESSING

Image processing and statistical analysis were implemented primarily via FSL.<sup>[64]</sup> Data were motion-corrected, intensity-normalized, temporally high-pass filtered, and spatially smoothed (FWHM = 5 mm). Temporal low-pass filtering was carried out using AFNI's 3dDespike.

Psychophysiological interaction analyses were performed on the functional time series. For each dIPFC ROI, the mean value across voxels was extracted per time point to create a dIPFC predictor. In each analysis, eight predictors were entered: (1) one dIPFC predictor, (2) a predictor modeling incongruent versus congruent (= 1 during incongruent, -1 during congruent, 0 all other times), (3) the interaction of these predictors, (4-6) three nuisance task predictors (incongruent+congruent, neutral, rest), and (7-8) two nuisance predictors modeling mean signal in white matter and cerebral-spinal fluid (to remove brain-wide fluctuations). Task predictors were HRF convolved prior to creating the interaction term.  $\beta$ -maps were nonlinearly warped to the 2009 MNI152 symmetrical 1 mm<sup>3</sup> template.<sup>[65]</sup>

Group-level mixed-effects were computed on the 1st-level  $\beta$ -maps associated with the interaction term. For each dIPFC ROI, PSWQ, MASQ-AA, and MASQ-AD were entered simultaneously as between-participant predictors. A nuisance covariate modeled whether participants completed the color-word Stroop first. AlphaSim was used to estimate overall significance level, with an individual-voxel threshold of 2.0537 and an overall corrected *P* of .05. For *a priori* directional hypotheses, one-tailed tests were used; two-tailed tests were used oth-

erwise. Masks of OFC and amygdala limited the voxels under consideration to relevant regions.

To examine the relationship between PPI coupling and behavior, mean coupling for each cluster was extracted and entered as a between-participant predictor in repeated-measures GLM (one accuracy outlier was excluded). Analyses were rerun with psychopathology scores entered as covariates to ensure that effects were not driven by shared variance. All analyses remained significant.

Task main effects were created by including only task predictors in 1st-level models and averaging across participants (using a gray-matter mask). Given the large sample and task effect size, a voxel threshold of 3.8906 was used.

Only significant effects are reported.

## ANALYSES TO RULE-OUT POTENTIAL CONFOUNDS

To ensure that findings were not driven by variance shared between anxiety/depression and approach/avoidance motivation,<sup>[25]</sup> analyses were rerun with motivation measures as covariates. To ensure that findings were not driven by differential motion-related variance or SNR, analyses were rerun with motion/SNR estimates covaried. Given significant shared variance between psychopathology measures, it is possible that the unique variance associated with each predictor is not measuring the construct it was meant to represent. Therefore, analyses were repeated individually for each predictor. To ensure that performance differences did not drive present findings, analyses were rerun with performance estimates (RT/accuracy interference) covaried. All findings remained highly significant for these analyses.

## OVERLAP WITH PREVIOUS STUDIES

Given that previous studies have used datasets that overlap with the present dataset, we provide the degree of sample overlap and a short summary of the analyses used in past studies (Table 1), along with correlations between present measures and those from past studies (Table 2). As evident in these tables, the present study builds on, but is distinct from, the two previous Spielberg et al. studies. Furthermore, the data examined in the present study are distinct from those used in<sup>[51,66]</sup> (fMRI vs. EEG connectivity) and<sup>[67]</sup> (connectivity vs. task effects). In summary, present findings are both conceptually and analytically distinct from previous work in our lab.

# RESULTS

## TASK MAIN EFFECTS

**Behavioral Data.** Participants had slower RT ( $t_{(168)} = 22.9$ ,  $P < .001$ ) and made more errors (RT;  $t_{(168)} = 11.0$ ,  $P < .001$ ) during incongruent trials.

**fMRI Data.** Twelve clusters emerged in which activation for incongruent was greater than for congruent trials, whereas seven clusters had the converse pattern (Table 3).

## ANXIETY AND DEPRESSION MODERATING RIGHT DLPFC ↔ OFC/AMYGDALA COUPLING

Consistent with hypothesis 1, MASQ-AD was uniquely associated with greater right dIPFC ↔ medial OFC coupling (Table 4, Fig. 2) when maintenance of the current goal was challenged. This OFC cluster overlapped the region that evidenced decreased activation for task main effects. Greater coupling in this circuit during the incongruent condition was related to more errors

