



Subclinical depression severity is associated with distinct patterns of functional connectivity for subregions of anterior cingulate cortex



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ABSTRACT

Depression is a prevalent psychiatric condition characterized by sad mood and anhedonia. Neuroscientific research has consistently identified abnormalities in a network of brain regions in major depression, including subregions of the anterior cingulate cortex (ACC). However, few studies have investigated whether the same neural correlates of depression symptom severity are apparent in subclinical or healthy subjects. In the current study, we used resting-state fMRI to examine functional connectivity for subregions of the ACC in $N = 28$ participants with subclinical levels of depression. In regression analyses, we examined relationships between depression severity and functional connectivity for pregenual ACC (pgACC), anterior subgenual ACC (sgACC), and posterior sgACC seed regions. Additionally, we examined relationships between ACC subregion connectivity and trait levels of positive and negative affect. We found distinct associations between depression severity and functional connectivity of ACC subregions. Higher depression severity was associated with reduced pgACC–striatum connectivity and reduced anterior sgACC–anterior insula connectivity. Consistent with resting-state findings in major depression, higher depression severity was also related to greater anterior sgACC–posterior cingulate connectivity and greater posterior sgACC–dorsolateral prefrontal connectivity. Lastly, there were distinct correlations between connectivity for anterior versus posterior ACC subregions and positive and negative affective traits. These findings provide novel support linking subclinical depression to the same neural substrates associated with major depression. More broadly, these results contribute to an emerging literature on dimensional approaches to psychiatric illness.

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1. Introduction

Depression is a prevalent psychiatric condition characterized by sad mood, anhedonia, and negative self-related thought (e.g., feelings of worthlessness). The societal costs of depression are substantial – with over 350 million individuals struggling with depression globally, it is the medical condition associated with the greatest number of years lost to disability (Smith, 2014). Understanding the psychological and neurobiological mechanisms underlying depression could have significant implications for early identification and treatment. While neuroscientific research has largely been devoted to identifying dysfunctional neural circuits in

major depression, fewer studies have examined the neural correlates of subclinical depression. There is increasing evidence that psychiatric conditions, including depression, may be dimensional rather than categorical (Widiger and Edmundson, 2014). Moreover, the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC) initiative has called for neuroscientific research into dimensions of psychopathology (Insel et al., 2010). Investigating the neural correlates of subclinical levels of depression severity constitutes a key step toward this dimensional approach. Establishing reliable neural markers for subclinical levels of depression could help guide preventative treatments aimed at curbing the development of more severe and debilitating symptoms.

Neuroimaging and lesion studies have associated depression with abnormalities in several limbic, cortical, and subcortical regions (Berman et al., 2011; Drevets et al., 2008a; Koenigs et al., 2008; Mayberg, 2003; Mayberg et al., 1999). Among those brain areas, subregions within the anterior cingulate cortex (ACC) (i.e., posterior subgenual ACC [sgACC], anterior sgACC, and pregenual

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ACC [pgACC]) have been consistently implicated in the pathophysiology of depression (Berman et al., 2011; Davey et al., 2012; Drevets et al., 2008b; Greicius et al., 2007; Koenigs et al., 2008; Mayberg et al., 1999; Mayberg et al., 2005). Heightened resting metabolism and resting-state functional connectivity with the posterior sgACC has been reliably identified in individuals with major depressive disorder (MDD) (Berman et al., 2011; Greicius et al., 2007; Mayberg et al., 1999; Zhu et al., 2012). In contrast to the hyperactivity observed in posterior sgACC, MDD has also been associated with decreased activity in the pgACC and anterior sgACC (Drevets et al., 1997, 1992). Additionally, ruminative thought and depression severity in MDD are positively correlated with elevated resting-state functional connectivity between anterior sgACC and posterior cingulate as well as between posterior sgACC and other regions within the DMN (Berman et al., 2011; Greicius et al., 2007). Importantly, various treatments for MDD normalize connectivity within the DMN and resting activity of the sgACC (anterior and posterior) and pgACC (Kennedy et al., 2007; Li et al., 2013; Liston et al., 2014; Mayberg et al., 2005; Yoshimura et al., 2014). For example, deep brain stimulation of the posterior sgACC for treatment-resistant depression has been associated with reductions in posterior sgACC resting-metabolism as well as depressive symptoms (Mayberg et al., 2005). In another study, increased resting-metabolism in anterior sgACC was found for patients with MDD responsive to treatment with cognitive behavioral therapy (Kennedy et al., 2007). Taken together, there is considerable neuroimaging evidence for dysfunction in the activity and functional connectivity of subregions of the ACC in MDD. Previous task-based neuroimaging studies using affective interference paradigms (i.e., emotional stroop) have implicated dysfunction in similar ACC subregions in subclinical depression (e.g., Kaiser et al., 2015a; Spielberg et al., 2014). However, to our knowledge no study has yet investigated the relationship between resting-state functional connectivity for subregions within the ACC and subclinical depression severity.

