◆ Human Brain Mapping 37:3214–3223 (2016) ◆

Reduced Global Functional Connectivity of the Medial Prefrontal Cortex in Major Depressive Disorder

James W. Murrough,[1,2,3]* Chadi G. Abdallah,[4,5] Alan Anticevic,[4,5] Katherine A. Collins,[1] Paul Geha,[4,5] Lynnette A. Averill,[4,5] Jaclyn Schwartz,[1] Kaitlin E. DeWilde,[1] Christopher Averill,[4,5] Genevieve Jia-Wei Yang,[5] Edmund Wong,[6] Cheuk Y. Tang,[6] John H. Krystal,[4,5] Dan V. Iosifescu,[1,2,3] and Dennis S. Charney[1,2,7]

[1]*Mood and Anxiety Disorders Program, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York*
[2]*Fishberg Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York*
[3]*Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York*
[4]*Clinical Neuroscience Division, VA National Center for PTSD, West Haven, Connecticut*
[5]*Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut*
[6]*Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, New York*
[7]*Department of Pharmacology and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, New York, New York*

Abstract: *Background:* Major depressive disorder is a disabling neuropsychiatric condition that is associated with disrupted functional connectivity across brain networks. The precise nature of altered connectivity, however, remains incompletely understood. The current study was designed to examine the coherence of large-scale connectivity in depression using a recently developed technique termed global brain connectivity. Methods: A total of 82 subjects, including medication-free patients with major depression ($n = 57$) and healthy volunteers ($n = 25$) underwent functional magnetic resonance imaging with resting data acquisition for functional connectivity analysis. Global brain connectivity was computed as the mean of each voxel's time series correlation with every other voxel and compared between study groups. Relationships between global connectivity and depressive symptom severity measured using the Montgomery-Åsberg Depression Rating Scale were examined by means of linear correlation. Results: Relative to the healthy group, patients with depression evidenced reduced global

Contract grant sponsor: National Institute of Mental Health of the National Institutes of Health (Career Development Award to Dr. Murrough); Contract grant number: K23MH094707; Contract grant sponsors: Iris & Junming Le Foundation (Award to Dr. Murrough) and Brain and Behavior Research Foundation (NARSAD award to Dr. Murrough); Contract grant sponsor: NIH National Center for Advancing Translational Sciences to Mount Sinai; Contract grant number: UL1TR000067; Contract grant sponsor: U.S. Department of Veterans Affairs via its funding of the VA National Center for PTSD – Clinical Neurosciences Division (to Drs. Averill and Abdallah) and the Office of Academic Affairs Advanced Fellowship in Mental Illness Research and Treatment (to Dr. Averill)

*Correspondence to: James W. Murrough, M.D., Mood and Anxiety Disorders Program, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1230, New York, NY 10029. E-mail: james.murrough@mssm.edu
J.W.M. and C.G.A. contributed equally to this work.

Received for publication 28 December 2015; Revised 28 March 2016; Accepted 19 April 2016.
DOI: 10.1002/hbm.23235
Published online 4 May 2016 in Wiley Online Library (wileyonlinelibrary.com).

connectivity bilaterally within multiple regions of medial and lateral prefrontal cortex. The largest between-group difference was observed within the right subgenual anterior cingulate cortex, extending into ventromedial prefrontal cortex bilaterally (Hedges' $g = -1.48$, $P < 0.000001$). Within the depressed group, patients with the lowest connectivity evidenced the highest symptom severity within ventromedial prefrontal cortex ($r = -0.47$, $P = 0.0005$). Conclusions: Patients with major depressive evidenced abnormal large-scale functional coherence in the brain that was centered within the subgenual cingulate cortex, and medial prefrontal cortex more broadly. These data extend prior studies of connectivity in depression and demonstrate that functional disconnection of the medial prefrontal cortex is a key pathological feature of the disorder. *Hum Brain Mapp 37:3214–3223, 2016*.

Key words: depression; neuroimaging; functional connectivity; resting state; prefrontal cortex; subgenual anterior cingulate cortex

INTRODUCTION

Major depressive disorder (MDD) is a complex neuropsychiatric syndrome characterized by pervasive disturbances in mood regulation, reward sensitivity, cognitive control, and neurovegetative functioning. Unipolar depressive disorders are associated with more disability than any other brain-based disorder, including all other psychiatric disorders and all neurological and substance use disorders [Collins et al., 2011]. Although the fundamental pathology underlying MDD or its component features remains elusive, significant progress has been made in characterizing abnormalities in depression at the level of neural system [Hamilton et al., 2012; Price and Drevets, 2010]. Behavioral neuroscience and neuroimaging studies provide convergent evidence for disordered functioning within distributed neural systems encompassing ventral, medial and lateral aspects of prefrontal cortex (PFC), rostral and ventral aspects of anterior cingulate cortex (ACC), and interconnected subcortical regions [Hamilton et al., 2012; Price and Drevets, 2010; Siegle et al., 2007]. The ventromedial prefrontal cortex (VMPFC) and subgenual anterior cingulate cortex (sgACC) in particular feature prominently in neurocircuit models of depression [Mayberg et al., 2005].

Techniques for computing functional connectivity based on analysis of low frequency fluctuations of the blood oxygen level dependent (BOLD) signal at rest [Fox and Raichle, 2007] have enabled important advances in the understanding of human brain function in vivo in MDD and other neuropsychiatric conditions [Kaiser et al., 2015; Sheline et al., 2010]. Prior studies in depression have partially converged on the ACC and other midline cortical structures have shown abnormal functional connectivity, although there is significant heterogeneity of findings in the literature and the precise nature of the alternations in connectivity that characterize MDD remain incompletely understood [Kaiser et al., 2015]. Contributing to this uncertainty, most research to date examining functional connectivity has relied on the a priori selection of "seed" regions by the investigator; this method involves determining to which brain area connectivity will be measured and therefore inherently restricts the interpretation of the results. This approach is useful for testing hypotheses regarding specific regions or networks but does not provide a comprehensive method of examining connectivity outside of pre-specified regions [Fox and Raichle, 2007].

