Original Investigation | META-ANALYSIS

Large-Scale Network Dysfunction in Major Depressive Disorder
A Meta-analysis of Resting-State Functional Connectivity

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IMPORTANCE Major depressive disorder (MDD) has been linked to imbalanced communication among large-scale brain networks, as reflected by abnormal resting-state functional connectivity (rsFC). However, given variable methods and results across studies, identifying consistent patterns of network dysfunction in MDD has been elusive.

OBJECTIVE To investigate network dysfunction in MDD through a meta-analysis of rsFC studies.

DATA SOURCES Seed-based voxelwise rsFC studies comparing individuals with MDD with healthy controls (published before June 30, 2014) were retrieved from electronic databases (PubMed, Web of Science, and EMBASE) and authors contacted for additional data.

STUDY SELECTION Twenty-seven seed-based voxel-wise rsFC data sets from 25 publications (556 individuals with MDD and 518 healthy controls) were included in the meta-analysis.

DATA EXTRACTION AND SYNTHESIS Coordinates of seed regions of interest and between-group effects were extracted. Seeds were categorized into seed-networks by their location within a priori functional networks. Multilevel kernel density analysis of between-group effects identified brain systems in which MDD was associated with hyperconnectivity (increased positive or reduced negative connectivity) or hypoconnectivity (increased negative or reduced positive connectivity) with each seed-network.

RESULTS Major depressive disorder was characterized by hypoconnectivity within the frontoparietal network, a set of regions involved in cognitive control of attention and emotion regulation, and hypoconnectivity between frontoparietal systems and parietal regions of the dorsal attention network involved in attending to the external environment. Major depressive disorder was also associated with hyperconnectivity within the default network, a network believed to support internally oriented and self-referential thought, and hyperconnectivity between frontoparietal control systems and regions of the default network. Finally, the MDD groups exhibited hypoconnectivity between neural systems involved in processing emotion or salience and midline cortical regions that may mediate top-down regulation of such functions.

CONCLUSIONS AND RELEVANCE Reduced connectivity within frontoparietal control systems and imbalanced connectivity between control systems and networks involved in internal or external attention may reflect depressive biases toward internal thoughts at the cost of engaging with the external world. Meanwhile, altered connectivity between neural systems involved in cognitive control and those that support salience or emotion processing may relate to deficits regulating mood. These findings provide an empirical foundation for a neurocognitive model in which network dysfunction underlies core cognitive and affective abnormalities in depression.

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Major depressive disorder (MDD) is a psychiatric illness with devastating social, personal, and medical consequences.[1,2] Moreover, MDD is ubiquitous, affecting more than 16 million people in the United States[3] and 350 million people worldwide[4] each year. Although significant progress has been made in understanding MDD and developing treatments, much is unknown about the pathophysiology of the disease, and rates of recurrence remain high.[5] Exploring the neurobiological signature of MDD from new perspectives has the potential to transform current conceptualizations of the disease and sharpen the search for treatment targets.[6]

Researchers have become increasingly interested in the role of abnormal communication among large-scale functional brain networks in the pathophysiology of MDD.[6,7] Functional networks can be defined as distributed sets of brain regions that exhibit correlated activity at rest, that is, resting-state functional connectivity (rsFC), or during task performance.[8,9] The recruitment of a highly synchronized network, in response to task demands or at rest, is believed to reflect distinct cognitive or emotional processes or mental states (eg, mind-wandering),[10-12] although these relationships are complex and remain a rapidly evolving field of study. Of particular relevance are networks putatively related to processes affected in depression, such as the frontoparietal network (FN), involved in top-down regulation of attention and emotion; the default network (DN) and the dorsal attention network (DAN), involved in internally or externally oriented attention, respectively; and the affective network (AN) and the ventral attention network (VAN) (sometimes together called the salience network[13]), involved in processing emotion or monitoring for salient events.[14-16] For example, abnormal communication within the FN may underlie deficits in cognitive control, which are commonly observed in depression[17] and may contribute to symptoms such as difficulty concentrating or regulating emotions. Likewise, aberrant communication between the FN and DN may reflect ongoing rumination or an underlying bias for control systems to allocate resources toward internal thoughts at the cost of engaging with the external world.[18] Hence, specific patterns of network dysfunction may contribute to core deficits in cognitive and affective functioning that are believed to underlie clinical symptoms.

Investigation of functional networks has surged in recent years, in particular in the domain of rsFC. Initial findings support the view that MDD is characterized by abnormal rsFC,[19] but inconsistency in the location and nature of effects makes it difficult to unify this research. Variability across studies may emerge for several reasons, including small sample sizes or differences in the networks selected for study. For example, prior research using seed-based rsFC[20], the most common analytic strategy, varies considerably in the location of seed regions of interest (ROIs). Although a spatially extensive set of seed ROIs provides a comprehensive view of rsFC across the brain, organizing results into a coherent model of network functioning is challenging. A theoretically informed strategy for categorizing seed ROIs and related findings (eg, by the location of seed ROIs within functional networks) would help organize the diverse set of findings and allow for a direct test of replication across studies. Meta-analysis is arguably the most powerful tool for synthesizing this research because it is capable of evaluating whether effects are robust across differences in methodologic details and disentangling consistent effects from false-positive results.[21,22] However, although rsFC abnormalities related to MDD have been reviewed,[19] meta-analysis of this burgeoning literature has, to our knowledge, never been performed.