Another important question is whether there are functional dissociations in positive and negative affect for different ACC subregions that are relevant to depression. Indeed, as mentioned above, MDD has been associated with increased posterior sgACC (BA25) activity (Mayberg et al., 1999; Mayberg et al., 2005), but decreased pgACC/anterior sgACC activity (Drevets et al., 1997, 1992). Interestingly, neuroimaging studies suggest these same regions tend to be associated with distinct types of affective information. Whereas posterior sgACC activity tends to be related to negative affect, anterior sgACC/pgACC activity tends to be associated with positive affect (i.e., reward) (Myers-Schulz and Koenigs, 2012 for review). However, it is unknown whether there would be similar distinctions between connectivity of ACC subregions and trait levels of positive and negative affect in subclinical depression.

In the current study, the primary aim was to test the hypothesis that subclinical depression severity would be associated with alterations in resting-state functional connectivity for subregions of the ACC previously implicated in major depression. We also examined the degree to which distinct patterns of functional connectivity for these ACC subregions would be differentially associated with trait levels of positive and negative affect, in order to draw more precise associations between specific facets of depression and the connectivity of ACC subregions.

2. Methods and materials

2.1. Participants

Twenty-eight healthy adult participants (15 male, 13 female; mean age = 56 ± 8.7) with no history of brain injury, neurological or

psychiatric illness, or current use of psychoactive medications were recruited from the local community. Participants had never been diagnosed with or treated for depression. To address potential differences in functional connectivity due to age and gender in the participant sample, all regression analyses included covariates for age and sex. All participants gave informed consent in accordance with the institutional review board at the University of Wisconsin–Madison.

2.2. Depression and affective measures

2.2.1. Depression inventory

To assess depression symptom severity, we administered the Beck Depression Inventory II (BDI-II) (Beck et al., 1996). Consistent with our exclusion criteria, no participants had BDI-II scores indicative of high severity (>20 ; range 0–17) and the average BDI-II score was within the non-depressed range (Table 1).

2.2.2. Positive and negative affect schedule

To measure positive and negative affect, we used the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988b), which includes 10-positive and 10-negative mood or feeling words (e.g., “inspired” or “scared”). The PANAS is a well-validated measure of self-reported positive and negative mood (Crawford and Henry, 2004; Watson et al., 1988b), used in healthy and psychiatric patient populations (Heller et al., 2013; Larsen and Ketelaar, 1991; Watson et al., 1988a). Participants rated the amount they generally experienced each item on a scale ranging from 1 to 5 (very slightly–extremely). The affect scores were calculated separately as the sum of all responses for positive and words, respectively. Both PANAS scores were used for correlations with the functional connectivity results.

2.3. Data acquisition

All structural and functional magnetic resonance imaging (MRI) data were acquired using a 3.0 T MRI scanner (Discovery MR750, General Electric Medical Systems) equipped with an 8-channel radio-frequency (RF) head coil array. High-resolution T1-weighted structural images were acquired axially using an inversion recovery spoiled GRASS sequence using the following parameters: voxel size = $1 \times 1 \times 1 \text{ mm}^3$; TR = 8.2 ms; TE = 3.2 ms; flip angle (FA) = 12° ; field of view (FOV) = $255 \times 256 \text{ mm}^2$; matrix = 256×256 ; slice thickness = 1 mm; number of slices = 1024.

Resting-state functional images were collected while subjects lay still and awake, passively viewing a fixation cross. T2*-weighted gradient-echo echoplanar images (EPIs) were acquired with the

Table 1

Means and correlations between depression severity and positive and negative affect.

Mean \pm SD	
BDI-II	4.2 \pm 3.9
PANAS-positive	37.7 \pm 6.1
PANAS-negative	13.6 \pm 3.6
Correlation (r)	
BDI-II x PANAS-positive	-.33 [#]
BDI-II x PANAS-negative	.56 [*]
PANAS-positive x PANAS-negative	-.40 [*]

Means, standard deviations (SD), and correlation results are reported (r-values) for all Pearson correlations. P-values: * = $p < .05$, [#] $p = .09$. Abbreviations: BDI-II = Beck Depression Inventory-II (Beck et al., 1996), PANAS = Positive and Negative Affect Scale (Watson et al., 1988b), SD = standard deviation.

following parameters: voxel size = $3.5 \times 3.5 \times 3.5 \text{ mm}^3$; TR = 2000 ms; TE = 22 ms; FA = 79° ; FOV = $224 \times 224 \text{ mm}^2$; matrix = 64×64 , slice thickness = 3 mm, gap = .5 mm, number of slices = 38 interleaved axial oblique. Rest-state scans lasted 5 min (150 volumes). To correct for geometric distortion of the EPIs, B0 field maps were acquired in two separate acquisitions with two different echo times, with the following parameters: voxel size = $.94 \times .94 \times 3.7 \text{ mm}^3$; TR = 600 ms; TE1 = 7 ms; TE2 = 10 ms; FA = 60° ; FOV = $240 \times 240 \text{ mm}^2$; matrix = 256×128 ; slice thickness = 4 mm, number of slices = 33.

2.4. Preprocessing of functional data

All functional MRI (fMRI) data analysis was performed using AFNI (Cox, 1996) and FSL (<http://www.fmrib.ox.ac.uk/fsl/>). The following preprocessing steps were performed: (1) EPI volumes were slice time corrected using the first slice as a reference, (2) motion corrected by rigid body alignment to the first EPI acquisition, (3) fieldmap correction, (4) images were deobliqued, (5) the first three volumes were omitted, (6) data were then motion corrected (3dvolreg), (6) despiked to remove extreme time series outliers, and (7) band-pass filtered ($.009 < f < .08$) and spatially smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel (Fox et al., 2005).