In order to further characterize the nature of functional connectivity alterations in MDD, in the current study we applied a recently developed measure of connectivity based on graph theory termed global brain connectivity (GBC) [Anticevic et al., 2013, 2014; Cole et al., 2010]. GBC provides a measure of the connectivity, or coherence, of all voxels in the brain relative to all other voxels. In the context of graph theory, GBC can be considered as weighted degree centrality normalized to the total number of possible functional connections [Bullmore and Sporns, 2009; Cole et al., 2010]. To date, GBC has been shown—using fully data-driven approaches—to be a powerful and replicable biomarker to identify major intrinsic brain networks (e.g., cognitive control and default mode networks) [Cole et al., 2010], to correlate with normal brain functions (e.g., cognition and intelligence) [Cole et al., 2012], and to be disrupted in bipolar disorder [Anticevic et al., 2013], schizophrenia [Anticevic et al., 2015], and obsessive-compulsive disorder (OCD) [Anticevic et al., 2014]. To our knowledge, this unique and reliable voxel-wise whole-brain data-driven GBC biomarker has not yet been fully investigated in MDD [Gong and He, 2015].

In the current study, we conducted a whole-brain study of GBC in patients with MDD free of concomitant antidepressant medication and healthy volunteers. Whole-brain analyses were followed by analyses restricted to the VMPFC (including the sgACC) because of the central role of this region in neurocircuit models of depression [Mayberg et al., 2005]. Based on the existing literature, we hypothesized that MDD would be characterized by abnormal connectivity primarily localized to midline prefrontal cortical structures.

METHODS AND MATERIALS

Participants

Male and female adults with MDD and healthy control (HC) volunteers were recruited for the current study

through an outpatient psychiatric research program at Icahn School of Medicine at Mount Sinai. Inclusion criteria for the MDD group included being in a current major depressive episode and having a primary diagnosis of MDD determined using the Structured Clinical Interview for DSM-IV. Lifetime history of anxiety disorders, substance use disorders, and other comorbidity was likewise assessed using the SCID. Healthy volunteers were free of lifetime psychiatric illness or significant medical conditions. Depressed patients were excluded if they had a lifetime history of a psychotic illness or bipolar disorder, met criteria for alcohol or substance abuse within one year of screening, significant medical illness, or had contraindications to magnetic resonance imaging (MRI). Participants were free of psychotropic medication for a minimum of one week prior scanning, and were free of substances of abuse as determined by a urine toxicology test on the day of scan. Women of childbearing potential were required to test negative on a urine pregnancy test on the day of scan. Depression and anxiety severity at the time of image acquisition was determined using the Montgomery-Åsberg Depression Rating Scale (MADRS) [Montgomery and Asberg, 1979], and the Hamilton Anxiety Rating Scale (HAM-A) [Hamilton, 1959], respectively. The Program for the Protection of Human Subjects at Icahn School of Medicine at Mount Sinai approved the study. After complete description of the study to potential participants, written informed consent was obtained prior to the conduct of any study procedures.

Neuroimaging Data Acquisition

Participants underwent MRI with a Philips Achieva 3.0T X-series system using an 8-channel birdcage headcoil for radio frequency transmission and reception. After a localization scan, high-resolution T1-weighted anatomical images were collected using a three-dimensional turbo field echo sequence (3D_TFE; RT: 7.5 ms; ET: 3.5 ms; voxel dimensions: 1 mm × 1 mm × 1 mm; FOV 224 mm × 224 mm; flip angle: 8°) and 172 sagittal planes. Resting-state functional data was acquired using a T2*-weighted gradient echo-planar imaging sequence (RT 2,000 ms; ET 26.6 ms; voxel dimensions: 2.2 mm × 2.2 mm × 3.25 mm; FOV 210 mm × 210 mm; flip angle = 90°, 120 frames) and 38 contiguous and ascending near-axial planes parallel to the intercommissural plane. Total resting state acquisition was 4 min. The relatively short scan time was selected to balance acquiring a sufficient amount of data while minimizing motion artifacts and patients' burden [Van Dijk et al., 2010]. At the beginning of each functional run, the MR signal was allowed to equilibrate over five TRs, which were subsequently excluded from the analysis. Participants were instructed to rest with their eyes open during the resting state scan.

Neuroimaging Processing and Analyses

Image processing and analyses were performed using previously validated pipelines utilizing FSL, AFNI, Freesurfer, and in-house written Matlab programs [Anticevic et al., 2013, 2014]. The preprocessing of each functional scan included the following: brain extraction, motion correction, slice-time correction, spatial smoothing (FWHM 5 mm), high-pass temporal filtering (100 s), boundary-based registration of fMRI to high-resolution T1 images, and nonlinear registration of structural images to a standard Montreal Neurological Institute (MNI) template. Considering recent evidence showing the contribution of high-frequency bands to functional connectivity, low-pass temporal filtering was not implemented [Chen and Glover, 2015; Gohel and Biswal, 2015; Lee et al., 2013]. To ensure BOLD quality across groups, all included scans passed the following criteria: signal-to-noise ratios (SNR) greater than 100, (i.e., the ratio of mean signal over standard deviation for a given slice across the BOLD run [Anticevic et al., 2013, 2014]) and no BOLD run with a single frame movement greater than 1 functional voxel. To remove spurious signal, the six rigid-body motion parameters, cerebrospinal fluid, white matter, and global brain signal were regressed out of each voxel's time series. Then, time series were extracted from all voxels within each individual's anatomically defined whole brain grey matter mask. All processing and analyses were conducted in the subject space, except for seconnd level group analyses. We opted not to regress out the temporal derivatives and the quadratic terms because such regression in the current data would have significantly reduced the degree of freedom [Saad et al., 2013]. In addition, while global signal regression is a contested processing step, it is very effective procedure for removing motion artifacts [Power et al., 2014].