The present study aimed to fill this important gap by conducting a meta-analysis of seed-based rsFC studies and unifying findings in a neurocognitive model of depression. Primary analyses tested for consistency in the location of brain systems exhibiting depression-related hyperconnectivity or hypoconnectivity with seed ROIs, which in turn were categorized within a priori networks. On the basis of evidence for broad deficits in cognitive control in MDD,[17] it was predicted that seed ROIs located within the FN would exhibit reduced connectivity with other areas of the FN. In addition, on the basis of the central role of ruminative, self-referential thinking in cognitive models of depression,[23,24] it was predicted that seed ROIs located within the DN would exhibit increased connectivity with other DN regions and increased connectivity with prefrontal regions of the FN involved in directing attention. Secondary analyses tested whether rsFC abnormalities were moderated by seed anatomy or by demographic or clinical factors.

Methods

Literature Search

A comprehensive literature search was conducted in Web of Science, PubMed, and EMBASE for articles in press as of June 30, 2014, using the keywords *rest*(-ing), connect*(-ivity),* and *depress*(-ion, -ive)*. Manual searches were conducted within the reference sections of empirical and review articles and for publications that cited those articles. Original functional magnetic resonance imaging studies using whole-brain seed-based rsFC to compare individuals with MDD with a healthy control (HC) group were eligible for inclusion (other rsFC methods, such as independent components analysis, adopt a distinct statistical approach that cannot be aggregated with seed-based data). If a published study did not report whole-brain effects or did not provide seed ROI or peak effect coordinates, authors were contacted for this information. Exclusion criteria were as follows: (1) no HC group or no current MDD group; (2) non–seed-based method; (3) whole-brain results could not be retrieved or did not survive correction (meta-analyses of functional magnetic resonance imaging data test for consistency in the spatial location of significant effects across studies[22]; thus, only studies that reported group differences in rsFC were eligible for inclusion); (4) entirely overlapping sample and seed ROIs reported in another publication; or (5) seed ROI or peak effect coordinates could not be retrieved (eFigure in the Supplement). Publications reporting on the same sample but using different seed ROIs were coded as a single study; publications in which distinct MDD groups were each compared with a single HC group were coded as distinct studies, and supplementary analyses were conducted to address the issue of partial nonindependence.[25] These searches and inclusion criteria yielded a sample of 27 studies from 25 publications[26-50] that reported on 556 individuals with MDD and 518 healthy controls in the HC group (eTable 1 and eTable2 in the Supplement).

Data Extraction and Coding

The present meta-analysis was coordinate based,[21,22,51] with coordinates reflecting the locations of significant group differences in functional connectivity at the time series level. Data extraction and coding included the following. First, coordinates for the center of mass of each seed ROI (91 seeds) and the peak of each significant between-group effect (346 effects) were extracted for each study and converted to Montreal Neurological Institute space as needed.[52] If the seed ROI was an anatomical region from a mask or standard brain atlas, the center of mass was calculated to obtain a representative coordinate. Second, each seed ROI was categorized into a seed-network based on the location of its center of mass within a priori rsFC networks defined by a previous whole-brain network parcellation in 1000 participants[14-16] (eTable 3 in the Supplement). This network parcellation was selected given its full coverage of cortex, cerebellum, and striatum; its definition in a large sample; its replication across an independent sample; and its close correspondence with networks derived from alternative rsFC analytic strategies and task-based patterns of coactivation.[53,54]

Effects were also categorized based on the direction of effect (ie, hyperconnectivity or hypoconnectivity in MDD groups). In previous work, hyperconnectivity has been defined as larger positive or reduced negative rsFC in individuals with MDD compared with healthy controls; hypoconnectivity has been defined as larger negative or reduced positive rsFC in individuals with MDD compared with healthy controls. Because the distinction between enhanced and weakened connectivity was inconsistently reported in the studies reviewed, it was not possible to test these forms of rsFC abnormality separately. However, when reported in the original publication, patterns of abnormal rsFC related to stronger or weaker connectivity in individuals with MDD are noted in the Results.

Multilevel Kernel Density Analysis

Meta-analysis[22] was performed using the multilevel kernel density analysis toolbox (http://wagerlab.colorado.edu), a Matlab (MathWorks) toolbox that incorporates tools from Statistical Parametric Mapping (http://www.fil.ion.ucl.ac.uk/spm/). Coordinates for peak effects from each study and seed-network comparison were convolved with a spherical kernel (r = 15 mm[55,56]) and thresholded at a maximum value of 1, yielding an indicator map in which a value of 1 indicated a significant effect in the neighborhood and a value of 0 indicated no significant effect. Next, the density of effects across studies was computed by averaging the indicator maps, weighted by study sample size.[21] The resulting density maps showed the proportion of studies in which hyperconnectivity or hypoconnectivity with each seed-network was observed in MDD within 15 mm of each voxel. Differences between density maps were calculated to test for directional effects (eg, either consistent hyperconnectivity or hypoconnectivity in MDD; unless otherwise noted, all effects were specific to one direction).

A Monte Carlo simulation was performed to establish the familywise error rate threshold used to correct for multiple comparisons. In this simulation, the locations of significant effects from indicator maps were randomized within a gray-matter mask in 15 000 iterations, yielding an estimate of the maximum density of effects predicted to occur by chance. A familywise error rate threshold of $P < .05$ was met when the density statistic exceeded the maximum null in 95% of the Monte Carlo maps. Density maps can be thresholded based on *height* (density at that voxel exceeds the maximum expected over the entire brain by chance) or *extent* (density at multiple contiguous voxels exceeds the maximum expected in a cluster of that size by chance). Because these thresholds provide complementary information, both are reported. Findings are discussed in terms of *within-network abnormalities* (effects fall within the same functional network as seed ROIs) or *between-network abnormalities* (effects fall outside the functional network in which seed ROIs are located).