**TABLE 1. Overlap with previous studies**

Study	Sample Overlap for fMRI Data	Analysis Strategy
Silton et al. (2010)	13.6%	Used CW Stroop fMRI data from sample subset to seed EEG source localization; examined EEG connectivity between left dlPFC and dACC.
Silton et al. (2011)	13.6%	Built on Silton et al. (2010); examined moderation of EEG connectivity between left dlPFC and dACC by depression and anxiety.
Spielberg et al. (2011)	44.6%	Examined relationship between CW Stroop task activation (in bilateral dlPFC) and measures of approach and avoidance temperament; resultant clusters were used as seed clusters for Spielberg et al. (2012) and the present study.
Spielberg et al. (2012)	97.2%	Built on Spielberg et al. (2011); examined fMRI psychophysiological connectivity between dlPFC seed clusters and OFC, amygdala, basal ganglia, and cingulate; examined moderation of connectivity by approach and avoidance temperament; resultant connectivity model used as the basis for the present study.
Warren et al. (2013)	40.8%	Examined relationship between CW Stroop task activation and two measures of inhibition (Stroop RT interference, self-report measure); examined whether depression and anxiety moderated activation in resultant clusters.

Note: fMRI = function magnetic resonance imaging; CW = color-word (Stroop); EEG = electroencephalography; dlPFC = dorsolateral prefrontal cortex; dACC = dorsal anterior cingulate; OFC = orbitofrontal cortex; RT = reaction time.

( $F_{(1,166)} = 4.42, P = .037$ ). Consistent with hypothesis 3, MASQ-AA was uniquely associated with greater right dlPFC↔left amygdala coupling.

**ANXIETY AND DEPRESSION MODERATING LEFT DLPFC↔OFC/AMYGDALA COUPLING**

Consistent with hypothesis 2, higher MASQ-AD was uniquely associated with reduced left dlPFC↔right-lateral OFC coupling (Table 4, Fig. 2).

**DISCUSSION**

The present study tested the hypothesis that trans-diagnostic dimensions of anxiety and depression are associated with processing differences in brain networks related to approach/avoidance motivation. Consistent with predictions, anxious arousal was uniquely associated with greater right dlPFC↔amygdala coupling (Fig. 2). This right dlPFC region has been previously linked with avoidance motivation,<sup>[43,44]</sup> both individually and as a central node in a network thought to implement avoidance goal pursuit.<sup>[24,25]</sup>

Anhedonic depression was uniquely associated with both increased and reduced dlPFC↔OFC coupling (Fig. 2). Specifically, *increased* coupling was observed

for *right* dlPFC and *reduced* coupling was evident with *left* dlPFC. As mentioned above, this right dlPFC region appears to play an important role in avoidance goal pursuit, and evidence suggests that the left dlPFC region examined is similarly central for approach goal pursuit.<sup>[24,25,43,44]</sup> Importantly, differences in coupling were specific to times when goal maintenance was challenged, rather than at rest as examined in most previous studies in this area.

**ANXIOUS AROUSAL AND RIGHT DLPFC↔AMYGDALA COUPLING**

In light of extensive evidence that dlPFC engages in top-down biasing,<sup>[41]</sup> one interpretation of present findings is that right dlPFC biases amygdala to overidentify goal-irrelevant stimuli as salient/threatening in high anxious arousal individuals. Given the correlational nature of present analyses, it is also possible that amygdala influences dlPFC, and this hypothesis has some support.<sup>[68]</sup> Specifically, amygdala may overidentify irrelevant stimuli as salient/threatening in anxious arousal, in turn increasing the maintenance of avoidance goals in right dlPFC via bottom-up influence.

**TABLE 2. Correlation between psychopathology scores and measures used in previous studies with some overlapping data**

Measure	Approach temperament (n = 174)	Avoidance temperament (n = 174)	BRIEF inhibition (n = 73)	Color-word Stroop Incongruent – Neutral RT (n = 73)
Anxious Apprehension (PSWQ)	–0.44**	0.80**	0.09	–0.13
Anxious Arousal (MASQ-AA)	–0.19**	0.41**	0.36**	–0.17
Anhedonic Depression (MASQ-AD)	–0.37**	0.60**	0.28*	–0.11

Note: \*P < .05; \*\*P < .01; fMRI = function magnetic resonance imaging; CW = color-word (Stroop); EEG = electroencephalography; dlPFC = dorsolateral prefrontal cortex; dACC = dorsal anterior cingulate; OFC = orbitofrontal cortex; RT = reaction time.