As in previous work [Cole et al., 2010], GBC was computed as the average of each voxel's time series correlation with every other voxel in the gray matter of the entire brain. The GBC procedure involves computing a Pearson correlation between a given voxel's time series and every voxel's time series, transforming all correlations to Fisher z-values, and computing the mean across those Fisher z-values (Fz). This procedure generates a map for each subject where each voxel value represents the mean connectivity of that voxel with the rest of the brain. Individual whole-brain GBC Fz maps were entered into a between-group t-test (MDD vs. HC), co-varying for age and gender. Whole brain analyses were followed by ROI analyses restricted to the vmPFC based on an anatomical atlas [Desikan et al., 2006]. Relationships between GBC and depressive symptom severity were examined by means of linear correlation. Type I error correction was based on peak and cluster extent [Forman et al., 1995] ascertained via AFNI's 3dClustSim using an estimate of smoothness through 3dFWHMx (uncorrected z-value > 2.58 and at least 88 or 23 contiguous voxels for whole-brain and VMPFC-restricted analyses respectively, providing $P < 0.05$

TABLE I. Study sample characteristics

	MDD ($n = 51$)	Healthy control ($n = 25$)
Age, yrs	41.6 (12.5)	39.0 (12.1)
Gender, male	22 (43%)	13 (52%)
Caucasian	21 (41%)	12 (48%)
Education, yrs	16.0 (2.8)	17.6 (2.4)
History of anxiety disorder	13 (25.4%)	—
History of substance use disorder	5 (9.8%)	—
Age at illness onset, yrs	19.8 (13.4)	—
No. of episodes[a]	2.5 (1–20)	
Duration of episode, yrs	8.0 (14.2)	—
Length of illness, yrs	19.9 (16.5)	—
No. of prior treatment failures[a,b]	2.0 (0–14)	—
Required medication washout[b]	9 (17.6%)	—
MADRS score	28.1 (6.5)	1.6 (3.2)
HAM-A score	16.7 (5.7)	1.3 (2.3)

[a]Values shown are means (SD) or count (%) except "*a*" indicates median (range).
Value reflects number of lifetime antidepressant medication failures as defined using the Antidepressant Treatment History Form criteria (see text).
[b]Subjects were required to be free of antidepressant medication for a minimum of 1 week prior to scan. Abbreviations: HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Asberg Depression Scale; MDD, major depressive disorder.

cluster-level correction per analysis). Standardize mean differences (SMD) are reported based on Hedges' *g*.

RESULTS

Participant Characteristics

Eighty-two subjects (57 MDD, 25 HC) completed all MRI procedures. Six subjects (all MDD) had to be excluded for excessive motion, yielding a final sample of 51 MDD and 25 HC subjects. Demographic and clinical characteristics of the study sample are summarized in Table I. The study groups had similar age and gender distributions.

GBC in Major Depression

There were no differences between the study groups in absolute motion (MDD: 0.19 ± 0.1, HC: 0.18 ± 0.1, $P = 0.9$), relative motion (MDD: 0.14 ± 0.1, HC: 0.12 ± 0.1, $P = 0.4$), or signal to noise ratio (MDD: 224.4 ± 7.9, HC: 223.8 ± 6.8, $P = 0.7$). To rule out the possibility that there may be group differences in signal variance that could drive any observed group difference in GBC, we examined the variance estimates of global signal variability and found no significant difference between the study groups ($P = 0.29$).

The largest effect size of between-group difference in GBC was observed within the right sgACC (BA 25), extending into the VMPFC bilaterally (BA 11, 32), wherein the MDD group evidenced significantly reduced connectivity compared to the HC group (MNI: 6, −14, −20; SMD = −1.48; Table II, Fig. 1). Patients with MDD also exhibited reduced GBC within bilateral regions of DLPFC, DMPFC, left VLPFC, and left dACC (Table II, Fig. 1).

Compared to the HC group, the MDD group evidence increased connectivity in two posterior brain regions: the posterior cerebellum and the middle occipital cortex (MOC), comprising the extrastriate visual cortex (Table II, Fig. 2). Post hoc analysis was conducted following motion scrubbing (i.e., removing the frames with high motion as well as 1 frame prior to and 2 frames following each of these high motion frames; see [Power et al., 2012]), which identified GBC alterations largely in the same brain regions described above (data not shown).

To examine the relationship between GBC abnormalities and the severity of depression within the MDD group, we conducted a voxel-wise correlation analysis limited to under or over-connected voxels (relative to HC). This approach has the advantage of specifically examining "abnormal" voxels, thereby reducing the risk of a type II error. We observed an inverse association between GBC and MADRS score within the VMPFC/sgACC (MNI: 2, 30, −16; $r = -0.44$), although this finding did not survive correction for multiple comparisons. We did not find a relationship between age, anxiety, number of prior antidepressant treatments, or number of depressive episodes and GBC within the MDD group. There was a weak inverse association between GBC and duration of illness within the left temporal pole (TP) and left MOC clusters that did not survive correction for multiple comparisons.

Global Connectivity of the VMPFC in Major Depression

Consistent with our whole-brain analysis, there was significantly reduced GBC in the MDD compared to HC group within the anatomically defined bilateral VMPFC (SMD = 0.82, $t = 3.4$, $P = 0.001$). Within the MDD group, there was an inverse association between GBC and MADRS score that remained significant following correction for multiple comparisons ($r = -0.47$, $P = 0.0005$; Fig. 3). Patients with the highest symptom severity had the lowest GBC within the VMPFC. The association between GBC and depression severity remained significant after controlling for age and gender ($r = -0.45$, $P = 0.001$).