As individual differences in subject motion can contribute to resting-state correlations (Power et al., 2012; Satterthwaite et al., 2013; Yan et al., 2013), we examined motion for each subject. No subjects were excluded based on the following criteria: mean framewise motion displacement (i.e., volume to volume movement across the time series) $> 2 \text{ mm}$, and/or total scan time $< 4 \text{ min}$ after censoring all time points with framewise motion displacement $> .2 \text{ mm}$ and extreme timeseries displacement (i.e., time points where $>10\%$ of voxels were outliers) (Power et al., 2012; Satterthwaite et al., 2013; Yan et al., 2013). These specific thresholds for motion (mean framewise motion displacement $< 2 \text{ mm}$ and $>4 \text{ min}$ remaining after censoring time points for both framewise motion $> .2 \text{ mm}$ and extreme timeseries displacement $> 10\%$ of voxels) were selected based on previous research to provide the most conservative criteria for motion correction. Importantly, there was no significant association between total censored time points and depression severity in the sample ($r = .26, p > .1$).

Normalized T1 anatomical images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) segments using FAST in FSL (Zhang et al., 2001). White matter and CSF segments were used as masks to extract a representative time series from each tissue type.

2.5. Anterior cingulate cortex seed regions of interest

To examine functional connectivity for key subregions of ACC implicated in depression, three bilateral seed regions of interest (ROI) were selected: pregenual ACC (pgACC: 1, 40, 16) (Andrews-Hanna et al., 2007) anterior subgenual ACC (anterior sgACC: 0, 38, -9) (Berman et al., 2011), and posterior subgenual ACC (posterior sgACC: 1, 25, -9) (Mayberg et al., 1999). The Wake Forest University (WFU) PickAtlas was used to generate a spherical 6-mm radius seed centered on the coordinates for each ROI (in MNI space) (Maldjian et al., 2003). Seed ROI masks in MNI space were then resampled to the EPI resolution, 3.5 mm, and aligned to native space to create subject-specific ROIs. All subject-specific ROIs were checked to verify accurate subject-specific placement before completing the functional connectivity analyses.

2.6. Functional connectivity analysis

Functional connectivity was assessed for each seed ROI (pgACC, anterior sgACC, posterior sgACC) using the mean resting-state BOLD time series, extracted for each participant. The mean time series from each seed ROI was included in a GLM with nine regressors of no interest: (1–6) six motion parameters (three translations, three rotations) obtained from the rigid body alignment of EPI volumes and their six derivatives, (7) the white matter time series, (8) the ventricular (CSF) time series, and (9) a second-order polynomial to model baseline signal and slow drift. To further control for subject motion during the GLM, volumes were censored for extreme timeseries displacement ($>10\%$ of voxels were outliers), and framewise motion displacement $> .2 \text{ mm}$ (Power et al., 2012; Yan et al., 2013).

To convert R^2 values output from the GLM to correlation coefficients (r), the following equation was used in AFNI: $3d\text{calc} - a \text{Corr_S1} + \text{tlrc}'[\text{sub-brick for } R^2] - b \text{Corr_S1} + \text{tlrc}'[\text{sub-brick for Beta}] - \text{expr 'ispositive(b)*sqrt(a) - isnegative(b)*sqrt(a)'$. Next, correlation coefficients for each seed ROI were converted to z-scores via Fisher's r-to-z transform and corrected for degrees of freedom using the following equation: $z = \log((1 + r)/(1 - r)) \times \sqrt{(n-3)/2}$, where $n = \text{degrees of freedom or time points remaining after motion censoring}$. The resulting z-score maps were aligned to a standard MNI template, resampled to 3-mm^3 voxels using AFNI, and entered into second-level statistical analyses.

2.7. Regression analyses for depression severity and functional connectivity

We performed linear regression analyses (3dRegAna in AFNI) to examine the relationship between depression and functional connectivity for the pgACC, anterior sgACC, and posterior sgACC seed ROIs. To correct for multiple comparisons, we implemented a family-wise error (FWE) correction approach at the cluster level using a whole-brain mask (3dClustSim in AFNI) (Carp, 2012; Forman et al., 1995) and applied cluster-extent thresholding to our regression results. The cluster-extent threshold corresponded to the statistical probability ($\alpha = .05$, or 5% chance) of identifying a random noise cluster at a predefined voxelwise threshold of $p < .005$ (uncorrected). In the present study, using this whole-brain FWE cluster correction, a cluster-corrected size of ≥ 84 voxels was significant at $p_{\text{FWE}} < .05$ in the regression analyses reported below for depression. Regression results were overlaid on the normalized mean anatomical image. For each regression, we also performed outlier tests (for residuals and leverage), and excluded anyone identified as an outlier. Depending on the regression, there were 0, 1, or 2 outliers.