**TABLE 3. Task main effects**

Region	Cluster size (mm <sup>3</sup> )	Mean z-value	Location		
			X	Y	Z
B IFG/MFG/SFG/OFC/insula/precentral/parahippocampus/ GP/putamen/thalamus/SN/caudate/dACC/PCC /paracingulate (BA 6/8/9/10/13/23/24/29/30/32/44/45/46/47)	168,250	5.45	-4	9	20
L ITG/MTG /fusiform (BA 20/21/37)	15,010	4.83	-45	-62	-17
L MTG/STG/MOG/SOG/IPL/SPL/cuneus/precuneus/supramarginal (BA 7/19/31/39 /40)	47,999	5.70	-26	-60	46
R MTG (BA 21)	129	4.06	59	-37	-6
R IOG/fusiform/B lingual (BA 17/18/37)	12,538	4.51	20	-83	-17
R ITG/fusiform (BA 20/37)	446	4.18	63	-53	-14
R STG/IPL/angular/supramarginal/precuneus (BA 7/31/39/40)	12,110	4.61	36	-60	42
L MFG/SFG (BA 9/10)	1,602	4.35	-27	49	21
R MFG (BA 10)	318	4.26	38	52	2
L cuneus/lingual (BA 18/30)	2,053	4.30	-6	-70	6
R cuneus/lingual (BA 18/30)	974	4.32	12	-72	8
M precuneus (BA 7)	197	4.20	-1	-50	70
M OFC (BA 11)	4,364	-4.59	0	41	-20
M sgACC (BA 25)	254	-4.19	0	18	-10
L insula/precentral (BA 13)	1,513	-4.49	-41	-18	15
R insula/precentral (BA 13)	666	-4.32	45	-14	13
R insula/precentral (BA 6/13)	482	-4.40	52	-6	3
R precentral/postcentral (BA 4/6/43)	129	-4.12	60	-5	21
L precentral/postcentral (BA 3/4)	302	-4.08	-63	-11	37

Note: L = left; R = right; B = bilateral; M = medial; BA = Brodmann's area; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus; OFC = orbitofrontal cortex; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus; IPL = inferior parietal lobule; SPL = superior parietal lobule; IOG = inferior occipital gyrus; MOG = middle occipital gyrus; SOG = superior occipital gyrus; dACC = dorsal anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex; PCC = posterior cingulate cortex; GP = globus pallidus; SN = substantia nigra; Location = coordinates are for the center of mass.

Regardless of whether present findings reflect dlPFC→amygdala influence or vice versa, findings delineate a potential neural mechanism supporting the attentional biases toward goal-irrelevant stimuli found in anxiety.<sup>[69]</sup> Given that this bias is observed across anxiety disorders<sup>[69]</sup> and that a transdiagnostic anxiety dimension (anxious arousal) was used in the present study, dysfunction in this circuit could serve as a biomarker for anxiety-related attentional biases. Considered in the

context of proposals that biased attention is an endophenotype for anxiety,<sup>[17]</sup> present findings further define this potential transdiagnostic endophenotype.

#### ANHEDONIC DEPRESSION AND DLPFC↔OFC COUPLING

Given evidence that OFC is key to maintaining average stimulus value, one interpretation of present findings

**TABLE 4. Moderation by psychopathology of coupling with dorsolateral prefrontal cortex**

Region	Cluster Size (mm <sup>3</sup> )	Mean z-value	Location		
			X	Y	Z
Anxious apprehension	-	-	-	-	-
Anxious arousal					
Coupling with Right dlPFC (Related to Avoidance Motivation)					
Left amygdala	587	2.42	-21	2	-21
Anhedonic depression					
Coupling with Left dlPFC (Related to Approach Motivation)					
Right lateral OFC (BA 47)	484	-2.38	51	29	-11
Coupling with Right dlPFC (Related to Avoidance Motivation)					
Medial OFC (BA 11)	578	2.46	-2	39	-16

Note: OFC = orbitofrontal cortex; dlPFC = dorsolateral prefrontal cortex; Location = coordinates are for the center of mass.

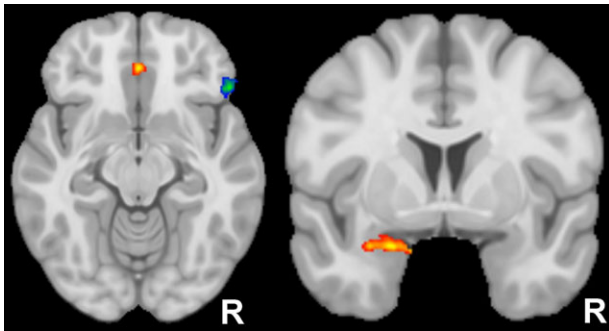


Figure 2. Regions where anhedonic depression or anxious arousal moderated coupling with dorsolateral prefrontal cortex. The axial slice above left ( $z = -12$ ) displays the two clusters in orbitofrontal cortex (OFC) exhibiting condition-dependent connectivity that was moderated by anhedonic depression. Specifically, depression was associated with decreased coupling between left dorsolateral prefrontal cortex (associated with approach motivation) and the blue/green OFC cluster. In contrast, depression was associated with increased coupling between right dorsolateral prefrontal cortex (associated with avoidance motivation) and the red/yellow cluster. The coronal slice above right ( $y = 3$ ) displays the amygdala cluster exhibiting condition-dependent connectivity that was moderated by anxious arousal. Specifically, anxious arousal was associated with increased coupling between right dorsolateral prefrontal cortex (associated with avoidance motivation) and the red/yellow amygdala cluster.

