Neuropsychopharmacology (2015), 1–15

www.neuropsychopharmacology.org

Resting-State Connectivity Predictors of Response to Psychotherapy in Major Depressive Disorder

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Despite the heterogeneous symptom presentation and complex etiology of major depressive disorder (MDD), functional neuroimaging studies have shown with remarkable consistency that dysfunction in mesocorticolimbic brain systems are central to the disorder. Relatively less research has focused on the identification of biological markers of response to antidepressant treatment that would serve to improve the personalized delivery of empirically supported antidepressant interventions. In the present study, we investigated whether resting-state functional brain connectivity (rs-fcMRI) predicted response to Behavioral Activation Treatment for Depression, an empirically validated psychotherapy modality designed to increase engagement with rewarding stimuli and reduce avoidance behaviors. Twenty-three unmedicated outpatients with MDD and 20 matched nondepressed controls completed rs-fcMRI scans after which the MDD group received an average of 12 sessions of psychotherapy. The mean change in Beck Depression Inventory-II scores after psychotherapy was 12.04 points, a clinically meaningful response. Resting-state neuroimaging data were analyzed with a seed-based approach to investigate functional connectivity with four canonical resting-state networks: the default mode network, the dorsal attention network, the executive control network, and the salience network. At baseline, the MDD group was characterized by relative hyperconnectivity of multiple regions with precuneus, anterior insula, dorsal anterior cingulate cortex (dACC), and left dorsolateral prefrontal cortex seeds and by relative hypoconnectivity with intraparietal sulcus, anterior insula, and dACC seeds. Additionally, connectivity of the precuneus with the left middle temporal gyrus and connectivity of the dACC with the parahippocampal gyrus predicted the magnitude of pretreatment MDD symptoms. Hierarchical linear modeling revealed that response to psychotherapy in the MDD group was predicted by pretreatment connectivity of the right insula with the right middle temporal gyrus and the left intraparietal sulcus with the orbital frontal cortex. These results add to the nascent body of literature investigating pretreatment rs-fcMRI predictors of antidepressant treatment response and is the first study to examine rs-fcMRI predictors of response to psychotherapy.
Neuropsychopharmacology advance online publication, 4 February 2015; doi:10.1038/npp.2015.12

INTRODUCTION

Unipolar major depressive disorder (MDD) is projected to be the second-leading contributor to the global burden of disease across the lifespan by 2020 (Murray and Lopez, 1996) and is currently the leading cause of global burden among all psychiatric and neurological disorders (Collins *et al*, 2011). The lifetime prevalence rate of MDD is 16%, with an estimated 32–35 million US residents expected to develop the disorder during their lifetimes (Kessler *et al*, 2003). Despite the societal burden of MDD, there has been relatively little progress in improving the efficacy of established antidepressant treatments (Fournier *et al*, 2010; Undurraga and Baldessarini, 2012): first-line FDA-approved pharmacotherapies demonstrate average response rates of 54 *vs* 37% for placebo (Levkovitz *et al*, 2011),with similar response rates to psychotherapy (Butler *et al*, 2006; Robinson *et al*, 1990). Although a number of novel antidepressant agents are currently under development (Murrough and Charney, 2012), one approach to ameliorating the societal burden of MDD is to improve response rates to currently available antidepressant treatments by developing methods to match specific patients to personalized, empirically validated treatments (Kapur *et al*, 2012; McGrath, *et al*, 2013; McGrath *et al*, 2013). To this end, the purpose of the current study was to evaluate rs-fcMRI differences in MDD relative to matched nondepressed controls and to examine whether pretreatment rs-fcMRI predicted response to psychotherapy.

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Received 20 August 2014; revised 24 November 2014; accepted 16 December 2014; accepted article preview online 12 January 2015

MDD is characterized by impaired cortico-limbic functioning, including dysfunction in (1) the cortical brain regions that mediate attention, reward-based decision making, and monitoring of emotional salience (Ressler and Mayberg, 2007; Seminowicz *et al*, 2004); (2) the subcortical brain regions that process affective stimuli (Kumar *et al*, 2008; Pizzagalli *et al*, 2009) and that modulate emotional memory formation and retrieval (Dillon *et al*, 2013); and (3) the coordinated interactions of distributed networks of limbic-cortical pathways during processing of cognitive and affective information (Drevets *et al*, 2008; Northoff *et al*, 2011). Neuroimaging treatment outcome research has shown that MDD remission is associated with decreased activity in orbitofrontal and medial prefrontal cortex (Goldapple *et al*, 2004; Kennedy *et al*, 2007), increased activity in hippocampus and dorsal cingulate cortex (Goldapple *et al*, 2004), and increased subcortical circuits involved in responses to rewards (Dichter *et al*, 2009; Stoy *et al*, 2012) and emotion regulation (Ressler and Mayberg, 2007).

Recent efforts to understand the pathophysiology of MDD have shifted toward a focus on network properties of resting-state brain activity in MDD. As summarized by Mayberg (2007), 'depression is unlikely a disease of a single gene, brain region, or neurotransmitter system. Rather, the syndrome is conceptualized as a systems disorder with a depressive episode viewed as the net effect of failed network regulation' (p. 729). This conceptualization of MDD as a network-level disorder suggests the importance of considering the functional connectivity among subcortical and cortical regions implicated in MDD. More broadly, there has been increased emphasis recently on conceptualizing MDD as a disorder of functional brain connectivity (Wang *et al*, 2012).

The brain is organized into multiple canonical functional networks, including the default mode network (DMN), the dorsal attention network (DAN), the executive control network (ECN), and the salience network (SN) (Damoiseaux *et al*, 2006; Fox and Raichle, 2007; Raichle, 2011). The DMN is active and synchronized when the brain is 'at rest' (ie, not engaged with an external task) and is comprised of the posterior cingulate cortex and adjacent precuneus, the medial prefrontal cortex, medial, lateral, and inferior parietal cortex, and medial and inferior temporal cortex (Buckner *et al*, 2008; Raichle and Snyder, 2007). The DMN supports internal mental activity, (Greicius *et al*, 2003; Mason *et al*, 2007) and deactivation of the DMN is associated with goal-directed behaviors (Harrison *et al*, 2011). Failure to deactivate the DMN is associated with a number of psychiatric disorders, including MDD (Pomarol-Clotet *et al*, 2008). In contrast to the DMN, the DAN shows increased synchronization during goal-directed processes (Corbetta *et al*, 1998; Kim, 2010) and includes the intraparietal sulcus/superior parietal lobule, frontal eye fields, and extrastriate visual areas (Corbetta and Shulman, 2002; Fox *et al*, 2006). The ECN, including the medial frontal gyrus, superior frontal gyrus, and the anterior cingulate cortex, is engaged during executive function tasks that require cognitive control and working memory (Seeley *et al*, 2007). The SN, comprised of the anterior insula, the dorsal anterior cingulate cortex (dACC), the amygdala, the substantia nigra/ventral tegmental area, and thalamus (Seeley *et al*, 2007), segregates internal and external stimuli to guide behavior (Menon and Uddin, 2010; Uddin, 2014) (Some studies have considered the amygdala to be part of the DMN (eg, Sheline *et al*, 2010). We here consider the amygdala to be part of the SN based on the work of Seely *et al* (2007) who demonstrated an independent network distinct from the ECN and the DMN that is comprised of the anterior insula, dACC, amygdala, substantia nigra/ventral tegmental area, and thalamus, as well as studies showing anatomical connectivity between the anterior insula and the amygdala (Menon and Uddin, 2010).