DISCUSSION

In the current study, MDD was characterized by reduced GBC within multiple regions of PFC, including VMPFC, MPFC, ACC, and DLPFC. The largest effect of reduced GBC in the PFC was centered within the sgACC extending into VMPFC bilaterally and higher depression severity was linked to low GBC uniquely within the

TABLE II. Whole-brain global connectivity in major depressive disorder

Region	Anatomical landmark	Hemisphere	Coordinates (peak)	Cluster size (mm^3)	Effect size	t	P^a
MDD < HC							
sgACC, VMPFC	SCG (BA 25, 11)	R[b]	6, 14, −20	1650	−1.48	−6.1	<0.000001
DMPFC	SFG (BA 8, 9)	R	4, 24, 52	1074	−1.25	−5.2	0.000002
dACC	SFG (BA 9, 32)	L	−6, 34, 28	926	−1.15	−4.8	0.000009
LPFC	MFG (BA 46)	R	42, 44, 10	570	−1.30	−5.3	0.000001
VLPFC	IFG (BA 47)	L	−46, 32, −4	360	−1.10	−4.5	0.00002
DLPFC	MFG (BA 9)	L	−32, 38, 32	338	−1.10	−4.4	0.00003
DMPFC	SFG (BA 46, 48)	L	−4, 10, 56	320	−1.27	−5.3	0.000001
DLPFC	MFG (BA 46)	R	46, 34, 24	234	−1.15	−4.7	0.00001
TP	STG (BA 38)	L	−46, 8, −18	184	−1.05	−4.3	0.00005
MDD > HC							
	Cerebellum	L	−30, −80, −24	3774	1.37	5.7	<0.000001
EVC	MOC (BA 18, 19)	L	−38, −86, 10	324	1.14	4.7	0.00001

Clusters demonstrating group effects are listed in descending order of cluster size. Effect size reflects standardized mean difference based on Hedge's g.

[a]Uncorrected P values are reported (all reported clusters survived correction based on $P < 0.05$ whole-brain cluster-level correction ($Z > 2.58$, extent 88 voxels).

[b]Cluster extends from right to left hemisphere.

Abbreviations: BA, Brodmann Area; dACC, dorsal anterior cingulate cortex; EVC, extrastriate visual cortex; IFG, inferior frontal gyrus; HC, healthy control; LPFC, lateral prefrontal cortex; MFG, middle frontal gyrus; MOC, middle occipital cortex; SFG, superior frontal gyrus; SCG, subcallosal gyrus; STG, superior temporal gyrus; TP, temporal pole; VMPFC, ventromedial prefrontal cortex.

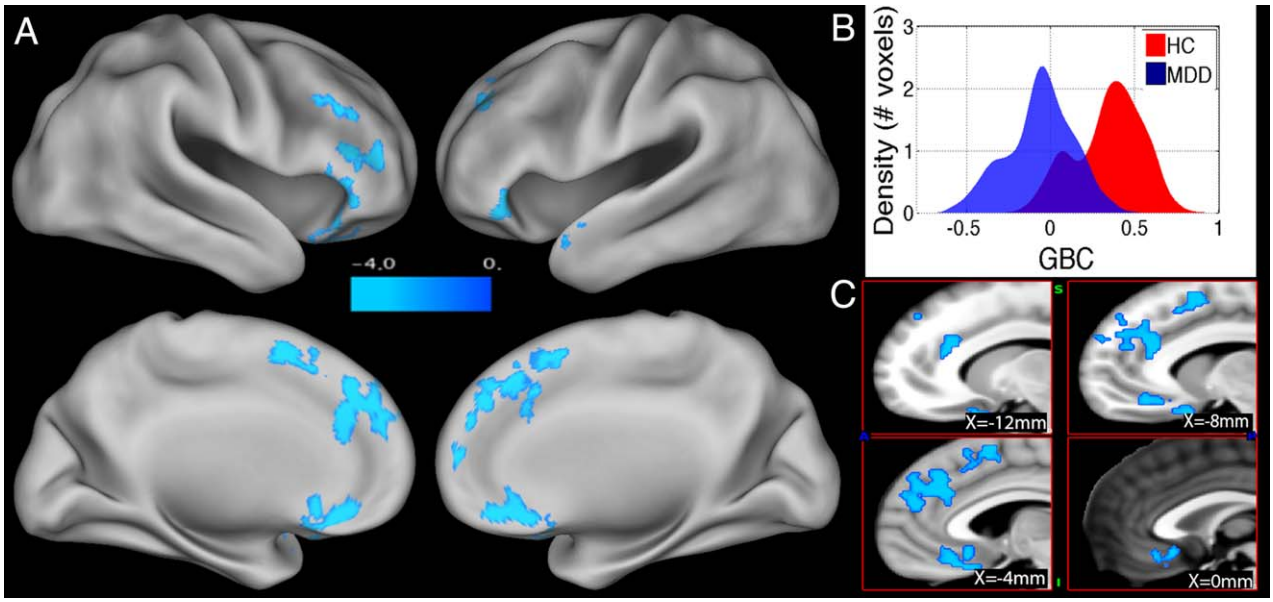

Figure 1.