Post Hoc Analyses

Three categories of post hoc tests were conducted. First, jackknife analyses were conducted to assess whether the inclusion of any partially nonindependent study disproportionately affected the results.[25] To accomplish this, the density statistic for each significant cluster was iteratively recalculated leaving out each partially nonindependent study, and a χ^2 test or Fisher exact test was performed between the original density statistic and the leave-one-out density statistic. Because these analyses failed to reveal disproportionate effects of any individual study, results reported here include all studies. Second, Fisher exact tests were conducted to investigate whether a specific anatomical region contributed more strongly to a significant effect than other regions of the same network. Although the primary analytic approach of grouping regions into functional networks made meta-analysis possible by boosting power across studies, this network-level approach made the assumption that distinct regions within each functional network show similar abnormalities in MDD. Therefore, post hoc region-level analyses were conducted by calculating the likelihood of a particular effect for seeds in distinct anatomical regions of a functional network and testing the difference in effect likelihood among regions. Third, analyses were performed to investigate moderation of effects by clinical and demographic factors (eTable 1 in the Supplement), including severity of depression (mild, moderate, or severe[57-59]), medication status (medication use or no use of medication in the MDD group), or age (teen, adult, or elder). For these analyses, the proportion of studies within each clinical or demographic group reporting the effect was calculated, and differences in proportions were tested between groups.

Results

Within-Network Abnormalities

Hypoconnectivity Within the FN

Major depressive disorder was associated with hypoconnectivity between the FN seeds and bilateral posterior parietal cortex (PPC), regions involved in attending to goal-relevant stimuli or features of an internal representation[60] (**Figure 1**A and **Table**). Examining the original empirical studies revealed that, when reported, hypoconnectivity was related to weaker positive connectivity between the FN seeds and the PPC.[26,27] Specifically, the FN seeds in the dorsolateral prefrontal cortex (DLPFC) or cerebel-

Table. Results of the Meta-analysis of Resting-State Functional Connectivity in Major Depressive Disorder[a]

Seed-Network (and Thresholding)	Seed Anatomy	Effect Network	Effect Anatomy	x	y	z	Voxels	Maximum P
FN	Caudate, cerebellum, DLPFC							
MDD < HC (hb)		FN	Right PPC	44	−50	50	162	.54
MDD < HC (eb)		FN and DAN	Right PPC extending to SPL	46	−54	46	2074	.40
MDD < HC (eb)		FN and DAN	Left PPC extending to SPL	−42	−52	48	2285	.34
DN	ACC, caudate, cerebellum, hippocampus, IPL, MPFC, MTG, PCC							
MDD > HC (hb)		DN	Right hippocampus extending to MTG	38	−30	−6	148	.30
MDD > HC (eb)		DN	MPFC	−2	38	12	7456	.20
MDD > HC (hb)		FN	Left DLPFC	−42	26	32	90	.30
MDD > HC (eb)		FN	Left DLPFC	−38	26	36	784	.29
MDD > HC (eb)		FN	Left DLPFC	−34	34	36	1125	.18
MDD < HC (eb)		VAN	Midcingulate extending to thalamus and putamen	−2	4	22	2476	.26
AN	ACC, amygdala, NACC							
MDD < HC (eb)		DN	MPFC	−2	46	16	3118	.37
VAN	ACC, cerebellum, insula, putamen							
MDD < HC (eb)		FN, DN, visual network	Precuneus extending to PCC and occipital cortex	18	−66	34	6194	.32

Abbreviations: ACC, anterior cingulate cortex; AN, affective network; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal cortex; DN, default network; eb, extent based; FN, frontoparietal network; hb, height based; HC, healthy control; MDD, major depressive disorder; MPFC, medial prefrontal cortex; MTG, middle temporal gyrus; NACC, nucleus accumbens; VAN, ventral attention network.

[a] Coordinates are Montreal Neurological Institute standard stereotaxic spaces. Voxels indicate the number of 1 × 1 × 1-mm voxels. Maximum P is the maximum proportion of studies exhibiting the effect at the peak density weighted by sample size.

lum exhibited hypoconnectivity with the PPC, and post hoc testing indicated that seeds in the DLPFC were more likely than cerebellar seeds to exhibit hypoconnectivity with right PPC (likelihood ratio, 5.29; $P = .04$), although no differences were detected for the left PPC ($P = .53$). Hypoconnectivity within the FN was not moderated by age, depression severity, or medication status ($P > .05$ for all; eTable 4 and eTable 5 in Supplement).

Hyperconnectivity Within the DN

Major depressive disorder was characterized by hyperconnectivity between the DN seeds and regions of the hippocampus extending to the middle temporal gyrus and areas of the medial prefrontal cortex (MPFC) (Figure 1B). These areas are believed to support internal mentation (eg, self-referential thinking and affective decision making).[61] When reported in the original studies, within-DN hyperconnectivity was related to enhanced positive connectivity in MDD.[27,30,32,34,45] Post hoc testing failed to reveal differences in the likelihood of hyperconnectivity as a function of seed anatomy ($P > .05$; eTable 4 and eTable 5 in Supplement). Neither age nor depression severity predicted DN hyperconnectivity ($P > .05$; eTable 4 and eTable 5 in Supplement), although trends emerged for greater likelihood of hyperconnectivity in unmedicated than medicated MDD between the DN seeds and the hippocampus (likelihood ratio, 6.01; $P = .09$) or the MPFC (likelihood ratio, 3.18; $P = .12$).