A few studies have investigated rs-fcMRI in MDD (for a review, see Wang *et al*, 2012). Sheline *et al* (2010) reported hyperconnectivity with bilateral dorsal medial prefrontal cortex across the ECN, the DMN, and the DAN and proposed that these patterns of hyperconnectivity may explain impaired concentration (ECN), increased rumination, self-focus, and vigilance (DMN), and emotional, visceral, and autonomic dysregulation (DAN) in MDD. These findings converge with other reports of aberrant affective network activation at rest and during emotional tasks in MDD (Johansen-Berg *et al*, 2008; Mayberg *et al*, 1999; Smoski *et al*, 2009), DMN hyperactivation during emotional tasks (Sheline *et al*, 2009), DMN hyperconnectivity at rest in MDD (Lemogne *et al*, 2009), and increased task-related connectivity (Schlosser *et al*, 2008; Vasic *et al*, 2009) and decreased task-related activation (Davidson *et al*, 2002; Panksepp, 2010) in the ECN in MDD.

To progress the field from cross-sectional studies examining MDD pathophysiology to prospective studies that evaluate potential neuroimaging predictors of response to antidepressant treatment, research is needed that examines baseline neuroimaging measures as putative treatment-specific biomarkers that predict patient-specific outcomes (Dichter *et al*, 2012). Indeed, it has been suggested that psychiatric research addressing resting-state network dynamics will be of maximal translational utility if it identifies risk or resilience factors, predicts treatment response or clinical outcomes, or aids in therapeutic targeting (Dietsche *et al*, 2014; Zhang *et al*, 2013). Pretreatment rs-fcMRI predictors of antidepressant treatment response appear to be highly contingent on treatment modality, and thus it is noteworthy that no study to date has addressed pretreatment rs-fcMRI predictors of psychotherapy response (Dichter *et al*, 2015). This omission is notable given that psychotherapy is an empirically validated first-line treatment for MDD (DeRubeis *et al*, 2008) with comparable efficacy to pharmacological treatment in all but perhaps the most severe cases of MDD (Elkin *et al*, 1995) and may offer better protection against relapse than pharmacological treatments (Hollon, 2011).

The purpose of the current study was to evaluate rs-fcMRI differences in MDD relative to matched nondepressed controls and to examine whether pretreatment rs-fcMRI predicted response to Behavioral Activation Treatment for Depression (BATD), a structured and validated psychotherapy designed to increase engagement with functional, potentially rewarding behaviors and reduce avoidance behaviors (Hopko *et al*, 2003). Behavioral activation treatments for MDD are theorized to work by facilitating engagement with potential positive reinforcers and to inhibit the behavioral withdrawal often characteristic of depression (Hopko *et al*, 2003; Jacobson *et al*, 2001). We thus focused on the DMN, the DAN, the ECN, and the SN because of linkages between these canonical resting-state networks,

cognitive and affective processes that are central to the pathophysiology of MDD (Seeley *et al*, 2007; Sheline *et al*, 2010; Zhu *et al*, 2012). We hypothesized cognitive mechanisms of action of BATD. Given the focus of BATD on decreasing avoidance behaviors and increasing behavioral engagement with clinically relevant goals, our strongest hypotheses concerned relations between connectivity in the SN, which has been shown to be over-reactive to negative stimuli in MDD (Hamilton *et al*, 2012), response to treatment, and anhedonic symptoms specifically.

MATERIALS AND METHODS

Overview

The study protocol was approved by the Institutional Review Boards at the University of North Carolina at Chapel Hill and Duke University Medical Centers, and all enrolled participants provided written informed consent. Participants with MDD were recruited via the Cognitive Behavioral Research and Treatment Program at the Duke University Medical Center and nondepressed control participants were recruited via listserves at UNC-Chapel Hill and Duke University. Potential participants completed an initial brief phone screen, and those who passed the phone screen were clinically evaluated, including administration of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (First *et al*, 2002) conducted by licensed clinical psychologists or trained clinicians to assess for Axis I disorders, and completed the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960) and Beck Depression Inventory-2 (BDI; Beck *et al*, 1996). If still eligible, they were invited to participate in the MRI scan session. Participants with MDD then began psychotherapy by trained and reliable study clinicians. HAMD scores were used to verify inclusion criteria, but only BDI scores are used in analyses.

After their fMRI scans, MDD outpatients received an average of 11.71 (SD = 4.08; range: 2–15) weekly sessions of brief BATD. Up to 15 sessions of BATD were offered in this intent-to-treat trial. Early responders were given the option to end therapy after eight sessions, and non-responders received the maximum number of sessions before being referred for additional treatment.

Participants

Participants in the MDD group met DSM-IV criteria for a current episode of MDD and scored $\geqslant 15$ on the HAMD. Participants in the control group scored $\leqslant 6$ on the HAMD and did not meet criteria for a current or lifetime episode of a mood disorder. Exclusion criteria included: (1) In the MDD group: current mood, anxiety, psychotic, or substance abuse disorder beyond unipolar MDD or dysthymia, (2) history of psychosis or mania; (3) active suicidal ideation, (4) evidence of organicity, (5) magnetic resonance imaging contraindication (eg, metal in body), (7) history of neurological injury or disease, (8) current pregnancy, or (9) age not between 18 and 50 years. All participants with MDD had been free of psychoactive medication use during the previous month and remained off of psychoactive medications during their participation in this study.

Participants were paid for participating in the clinical assessments and neuroimaging sessions. Twenty-four outpatients with MDD (19 females) and 20 nondepressed controls (14 females) enrolled in the study. One MDD participant was taking antidepressant medication and was excluded from the analyses. Thus the final sample was 23 outpatients with MDD (19 female) and 20 nondepressed controls (14 females). Groups did not differ in age, estimated IQ (measured by the North American Adult Reading Test (Blair and Spreen, 1989), or gender distribution, $ps > 0.35$ (see Table 1 for participant characteristics).

Sleepiness

Given that sleepiness is a common symptom of MDD and recent evidence that a substantial proportion of individuals show a loss of wakefulness during the first 3 min of resting-state scans (Tagliazucchi and Laufs, 2014), just prior to scans participants completed the Karolinska Sleepiness Scale (KSS; Akerstedt and Gillberg, 1990), a common and well-validated measures of subjective sleepiness that includes a single item with anchor points from 1 (extremely alert) to 9 (extremely sleepy—fighting sleep). Participants with and without MDD reported similar subjective sleepiness: MDD mean (SD) = 5.5 (1.4); control mean (SD) = 4.6 (1.8), $t(p) = 1.68$ (0.10) (KSS data were not available from two control and three MDD participants). Additionally, participants' eyes were monitored via a camera mounted on the head coil to ensure that participants kept their eyes open throughout the scan session.