2.8. Correlation between functional connectivity and positive and negative affect

As a follow-up analysis, we investigated whether the patterns of abnormal functional connectivity that were associated with depressive symptoms for the pgACC and sgACC (anterior and posterior seed ROIs) were also associated with positive or negative affect. We focused on the significant clusters identified in the regression analyses for each seed. The mean z-scores for voxels within each significant cluster were computed for this correlation analysis. We then computed the Pearson's correlation between the mean z-score for each cluster and total PANAS positive and negative scores.

3. Results

3.1. Depression severity linked to distinct connectivity patterns for anterior cingulate subregions

To test our main hypothesis that depression severity would be associated with distinct patterns of functional connectivity for ACC subregions, we performed three separate linear regressions for depression, using pgACC, anterior sgACC, and posterior sgACC seed ROIs.

3.1.1. Pregenual anterior cingulate cortex

Higher depression scores were associated with significantly decreased connectivity between pgACC and striatum bilaterally (right caudate extending to putamen, overall model $r^2 = .57$, $F_{1,26} = 34.1$, $p_{FWE} < .05$; left caudate, overall model $r^2 = .47$, $F_{1,26} = 23.5$, $p_{FWE} < .05$) (Fig. 1, Table 2). Additionally, higher depression scores were associated with significantly increased connectivity between pgACC and right lingual gyrus (overall model $r^2 = .43$, $F_{1,26} = 20.0$, $p_{FWE} < .05$) (Fig. 1, Table 2). All results for the pgACC remained significant after including covariates for age and sex, and after excluding subjects identified as statistical outliers ($p_{FWE} < .05$).

3.1.2. Anterior subgenual anterior cingulate cortex

By contrast, higher depression scores were associated with significantly increased functional connectivity between the anterior sgACC and bilateral posterior cingulate (overall model $r^2 = .43$, $F_{1,26} = 26.3$, $p_{FWE} < .05$), but significantly decreased functional connectivity between anterior sgACC and right anterior insula (overall model $r^2 = .52$, $F_{1,26} = 28.4$, $p_{FWE} < .05$) (Fig. 2, Table 2). Similar to the pgACC, all results for the anterior sgACC remained significant after including covariates for age and sex ($p_{FWE} < .05$). There were no subjects identified as outliers.

3.1.3. Posterior subgenual anterior cingulate cortex

For the posterior sgACC, higher depression scores were associated with significantly increased functional connectivity with right

inferior frontal gyrus extending to dorsolateral prefrontal cortex (dlPFC) (overall model $r^2 = .66$, $F_{1,26} = 51.5$, $p_{FWE} < .05$), left inferior frontal gyrus (overall model $r^2 = .52$, $F_{1,26} = 28.2$, $p_{FWE} < .05$), bilateral parahippocampal gyrus (overall model overall model $r^2 = .53$, $F_{1,26} = 29.3$, $p_{FWE} < .05$), and right cerebellum (overall model overall model $r^2 = .61$, $F_{1,26} = 40.1$, $p_{FWE} < .05$) (Fig. 3, Table 2). All results for the posterior sgACC remained significant after controlling for age and sex, and after excluding subjects identified as statistical outliers ($p_{FWE} < .05$).

3.2. Relationships between anterior cingulate connectivity and affect

To examine the relationship between ACC connectivity and positive versus negative affect, we computed the correlations between PANAS positive and negative scores and connectivity for significant clusters identified in the regression analyses above. We found that the three ACC subregions exhibited distinct relationships between functional connectivity and positive and negative affect (Table 3). For the pgACC, there was a negative correlation between caudate connectivity and negative affect, and a positive correlation between caudate connectivity and positive affect. For the anterior sgACC, there was only a negative correlation between insula connectivity and negative affect. There were no significant associations between anterior sgACC-posterior cingulate connectivity and positive or negative affect. For the posterior sgACC, there were significant positive correlations between all clusters and negative affect, and a significant negative correlation between posterior sgACC-right inferior frontal gyrus/dIPFC and positive affect. There were no significant associations between posterior sgACC-parahippocampal, right cerebellum, or left inferior frontal gyrus connectivity and positive affect. All results for these relationships with affect remained significant after including covariates for age and sex ($p < .05$).

We also computed partial correlations between with PANAS measures and connectivity, to determine whether relationships between positive or negative affect and connectivity would remain after covarying for the other affect score. All ACC subregions and