Reduced global brain connectivity in major depressive disorder. (**A**) Clusters where MDD patients showed significantly less GBC compared to healthy volunteers. (**B**) Histogram of GBC reduction in major depressive disorder relative to healthy volunteers across all voxels showing significant group differences. (**C**) Zoomed in view of clusters of significant dysconnectivity in major depressive disorder relative to healthy volunteers within the medial prefrontal cortex and subgenual anterior cingulate. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

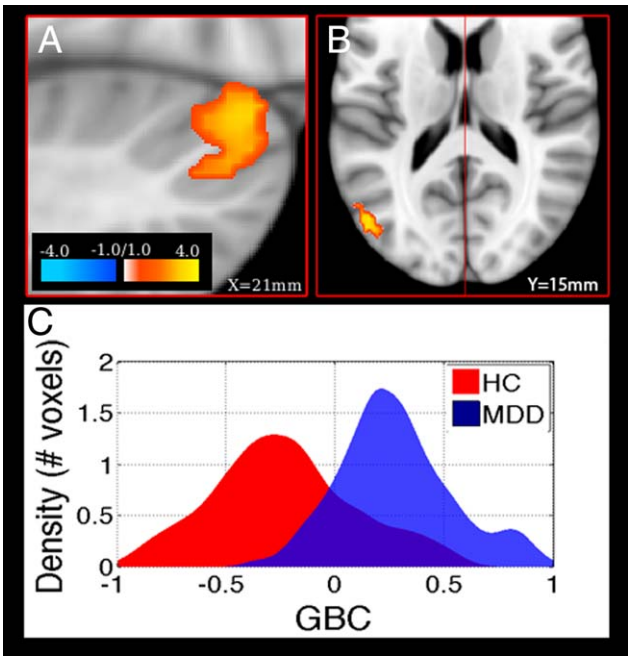

Figure 2.

Increased global brain connectivity in major depressive disorder. (**A**) Significantly increased GBC in major depressive disorder compared to healthy volunteers within the posterior cerebellum. (**B**) Significantly increased GBC in major depressive disorder compared to healthy volunteers within the left extrastriate visual cortex. (**C**) Histogram of GBC increases in major depressive disorder relative to healthy volunteers across all voxels showing significant group differences. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

VMPFC. In addition, we found that MDD was characterized by increased GBC within the cerebellum and visual processing cortex, although these increases were not associated with symptom severity.

The GBC metric used in the current study reliably identifies brain regions of high connectivity, potentially reflecting coordinating hubs in large-scale brain networks [Cole et al., 2010]. Our finding of reduced GBC of the medial and lateral PFC in MDD is consistent with decreased participation or coordination of these critical integrative regions within their associated networks. The VMPFC and sgACC in particular are key regions within both the DMN and the salience network [Seeley et al., 2007]. Including medial PFC structures more broadly, the PCC and regions of parietal cortex, the DMN supports internally directed and self-referential thought and has been implicated in pathological rumination in MDD [Johnson et al., 2009]. Previous studies indicate increased activity or failure to reduce activity in these regions in MDD in response to a cognitive or affective challenge [Sheline et al., 2009]. Resting state studies utilizing seed based or ICA approaches suggest increased contribution of the VMPFC or ACC to the DMN in MDD [Kaiser et al., 2015]. Notably, our finding of reduced GBC in this region is consistent with and extends prior studies since reduced GBC suggests reduced coordination or coherence with other brain structures and networks. Reduced global connectivity of sgACC/VMPFC is consistent with a pathological autonomy of this network hub and its attendant functional consequences of dominating self-referential mental processes and a relative resistance to regulation by cognitive control systems.

We observed reduced GBC within regions of lateral PFC and DMPFC, key regions within a cognitive control network that are known to participate in emotion regulation [Cole and Schneider, 2007; Ochsner and Gross, 2005]. Prior activation studies have reported under activation of the DLPFC in patients with depression, and enhanced DLPFC activation following antidepressant treatment [Siegle et al., 2007]. Our primary findings of reduced GBC within lateral and medial PFC regions are consistent with reduced cognitive flexibility, poor concentration, and reduced emotion regulation capacity associated with MDD [Gotlib and Joormann, 2010; Murrough et al., 2011]. Interestingly, Anticevic et al. also reported reduced medial PFC GBC in patients with bipolar disorder compared to healthy volunteers using an analytic method very similar to the method used in the current study [Anticevic et al., 2013]. In that study, that majority of patients were receiving medication at the time of scan, and the effect of diagnosis on GBC was driven exclusively by the patients with a history of psychosis. While we likewise observed reduced GBC within overlapping regions of medial PFC, our patients were all unipolar, unmedicated at the time of scan, and without a history of psychosis. Although it is unclear why precisely the patients without a history of psychosis did not show reduced medial PFC connectivity in the Anticevic et al. study, the two studies are broadly congruent in their implication of medial PFC circuitry as critical to the pathophysiology of mood disorders.

While the bulk of our findings consisted of reduced GBC localized to components of the PFC, we also found increased GBC within the dorsal lateral part of the posterior lobe of the cerebellum in MDD compared to HC. The cerebellum is classically involved in motor learning and coordination, although the important role of the cerebellum in cognitive and affective processes has gained increased recognition [Paradiso et al., 1999]. The cerebellum has a preponderance of reciprocal connections with subcortical regions important for emotion and autonomic regulation and several studies have linked enhanced cerebellar functioning during an affective challenge specifically to negative affect in humans [Paradiso et al., 1999]. A seed-based connectivity analysis in geriatric depression demonstrated reduced cerebellar connectivity with prefrontal regions and increased connectivity with basal ganglia [Alalade et al., 2011]. A more recent seed-based connectivity study focusing on the DMN found increased connectivity between the cerebellum and components of the DMN in MDD compared to healthy volunteers