Brief BATD

Behavioral activation treatments have gained increasing interest since the seminal dismantling study of cognitive

Table 1 Participant Characteristics

	MDD, $N = 23$		Con, $N = 20$		p
	Mean (SD)	Range	Mean (SD)	Range	
Sex (M/F)	5/18		6/14		0.546
Age (years)	33.09 (7.45)	21–45	31.1 (8.82)	20–44	0.443
NAART	110.87 (5.34)	99.2–117.3	112.03 (3.83)	102.6–118.1	0.430
Pretreatment BDI	26.04 (7.46)	18–44	1.1 (1.65)	0–5	<0.0001
Previous major depressive episodes	3.39 (1.80)	1–7	0	0	—
Duration of current episode (months)	32.96 (80.697)	1–384	—	—	—

behavioral therapy by Jacobson *et al* (2001) in which behavioral activation appeared equally effective as cognitive therapy in reducing MDD symptoms. At follow-up, behavioral activation was also as effective as cognitive therapy in preventing relapse (Gortner *et al*, 1998), and a subsequent large-scale randomized trial found that behavioral activation was equivalent to paroxetine in reducing symptoms in moderately to severely depressed individuals (Dimidjian *et al*, 2006). Recently, Lejuez *et al* (2001) developed a brief BATD. Although sharing many common elements with previous approaches, BATD is unique in that it is shorter than traditional treatments (only 8–15 sessions) and does not require as extensive skills on the part of the therapist or the patient (Hopko *et al*, 2003). Treatment proceeds through a series of structured units that (a) provide psychoeducation about MDD and a rationale for the treatment approach; (b) assess and monitor baseline activity levels; (c) develop personally valued goals and a hierarchical plan for goal attainment; and (d) monitor, support, and reward achieving behavioral goals. Preliminary studies have demonstrated that BATD effectively reduces MDD symptoms and is well tolerated in both outpatient (Hopko *et al*, 2005; Lejuez *et al*, 2001) and inpatient (Hopko *et al*, 2003) settings.

Treatment Outcomes

Treatment outcomes in the MDD group were evaluated by examining changes in BDI scores that were collected at the scan session, every 2 weeks during treatment, and at the last psychotherapy session. BDI scores of 0–13 indicates minimal MDD, 14–19 indicates mild MDD, 20–28 indicates moderate MDD, and 29–63 indicates severe MDD (Beck *et al*, 1996). The BDI provides an overall measure of MDD severity and includes items that tap multiple MDD symptom dimensions. Because specific psychological processes are mediated by specific resting-state networks (Raichle, 2011), we examined anhedonia, cognitive, and somatic subscale scores of the BDI in addition to total BDI scores to address whether specific resting-state networks might be predictive of changes in specific MDD constructs. The BDI anhedonia subscale includes items 4, 12, 15, and 21 (Joiner *et al*, 2003); the cognitive BDI subscale includes items 2, 3, 5–9, and 14 (Siegert *et al*, 2009); and the somatic BDI subscale includes items 1, 4, 10, 11–13, and 15–21 (Siegert *et al*, 2009). Supplementary analyses evaluated relations between pretreatment rs-fcMRI and psychotherapy motivation, measured by the Situational Motivation Scale (SIMS; Guay *et al*, 2000), which was also administered every 2 weeks during treatment.

Imaging Methods

Functional images were acquired at the Duke-UNC Brain Imaging and Analysis Center (BIAC) on a General Electric (Waukesha, WI, USA) MR750 3.0 T scanner equipped with 50 mT/m gradients (200 T/m/s slew rate) and an eight-channel head coil for parallel imaging. High-resolution T1-weighted anatomical images were acquired with 162 axial slices using a FSPGR pulse sequence (TR = 7.584 ms; TE = 2.936 ms; FOV = 256 mm; image matrix = 256 × 256; voxel size = 1 × 1 × 1 mm; flip angle = 12°) and were used for normalization and coregistration with the functional data. This structural image was aligned in a near axial plane defined by the anterior and posterior commissures. Whole-brain functional images were acquired using a spiral-in SENSE sequence (TR = 1500 ms; TE = 30 ms; FOV = 240 mm; image matrix, 64 × 64; flip angle = 60°; voxel size, 3.75 × 3.75 × 4.0 mm; 34 axial slices) to reduce susceptibility artifacts and recover signal in orbital frontal regions (Pruessmann *et al*, 2001; Truong and Song, 2008). The resting-state functional scan was 300 s long, and participants were instructed to rest comfortably with their eyes open while viewing a gray fixation cross. A semi-automated high-order shimming program ensured global field homogeneity.

Imaging Data Preprocessing

The first four volumes of each functional imaging data set were discarded to allow for magnetic field stabilization. Heart rate and respiration were acquired from each participant during the scan, and retrospective correction for physiological motion was performed using AFNI 3dretroicor (Glover *et al*, 2000), and signal outliers were removed from the data using AFNI 3dDespike. Brain extraction, motion correction, spatial smoothing, and slice-timing correction were then performed using FSL version 5.0.1 (FMRIB Software Library, FMRIB Centre, Oxford University, UK) as previously described (Schiller *et al*, 2013). Data were affine-registered to MNI152 standard space using MCFLIRT in FSL using an intermodal registration tool (Jenkinson *et al*, 2002; Smith *et al*, 2004). Next, white matter and cerebrospinal fluid were regressed out using FMRIB's Automated Segmentation Tool (FAST) in FSL. Voxel-wise temporal autocorrelation was estimated and corrected using FMRIB's Improved Linear Model (Jenkinson and Smith, 2001), and data were bandpass filtered between 0.008 and 0.1 Hz using custom python scripts. Volumes that exceeded framewise displacement of 0.5 or DVARS (DVARS is a measure of how much the intensity of a brain image changes in comparison to the previous timepoint (Power *et al*, 2012)) of 0.5% (mean global intensity of a single volume over brain mask intensity) were removed prior to connectivity analyses (Power *et al*, 2012). We did not regress global signal intensity (Saad *et al*, 2012).

Functional Connectivity Analysis

Functional connectivity was analyzed via a whole-brain seed-based approach. Standard seed regions were used to analyze each canonical resting-state network (Schmidt *et al*, 2013; Woodward *et al*, 2011). These seeds were the anterior insula (Elton and Gao, 2013) and dACC (Seeley *et al*, 2007) for the SN; the posterior intraparietal sulcus/superior parietal lobule (Schmidt *et al*, 2013; Vincent *et al*, 2008) for the DAN; the dorsolateral prefrontal cortex (Elton and Gao, 2013; Seeley *et al*, 2007; Sheline *et al*, 2010) for the ECN; and the precuneus and medial prefrontal cortex for the DMN (Sheline *et al*, 2010). Seed regions were 5-mm spheres with centers as described in Raichle (2011) (see Table 2).