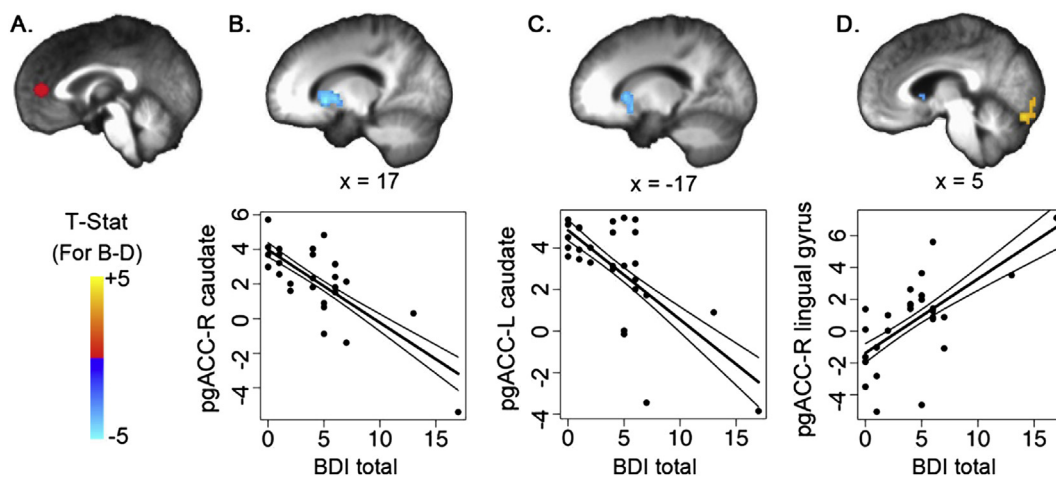


Fig. 1. Depression severity was associated with distinct functional connectivity between pgACC, striatum, and visual cortex. A. pgACC seed ROI; B. *Top row*: Higher depression severity was associated with diminished connectivity between pgACC and right caudate, *Bottom row*: Scatterplot shows the relationship between total BDI score and pgACC-right caudate connectivity values; C. *Top row*: Higher depression severity was associated with diminished connectivity between pgACC and left caudate, *Bottom row*: Scatterplot shows the relationship between total BDI score and pgACC-left caudate connectivity values; D. *Top row*: Higher depression severity was associated with increased connectivity between pgACC and right lingual gyrus, *Bottom row*: Scatterplot shows the relationship between total BDI score and pgACC-right lingual gyrus connectivity values. The seed ROI and all results are displayed on the group average structural MRI in MNI-space. All results survived whole-brain cluster correction ($p_{FWE} < .05$). Each regression line (plotted in black) depicts the predicted model for total BDI score and pgACC connectivity; confidence intervals are plotted in thin black lines. Color bar indicates uncorrected t-values for panels B–D. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Resting-state functional connectivity results for anterior cingulate subregions.

Seed	Brain region	MNI coordinates	Cluster size (voxels), t-value
pgACC	Right caudate	17, 15, -3	161, -5.84
pgACC	Left caudate	-19, 18, 3	87, -4.84
pgACC	Right lingual gyrus	5, -87, -18	90, 4.47
Anterior sgACC	Bilateral posterior cingulate cortex	-10, -48, 36	288, 4.39
Anterior sgACC	Right insula	53, 12, -6	192, -5.34
Posterior sgACC	Right inferior frontal gyrus/dorsolateral prefrontal cortex	44, 33, 9	319, 7.17
Posterior sgACC	Left inferior frontal gyrus	-43, 27, 6	114, 5.31
Posterior sgACC	Bilateral parahippocampal gyrus extending to thalamus	-7, -9, -15	179, 5.41
Posterior sgACC	Right cerebellum	56, -54, -39	134, 6.33

All regression results were significant at whole-brain cluster-corrected $p_{FWE} < .05$. Abbreviations: pgACC = pregenual anterior cingulate, sgACC = subgenual anterior cingulate.