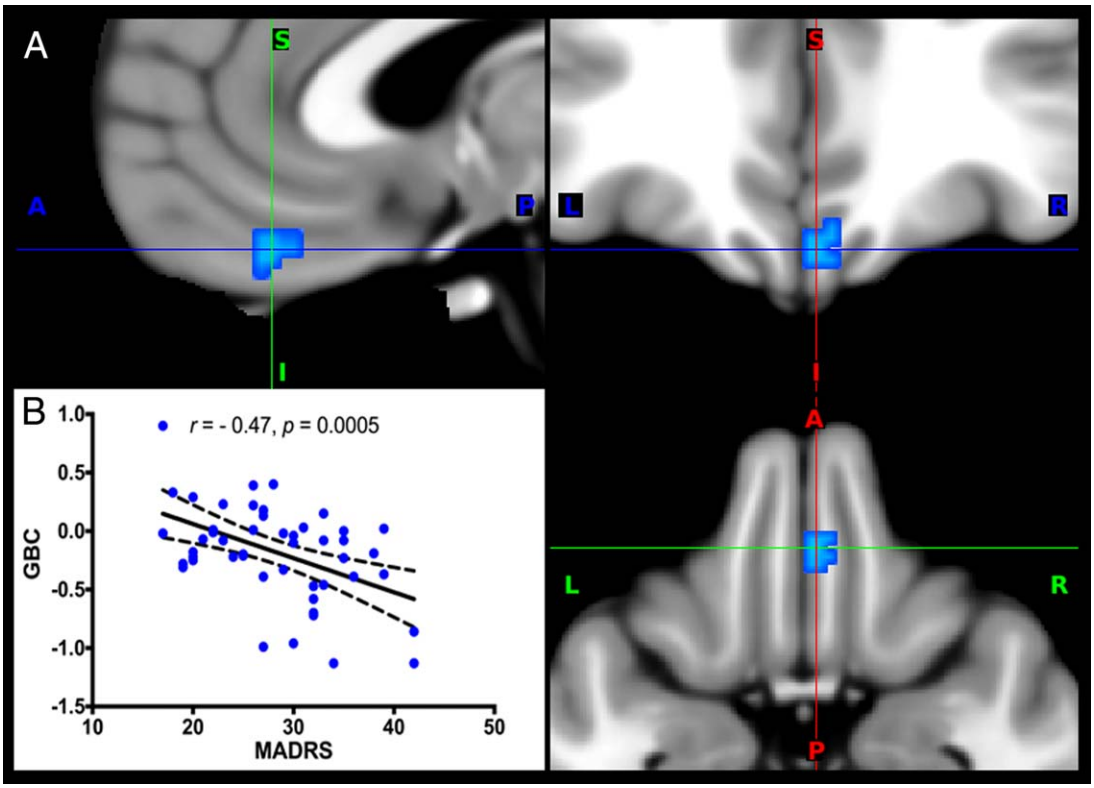

Figure 3.

Global brain connectivity within the ventromedial prefrontal cortex in major depressive disorder and association with symptom severity. (**A**) Cluster depicts significantly reduced GBC in major depressive disorder patients relative to healthy volunteers within an anatomically defined bilateral VMPFC. (**B**) Inverse linear correlation between GBC within the VMPFC and depressive severity as measured by Montgomery-Åsberg Depression Rating Scale score. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

[Guo et al., 2015]. Although the functional significance of the increased cerebellar GBC in our study remains speculative, hyper-connectivity of phylogenetically old circuitry subserving autonomic regulation is consistent with neurovegetative alterations and exaggerated stress responses observed in MDD.

The second region that demonstrated greater GBC in MDD compared to HC in our study was extrastriate visual cortex. As a sensory processing region, the visual cortex is often not included in neurocircuit models of MDD. Prior studies, however, have suggested that components of the visual system may be over-responsive to negative stimuli in MDD, consistent with a negative perceptual bias in MDD [Keedwell et al., 2010; Surguladze et al., 2005]. Studies have also linked neural responses within the visual cortex to treatment outcomes in MDD [Furey et al., 2013; Keedwell et al., 2010]. Within this context, our finding of heighten GBC within the visual cortex in MDD may reflect a pathological broadening of the interaction between the visual system and other brain systems, which potentially contributes to a negative perceptual bias in MDD.

As noted above, our GBC approach provides a unique assessment of whole-brain functional coherence appropriate for examining the large-scale functional organization of the brain and differences in large-scale organization as a function of disease. Seed-based approaches have the potential to bias outcomes since analyses are inherently restricted to the selected regions. Likewise, meta-analyses utilizing seed-based studies inherit the same limitations. A recent study utilizing a FC metric related to degree centrality within the context of graph theory found reduced FC within multiple PFC regions, including the VMPFC, in the MDD compared to the HC group [Wang et al., 2014]. Our results are largely consistent with these findings and extend them by utilizing a validated measure of GBC, including MDD patients free of concomitant antidepressant medication, and utilizing a larger sample size. Additional difference between our study and that of Wang et al is that the prior study utilized an arbitrary threshold of $r = 0.2$, which excluded low or negative correlations, potentially ignoring functionally and clinically relevant connections [Cole et al., 2010]. Several other studies have

utilized approaches based on graph theory to investigate large-scale network organization in MDD [Gong and He, 2015]. These studies provide initial evidence for perturbations in network organization in MDD beyond what is assessed using metrics of coherence or centrality, including modular structure [Lord et al., 2012] and small-world efficiency [Zhang et al., 2011].

The current study methods do not allow the interrogation of the underlying molecular processes that give rise to the observed prefrontal dysconnectivity in MDD. However, it is important to highlight that these findings are congruent with the well-described loss of synaptic connectivity in animal models of depression and prolonged stress [Duman and Aghajanian, 2012]. Repeated stress exposure in rodents alters synaptic homeostasis and results in reductions in synaptic plasticity and decreased synaptic connectivity within the medial PFC, which drive depressive behavior [Li et al., 2010]. Behavioral antidepressant effects following treatment with classic antidepressants or ketamine—a putative rapidly acting antidepressant—are dependent on increases in synaptic structure and function, indicating that this form of neuroplasticity represents a state-dependent effect and that amelioration of deficits in synaptic plasticity may be a mechanism of antidepressant action [Abdallah et al., 2015]. While still speculative, our observed reductions in PFC GBC in human depression may reflect underlying deficits in synaptic plasticity and connectivity, akin to what is observed in animal stress models of depression. Alternations within the hypothalamic-pituitary-adrenal (HPA) axis may also contribute to the observed reductions in cortical FC in patients with depression via the impact of glucocorticoids on neuronal plasticity [McEwen et al., 2015; Pariante and Lightman, 2008]. Finally, elevated levels of pro-inflammatory cytokines or other immune factors reported in patients with depression may contribute maladaptive changes in mood-related neurocircuits via both HPA axis-dependent and HPA axis-independent mechanisms [Felger et al., in press; Hodes et al., 2014, 2015].