Mean fMRI timeseries were extracted from seed ROIs using FSL fslmeants and analyzed as regressors to identify voxels correlated with seed timeseries for each participant in FSL FEAT as a first-level explanatory variable using a

Table 2 Centers of 5 mm Sphere of Seed Regions (From Raichle, 2011)

Network	Seed regions	MNI coordinates		
		X	*Y*	*Z*
Default mode	Precuneus	0	−52	27
	Medial prefrontal cortex	−1	54	27
Dorsal attention	Left intraparietal sulcus	41	−39	45
	Right intraparietal sulcus	−44	−39	45
Salience	Left anterior insula	41	3	6
	Right anterior insula	−41	3	6
	Dorsal anterior cingulate cortex	0	21	36
Executive control	Left dorsal lateral prefrontal cortex	32	45	30
	Right dorsal lateral prefrontal cortex	−35	45	30

Table 3 Change in BDI Total and Subscale Scores After Treatment in the MDD Group

	Pretreatment		Posttreatment		*p*
	Mean (SD)	Range	Mean (SD)	Range	
BDI total score	26.04 (7.46)	18–44	14.00 (8.40)	0–25	<0.001
BDI anhedonia subscale	4.97 (2.05)	3–10	2.58 (2.02)	0–8	<0.001
BDI somatic subscale	15.06 (4.98)	7–23	9.36 (6.20)	2–22	<0.001
BDI cognitive subscale	10.21 (3.89)	5–21	5.26 (3.89)	0–11	<0.001

Pretreatment BDI scores were obtained at the scan session; posttreatment BDI scores were obtained at the last therapy session. Posttreatment BDI subscale scores were not available from one MDD participant.

general linear model approach with FILM prewhitening (Jenkinson *et al*, 2012). The resulting parameter estimate maps for each participant were entered into group-level analyses calculated by a mixed effects analysis using Bayesian estimation techniques (FILM, Woolrich *et al*, 2001) to compare MDD and control groups with respect to seed-based connectivity using FMRIB Local Analysis of Mixed Effects (FLAME 1 + 2, Beckmann *et al*, 2003) using *Z*-statistic images cluster thresholded at $Z>2.3$ with a corrected cluster significance threshold of $p<0.05$. This method of cluster correction, implemented via the cluster thresholding option within FSL FEAT, compares each cluster's estimated significance level (from Gaussian random field theory) with the cluster probability threshold to eliminate clusters below this threshold. Average *Z*-scores from clusters with significantly different connectivity between groups were extracted for each participant to examine relations with antidepressant treatment outcomes in the MDD group. Cluster localizations were based on Harvard–Oxford cortical and subcortical structural probabilistic atlases in FSLView v3.1.8.

RESULTS

Treatment Response

Table 3 illustrates that BDI total and subscale scores showed a significant decline from pretreatment to posttreatment. The average decline in BDI total scores was 12.04 ($p<0.001$), a clinically meaningful response (Jacobson and Truax, 1991). Supplementary Materials SI presents correlations between BDI total and subscale scores at pretreatment and posttreatment.

Head Motion

There were no significant differences between groups with respect to mean relative or absolute displacement across three dimensions, p's >0.05 (control mean (SD) absolute displacement = 0.255 (0.241); MDD mean (SD) absolute displacement = 0.189 (0.146)), calculated with FSL MCFLIRT.

Group Differences in Functional Connectivity

Table 4 and Figure 1 illustrate clusters with group differences in seed-based functional connectivity. The MDD group was characterized by relatively increased connectivity between: (1) right anterior insula and left visual cortex; (2) left anterior insula and left superior parietal lobule; (3) dACC and left visual cortex; (4) precuneus and left middle temporal gyrus; and (5) left dorsolateral prefrontal cortex and right motor cortex. The MDD group was characterized by relatively decreased connectivity between: (1) right anterior insula and clusters within left and right middle temporal lobes; (2) left anterior insula seed and the left middle temporal lobe; (3) dACC and left parahippocampal gyrus; and (4) left intraparietal sulcus and left orbitofrontal cortex.

Figure 2 illustrates the high degree of overlap in the left middle temporal gyrus between clusters showing differential connectivity in the MDD group (ie, greater connectivity with the precuneus seed and decreased connectivity with right and left anterior insula seeds).

Supplementary Materials SII presents within-group connectivity maps for each seed regions to illustrate the extent to which group differences in connectivity are related to connectivity maps within the control and MDD samples. Supplementary Materials SIII presents between-group results with the exclusion of the four participants who completed fewer than eight therapy sessions and illustrates highly similar patterns of findings.

Relations between Pretreatment Functional Connectivity and Symptom Severity

Correlation analyses between pretreatment BDI scores and connectivity magnitude in regions that yielded different connectivity between groups (ie, the nine pairs of regions listed in Table 4) indicated significant relations between MDD severity, as measured by total BDI scores, and connectivity between the precuneus and left middle temporal gyrus connectivity (inverse relation) and connectivity between the dACC and the parahippocampal gyrus (direct relation), as illustrated in Figure 3. Correlations with BDI subscale scores were not significant.

Table 4 Between Group Differences in Connectivity (Cluster-Corrected $p<0.05$)

Seed (network)	Region (BA)	MNI coordinates			Peak z-score
		X	*Y*	*Z*	
MDD > control					
Right anterior insula (salience network)	Left visual cortex (BA17)	−2	−88	−8	3.87
Left anterior insula (salience network)	Left superior parietal lobule (BA7)	−10	−66	58	3.97
Dorsal ACC (salience network)	Left visual cortex (BA17)	−20	−98	8	3.98
Precuneus (default mode network)	Left middle temporal lobe (BA21)	−60	−42	0	4.33
Left dorsolateral PFC (executive control network)	Right motor cortex (BA4)	38	−24	60	3.91
Control > MDD					
Right anterior insula (salience network)	Left middle temporal lobe (BA21)	−60	−44	4	4.53
Right anterior insula (salience network)	Right middle temporal lobe (BA22)	48	−38	8	4.29
Left anterior insula (salience network)	Left middle temporal lobe (BA22)	−48	−28	−12	4.37
Dorsal ACC (salience network)	Left parahippocampal gyrus	−12	−34	−16	4.18
Left IPS (dorsal attention network)	Left orbitofrontal cortex (BA47)	−32	24	−18	3.79

Abbreviation: BA, Brodmann area.

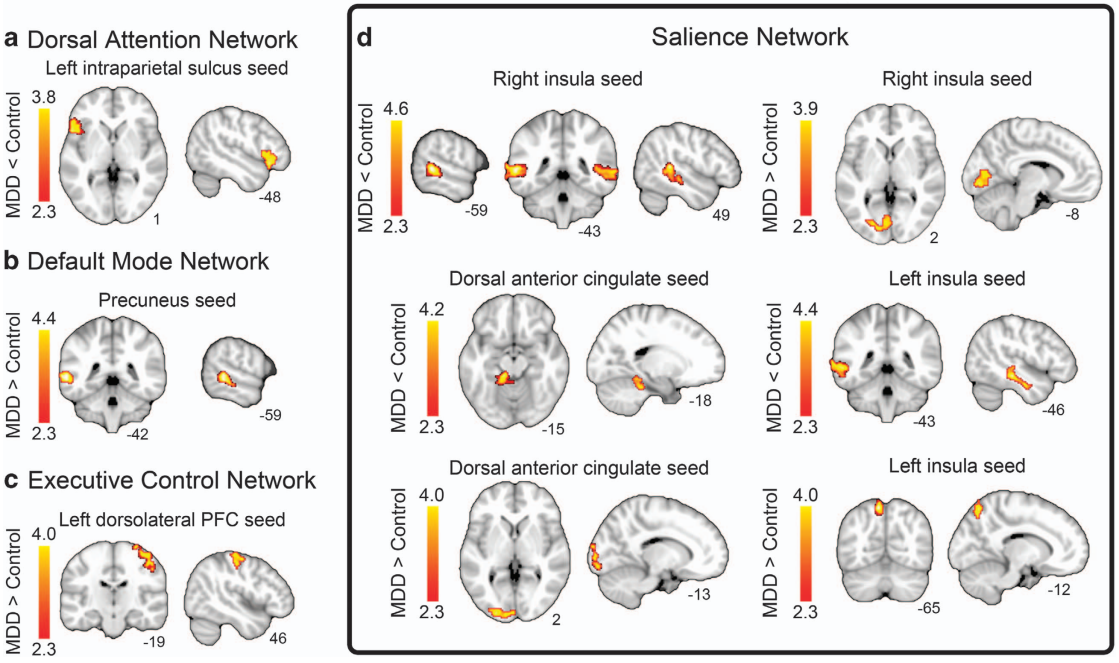

Figure 1 Group differences in resting-state connectivity in (a) the dorsal attention network (DAN); (b) the default mode network (DMN); (c) the executive control network (ECN); and (d) the salience network (SN). All results are cluster-corrected, $p<0.05$.