Between-Network Abnormalities

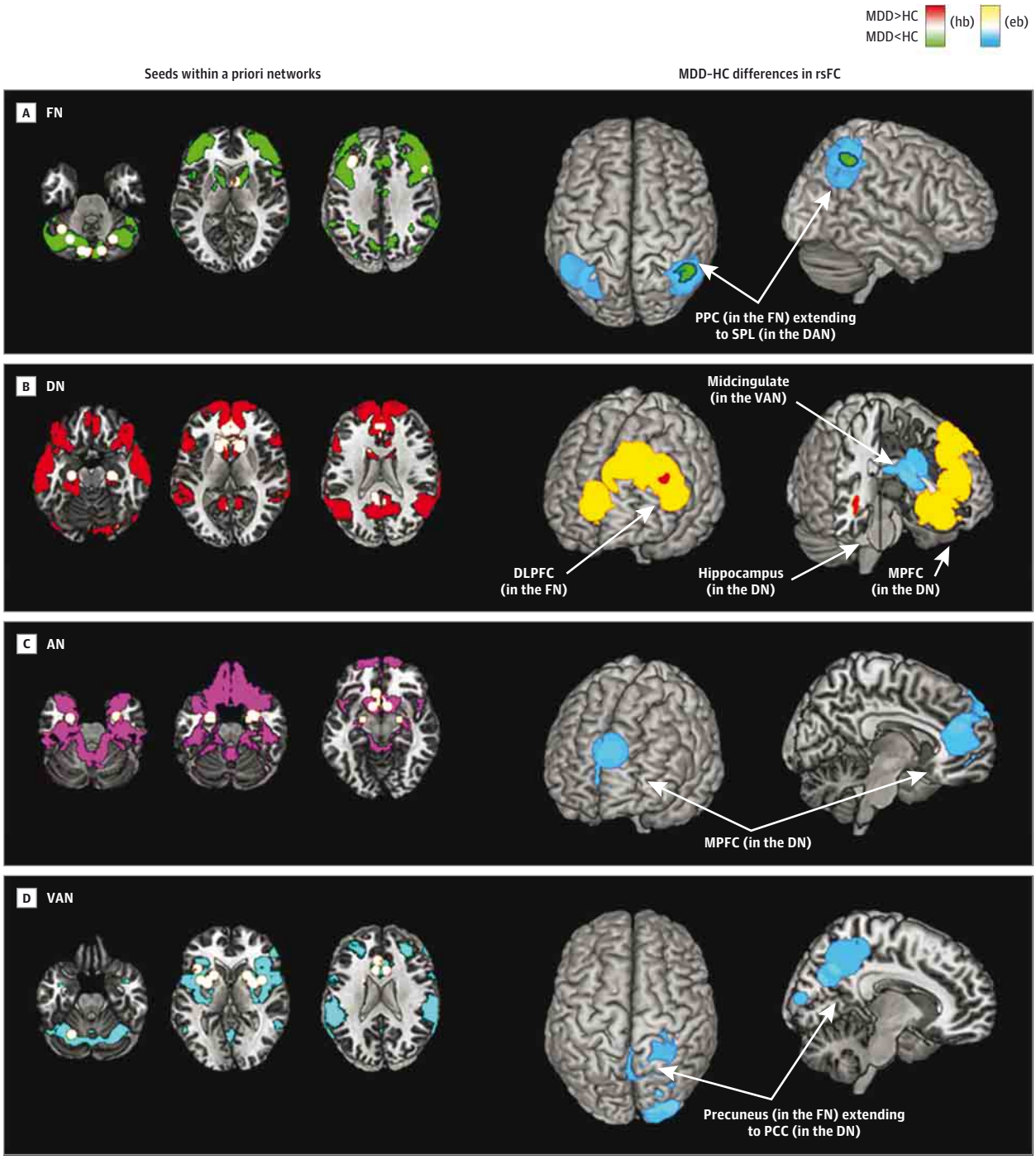
Altered Connectivity Between the FN and Regions of the DAN or DN Involved in Externally or Internally Oriented Attention

As reported above, MDD was associated with weaker rsFC between the FN seeds and regions of bilateral parietal cortex; these clusters extended to regions of the superior parietal lobule involved in attending to perceptual cues in the environment[60] that fall within the DAN (Figure 1A). In addition, MDD was associated with hyperconnectivity between the DN seeds and a region of left DLPFC believed to be critical for goal-directed regulation of attention and emotion[60,62-64] (Figure 1B). When reported, DN hyperconnectivity with lateral prefrontal regions was predominantly related to enhanced positive[32,34,45] but also weaker negative[31] connectivity in MDD. No differences were detected among anatomical regions of the DN in the likelihood of hyperconnectivity with DLPFC ($P > .05$; eTable 4 and eTable 5 in Supplement), and effects were not moderated by clinical or demographic variables ($P > .05$; eTable 4 and eTable 5 in Supplement).

