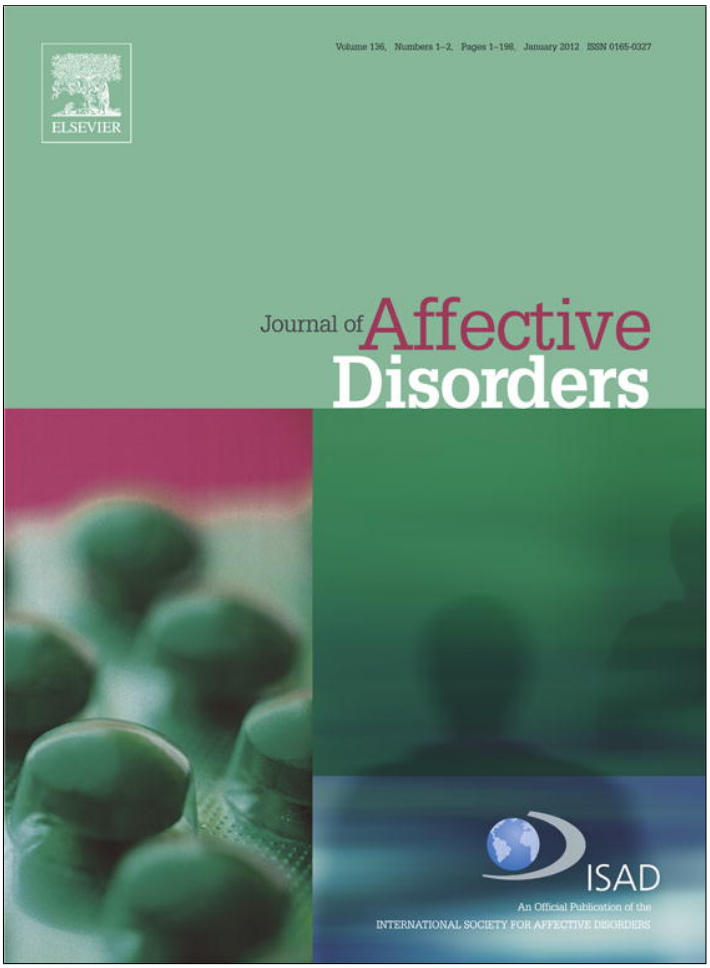

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Review

# A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder

Gabriel S. Dichter [a,*], Devin Gibbs [a], Moria J. Smoski [b]

[a] Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC 27599, USA
[b] Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710, USA

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ABSTRACT

*Background:* Resting-state functional magnetic resonance imaging (fMRI) is a promising predictor of treatment response in major depressive disorder (MDD).
*Methods:* A search for papers published in English was conducted using PubMed with the following words: depression, treatment, resting-state, connectivity, and fMRI. Findings from 21 studies of relations between resting-state fMRI and treatment response in MDD are presented, and common findings and themes are discussed.
*Results:* The use of resting-state fMRI in research on MDD treatment response has yielded a number of consistent findings that provide a basis for understanding the potential mechanisms of action of antidepressant treatment response. These included (1) associations between response to antidepressant medications and increased functional connectivity between frontal and limbic brain regions, possibly resulting in greater inhibitory control over neural circuits that process emotions; (2) connectivity of visual recognition circuits in studies that compared treatment resistant and treatment sensitive patients; (3) response to TMS was consistently predicted by subcallosal cortex connectivity; and (4) hyperconnectivity of the default mode network and hypoconnectivity of the cognitive control network differentiated treatment-resistant from treatment-sensitive MDD patients.
*Limitations:* There was also considerable variability between studies with respect to study designs and analytic strategies that made direct comparisons across all studies difficult.
*Conclusions:* Continued standardization of study designs and analytic strategies as well as aggregation of larger datasets will allow the field to better elucidate the potential mechanisms of action of treatment response in patients with MDD to ultimately generate algorithms to predict which patients will respond to which antidepressant treatments.