is that the biases in valuation observed in depression<sup>[31,32]</sup> are due to differences in top-down dlPFC regulation of OFC. Specifically, when healthy individuals maintain approach goals, left dlPFC may bias OFC to represent the value of goal-relevant stimuli as more rewarding than that of irrelevant stimuli, whereas this adaptive process may not occur in depression. Similarly, present findings suggest that, when individuals with depression maintain avoidance goals, right dlPFC biases OFC to overvalue the aversive aspects of stimuli. If so, present findings indicate that changing biased valuation in depression may be accomplished by targeting this circuit (i.e., upregulating *left* dlPFC $\leftrightarrow$ OFC coupling/downregulating *right* dlPFC $\leftrightarrow$ OFC coupling).

Interestingly, the medial OFC region found to have increased coupling with right dlPFC largely overlapped the region evidencing decreased activation for task main effects (incongruent-congruent). Thus, potential upregulation of this region by dlPFC may actually impair performance, which is supported by the finding that increased coupling in this circuit was related to more errors.

As mentioned earlier, present analyses cannot determine direction of effects. Thus, it is possible that, in depression, biased valuation in OFC influences goal-maintenance processes in dlPFC. For example, when healthy individuals encounter potentially rewarding stimuli, OFC may increase the likelihood of pursuing approach goals via upregulation of relevant left dlPFC processing. Thus, decreased coupling in this circuit is a

potential mechanism by which individuals high in anhedonic depression fail to pursue approach goals.

Regardless of the direction of effect, present findings provide insight into the manner in which biases in stimulus valuation interact with the pursuit of goals in depression. Importantly, anhedonic depression was associated with differences in coupling with both approach- and avoidance-related dlPFC regions, in contrast to anxious arousal, which evidenced only differential coupling of the avoidance-related area. This is consistent with previous research indicating that dysfunction in approach motivation is depression-specific.<sup>[23]</sup> Present findings provide insight into one potential source of this difference, namely coupling with left dlPFC. Thus, it is possible that hypocoupling with left dlPFC serves as a predisposing/maintaining factor for depression uniquely, whereas hypercoupling with right dlPFC is relevant for both anxiety and depression.

Contrary to prediction, no findings emerged for anxious apprehension. It is possible that dlPFC $\leftrightarrow$ amygdala/OFC coupling is not central to this anxiety dimension. For example, recent research indicates that anxious apprehension involves dysfunctional coupling between Broca's area and attention-related regions.<sup>[60]</sup> Furthermore, the task used in the present study may not have engaged processes relevant to the core pathology of anxious apprehension. For example, given the future orientation of anxious apprehension,<sup>[70]</sup> future-oriented tasks (e.g., intertemporal choice) may be needed to elicit biased coupling. Given evidence of strong biases in punishment-related valuation<sup>[71]</sup> and a strong tendency to pursue avoidance goals<sup>[23]</sup> in anxious apprehension, future research should examine right dlPFC $\leftrightarrow$ OFC coupling during a future-oriented task.

## STRENGTHS AND LIMITATIONS

The present study benefited from an unusually large fMRI sample and examination of transdiagnostic anxiety/depression dimensions rather than DSM diagnoses. Examining anxiety and depression simultaneously allowed for appropriate parsing of variance, despite considerable comorbidity. As well, the present study examined network activity while goal maintenance was challenged rather than at rest, ensuring that dysfunctional activation evident only when the system is challenged would not be missed<sup>[19]</sup>. Finally, the present study examined brain circuits rather than only activation in specific regions, increasing the level of complexity in representing and understanding the neuropathology of anxiety/depression.

Limitations of the present study include the correlational nature of analyses, leaving direction of influence unresolved. Also, the present design is cross-sectional, leaving unclear whether observed differences are predisposing or maintaining factors or consequences of having anxiety/depression. Future research with a prospective design is needed to discern the degree to which dysfunctional coupling is part of the etiological chain

causing or maintaining anxiety/depression. Finally, the present study administered just one of many relevant challenges that may reveal dysfunctional coupling. On balance, present findings suggest specific elements of a model of the neural instantiation of anxiety and depression, including both shared and distinct mechanisms.

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