Altered Connectivity Between the AN and Regions of the DN Involved in Mediating Emotion Regulation

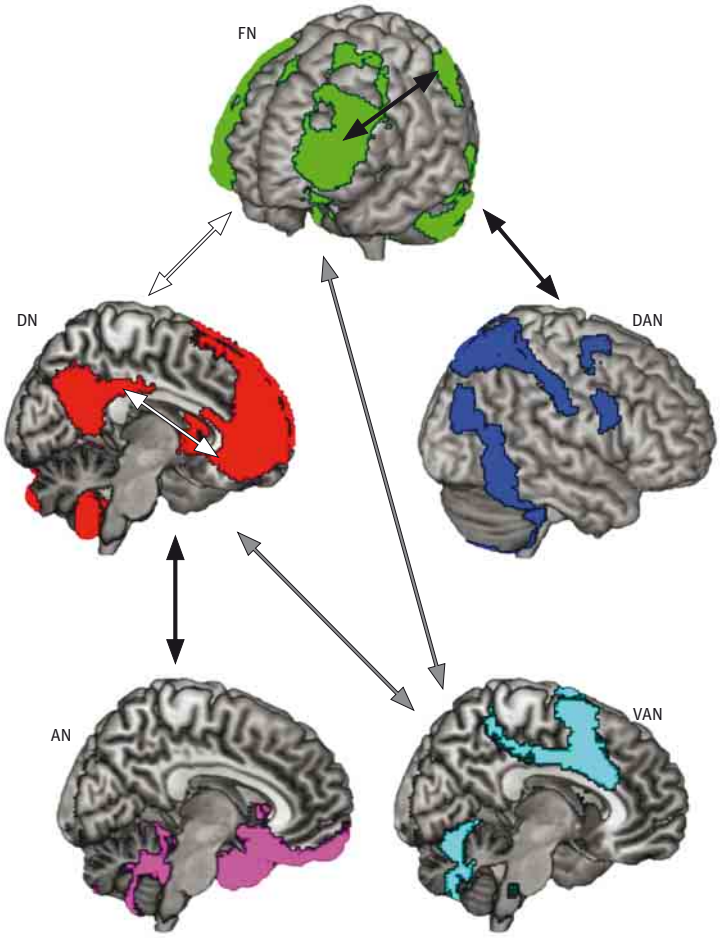
Hypoconnectivity was observed between the AN seeds and regions of the MPFC involved in mediating emotion regulation[65] (Figure 1C). When reported, hypoconnectivity was related to both weaker positive (between the nucleus accumbens and the

Figure 1. Meta-anaysis of Abnormal Resting-State Function Connectivity (rsFC) in Major Depressive Disorder (MDD)



Shown are seed regions of interest categorized by a priori functional network and brain regions in which abnormal rsFC was observed in MDD compared with healthy control (HC) individuals. A, Individuals with MDD exhibited hypoconnectivity within the frontoparietal network (FN) between the FN seeds and the posterior parietal cortex (PPC) and hypoconnectivity between the FN seeds and a region of superior parietal lobule (SPL) within the dorsal attention network (DAN). B, MDD was associated with hyperconnectivity within the default network (DN) between the DN seeds and the medial prefrontal cortex (MPFC) and hippocampus and hyperconnectivity between the DN seeds and the dorsolateral prefrontal cortex (DLPFC), a key hub of the FN. C, MDD was linked to hypoconnectivity between seeds in the affective network (AN) and regions of the MPFC. D, MDD was related to hypoconnectivity between the ventral attention network (VAN) seeds and the precuneus extending to the occipital and posterior cingulate cortex (PCC), although post hoc analyses also indicated hyperconnectivity between the VAN and posterior regions. Shown here are results of both height-based (hb) thresholding (proportion of studies reporting an effect at that voxel exceeds chance) and extent-based (eb) thresholding (proportion of studies reporting an effect at contiguous voxels exceeds chance). All results are significant at $P < .05$, corrected for familywise error rate.

Figure 2. A Neurocognitive Network Model of Major Depressive Disorder (MDD)



Reduced connectivity among regions of the frontoparietal network (FN) may underlie general deficits in cognitive control, whereas increased connectivity between the FN and default network (DN) and reduced connectivity between the FN and dorsal attention network (DAN) may reflect biases toward ruminative thoughts at the cost of attending to the external world. Meanwhile, reduced connectivity between the affective network (AN) and medial prefrontal cortex regions that mediate top-down regulation may reflect impaired ability to upregulate or downregulate emotions or arousal, whereas abnormal connectivity between the ventral attention network (VAN) and posterior regions may reflect altered or biased salience monitoring. Black arrows indicate hypoconnectivity in MDD; white arrows, hyperconnectivity in MDD; and gray arrows, generally abnormal (both hypoconnectivity and hyperconnectivity in MDD).

MPFC[35]) and enhanced negative (between the amygdala and the MPFC[46]) connectivity. The likelihood of MPFC hypoconnectivity did not differ among anatomical regions of the AN ($P > .05$; eTable 4 in Supplement) and was not moderated by clinical or demographic variables ($P > .05$; eTable 5 in Supplement).

Altered Connectivity Between the VAN and Regions of the FN or DN

Major depressive disorder was linked to hypoconnectivity between the VAN seeds and regions of the precuneus extending to the occipital and posterior cingulate cortex (Figure 1D), a functionally diverse set of regions involved in visual attention and internal thought.[60,61] There was no difference in likelihood of hyperconnectivity vs hypoconnectivity, suggesting generally abnormal connectivity between the VAN and posterior systems. Hypoconnectivity was also observed between the DN seeds and a region of the midcingulate extending to the thalamus and putamen (Figure 1B), areas involved in relaying information about salience and somatosensation.[13,16] When reported, such hypoconnectivity was related to weaker positive connectivity in MDD.[26,34] Post hoc analyses failed to reveal differences among anatomical seeds in the likelihood of abnormal rsFC ($P > .05$; eTable 4 in Supplement) or moderation by clinical or demographic variables ($P > .05$; eTable 5 in Supplement).

Discussion

The present study provides the first meta-analytic evidence, to our knowledge, that individuals with MDD exhibit abnormal connectivity within and between brain networks involved in internally (DN) or externally (DAN) oriented attention, processing of emotion (AN) or salience (VAN), and goal-directed regulation of these functions (FN) (**Figure 2**). These findings motivate a neurocognitive model in which network dysfunction is tightly linked to deficits regulating attention and mood.[6,7,23] In this model, reduced coordination among brain systems critical for cognitive control and altered communication between such control systems and other networks engaged for internal thought or emotional regulation may underlie the biased cognitive style and persistent negative mood that characterize MDD.