Prediction of Treatment Response from Pretreatment Functional Connectivity

We used hierarchical linear models (HLM), implemented via SAS 'proc mixed' (SAS version 9.3, Cary, NC) to evaluate the predictive effects of pretreatment functional connectivity on response to psychotherapy, as measured by BDI scores (Supplementary Materials SIV present results of correlational analyses testing for relations between baseline rs-fcMRI values and change in BDI scores, calculated as simple differences between pretreatment and posttreatment BDI scores). HLM models analyzed the capacity of baseline rs-fcMRI data to predict change in symptoms using nine BDI timepoints over 15 weeks. HLM controls for the non-independence that arises through repeated measures by the inclusion of random effects, and we included random effects for BDI intercept and time. In traditional regression analyses, participants are removed listwise when any of

their timepoints are missing. In HLM, repeated measures are handled by treating each timepoint for each participant as a separate observation. For this reason, participants with at least one observation (ie, all MDD participants) are included in these analyses.

We used models that tested whether linear change in BDI scores over time was moderated by baseline connectivity included as a time-invariant variable. To address the potential for nonlinear change of time, for all models presented below, we tested models that also included quadratic and cubic effects for time, which were all nonsignificant, indicating that change was indeed linear (all $F<0.57$, all $p>0.45$). Models included main effects for time and connectivity plus their interaction terms. Data were centered such that the main effect for connectivity was estimated at time = 0 (ie, pretreatment), and the main effects for time were estimated at the mean of connectivity values. We examined models separately that assessed the predictive capacity of the nine region pairs that differentiated the MDD and control groups at baseline listed in Table 4 to predict BDI total and BDI anhedonia, cognitive, and somatic subscale scores. Figure 4 illustrates biweekly BDI scores from individual MDD participants and average biweekly BDI scores from all MDD participants. As described earlier, given the focus of BATD on decreasing avoidance behaviors and increasing behavioral engagement with clinically relevant goals, our strongest hypotheses focused on relations between connectivity, response to treatment, and anhedonic symptoms, as well as the severity of MDD symptoms overall. Thus *a priori* hypotheses focused on BDI total scores and BDI anhedonia subscale scores, and analyses of other BDI subscales should be considered exploratory. Four models yielded significant or marginally significant connectivity × time interaction effects, as described here:

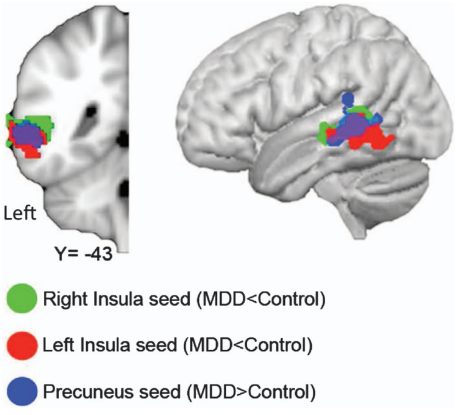

Figure 2 Overlap in the left middle temporal gyrus clusters that demonstrated differential connectivity with the right insula (in green), the left insula (in red), and the precuneus (in blue).

Prediction of change in BDI anhedonia subscale scores from right insula connectivity with right middle temporal gyrus. Tests of random effects indicated a significant effect for the intercept ($z=2.82$ $p<0.003$) and a significant effect for time ($z=1.79$, $p<0.04$). The fixed effects indicated a significant negative effect for time ($t=-5.17$, $p<0.0001$), indicating that BDI anhedonia subscale scores decreased with time for all participants, as well as for connectivity ($t=2.01$, $p<0.05$), indicating that connectivity was associated with BDI anhedonia subscale scores. The critical connectivity × time interaction was significant ($t=-2.19$, $p<0.04$), indicating that varying levels of connectivity were associated with differential change in anhedonia subscale BDI scores over time, and more specifically that the amount of change in BDI anhedonia subscale scores was greatest for those with greater connectivity and least for those with lower connectivity. This effect is illustrated in the top left of Figure 5.

Prediction of change in BDI somatic subscale scores from left intraparietal sulcus connectivity with orbital frontal cortex. Tests of random effects indicated significant effects for the intercept ($z=2.91$, $p<0.002$) and for time ($z=1.93$, $p<0.03$). The fixed effects indicated a significant negative effect for time ($t=-6.80$, $p<0.0001$), indicating that BDI somatic subscale scores decreased with time for all

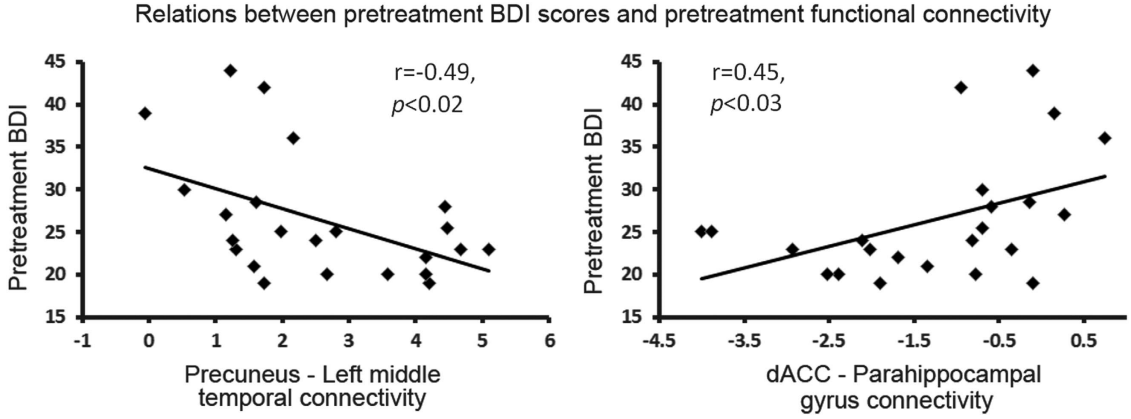

Figure 3 Left: Relations between pretreatment precuneus—left middle temporal gyrus connectivity and pretreatment BDI scores. At pretreatment, the MDD group was characterized by greater precuneus—left middle temporal gyrus connectivity relative to controls. Right: Relations between pretreatment dACC–parahippocampal connectivity and pretreatment BDI scores. At pretreatment, the MDD group was characterized by decreased dACC–parahippocampal connectivity relative to controls.