**Contents**



*Abbreviations:* ↑, increased; ↓, decreased; A_DM, anterior default mode; ALFF, amplitude of low-frequency fluctuations; b/w, between; BC, Betweeness centrality; CCN, Cognitive Control Network; DMPFC, Dorsomedial prefrontal cortex; DLPFC, Dorsolateral Prefrontal Cortex; DMN, Default Mode Network; END, early treatment nonresponsive major depressive disorder; ERD, early treatment responsive major depressive disorder; FC, Functional Connectivity; HC, healthy controls; IPL, Inferior parietal lobule; L_, left; NDD, Not treatment refractory depression; Pcu, precuneus; p_DM, Posterior default mode; PFG, Posterior fusiform gyrus; R_, right; ReHo, Regional Homogeneity; SCC, Subcallosal Cingulate Gyrus; SNRI, Serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TR, repetition time; TRD, Treatment-resistant depression; TSD, Treatment-sensitive depression; Tx, Treatment; VMHC, Voxel mirrored homotopic connectivity

* Corresponding author.
*E-mail address:* dichter@med.unc.edu (G.S. Dichter).

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## 1. Introduction

Major depressive disorder (MDD) affects over 150 million people worldwide (WHO, 2008) and in 2004 was the third leading cause of global burden of disease. The lifetime prevalence rate of MDD is 16%, with an estimated 32–35 million US residents expected to develop the disorder during their lifetimes (Kessler et al., 2003). Brain imaging has proven to be a powerful tool to elucidate the pathophysiology and possible etiology of MDD, with numerous studies highlighting the critical role of dysfunction in an extended network that includes the medial prefrontal cortex and limbic, striatal, thalamic and basal forebrain structures involved in affect processing, mood regulation, and cognitive control (Diener et al., 2012; Pizzagalli, 2011; Price and Drevets, 2012). Though activation and connectivity in these networks differentiates those with MDD from controls, less is known about relations between functional brain connectivity and antidepressant treatment outcomes.

Though there are many effective interventions for MDD, there is significant variability in treatment response: over a third of patients with MDD will fail to respond to a given treatment (Fava and Davidson, 1996). One obstacle to improved treatment response rates is the lack of biomarkers to predict who will respond to a given treatment. Indeed, there has been relatively little progress improving the efficacy of established antidepressant treatments (Fournier et al., 2010; Undurraga and Baldessarini, 2012), with first-line FDA-approved treatments demonstrating average response rates of 54% versus 37% for placebo (Levkovitz et al., 2011). Too frequently, clinical practice involves a trial-and-error approach to identifying the right antidepressant treatment. Part of the challenge of improving antidepressant treatment response is the heterogeneity of MDD. The disorder is diagnosed on the basis of a polythetic criterion set and thus patients vary widely in the constellation of symptoms they express, suggesting that different patients likely manifest with different etiologies and disease processes.

A powerful method to investigate the pathophysiology of MDD and aid in the identification of biomarkers of treatment response is functional magnetic resonance imaging (fMRI). Decades of task-based fMRI studies have identified brain circuits with altered functional activity while patients with an MDD process affective stimuli. More recently, resting-state fMRI has become increasingly popular to study the pathophysiology of MDD. Resting-state fMRI allows for the identification of spontaneous neural activity that coincides temporally to form neural networks. Spontaneous neural activity (i.e., non-task related activity) represents the largest energy expenditure of the brain and is thus critical to understanding brain network dynamics (Fox and Raichle, 2007).

Resting-state brain activity is altered across a spectrum of psychiatric disorders, including MDD, schizophrenia, autism spectrum disorder, and anxiety disorders. MDD is increasingly recognized as a disorder of dysregulated neural networks rather than as a disruption of single brain regions, and brain networks alterations have been identified in MDD, including the default mode network (DMN), the salience network (SN), the cognitive control network (CCN), the affective network (AN), and parts of the limbic system (for a review, see Wang et al. (2012)). For example, a number of studies have reported the DMN to be hyperactive in MDD (Nejad et al., 2013; Sheline et al., 2010). The DMN is most active when the brain is not engaged in goal-directed tasks, and DMN hyperactivity is thought to underlie rumination states in MDD (Broyd et al., 2009). The salience network directs attention to important stimuli in the environment (Menon and Uddin, 2010), and dysregulation of this network in MDD may explain the negative interpretation bias common in MDD ( Hamilton et al., 2012). The affective network, composed of the subgenual and pregenual cingulate and amygdala, is involved in appetite, libido and sleep, and hyperactivity of this network in MDD may account for vegetative disturbances (Sheline et al., 2010).