Reduced connectivity was observed in individuals with MDD among frontoparietal systems involved in cognitive control, and imbalanced connectivity was observed between control systems and regions engaged for externally directed attention or internal mentation. These findings converge with theoretical models in which depression is defined by the tendency to become mired in negative rumination,[24] which in turn stems from abnor-

mal communication among brain regions supporting goal-directed control of attention, emotion, and self-referential thought.[23] A coordinate-based search of prior studies (using BrainMap.org[66]) indicated that the same areas of the DLPFC that exhibited hypoconnectivity with external-attention systems and hyperconnectivity with internal-attention systems have been implicated in top-down control of cognitive functions.[62-64] Critically, overlapping regions of the DLPFC exhibit abnormal activity in depressed individuals exerting cognitive control.[67] Meanwhile, regions of the MPFC that were hyperconnected with other DN systems in the present meta-analysis have been implicated in functions such as self-referential thinking[68] and autobiographical memory retrieval[69] and are hyperactive in depressed individuals instructed to direct attention away from self-focused thinking.[70] Hence, the present patterns of poorly coordinated or imbalanced network functioning in MDD may reflect weaknesses in cognitive control that contribute to both general deficits in goal-directed behavior and specific biases toward internal thought at the cost of attending to the external world.

The present meta-analysis also revealed hypoconnectivity in MDD between the MPFC and limbic regions. This pattern, considered in light of reduced connectivity among frontoparietal systems, suggests abnormal communication among networks involved in emotion regulation. Previous research has indicated that successful upregulation or downregulation of emotion relies on communication between lateral prefrontal cortex regions responsible for top-down control, areas of MPFC that mediate regulation, and limbic regions involved in affective responses.[65,71] Altered activity and connectivity in this circuit have been observed in depressed individuals during emotion regulation tasks.[72] Here, abnormal connectivity between regulatory and affective systems appeared to stem from both blunted positive communication (between the MPFC and nucleus accumbens) and excessive negative communication (between the MPFC and amygdala). Thus, hypoconnectivity between the MPFC and regions of the AN may stem from abnormalities in multiple subnetworks engaged for distinct facets of emotional processing.

Although mixed, the present meta-analysis also provides evidence of hypoconnectivity between brain systems involved in processing salience and regions supporting cognitive control or internal mentation. The VAN is believed to play a role in signaling when to allocate resources to cognitive control systems in response to salient events or sensory experiences.[73] Accordingly, decreased connectivity between the VAN and control systems could reflect reduced reorientation of attention in response to salient cues. However, the observed pattern of altered VAN connectivity included both hypoconnectivity and hyperconnectivity, suggesting that the nature of the VAN abnormality in MDD may depend on additional factors. For example, previous research revealed that, in response to negative emotional distractors, depression was associated with hyperconnectivity between regions responsive to salience and regions involved in internal mentation.[18] Thus, the nature of communication between networks involved in salience and attention may be affected by the presence of environmental cues that correspond to the content of internal thoughts.

Two general patterns emerged in this meta-analysis. First, the sources of abnormal connectivity within seed-networks tended to be spatially distributed, highlighting the importance of considering anatomical regions within functional networks. However, given the low frequency of any single seed ROI implemented across studies, the absence of anatomical specificity should be interpreted with caution. Second, network abnormalities were similar across demographic and clinical groups. However, these analyses could only compare differences in the likelihood (but not magnitude) of network abnormalities between clinical or demographic groups and only for groups that were consistently identified across the original studies. Future studies investigating additional clinical constructs will provide a more nuanced view of rsFC in depression.

Several limitations warrant attention and suggest directions for future research. First, the present meta-analysis was necessarily limited to seed-based rsFC studies and seed ROIs selected by those studies (eTable 3 in the Supplement). Hence, particular networks and anatomical regions were better represented than others. In addition, it was not possible to include findings from studies that adopted alternative analytic methods (eg, independent components analysis). Because relatively few prior studies have implemented these methods with MDD samples (eTable 2 in the Supplement), separate meta-analyses for each analytic approach could not be conducted. However, as this literature increases, an important next step will be to test the replicability of rsFC abnormalities across other analytic methods and network parcellations.

Second, because rsFC is a rapidly evolving field, standards for data acquisition and processing varied considerably among the studies reviewed here (eTable 6 in the Supplement). Differences in motion correction or instructions to rest with eyes open vs closed may substantially affect results.[74] Unfortunately, it was not possible to test the moderating effects of such variables because of the low frequency of studies within methodologic categories, but these effects merit future investigation.

Third, an important question unanswered by the present meta-analysis is the extent to which aberrant functional connectivity could be related to structural abnormalities.[23] For example, decreased cortical thickness has been associated with altered functional connectivity in depressed adults.[75] Future studies that integrate structural and functional perspectives may provide a more comprehensive view of neurobiological abnormalities in mood disorders.

Fourth, it is unclear to what extent depression-related abnormalities in rsFC would persist during performance of other tasks. Resting-state functional connectivity appears to reflect both static (eg, related to anatomical connections) and dynamic (eg, related to changing goals or states of arousal) components, but the precise contribution of these components to rsFC is unknown.[74] Abnormal rsFC in MDD may be a transient consequence of internally biased attention, related to ruminating while resting in the scanner, rather than a persistent cause for biased or poorly controlled attention when engaged in other tasks. To disentangle these non–mutually exclusive possibilities, studies will be required that compare network functioning at rest and during tasks that challenge attention and mood regulation.