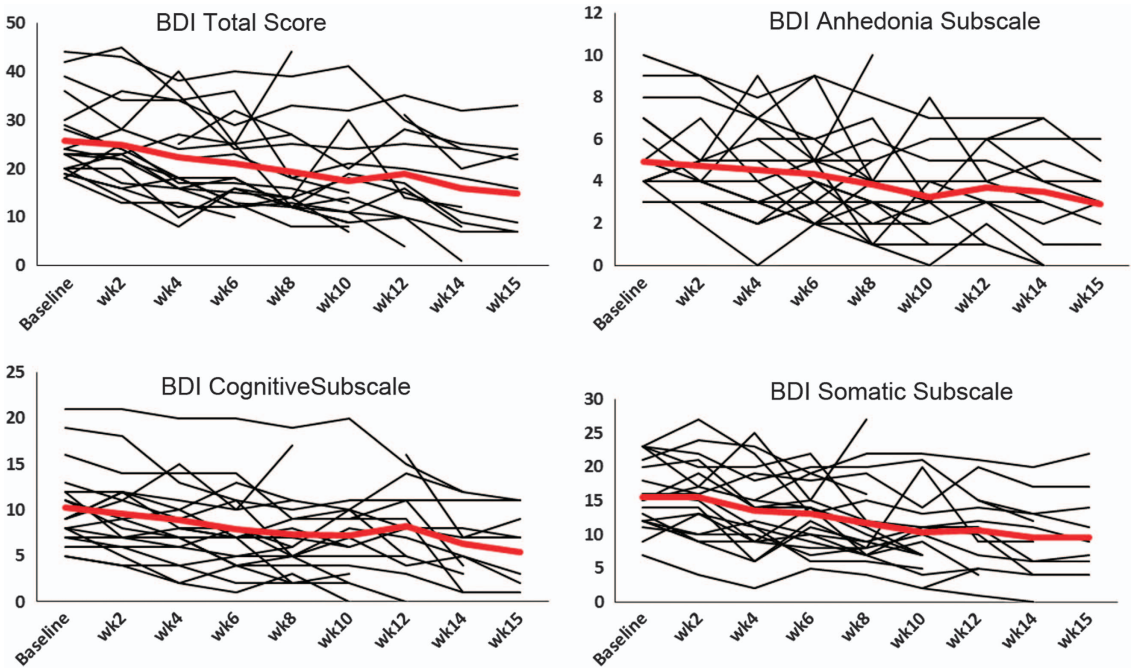

Figure 4 Biweekly BDI scores from individual MDD participants (thin lines) and average biweekly BDI scores from all MDD participants (thick line). Baseline assessments occurred before the start of treatment. Fourteen data points were not available.

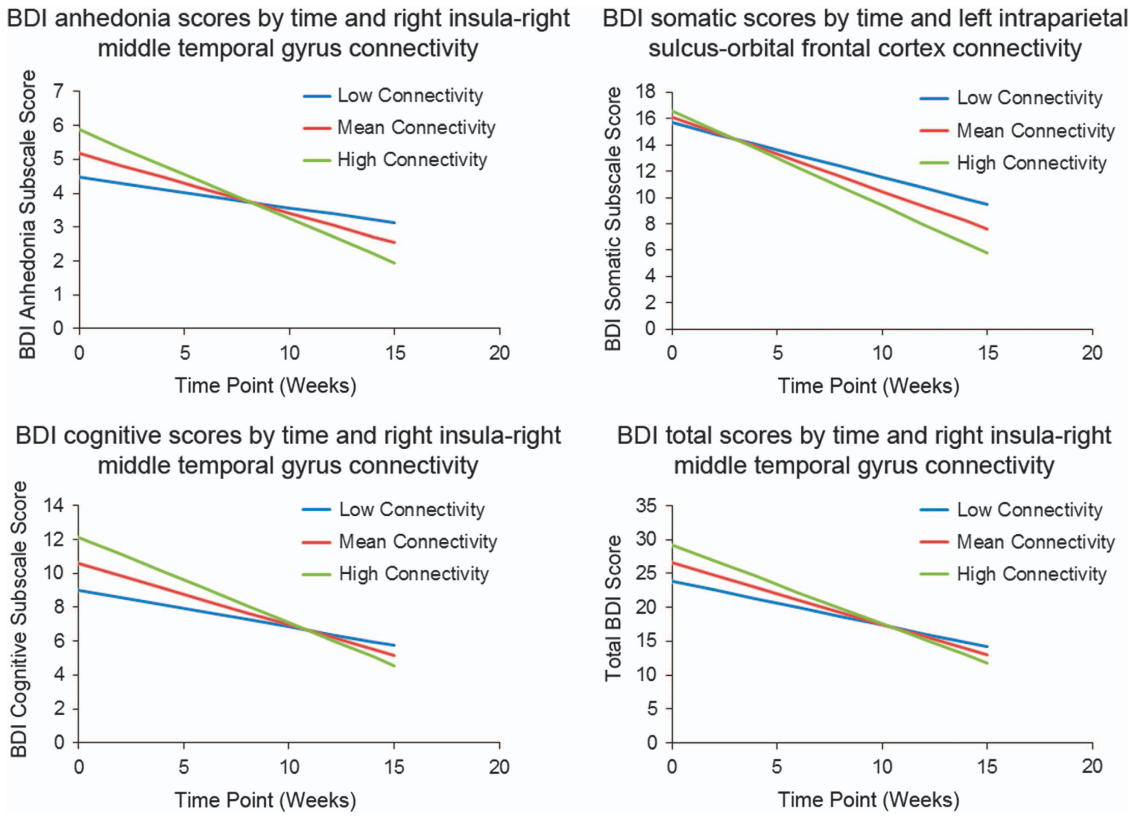

Figure 5 Graphical illustration of the significant interaction between baseline connectivity and time predicting change in BDI scores from the HLM models. The lines represent the range of variability on connectivity: 'low' represents the expectation for change in an individual who is a SD below the mean, 'mean' for someone at the average, and 'high' for someone a SD above. Note that the lines are model-based estimates and do not represent averages but rather ranges of brain connectivity variability.

participants, but no effect for connectivity ($t = 0.51$, $p > 0.60$), indicating that connectivity was not associated with BDI somatic subscale scores. The critical connectivity × time interaction was marginally significant ($t = -1.88$, $p = 0.06$), indicating that varying levels of connectivity were associated with differential change in BDI somatic subscale scores over time, and more specifically that the amount of change in BDI somatic subscale scores was greatest for those with greater connectivity and least for those with lower connectivity. This effect is illustrated in the top right of Figure 5.

Prediction of change in BDI cognitive subscale scores from right insula connectivity with right middle temporal gyrus. Tests of random effects indicated a significant effect for the intercept ($z = 2.98$, $p < 0.002$) and a marginally significant effect for time ($z = 1.53$, $p < 0.07$). The fixed effects indicated a significant negative effect for time ($t = -7.15$, $p < 0.0001$), indicating that BDI cognitive subscale scores decreased with time for all participants, as well as for connectivity ($t = 2.09$, $p < 0.04$), indicating that connectivity was associated with BDI cognitive subscale scores. The critical connectivity × time interaction was significant ($t = 2.55$, $p < 0.02$), indicating that varying levels of connectivity were associated with differential change in BDI cognitive subscale scores over time, and more specifically that the amount of change in BDI cognitive subscale scores was greatest for those with greater connectivity and least for those with lower connectivity. This effect is illustrated in the bottom left of Figure 5.