There has recently been increased use of resting state fMRI in the context of studies addressing brain network dynamics involved in response to antidepressant treatments, both in terms of predicting response to treatment as well as understanding changes in functional brain connectivity after effective treatments. These studies have focused on medication and neurostimulation treatments for MDD, and such studies have the potential to elucidate resting state biomarkers of treatment response. The goal of this review is to examine studies addressing linkages between resting state fMRI and treatment response in MDD to identify common patterns and themes both within and across antidepressant treatment modalities to guide future research in this area.

## 2. Methods

Studies were identified by searching PubMed using varying combinations of the following search terms: depression, treatment, resting-state, connectivity, and fMRI. Articles were excluded if they did not include a dedicated resting-state fMRI scan (i.e., studies examining psychophysiological interactions in the context of tasks were excluded), did not include a treatment component, or did not include patients with MDD. A total of 21 articles met these criteria and were included in this review.

## 3. Results

### 3.1. Experimental designs

There were a variety of experimental designs in the articles reviewed. Seven studies (Guo et al., 2012a, 2012b, 2013a, 2013b; Lui et al., 2011; Ma et al., 2012; Wu et al., 2011) compared resting-state fMRI between participants with treatment resistant depression (TRD) and treatment sensitive depression (TSD), with

**Table 1**
Studies of antidepressant medication.

| Study | Tx modality | Sample characteristics | Study design | Analytic method | RS scan details* | Principle findings | Conclusions |
|---|---|---|---|---|---|---|---|
| (Alexopoulos et al., 2012) | Open-label escitalopram at mean dose of 16.25 mg (SD: 5.0, range 10–20) daily for 12 weeks following 2 week single-blind placebo | 16 MDD, 69 ± 5.5 years 10 controls, 68.6 ± 7.0 years | MDD scanned once before tx. Controls scanned once. | Seed-based; Seeds: DMN (posterior cingulate cortex) and CCN (dorsal ACC and DLPFC) | Eyes closed, TR=2000 ms | ↑ FC in DMN did not predict tx response, but associated with pessimism.↓ FC in CCN associated with low remission rate and persistence of symptoms, associated with apathy and dysexecutive behavior | Low CCN FC predicted poor antidepressant outcomes in older adults |
| (Anand et al., 2007) | Open-label sertraline (6 weeks) 50 mg q.d. Dosage was ↑ to 100 mg after 1 week. After the first two weekly visits, sertraline was ↑ by 50 mg every 2 weeks to a max of 200 mg, depending on patient's response and tolerance | 12 MDD, 3/9 M/F, 30 ± 9 years. Medication free for 2 weeks. 11 controls, 3/8 M/F, 29 ± 8 years | MDD scanned before and after tx. Controls scanned twice | Seed-based; Seed=pre-genual ACC. Looked at FC b/w seed and limbic regions—amygdala, pallidostriatum and medial thalamus | Eyes closed, Time=307 s, TR=400 ms | After 6 weeks of sertraline tx, ↑ FC b/w the ACC and limbic regions (thalamus, pallidostriatum, amygdala) | Antidepressant tx had reciprocal effects on corticolimbic FC |
| (Guo et al., 2012b) | Open-label TCA, SSRI, or SNRI. Min. dose of 150 mg/day of imipramine equivalents for 6 weeks given to tx-naïve after scan | 18 TRD, 11/7 M/F, 27.39 ± 7.74 years. 17 TSD, 10/7 M/F, 26.71 ± 7.73 years. 17 HC, 10/7 M/F, 24.24 ± 4.41 years | MDD scanned before tx. Controls scanned once | ALFF | Eyes closed, Time=360 s, TR=2000 ms | In TRD, posterior lobes of the cerebellum and default circuit (ACC and medial frontal gyrus) had ↑ ALFF, the visual recognition circuit (lingual gyrus and cuneus) had ↓ ALFF relative to TSD | Differences in brain circuits b/w TRD and TSD were mainly in the cerebellum, the visual recognition circuit and the default circuit |