Our study has several limitations. This cross-sectional study included only patients with MDD in a current major depressive episode, and therefore, we are unable to distinguish between state and trait effects. Likewise, longitudinal studies of high-risk individuals would be required to disentangle predisposing vulnerabilities from consequences of the illness. Although GBC is a simple, potentially powerful tool to identify brain regions with impaired overall coherence, GBC cannot capture connectivity impairments between two regions with opposing effects, for example, if one region increased correlation by 0.2, while the other decreased correlation by 0.2. Finally, the specific functional consequences of our findings require further study. Our primary finding of reduced GBC within the PFC in MDD spanned several anatomical regions known to participate in multiple large-scale networks, including the DMN, an executive/cognitive control network, and an affective or salience network. Future studies utilizing more detailed behavioral evaluations of network-specific functions, such as self-directed processing, emotion perception and threat detection, and emotion regulation will be required to provide a finer mapping of disordered connectivity to behavioral dysfunction in MDD.

In conclusion, we found that MDD was characterized by robust reductions in global functionally connectivity of the sgACC, VMPFC, and other PFC regions and that low levels of connectivity were linked to the severity of depressive symptoms. These data are consistent with the loss of synaptic connectivity in animal models of depression and suggest a potential human biomarker of depressive pathology. Future studies will be required to determine the molecular causes and functional consequences of these changes in depressive disorders.

ACKNOWLEDGMENTS

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or other organizations. The sponsors had no role in the design or conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Drs. Murrough and Abdallah had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Disclosures: In the past 3 years, Dr. Murrough has served on advisory boards for Janssen Research and Development and Genentech, has provided consultation services for ProPhase, LLC and Impel Neuropharma and has received research support from Janssen and Avanir Pharmaceuticals; he is named on a patent pending for neuropeptide Y as a treatment for mood and anxiety disorders and on a patent pending for the combination of ketamine and lithium for suicidal ideation. He is an employee of the Icahn School of Medicine at Mount Sinai and has received external funding from the National Institutes of Health, the Brain and Behavioral Research Foundation, and the American Foundation for Suicide Prevention. Dr. Abdallah has served on advisory boards for Genentech. He is an employee of the Yale School of Medicine and has received funding from the National Institutes of Health, the Brain and Behavioral Research Foundation, the VA National Center for PTSD, the Department of Defense, the American Psychiatric Foundation, and the Robert E. Leet and Clara Guthrie Patterson Trust. Dr. Iosifescu has consulted for Avanir, CNS Response, INSYS Therapeutics, Lundbeck, Otsuka, Servier, Sunovion and he has received grant/research support through Mount Sinai School of Medicine from Alkermes, Astra Zeneca, Brainsway, Euthymics Bioscience Inc, Neosync, Roche and Shire. Dr. Krystal is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance,

Inc., FORUM Pharmaceuticals, Janssen Research & Development, Lundbeck Research USA, Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Medical Sciences; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued Sep 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued Jul 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression. U.S. Application No. 14/197,767 (filed on Mar 5, 2014); U.S. application or Patent Cooperation Treaty international application No. 14/306,382 (filed on Jun 17, 2014). Dr. Dennis Charney (Dean of Icahn School of Medicine at Mount Sinai), and Icahn School of Medicine at Mount Sinai have been named on a use patent on ketamine for the treatment of depression. Dr. Charney and Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine were to gain approval for the treatment of depression. Dr. Charney is named on a patent pending for ketamine as a treatment for PTSD and for neuropeptide Y as a treatment for mood and anxiety disorders; he has received funding from the U.S. Department of Defense, NIH, NIH/NIMH, NARSAD, USAMRAA; he has severed on the scientific advisory board for the Institute of Medicine Committee on DHS Workforce Resilience and on the editorial board of CNS Spectrums. All other authors declare no conflict of interest.

REFERENCES

Abdallah CG, Sanacora G, Duman RS, Krystal JH (2015): Ketamine and rapid-acting antidepressants: A window into a new neurobiology for mood disorder therapeutics. Annu Rev Med 66:509–523.

Alalade E, Denny K, Potter G, Steffens D, Wang L (2011): Altered cerebellar-cerebral functional connectivity in geriatric depression. PLoS One 6:e20035.

Anticevic A, Brumbaugh MS, Winkler AM, Lombardo LE, Barrett J, Corlett PR, Kober H, Gruber J, Repovs G, Cole MW, Krystal JH, Pearlson GD, Glahn DC (2013): Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history. Biol Psychiatry 73:565–573.

Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, Repovs G, Cole MW, Bednarski S, Krystal JH, Bloch MH, Li CS, Pittenger C (2014): Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. Biol Psychiatry 75:595–605.

Anticevic A, Hu X, Xiao Y, Hu J, Li F, Bi F, Cole MW, Savic A, Yang GJ, Repovs G, Murray JD, Wang XJ, Huang X, Lui S, Krystal JH, Gong Q (2015): Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. J Neurosci 35:267–286.

Bullmore E, Sporns O (2009): Complex brain networks: Graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198.

Chen JE, Glover GH (2015): BOLD fractional contribution to resting-state functional connectivity above 0.1 Hz. Neuroimage 107:207–218.

Cole MW, Schneider W (2007): The cognitive control network: Integrated cortical regions with dissociable functions. Neuroimage 37:343–360.

Cole MW, Pathak S, Schneider W (2010): Identifying the brain's most globally connected regions. Neuroimage 49:3132–3148.

Cole MW, Yarkoni T, Repovs G, Anticevic A, Braver TS (2012): Global connectivity of prefrontal cortex predicts cognitive control and intelligence. J Neurosci 32:8988–8999.

Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS; Scientific Advisory Board and the Executive Committee of the Grand Challenges on Global Mental Health, Anderson W, Dhansay MA, Phillips A, Shurin S, Walport M, Ewart W, Savill SJ, Bordin IA, Costello EJ, Durkin M, Fairburn C, Glass RI, Hall W, Huang Y, Hyman SE, Jamison K, Kaaya S, Kapur S, Kleinman A, Ogunniyi A, Otero-Ojeda A, Poo MM, Ravindranath V, Sahakian BJ, Saxena S, Singer PA, Stein DJ, (2011): Grand challenges in global mental health. Nature 475:27–30.

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.

Duman RS, Aghajanian GK (2012): Synaptic dysfunction in depression: Potential therapeutic targets. Science 338:68–72.

Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, Miller AH: Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry (in press).

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. Magn Reson Med 33:636–647.

Fox MD, Raichle ME (2007): Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711.

Furey ML, Drevets WC, Hoffman EM, Frankel E, Speer AM, Zarate CA Jr (2013): Potential of pretreatment neural activity in the visual cortex during emotional processing to predict treatment response to scopolamine in major depressive disorder. JAMA Psychiatry 70:280–290.

Gohel SR, Biswal BB (2015): Functional integration between brain regions at rest occurs in multiple-frequency bands. Brain Connect 5:23–34.

Gong Q, He Y (2015): Depression, neuroimaging and connectomics: A selective overview. Biol Psychiatry 77:223–235.

Gotlib IH, Joormann J (2010): Cognition and depression: Current status and future directions. Annu Rev Clin Psychol 6:285–312.

Guo W, Liu F, Liu J, Yu M, Zhang Z, Liu G, Xiao C, Zhao J (2015): Increased cerebellar-default-mode-network connectivity in drug-naive major depressive disorder at rest. Medicine (Baltimore) 94:e560.

Hamilton M (1959): The assessment of anxiety states by rating. Br J Med Psychol 32:50–55.

Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH (2012): Functional neuroimaging of major depressive

disorder: A meta-analysis and new integration of base line activation and neural response data. Am J Psychiatry 169:693–703.

Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL, Lebonte B, Horn S, Lapidus KA, Stelzhammer V, Wong EH, Bahn S, Krishnan V, Bolanos-Guzman CA, Murrough JW, Merad M, Russo SJ (2014): Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. Proc Natl Acad Sci USA 111:16136–16141.

Hodes GE, Kana V, Menard C, Merad M, Russo SJ (2015): Neuroimmune mechanisms of depression. Nat Neurosci 18:1386–1393.

Johnson MK, Nolen-Hoeksema S, Mitchell KJ, Levin Y (2009): Medial cortex activity, self-reflection and depression. Soc Cogn Affect Neurosci 4:313–327.

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015): Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72:603–611.

Keedwell PA, Drapier D, Surguladze S, Giampietro V, Brammer M, Phillips M (2010): Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. J Affect Disord 120:120–125.

Lee HL, Zahneisen B, Hugger T, LeVan P, Hennig J (2013): Tracking dynamic resting-state networks at higher frequencies using MR-encephalography. Neuroimage 65:216–222.

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS (2010): mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.

Lord A, Horn D, Breakspear M, Walter M (2012): Changes in community structure of resting state functional connectivity in unipolar depression. PLoS One 7:e41282.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH (2005): Deep brain stimulation for treatment-resistant depression. Neuron 45:651–660.

McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, Nasca C (2015): Mechanisms of stress in the brain. Nat Neurosci 18:1353–1363.

Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.

Murrough JW, Iacoviello B, Neumeister A, Charney DS, Iosifescu DV (2011): Cognitive dysfunction in depression: Neurocircuitry and new therapeutic strategies. Neurobiol Learn Mem 96:553–563.

Ochsner KN, Gross JJ (2005): The cognitive control of emotion. Trends Cogn Sci 9:242–249.

Paradiso S, Johnson DL, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, Hichwa RD (1999): Cerebral blood flow changes associated with attribution of emotional valence to pleasant, unpleasant, and neutral visual stimuli in a PET study of normal subjects. Am J Psychiatry 156:1618–1629.

Pariante CM, Lightman SL (2008): The HPA axis in major depression: Classical theories and new developments. Trends Neurosci 31:464–468.

Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE (2012): Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59:2142–2154.

Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE (2014): Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84: 320–341.

Price JL, Drevets WC (2010): Neurocircuitry of mood disorders. Neuropsychopharmacology 35:192–216.

Saad ZS, Reynolds RC, Jo HJ, Gotts SJ, Chen G, Martin A, Cox RW (2013): Correcting brain-wide correlation differences in resting-state FMRI. Brain Connect 3:339–352.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007): Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356.

Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, Mintun MA, Wang S, Coalson RS, Raichle ME (2009): The default mode network and self-referential processes in depression. Proc Natl Acad Sci USA 106:1942–1947.

Sheline YI, Price JL, Yan Z, Mintun MA (2010): Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci USA 107:11020–11025.

Siegle GJ, Thompson W, Carter CS, Steinhauer SR, Thase ME (2007): Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent features. Biol Psychiatry 61:198–209.

Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, Williams SC, Phillips ML (2005): A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol Psychiatry 57: 201–209.

Van Dijk KR, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL (2010): Intrinsic functional connectivity as a tool for human connectomics: Theory, properties, and optimization. J Neurophysiol 103:297–321.

Wang L, Dai Z, Peng H, Tan L, Ding Y, He Z, Zhang Y, Xia M, Li Z, Li W, Cai Y, Lu S, Liao M, Zhang L, Wu W, He Y, Li L (2014): Overlapping and segregated resting-state functional connectivity in patients with major depressive disorder with and without childhood neglect. Hum Brain Mapp 35:1154–1166.

Zhang J, Wang J, Wu Q, Kuang W, Huang X, He Y, Gong Q (2011): Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biol Psychiatry 70:334–342.