Prediction of change in total BDI scores from right insula connectivity with right middle temporal gyrus. Tests of random effects indicated significant effects for the intercept ($z = 2.89$, $p < 0.002$) and for time ($z = 1.86$, $p < 0.04$). The fixed effects indicated a significant negative effect for time ($t = -6.99$, $p < 0.0001$), indicating that BDI scores decreased with time for all participants, and a marginal positive effect for connectivity ($t = 1.81$, $p = 0.075$), indicating that connectivity was marginally positively associated with BDI scores. The critical connectivity × time interaction was marginally significant ($t = 1.80$, $p = 0.074$), indicating that varying levels of connectivity were associated with differential change in BDI scores over time, and more specifically that the amount of change in BDI scores was greatest for those with greater connectivity and least for those with lower connectivity. This effect is illustrated in the bottom right of Figure 5.

Prediction of Change in SIMS Scores from Pretreatment rs-fcMRI

Supplementary Materials SV presents HLM models that predict changes in SIMS scores (Guay *et al*, 2000) during the course of psychotherapy from rs-fcMRI.

DISCUSSION

This purpose of this study was to examine differences in resting-state functional connectivity between outpatients with MDD and matched control participants and to investigate whether pretreatment rs-fcMRI connectivity predicted response to behavioral activation psychotherapy. Specifically, we examined whether groups differed in connectivity with seeds previously identified as network hubs in four canonical resting-state networks relevant to the pathophysiology of MDD: the SN, the DAN, the ECN, and the DMN. We examined response to BATD, a validated psychotherapy designed to increase engagement with functional, potentially rewarding behaviors and to reduce avoidance behaviors (Hopko *et al*, 2003). This psychotherapy modality has been shown to be equally effective as cognitive psychotherapy (Jacobson *et al*, 1996) and paroxetine treatment (Dimidjian *et al*, 2006) in reducing MDD symptoms and as effective as cognitive therapy in preventing MDD relapse (Gortner *et al*, 1998).

The clinical effectiveness of BATD in the current study was consistent with prior trials (Dichter *et al*, 2009; Hopko *et al*, 2003): average BDI scores declined 12.25 points, a clinically meaningful response (Jacobson and Truax, 1991). Nevertheless, there was substantial variability in response (ie, the range of change in BDI scores for individual patients was between −6 and +25 points), highlighting the need to develop methods to match specific patients to empirically validated treatments in order to maximize treatment success (Kapur *et al*, 2012).

We found that connectivity between nine region pairs differentiated the MDD and control groups. Consistent with *a priori* hypotheses, a number of findings converged on the SN, a brain network that directs attention to salient stimuli in the external environment (Menon and Uddin, 2010). First, we found evidence of decreased connectivity in the MDD group between the dACC (a SN hub) with the left parahippocampal gyrus. The dACC is part of a distributed attentional network that maintains strong reciprocal interconnections with lateral prefrontal, parietal, and motor areas and is implicated in the modulation of attention by influencing sensory and response selection, conflict monitoring, and error detection (eg, Bush *et al*, 1999; Carter *et al*, 1999). More recent formulations of the functions of the dACC stress the evaluative, rather than regulatory, role of this region (see, eg, Botvinick, 2007 for a review), highlighting that the dACC detects internal states indicating a need to strengthen top–down control (Badre and Wagner, 2004). Additionally, the dACC serves to integrate the emotional or motivational relevance of stimuli with attentional functions, due to its connections between the limbic system and sensory processing areas (Mayberg, 1997; Mesulam, 1981). Notably, dACC–parahippocampal connectivity was associated with pretreatment BDI scores within the MDD group. Decreased connectivity in the MDD group between the dACC and the parahippocampal gyrus, a component of the limbic system that is differentially active in MDD in the context of memory tasks (Dietsche *et al*, 2014), emotional processing (Lai, 2014), and reward tasks (Zhang *et al*, 2013) suggests aberrant dACC regulatory connectivity with this affective processing region in the MDD group that is predictive of symptom severity, suggesting a mechanistic account of negative interpretation biases that characterize MDD (Lawson and MacLeod, 1999).

Also implicating the SN, the left and right anterior insula seeds showed differential connectivity with clusters in visual cortex, the superior parietal lobule and the middle temporal

gyrus. The anterior insula is sensitive to salient external stimuli and critical for externally oriented attention and internally oriented or self-related cognitions, and the SN more broadly functions to identify relevant stimuli to guide goal-oriented behaviors (Menon and Uddin, 2010). Additionally, the anterior insula has been implicated in high-level social cognition (Baumgartner *et al*, 2009), empathy (Singer, 2006), and compassion for social or psychological pain (Immordino-Yang *et al*, 2009), as well as categorization of negative information and the experience of emotion more generally (Beatty *et al*, 2014). Differential anterior insular connectivity dovetails with models of MDD that emphasize altered motivational context to personally relevant stimuli and difficulty engaging in cognitively demanding tasks while ignoring irrelevant, negatively valenced stimuli (Yuen *et al*, 2014), and the current results suggest that greater anterior insula connectivity facilitated response to BA, despite higher initial anhedonia scores.

It is noteworthy that the MDD group was characterized by differential connectivity of the right anterior insula with visual cortex and left anterior insula with left superior parietal lobule. The visual cortex and the superior parietal lobule are critical components of the visual information processing system, with the superior parietal lobule in particular involved in spatial orientation. Visual recognition circuits have been implicated in studies of relations between rs-fcMRI and response to antidepressant treatments (Guo *et al*, 2013b; Guo *et al*, 2012; Wang *et al*, 2014), though the precise functional role of connectivity between the anterior insula and visual processing regions in antidepressant treatment response remains to be elucidated.

The primary focus of the present study was to investigate pretreatment rs-fcMRI predictors of response to BATD. We evaluated this with hierarchical linear regression that modeled BDI scores at nine time points during the course of treatment and that allowed for the inclusion of participants with missing data. In contrast to an approach that examines response to treatment calculated as a simple pretreatment minus posttreatment scores, this approach models scores during the entire course of treatment, mitigating the effect of outlier BDI scores and captures a more detailed picture of the course of treatment response. Four pretreatment connectivity pairs were found to predict treatment response, and three of these involved the anterior insula. Specifically, (1) change in BDI anhedonia subscale scores were predicted by pretreatment right insula–right middle temporal gyrus connectivity; (2) change in BDI cognitive subscale scores were predicted by pretreatment right insula–middle temporal gyrus connectivity; and (3) change in BDI total scores were marginally predicted by pretreatment right insula–middle temporal gyrus connectivity.