| (Guo et al., 2012a) | Open-label TCA, SSRI, or SNRI. Min. dose of 150 mg/day of imipramine equivalents for 6 weeks given to tx-naïve after scan | 23 TRD, 11/12 M/F, 27.35 ± 7.26 years. 22 TSD, 12/10 M/F, 28.09 ± 9.91 years. 19 HC, 10/9 M/F, 24.37 ± 4.18 years | MDD scanned before tx. Controls scanned once. | Cohe-ReHo | Eyes closed, Time=360 s, TR=2000 ms | ↓ Cohe-Reho in TRD in bilateral superior frontal gyrus, left cerebellum.↓ Cohe-Reho in TSD in bilateral superior frontal gyrus. TRD < TSD in bilateral cerebellum. TSD > TRD left fusiform gyrus. (–) correlation b/w Cohe-Reho in fusiform gyrus and duration | ↓ Cohe-ReHo in the cerebellum may differentiate TRD from TSD |
| (Guo et al., 2013a) | Open-label TCA, SSRI, or SNRI. Min. dose of 150 mg/day of imipramine equivalents for 6 wks given to tx-naïve after scan | 23 TRD, 11/12 M/F, 27.35 ± 7.26 years. 22 TSD, 12/10 M/F, 28.09 ± 9.91 years. 19 HC, 10/9 M/F, 24.37 ± 4.18 years. (Same data set as (Guo et al., 2012a)) | MDD scanned before tx. Controls scanned once | Seed-based; Seeds= cerebellar regions. Seeds used to identify executive, DMN, affective-limbic, and motor networks in cerebellum, which had been demonstrated to have cerebral–cerebellar FC | Eyes closed, Time=360 s, TR=2000 ms | Relative to HC, both patient groups showed significantly ↓cerebellar–cerebral FC with the prefrontal cortex (superior, middle, and inferior frontal gyrus) and (DMN) [superior, middle, and inferior temporal gyrus, precuneus, and inferior parietal lobule], and ↑ FC with visual recognition network (lingual gyrus, middle occipital gyrus, and fusiform) and parahippocampal gyrus. The TRD group exhibited a more ↓ FC than the TSD group, mainly in connected regions within DMN [PCu, angular gyrus (AG) and IPL] | Decreased FC b/w the cerebellum and regions within DMN may differentiate TRD from TSD |
| (Guo et al., 2013b) | Open-label TCA, SSRI, or SNRI. minimum dose of 150 mg/day of imipramine equivalents for 6 weeks given to tx-naïve after scan | 23 TRD, 11/12 M/F, 27.35 ± 7.26 years. 22 TSD, 12/10 M/F, 28.09 ± 9.91 years. 19 HC, 10/9 M/F, 24.37 ± 4.18 years. (Same data set as (Guo et al., 2012a)) | MDD scanned before tx. Controls scanned once | VMHC and seed-based; Seeds=right and left calcarine sulcus | Eyes closed, Time=360 s, TR=2000 ms | TRD VMHC < TSD in calcarine sulcus, fusiform gyrus, hippocampus, superior temporal gyrus, middle cingulum, precentral gyrus | Lower VMHC values in TRD than TSD; calcarine cortex connectivity may differentiate TRD from TSD |
| (Kozel et al., 2011) | 8 weeks of open-label antidepressant tx: 10 took bupropion SR 150 mg twice a day as part of a clinical trial, two took escitalopram 20 mg once a day, and | 13 participants 3/10 M/F, 33.7 ± 7.4 years | MDD participants scanned before tx. | Seed-based; Seeds=left and right amygdala, hippocampus, anterior cingulate gyrus, posterior cingulate gyrus, medial frontal | Eyes open, time= 502 ssecond, TR=2000 ms. | The magnitude of negative correlation b/w subcallosal cortex and the anterior cingulate cortex was associated with the degree of tx response. Of the 15 most significant | FC measures in several regions, especially the subcallosal cortex, were highly correlated with tx outcome |