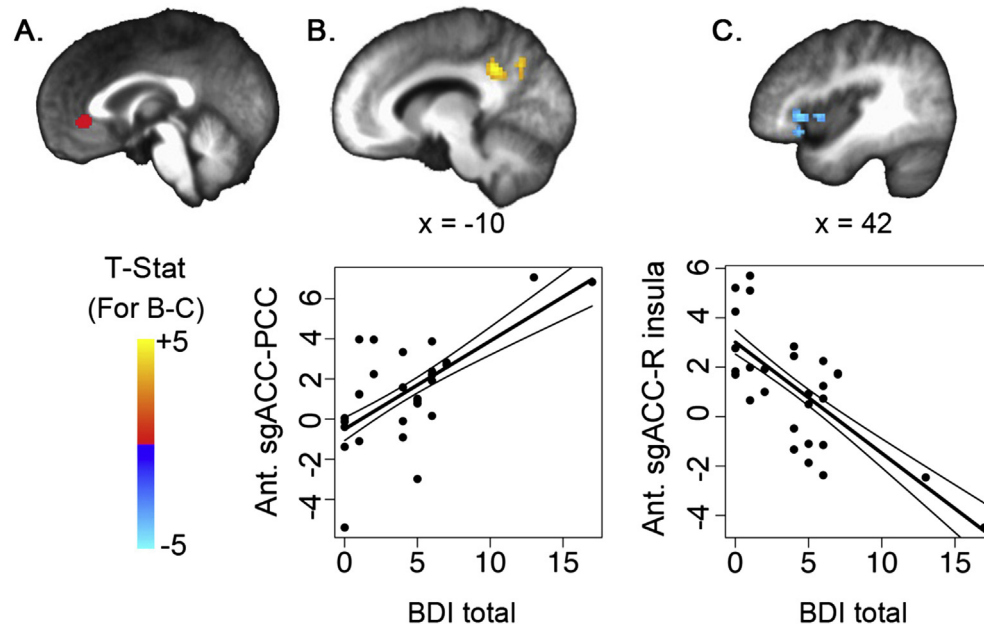


Fig. 2. Depression severity was associated with distinct functional connectivity between anterior sgACC, posterior cingulate, and insula. A. Anterior sgACC seed ROI; B. *Top row*: Higher depression severity was associated with enhanced connectivity between anterior sgACC and bilateral posterior cingulate cortex (PCC), *Bottom row*: Scatterplot shows the relationship between total BDI score and the anterior sgACC-bilateral PCC connectivity values; C. *Top row*: Higher depression severity was associated with diminished connectivity between anterior sgACC and right insula, *Bottom row*: Scatterplot shows the relationship between total BDI score and anterior sgACC-right insula connectivity values. The seed ROI and all results are displayed on the group average structural MRI in MNI-space. All results survived whole-brain cluster correction ($p_{FWE} < .05$). Each regression line (plotted in black) depicts the predicted model for total BDI score and pgACC connectivity; confidence intervals are plotted in thin black lines. Color bar indicates uncorrected t-values for panels B–C. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

negative affect remained significant after covarying for positive affect ($p < .05$), with the exception of posterior sgACC-left inferior frontal gyrus connectivity ($p = .053$). By contrast, no correlations with positive affect remained significant after covarying for negative affect (each $p > .1$).

4. Discussion

In this study, we used resting-state fMRI to determine whether subclinical levels of depression were associated with functional connectivity for subregions of the ACC previously implicated in major depression. Indeed, our results revealed several significant relationships between depression severity and functional connectivity between the ACC, subcortical, and cortical regions. For the pregenual ACC, depression severity was associated with diminished connectivity with the striatum. For the anterior subgenual ACC, by contrast, depression severity was related to heightened connectivity with posterior cingulate, but diminished connectivity with anterior insula. For the posterior subgenual ACC, depression was

associated with heightened connectivity with lateral prefrontal, hippocampal, and cerebellar regions. Lastly, there were distinct correlations between connectivity for ACC subregions and measures of positive and negative affect. Below, we discuss each of the major findings in turn.

Our observed relationship between depression severity and diminished pgACC-striatum connectivity mirrors a previous resting-state fMRI finding in individuals with major depressive disorder (MDD) (Davey et al., 2012). The present findings are also consistent with structural and functional neuroimaging research associating striatal and medial prefrontal abnormalities with MDD (Kim et al., 2008; Matsuo et al., 2008; Pizzagalli et al., 2009; Wacker et al., 2009). For example, several structural MRI studies have reported reduced caudate volume in MDD (e.g., Kim et al., 2008; Matsuo et al., 2008; Pizzagalli et al., 2009). Moreover, task-based functional imaging research has frequently found lower striatal activity to positive affect (Epstein et al., 2006; Heller et al., 2009; Keedwell et al., 2005; Surguladze et al., 2005; Tremblay et al., 2005) and rewarding stimuli (Pizzagalli et al., 2009; Smoski et al.,

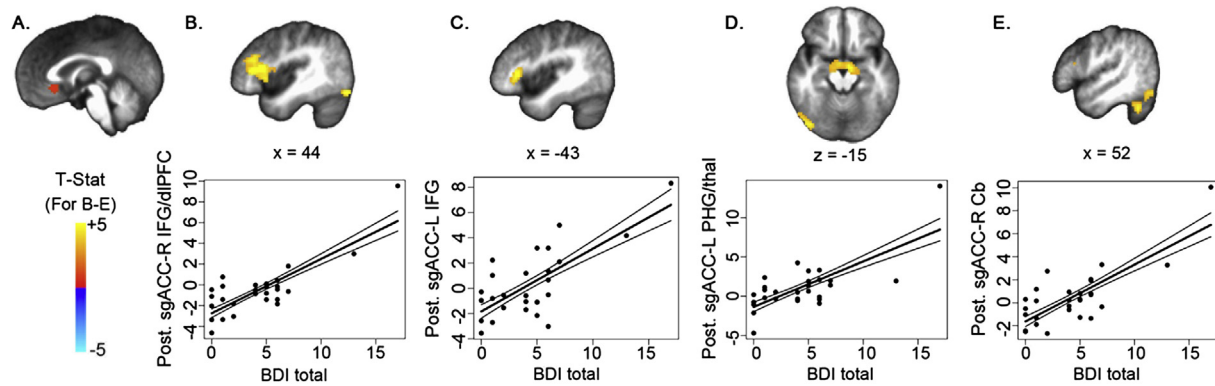


Fig. 3. Depression severity was associated with enhanced functional connectivity between posterior sgACC, bilateral inferior frontal gyrus, parahippocampal gyrus, and cerebellum. A. Posterior sgACC seed ROI; B. *Top row:* Higher depression severity was associated with enhanced connectivity between posterior sgACC and right inferior frontal gyrus/dorsolateral prefrontal cortex (IFG/dlPFC), *Bottom row:* Scatterplot shows the relationship between total BDI score and posterior sgACC-right IFG/dlPFC connectivity values; C. *Top row:* Higher depression severity was associated with increased connectivity between posterior sgACC and left IFG, *Bottom row:* Scatterplot shows the relationship between total BDI score and posterior sgACC-left IFG connectivity values; D. *Top row:* Higher depression severity was associated with enhanced connectivity between posterior sgACC and left parahippocampal gyrus/thalamus (PHG/thal), *Bottom row:* Scatterplot shows the relationship between total BDI score and posterior sgACC-left PHG/thal connectivity values; E. *Top row:* Higher depression severity was associated with enhanced connectivity between posterior sgACC and right cerebellum (Cb), *Bottom row:* Scatterplot shows the relationship between total BDI score and posterior sgACC-right Cb connectivity values. The seed ROI and all results are displayed on the group average structural MRI in MNI-space. All results survived whole-brain cluster correction ($p_{FWE} < .05$). Each regression line (plotted in black) depicts the predicted model for total BDI score and pgACC connectivity; confidence intervals are plotted in thin black lines. Color bar indicates uncorrected t-values for panels B–E. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3

Correlations between functional connectivity for anterior cingulate subregions and positive and negative affect.