Conclusions

To our knowledge, this study provides the first meta-analytic evidence of large-scale network dysfunction in MDD, including imbalanced connectivity among networks involved in regulating attention to the internal or external world and decreased connectivity among networks involved in regulating or responding to emotion or salience. These findings are consistent with a neurocognitive model of MDD in which abnormal communication among functional networks may mediate the core cognitive and affective biases that characterize this serious disorder.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kaiser, Andrews-Hanna.
Critical revision of the manuscript: All authors.
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REFERENCES

1. Kessler RC. The costs of depression. *Psychiatr Clin North Am*. 2012;35(1):1-14.

2. Merikangas KR, Ames M, Cui L, et al. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. *Arch Gen Psychiatry*. 2007;64(10):1180-1188.

3. Substance Abuse and Mental Health Services Administration. *Results From the 2012 National Survey on Drug Use and Health: Mental Health Findings*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.

4. World Health Organization W. *World Health Statistics*. Geneva, Switzerland: World Health Organization Press; 2010.

5. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012;21(3):169-184.

6. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology*. 2011;36(1):183-206.

7. Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct*. 2008;213(1-2):93-118.

8. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995;34(4):537-541.

9. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A*. 2003;100(1):253-258.

10. Buckner RL, Krienen FM. The evolution of distributed association networks in the human brain. *Trends Cogn Sci*. 2013;17(12):648-665.

11. Chang C, Liu Z, Chen MC, Liu X, Duyn JH. EEG correlates of time-varying BOLD functional connectivity. *Neuroimage*. 2013;72:227-236.

12. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb Cortex*. 2012;22(1):158-165.

13. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349-2356.

14. Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BTT. The organization of the human cerebellum estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(5):2322-2345.

15. Choi EY, Yeo BTT, Buckner RL. The organization of the human striatum estimated by intrinsic functional connectivity. *J Neurophysiol*. 2012;108(8):2242-2263.

16. Yeo BTT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125-1165.

17. Snyder HR. Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull*. 2013;139(1):81-132.

18. Kaiser RH, Andrews-Hanna JR, Spielberg JM, et al. Distracted and down: neural mechanisms of affective interference in subclinical depression [published online July 25, 2014]. *Soc Cogn Affect Neurosci*. doi:10.1093/scan/nsu100.

19. Wang L, Hermens DF, Hickie IB, Lagopoulos J. A systematic review of resting-state functional-MRI studies in major depression. *J Affect Disord*. 2012;142(1-3):6-12.

20. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci*. 2007;8(9):700-711.

21. Wager TD, Lindquist M, Kaplan L. Meta-analysis of functional neuroimaging data: current and future directions. *Soc Cogn Affect Neurosci*. 2007;2(2):150-158.

22. Wager TD, Lindquist MA, Nichols TE, Kober H, Van Snellenberg JX. Evaluating the consistency and specificity of neuroimaging data using meta-analysis. *Neuroimage*. 2009;45(1)(suppl):S210-S221.

23. Hasler G, Northoff G. Discovering imaging endophenotypes for major depression. *Mol Psychiatry*. 2011;16(6):604-619.

24. Holtzheimer PE, Mayberg HS. Stuck in a rut: rethinking depression and its treatment. *Trends Neurosci*. 2011;34(1):1-9.

25. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476-1488.

26. Alalade E, Denny K, Potter G, Steffens D, Wang L. Altered cerebellar-cerebral functional connectivity in geriatric depression. *PLoS One*. 2011;6(5):e20035.

27. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, Murphy CF, Lim KO, Gunning FM. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord*. 2012;139(1):56-65.

28. Alexopoulos GS, Hoptman MJ, Yuen G, et al. Functional connectivity in apathy of late-life depression: a preliminary study. *J Affect Disord*. 2013;149(1-3):398-405.

29. Andreescu C, Tudorascu DL, Butters MA, et al. Resting state functional connectivity and treatment response in late-life depression. *Psychiatry Res*. 2013;214(3):313-321.

30. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J. Depression, rumination and the default network. *Soc Cogn Affect Neurosci*. 2011;6(5):548-555.

31. Cao X, Liu Z, Xu C, et al. Disrupted resting-state functional connectivity of the hippocampus in medication-naïve patients with major depressive disorder. *J Affect Disord*. 2012;141(2-3):194-203.

32. Connolly CG, Wu J, Ho TC, et al. Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. *Biol Psychiatry*. 2013;74(12):898-907.

33. Cullen KR, Gee DG, Klimes-Dougan B, et al. A preliminary study of functional connectivity in comorbid adolescent depression. *Neurosci Lett*. 2009;460(3):227-231.

34. Davey CG, Harrison BJ, Yucel M, Allen NB. Regionally specific alterations in functional connectivity of the anterior cingulate cortex in major depressive disorder. *Psychol Med*. 2012;42 (10):2071-2081.

35. Furman DJ, Hamilton JP, Gotlib IH. Frontostriatal functional connectivity in major depressive disorder. *Biol Mood Anxiety Disord*. 2011; 1(1):11.

36. Gabbay V, Ely BA, Li Q, et al. Striatum-based circuitry of adolescent depression and anhedonia. *J Am Acad Child Adolesc Psychiatry*. 2013;52(6): 628-41.e13.

37. Guo W, Liu F, Xue Z, et al. Abnormal resting-state cerebellar-cerebral functional connectivity in treatment-resistant depression and treatment sensitive depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;44: 51-57.