**Table 1** (*continued*)

| Study | Tx modality | Sample characteristics | Study design | Analytic method | RS scan details* | Principle findings | Conclusions |
|---|---|---|---|---|---|---|---|
| | one took aripiprazole 5 mg once a day | | | cortex, orbitofrontal cortex, middle frontal cortex, and subcallosal cortex | | correlations b/w structures (of 120 possible), 11 involved the subcallosal cortex (six left, five right hemisphere) | |
| (Lai and Wu, 2012) | Open-label duloxetine 60 mg/d for 6 weeks. The only approved psychotropic was alprazolam 1 mg/day for panic attacks | 15 first episode MDD with panic disorder, 5/10 M/F, 35.87 ± 9.59 years 15 HC, 4/11 M/F, 34.30 ± 9.87 years | MDD participants scanned before and after tx. Controls scanned twice within 6 weeks | ReHo | Eyes closed, time =400 s, TR=2000 ms | ReHo ↑ in right superior frontal cortex, right medial frontal cortex and ↓ in right superior temporal cortex after remission of symptoms in these MDD patients within 6 weeks | Differential modulations inside the default mode network were associated with tx response |
| (Li et al., 2013) | Either open-label alprazolam (20–60 mg/day), venlafaxine (75–225 mg/day), duloxetine (60–90 mg/day), or citalopram (20–40 mg/day) for 12 weeks. 7/33 patients also received benzodiazepine (lorazepam,0.5–1.5 mg/day) during the first 2 weeks of tx | 24 Pre-tx MDD, 8/16 M/F, 31.83 ± 11.11 years. 16 Post-tx MDD. 3/13 M/F, 32.6 ± 11.84 years. 29 HC, 9/20 M/F, 33.62 ± 10.29 years | MDD participants scanned before and after tx. Controls scanned once | ICA looking specifically for subnetworks in the DMN | Eyes closed, Time=650 s, TR_=2000 ms | The anterior subnetwork and the posterior subnetwork showed ↑ FC in pre-tx MDD participants, relative to controls. Differences in the posterior subnetwork were normalized after antidepressant tx, while abnormal FC persisted within the anterior subnetwork | Persistent abnormal FC within the anterior DMN subnetwork in recovered MDD may constitute a biomarker of asymptomatic MDD and potential for relapse |
| (Lui et al., 2011) | Open-label TCA, SSRI, or SNRI. Tx refractory and non-refractory groups separated after 2 tx trials. Tx trial defined as 6 weeks | 28 tx refractory, 18/10 M/F, 33 ± 11 years. 32 tx nonrefractory, 21/11 M/F, 32 ± 10 years. 48 HC, 31/17 M/F, 35 ± 12 years | MDD participants scanned before tx. Controls scanned once | Seed-based; 13 seeds: left and right hippocampus, insula, dorsal lateral prefrontal areas, amygdala, putamen, and thalamus and anterior cingulate cortex | Eyes closed, 400 s, TR=2000 ms | MDD < HC: prefrontal-limbic-thalamic areas Nonrefractory > Refractory: more distributed ↓ in ACC, amygdala, hippocampus, insula Refractory: ↓ FC in prefrontal areas/thalamus FC of refractory > nonrefractory: l_amygdala with cingulate cortex, R_Insula with Cingulate cortex and precuneus | Refractory MDD associated with disrupted FC in thalamocortical circuits. Nonrefractory MDD associated with more distributed ↓ FC in limbic-striatal-pallidal-thalamic circuit |
| (Ma et al., 2012) | Open-label TCA, SNRI, or SSRI at a min. dose of 150 mg/day of imipramine equivalents for 6 weeks given to all patients | 18 TRD, 11/7 M/F, 27.39 ± 7.74 years. 17 TSD, 10/7 M/F, 26.71 ± 7.73 years. 17 HC, 10/7 M/F, 24.24 ± 4.41 years | MDD participants scanned before tx. Controls scanned once | Seed-based; regions showing significantly altered gray matter volume defined as seed ROIs for subsequent FC analysis: right MTG and bilateral caudate | Eyes closed, Time= 300 s, TR=2000 ms | For R_MTG seed, TSD showed ↑ FC in the right superior temporal gyrus and ↓ FC in the right angular gyrus, rectus, precuneus, medial frontal gyrus and bilateral superior frontal gyrus relative to TRD. For the r_caudate seed, TRD had ↑ FC in the right superior frontal gyrus and middle frontal gyrus, and ↓ FC in the right inferior frontal gyrus and corpus callosum compared to TSD | TRD and TSD both showed altered MTG FC mainly in the DMN and altered r_caudate FC with frontal regions |
| (Posner et al., 2013) | 10-week prospective, double blind, placebo-controlled trial of duloxetine. Dosing began at 30 mg daily and could be ↑ to a max of 120 mg daily in the absence of sufficient response | 41 dysthymic patients (DD), 37.8 ± 9.0 years, 24/17 M/F. 9 DD did not complete F/U scan. 25 HCs, 33.0 ± 11.9 years, 17/8 M/F | MDD participants scanned before and after tx. Controls scanned once | Seed-based; seed=PCC for DMN | Eyes closed, Time=two 5 min scans, TR=2200 ms | Patients had ↑ FC b/w the PCC and the mesial prefrontal cortex bilaterally, lateral parietal lobes bilaterally, and precuneus. The PCC–right lateral parietal cortex and PCC–right inferior temporal gyrus connections normalized after Duloxetine tx | ↑ FC within DMN implicated in MDD. Treatment resulted in normalization of DMN FC |
| (Wang et al., 2014) | Open-label SSRIs at the min. effective dose fluoxetine 20 mg/day, paroxetine 20 mg/day, sertraline 50 mg/day, citalopram 20 mg/day | 26 ERD, 16/10 M/F, 32.54 ± 11.23 years. 30 END, 17/13 M/F, 35.70 ± 9.39 years. 33 controls, 19/14 M/F, 31.45 ± 11.01 | MDD participants scanned before tx. Controls | ALFF | Time=350 s, TR=2000 ms | END > ERD cerebellum. ERD > END right lingual gyrus. ERD < Control PCC+R_cerebellum. END < control PCC. | ERD and END differentiated by ALLF in the lingual gyrus and cerebellum |