Functional connectivity for significant clusters	Positive affect (r-value)	Negative affect (r-value)
pgACC-R caudate	.41*	-.54**
pgACC-L caudate	.31	-.58**
pgACC-R lingual gyrus	-.21	.54**
Anterior sgACC-B PCC	-.10	.19
Anterior sgACC-R insula	.17	-.46*
Posterior sgACC-R inferior frontal gyrus/dlPFC	-.45*	.50**
Posterior sgACC-L inferior frontal gyrus	-.17	.41*
Posterior sgACC-parahippocampal gyrus	-.29	.48*
Posterior sgACC-R cerebellum	-.23	.48*

Correlation results are reported (r-values) for all Pearson correlations. P-values: * = $p < .05$, ** = $p < .01$. Abbreviations: R = right hemisphere, L = left hemisphere, B = bilateral, PCC = posterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, pgACC = pregenual anterior cingulate, sgACC = subgenual anterior cingulate.

2009; Tremblay et al., 2005) in depression. Similarly, dysfunction in the medial prefrontal cortex, including the pgACC, has been reported in MDD during the processing of reward-related stimuli (Epstein et al., 2006; Heller et al., 2009; Keedwell et al., 2005; Smoski et al., 2009). Additionally, neuroimaging research has shown an association between increased in positive affect after antidepressant treatment in MDD and increased prefrontal-striatal connectivity (Heller et al., 2013). Together, these findings have lead researchers to suggest that abnormalities in reward circuitry, in particular medial prefrontal (including pgACC) and striatal regions, could contribute to the loss of interest/pleasure in previously rewarding activities, or anhedonia, a core symptom in MDD as well as in other psychiatric conditions (Der-Avakian and Markou, 2012; Pujara and Koenigs, 2014; Russo and Nestler, 2013; Treadway and Zald, 2013). Our follow-up analyses, which considered positive and negative affective traits separately, support this hypothesis; pgACC-caudate connectivity was significantly associated with positive affective traits. Understanding the neurobiological mechanisms underlying anhedonia or reward-related processing more generally could have important implications for the diagnosis and treatment of several psychiatric illnesses. Future research could explore the relationship between pgACC-striatum connectivity, anhedonia, and treatment response across a variety of psychiatric conditions.

With respect to increased anterior sgACC-posterior cingulate connectivity, our results demonstrate remarkable overlap with research associating MDD with enhanced resting-state connectivity between posterior cingulate and sgACC (including anterior and posterior subregions) (Berman et al., 2011; Greicius et al., 2007; Kaiser et al., 2015b; Zhu et al., 2012), two key regions of the default mode network (DMN). Although previous studies have found correlations between depression severity and heightened DMN connectivity in individuals with MDD (Greicius et al., 2007; Hamilton et al., 2011), our results are novel as we demonstrate the same relationship across participants with subclinical levels of depression. Building on neuroscientific research linking the DMN with self-related thought (Buckner et al., 2008; Gusnard et al., 2001; Qin and Northoff, 2011; Whitfield-Gabrieli et al., 2011), several researchers have proposed that increased rumination, or negative self-focused cognition, in MDD could be linked to the DMN hyperconnectivity found in depression (Berman et al., 2011; Philippi and Koenigs, 2014; Sheline et al., 2009; Whitfield-Gabrieli and Ford, 2012). In support of these claims, neuroimaging studies have reported significant correlations between rumination and DMN connectivity in depression (Berman et al., 2014; Hamilton et al., 2011; Zhu et al., 2012). Moreover, various therapeutic interventions for depression have been shown to normalize activity in the DMN and reduce depressive symptoms (Li

et al., 2013; Liston et al., 2014; Yoshimura et al., 2014). Taken together, elevated DMN connectivity in depression, in particular with the sgACC, could constitute a neurobiological marker or risk factor for developing the disorder. From a dimensional perspective, future work in a large sample with a broad distribution of depression severity (i.e., subclinical to clinical levels) will be required to determine whether there is a linear relationship between depression, rumination, and DMN connectivity.