38. Guo W, Liu F, Xue Z, et al. Decreased interhemispheric coordination in treatment-resistant depression: a resting-state fMRI study. *PLoS One*. 2013;8(8):e71368.

39. Guo W, Liu F, Dai Y, et al. Decreased interhemispheric resting-state functional connectivity in first-episode, drug-naive major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;41:24-29.

40. Guo W, Liu F, Liu J, et al. Is there a cerebellar compensatory effort in first-episode, treatment-naive major depressive disorder at rest? *Prog Neuropsychopharmacol Biol Psychiatry*. 2013; 46:13-18.

41. Hamilton JP, Chen G, Thomason ME, Schwartz ME, Gotlib IH. Investigating neural primacy in major depressive disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. *Mol Psychiatry*. 2011;16(7):763-772.

42. Horn DI, Yu C, Steiner J, et al. Glutamaterigic and resting-state functional connectivity correlates of severity in major depression: the role of pregenual anterior cingulate cortex and anterior insula [published online July 15, 2010]. *Front Syst Neurosci*. doi:10.3389/fnsys.2010.00033.

43. Kenny ER, O'Brien JT, Cousins DA, et al. Functional connectivity in late-life depression using resting-state functional magnetic resonance imaging. *Am J Geriatr Psychiatry*. 2010;18(7): 643-651.

44. Lui S, Wu Q, Qiu L, et al. Resting-state functional connectivity in treatment-resistant depression. *Am J Psychiatry*. 2011;168(6):642-648.

45. Ma C, Ding J, Li J, et al. Resting-state functional connectivity bias of middle temporal gyrus and caudate with altered gray matter volume in major depression. *PLoS One*. 2012;7(9):e45263.

46. Pannekoek JN, van der Werff SJA, Meens PHF, et al. Aberrant resting-state functional connectivity in limbic and salience networks in treatment: naïve clinically depressed adolescents. *J Child Psychol Psychiatry*. 2014;55(12):1317-1327.

47. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci U S A*. 2010;107 (24):11020-11025.

48. Tahmasian M, Knight DC, Manoliu A, et al. Aberrant intrinsic connectivity of hippocampus and amygdala overlap in the fronto-insular and dorsomedial-prefrontal cortex in major depressive disorder. *Front Hum Neurosci*. 2013;7:639.

49. Tang Y, Kong L, Wu F, et al. Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: a resting-state functional magnetic resonance imaging study. *Psychol Med*. 2013;43(9):1921-1927.

50. Ye T, Peng J, Nie B, et al. Altered functional connectivity of the dorsolateral prefrontal cortex in first-episode patients with major depressive disorder. *Eur J Radiol*. 2012;81(12):4035-4040.

51. Salimi-Khorshidi G, Smith SM, Keltner JR, Wager TD, Nichols TE. Meta-analysis of neuroimaging data: a comparison of image-based and coordinate-based pooling of studies. *Neuroimage*. 2009;45(3):810-823.

52. Brett M, Christoff K, Cusack R, Lancaster J. Using the Talairach atlas with the MNI template. *Neuroimage*. 2001;13(6, pt 2):85-85.

53. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A*. 2009;106(31):13040-13045.

54. Smith SM. The future of FMRI connectivity. *Neuroimage*. 2012;62(2):1257-1266.

55. Nee DE, Wager TD, Jonides J. Interference resolution: insights from a meta-analysis of neuroimaging tasks. *Cogn Affect Behav Neurosci*. 2007;7(1):1-17.

56. Thayer JF, Ahs F, Fredrikson M, Sollers JJ III, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev*. 2012;36(2):747-756.

57. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996; 67(3):588-597.

58. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.

59. Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton depression rating scale. *J Affect Disord*. 2013;150(2):384-388.

60. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J Neurophysiol*. 2008;100(6):3328-3342.

61. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron*. 2010;65(4):550-562.

62. Fales CL, Barch DM, Rundle MM, et al. Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biol Psychiatry*. 2008;63(4):377-384.

63. Kerns JG. Anterior cingulate and prefrontal cortex activity in an FMRI study of trial-to-trial adjustments on the Simon task. *Neuroimage*. 2006; 33(1):399-405.

64. Veltman DJ, Rombouts SA, Dolan RJ. Maintenance versus manipulation in verbal working memory revisited: an fMRI study. *Neuroimage*. 2003;18(2):247-256.

65. Ochsner KN, Ray RD, Cooper JC, et al. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage*. 2004;23(2):483-499.

66. Laird AR, Lancaster JL, Fox PT. BrainMap: the social evolution of a human brain mapping database. *Neuroinformatics*. 2005;3(1):65-78.

67. Dichter GS, Felder JN, Smoski MJ. Affective context interferes with cognitive control in unipolar depression: an fMRI investigation. *J Affect Disord*. 2009;114(1-3):131-142.

68. Gusnard DA, Akbudak E, Shulman GL, Raichle ME. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci U S A*. 2001;98(7): 4259-4264.

69. Kim H. A dual-subsystem model of the brain's default network: self-referential processing, memory retrieval processes, and autobiographical memory retrieval. *Neuroimage*. 2012;61(4):966-977.

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

71. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron*. 2008;59(6):1037-1050.

72. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *J Neurosci*. 2007;27(33):8877-8884.

73. Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron*. 2008;58 (3):306-324.

74. Buckner RL, Krienen FM, Yeo BTT. Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci*. 2013;16(7):832-837.

75. van Tol MJ, Li M, Metzger CD, et al. Local cortical thinning links to resting-state disconnectivity in major depressive disorder. *Psychol Med*. 2013;44(10):1-13.