**Table 1** (*continued*)

| Study | Tx modality | Sample characteristics | Study design | Analytic method | RS scan details* | Principle findings | Conclusions |
|---|---|---|---|---|---|---|---|
| | or escitalopram 10 mg/day. Classified as ERD/END at 2 weeks | years. All MDD: first-episode, drug naïve | scanned once | | | END > control mOFC, L_cerebellum | |
| (Wu et al., 2011) | Open-label TCA, SNRI, or SSRI. TRD/NDD separated after 2 tx trials. Tx trial defined as 6 weeks | 22 TRD, 15/7 M/F, 35 ± 13 years 22 NDD, 10/12 M/F, 35 ± 13 years 26 Controls, 16:10 M/F, 33 ± 8 years | MDD participants scanned before tx. Controls scanned once | ReHo | Eyes closed, Time = 400 s, TR = 2000 ms | MDD > HC: ACC, mPFC, R_insula, R_parahippocampal gyrus. MDD < HC: L_PFG, L_inferior frontal area, L_IPL, L_caudate body, L_rectal gyrus TRD > NDD: R_mid temporal gyrus, R_insula, mid cingulated TRD < NDD: L_precuneus, L_inferior frontal gyrus. NDD > HC: mPFC, parahippocampal NDD < HC:L_PFG TRD > HC: ACC, mPFC, R_insula, R_transverse temporal gyrus, superior/mid temporal gyrus, L_posterior medial frontal gyrus TRD < HC: L_lateral inferior frontal gyrus, L_PFG, L_IPL, L_superior parietal lobule, L_precuneus | TRD had more widely distributed regions with altered ReHo. Tx refractoriness resulted from disruption of cortico-limbic networks |
| (Yang et al., 2014) | Open-label sertraline in a fixed-dosing design over 8 weeks (50–100 mg/day) | 12 MDD, 7/5 M/F, 34.91 ± 12.16 years | MDD participants scanned before and after tx | Seed = hypothalamus | Eyes closed, TR = 2500 ms | After 8 weeks of tx, MDD patients showed↑FC b/w the hypothalamus and DLPFC, OFC, ACC, insula, putamen, caudate, and claustrum. ↓ FC of the hypothalamus was primarily with the inferior frontal gyrus, medial frontal gyrus, cingulated gyrus, precuneus, thalamus, and cerebellum | Sertraline tx caused ↑ FC b/w prefrontal-limbic-hypothalamus pathways |

* Note: Scan parameters (i.e. eyes open or closed, scan length, and TR) are included when reported.

treatment resistance defined as less than 50% reduction in the Hamilton Depression Rating Scale (Hamilton, 1960) after at least two adequate trials of different classes of antidepressants, defined as appropriate dosage and compliance for at least 6 weeks. One study compared treatment responders to nonresponders but defined response as a ≥20% decrease in Hamilton Depression Rating Scale scores after 2 weeks (Wang et al., 2014).

Studies also differed with respect to when resting-state fMRI scans were obtained. In eight studies (Abbott et al., 2013; Anand et al., 2007; Lai and Wu, 2012; Li et al., 2013; Liston et al., 2014; Posner et al., 2013; Salomons et al., 2014; Yang et al., 2014), participants were scanned before and after treatment, whereas in the remaining studies participants were scanned only prior to treatment. These two approaches are designed to answer different research questions: the former addresses changes in functional connectivity due to treatment, whereas the latter examines predictors of antidepressant treatment response from pre-treatment scans.