We also observed an association between depression severity and reduced connectivity between anterior sgACC and anterior insula, a region consistently implicated in major depression (Mayberg et al., 1999; McGrath et al., 2013; Sprengelmeyer et al., 2011; Takahashi et al., 2010). Moreover, several studies have shown changes in insula metabolism following successful treatment response in MDD across different therapeutic interventions (Kennedy et al., 2001; Mayberg et al., 2005; McGrath et al., 2013). More broadly, a recent meta-analysis found that gray matter reductions in the right and left insula were common across six different psychiatric diagnoses, including MDD (Goodkind et al., 2015). Although the role of insula dysfunction in MDD is not completely understood, the insula has been associated with affective and behavioral processes relevant to depression (i.e., interoceptive and emotional awareness) (Craig, 2009; Critchley et al., 2004; Critchley, 2005). From a network perspective, the insula has been identified as a key region involved in switching between the DMN and the central executive network (Sridharan et al., 2008). Thus, in MDD, abnormalities in insula activity could impair the ability to flexibly move between internally-focused and externally-focused cognitive states, or DMN and central executive network respectively. Consistent with this possibility, a study showed that abnormalities in switching between these two networks, or dominance in the DMN in MDD, was correlated with maladaptive rumination (Hamilton et al., 2011).

Our results associating depression severity with increased functional connectivity between posterior sgACC and dlPFC are directly relevant to literature identifying the sgACC and the dlPFC as key regions altered in depression (Drevets et al., 2008b; Koenigs et al., 2008; Koenigs and Grafman, 2009; Mayberg, 2003). Specifically, neuroimaging studies have found evidence for heightened resting activity in sgACC (Drevets et al., 1992; Greicius et al., 2007; Mayberg et al., 1999), but reduced resting activity in dlPFC in major depression (Baxter et al., 1989; Mayberg et al., 1999). Additionally, resting-state fMRI studies have demonstrated aberrant functional connectivity between the medial prefrontal cortex, including the posterior sgACC, and dlPFC in MDD (Davey et al., 2012; Kaiser et al., 2015b). Moreover, neuromodulatory treatments for major depression, such as transcranial magnetic stimulation (TMS) and deep brain stimulation, target the dlPFC and posterior sgACC (Fox et al., 2012; Mayberg et al., 2005). While the precise mechanisms underlying the therapeutic effects of these neural stimulation treatments for depression remain unknown, researchers have suggested that TMS targeted at increasing activity in dlPFC may function by reducing activity in distant limbic regions, including the posterior sgACC (Fox et al., 2012; George et al., 1997; Padberg and George, 2009). However, additional research is warranted to understand the relationship between posterior sgACC-dlPFC connectivity, depressive symptoms, and therapeutic changes after treatment in MDD.

Overall, the pattern of the connectivity findings in the present study is consistent with research associating major depression with reduced or hypoconnectivity between ACC subregions and brain regions within limbic and cognitive control networks (e.g., Davey et al., 2012; Kaiser et al., 2015b). For example, we found a relationship between higher levels of depression and weaker positive connectivity between the pgACC and caudate as well as weaker

negative correlations between the posterior sgACC and dlPFC. However, more research is necessary to investigate the specific relationship between depression severity and large-scale network dysfunction, including for ACC subregions.

With respect to ACC subregion connectivity and affect, we found evidence for distinct relationships for anterior versus posterior subregions. More specifically, anterior ACC subregion connectivity (including pgACC and anterior sgACC) tended to be negatively correlated with negative affect, but positively correlated with positive affect. By contrast, posterior sgACC connectivity was positively correlated with negative affect, but negatively correlated with positive affect. In other words, anterior ACC subregions were associated with positive affect, whereas posterior ACC subregions were associated with negative affect. These results are consistent with neuroscientific research linking anterior sgACC/perigenual ACC regions with positive emotional stimuli, and more posterior sgACC regions with negative emotional stimuli (Myers-Schulz and Koenigs, 2012 for review). Additionally, as Myers-Schulz and Koenigs (2012) proposed, these findings could help explain the apparently contradictory findings in major depression of diminished activity in anterior sgACC, but heightened activity in posterior sgACC (Drevets et al., 1997; Mayberg et al., 1999). Lastly, in the partial correlation analyses with positive and negative affect, only negative affect (after controlling for positive affect) remained significantly associated with ACC subregion connectivity. Together, trait levels of negative affect and depression severity predicted similar associations with ACC subregion connectivity and trait levels of negative affect and depression were significantly correlated. Thus, further research using both trait and state measures of positive and negative affect is necessary to distinguish among the unique contributions of positive versus negative affect in the pathophysiology of depression.

The current study focused on subclinical levels of depression severity. While we used a well-validated measure of depression severity, additional research will be crucial to determine whether these results replicate across different clinical and experimental depression measures.

4.1. Conclusions

In sum, we have presented novel results linking subclinical depression severity to the same alterations within neural circuits observed in major depression. Importantly, these findings are consistent with recent efforts in psychiatry and at the NIMH to move toward a dimensional approach to classifying mental conditions based on psychological, behavioral, and neurobiological measures. Future work will be necessary to explore whether neurobiological measures, such as anterior cingulate connectivity, can be used to predict psychopathology severity across both clinical and subclinical samples.

Conflicts of interest

The authors report no potential conflicts of interest.

Contributors

C.L.P. analyzed the data and wrote the first draft of the manuscript. M.K., J.C.M., and M.S.P. revised and edited subsequent versions of the manuscript. J.C.M. and M.S.P. collected the neuroimaging data, and C.L.P. collected the behavioral data. All authors have contributed to and approved the final version of this manuscript.

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