One additional BATD-response predictor was identified: change in BDI somatic subscale scores were predicted by pretreatment left intraparietal sulcus–orbital frontal cortex connectivity. The DAN network shows increased synchronization during goal-directed processes (Corbetta *et al*, 1998; Kim, 2010), and MDD is characterized by poor performance in cognitive control tasks (Veiel, 1997; Zakzanis *et al*, 1998) as well as dysfunction in dorsolateral and ventrolateral prefrontal cortex and anterior cingulate cortex during cognitive control tasks (Brody *et al*, 2001; Rogers *et al*, 2004). MDD is also characterized by altered orbital frontal cortex activation in the context of processing rewards (Dichter *et al*, 2012; Smoski *et al*, 2009), anticipating rewards (Dichter *et al*, 2012), and while processing sad distracting information (Elliott *et al*, 2002). Thus our finding of decreased connectivity between a DAN network hub and orbitofrontal gyrus may reflect the well-replicated finding of decreased cognitive control over emotion processing in MDD (Dichter *et al*, 2009) and prevailing neural models of MDD that highlight decreased modulatory control of prefrontal cortical brain regions over limbic brain regions, particularly in the context of emotion processing and emotion regulation (Johnstone *et al*, 2007; Joormann and Gotlib, 2010; Ray *et al*, 2005). Additionally, recent studies investigating response to antidepressant medications in MDD highlight that treatment response is associated with increased connectivity between prefrontal cortical and limbic brain regions, possibly implicating greater inhibitory control over neural circuits that process emotions in positive treatment response (Alexopoulos *et al*, 2012; Lai and Wu, 2012; Lui *et al*, 2011; Wu *et al*, 2011; Yang *et al*, 2014). The somatic subscale as defined by Siegert *et al* (2009) encompasses mood (sadness), vegetative (eg, sleep, fatigue), attention/concentration, and motivation-related (interest, energy) symptoms and thus may be especially sensitive to disruptions in circuits that underlie both attention and goal-directed behaviors.

It was striking that of the nine region pairs that differentiated groups, four involved connectivity with the middle temporal gyrus (ie, differential connectivity with the precuneus (DMN), anterior insula (SN), and dACC (SN)). Differential precuneus connectivity in MDD is consistent with previous reports of DMN hyperconnectivity in MDD (Broyd *et al*, 2009; Sheline *et al*, 2010). Given that the DMN is most active when the brain is at rest (ie, not engaged in goal-directed tasks), and involved in introspective thought and attention orienting, it has been theorized that differential DMN connectivity may be responsible for the negative rumination states that characterize MDD (Broyd *et al*, 2009). It is also noteworthy that precuneus–left middle temporal gyrus connectivity inversely predicted the severity of pretreatment symptoms in the MDD sample, suggesting a mechanistic linkage between DMN connectivity and MDD severity.

The MDD group was also characterized by aberrant middle temporal gyrus connectivity with a number of seeds. The temporal lobes have a critical role in the subjective experience of emotion (Beatty *et al*, 2014), and the posterior and superior portions of the temporal sulcus are critically involved in imitation, social cognition (Grossman and Blake, 2002; Iacoboni, 2005), and mentalizing (Sommer *et al*, 2014). These findings may suggest differential awareness (DMN), salience (SN), and cognitive control (ECN) of mental states in MDD that may contribute to rumination or impaired planful action based on awareness of one's own mental states. Although the current study did not include measures of these constructs, this interpretation is consistent with prevailing cognitive theories of MDD (eg, Watters and Williams, 2011). Specific to the prediction of treatment response, connectivity between anterior insula and middle temporal gyrus may subserve attention to internal affective states and social comparisons that interacted with cognitive symptoms of MDD (eg, guilt,

worthlessness). In addition, this circuit may also impact the perceived salience of goals and awareness of one's progress toward those goals, interacting with anhedonic symptoms of MDD.

Also of note is that all of the connectivity pairs that predicted better treatment response were consistent with patterns of connectivity closer to that observed in controls. In each case, the region pairs that demonstrated hypoconnectivity relative to the control group and relative hyperconnectivity within the MDD group predicted better treatment response. Contrary to what one might expect, this relatively normalized connectivity was also associated with greater symptom severity in anhedonic and cognitive symptoms of MDD at baseline. This suggests that hypoconnectivity between anterior insula and middle temporal gyrus may serve a compensatory function, and individuals with MDD who do not demonstrate compensatory pretreatment hypoconnectivity may be more amenable to other forms of remediation. Clinically, it is promising to note that greater severity of anhedonic and cognitive symptoms were also associated with greater response, suggesting that treatments such as BATD may be especially useful in targeting individuals with these symptom clusters, although the fact that these patients also had higher BDI total scores suggests the possibility that more severely depressed patients benefited the most from BATD.

The current study has a number of limitations to be addressed in future research. First, a comparison treatment condition (eg, another psychotherapy modality, psychopharmacologic treatment, or magnetic stimulation treatment) was not included, and thus it is not possible to attribute findings specifically to BATD psychotherapy relative to alternative treatments. Indeed, pretreatment rs-fcMRI predictors of antidepressant treatment response appear to be highly contingent on treatment modality (Dichter *et al*, 2015). Additionally, there were no group differences in connectivity with the DLPFC, a hub of the ECN. The ECN is active during executive function tasks, such as maintaining attention to salient stimuli (Seeley *et al*, 2007), and recent reports highlight hyperconnectivity of dorsal medial prefrontal cortex with multiple brain networks in MDD (Sheline *et al*, 2010). Future studies with larger samples will be needed to address the replicability of altered ECN connectivity in MDD. Undoubtedly, robust algorithms predicting treatment response will need to incorporate genetic testing (Frieling and Tadic, 2013), pharmacogenetics (de Leon, 2009), and neuroendocrine function (Holsboer, 2000). It is also well documented that a number of patient factors predict response to antidepressant treatment across treatment modalities, including disease severity, longer duration and frequency of the episodes, comorbid anxiety disorders, and an older age of onset (Kemp *et al*, 2008). Moreover, longitudinal clinical follow-up data would be critical to assess relapse after BATD termination as well as rs-fcMRI predictors of relapse, and posttreatment resting-state scans would be needed to address potential mechanisms of antidepressant action on canonical resting-state brain networks. Finally, although *a priori* hypotheses focused on BDI total and anhedonia subscale scores, findings from other BDI subscales were exploratory in nature and thus should be interpreted with caution until replicated.

In summary, the present study found that MDD is characterized by rs-fcMRI differences in connectivity with a number of canonical brain network hubs. Of note, a number of findings highlight altered connectivity with middle temporal gyrus, a brain area that is involved in imitation, social cognition, and mentalizing, implicating brain regions that code for awareness, salience, and cognitive control of mental states in the pathophysiology of MDD. Additionally, pretreatment connectivity of the anterior insula and intraparietal sulcus predicted response to psychotherapy, a pattern of results consistent with other reports of pretreatment anterior insula metabolism (McGrath *et al*, 2013) and connectivity (Downar *et al*, 2013) as predictors of response to psychotherapy and parietal lobe connectivity predicting response to antidepressant medication treatment (Guo *et al*, 2013a; Wu *et al*, 2011). More generally, the present study adds to the nascent but growing body of evidence linking pretreatment neuroimaging endophenotypes to antidepressant treatment outcomes (McGrath *et al*, 2013; McGrath *et al*, 2013). This line of research has the ultimate goal of improved response rates to currently available antidepressants through matching patients to specific, empirically validated treatment options (Kapur *et al*, 2012).

FUNDING AND DISCLOSURE

The project was funded by R21 MH094781 and R21 MH094781 S1 to GSD and MJS, by NIMH K23 MH087754 to MJS, and by NIMH K23 MH081285 to GSD. CES was supported by the UNC Building Interdisciplinary Careers in Women's Health (BIRCWH) Career Development Program (K12 HD001441) and by R21 MH101409. AC was supported by the UNC Neuroscience Center predoctoral training grant, T32NS007431. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The authors thank MRI technologists Susan Music, Natalie Goutkin, and Luke Poole for assistance with data acquisition, and BIAC Director Dr Allen Song for assistance with various aspects of this project.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)