In four studies (Abbott et al., 2013; Li et al., 2013; Liston et al., 2014; Posner et al., 2013), the MDD group was scanned twice whereas the control group was scanned only once; in all other studies, the MDD and control groups were scanned the same number of times (once or twice). As reviewed elsewhere (Dichter et al., 2012), fully balanced designs are optimal to assess treatment effects with neuroimaging to model the effects of repeated scans and other non-treatment factors related to repeated scanning.

### 3.2. Resting state analysis methods

In addition to varieties in experimental designs, a number of different analysis methods were used. Here we provide a brief overview of each analytic method used in the reviewed studies.

#### 3.2.1. Regional homogeneity

The amplitude of low frequency fluctuations (ALFF) evaluates the intensity of spontaneous changes in the blood oxygen level dependent (BOLD) signal in a given region (Zuo et al., 2010), whereas regional homogeneity (ReHo) methods use Kendall's Correlation Coefficient to measure how similar or synchronized a voxel is to its neighbors within a cluster of voxels (Zang et al., 2004). A larger ReHo value indicates higher synchronization of regional activation. Finally, coherence-based ReHo (Cohe-ReHo) has the added benefit of being insensitive to random noise in a time-series (Liu et al., 2010).

#### 3.2.2. Seed-based analyses

A seed-based approach identifies temporal correlations between an *a priori* region of interest (ROI) seed and other voxels. This approach allows for identification of networks linked to a hypothesized ROI, but will not detect network activity not associated with the ROI (Fox and Raichle, 2007). Betweeness Centrality (BC) is a graph theory approach that builds on the seed-based

**Table 2**
Studies of TMS.

| Study | Tx modality | Sample characteristics | Study design | Analytic method | RS scan details* | Principle findings | Conclusions |
|---|---|---|---|---|---|---|---|
| (Downar et al., 2014) | 20 sessions of open-label magnetic resonance imaging-guided rTMS to the dmPFC, 3000 pulses of 10 Hz stimulation at 120% resting motor threshold were applied to the left then right hemisphere at each session | 47 consecutive medication resistant MDD patients 20/27 M/F, 42.2 ± 12.7 years, with either unipolar ($n$=38) or bipolar ($n$=9) MDD | MDD participants scanned before tx | BC-mapping (a graph theoretic approach) | Eyes closed, Time=10 min, TR=2000 ms | L_VMPFC showed higher BC in nonresponders than in responders. Compared with responders, nonresponders showed ↓ FC to L_VMPFC in the ventral tegmental area, L_caudate nucleus, L_DMPFC, L_DLPFC, L_inferior parietal lobule, and L_anterior insula. Compared with responders, nonresponders showed ↑ FC to L_VMPFC in R_ DMPFC, R_ DLPFC, R_ frontopolar cortex, and R_PCC | Results suggest distinct MDD subtypes, one with preserved hedonic function and responsive to dorsomedial rTMS and another with disrupted hedonic function, abnormally lateralized FC through ventromedial prefrontal cortex, and unresponsive to dorsomedial rTMS |
| (Fox et al., 2012) | No TMS administered, but examined relations between different common left DLPFC TMS targets, FC, and antidepressant efficacy | Two pre-existing datasets. Validation Sample: 98 healthy participants 48/50 M/F, 22 ± 3.2 years. Test Sample: 13 MDD 3/10 M/F, mean age 40.2 years. 11 healthy subjects, 5/6 M/F, mean age 29 years | Identified areas within DLPFC with highest FC anticorrelation with subgenual cingulate activity in the 98 healthy controls. Compared DLPFC target regions with clinical efficacy in MDD dataset | Seed-based; Seeds=Subgenual region and left DLPFC | Validation Sample: Eyes open, 372 s, TR=3000 ms; Test Sample: Eyes closed, 600 s, TR=2000 ms | Clinical efficacy of TMS negatively correlated with L_DLPFC FC to subgenual cortex | Using connectivity-based optimized TMS to identify DLPFC subregions that were anti-correlated with subgenual cingulate activity, TMS to the DLPFC may suppress subgenual cingulate activity |
| (Liston et al., 2014) | 25 sessions of open-label TMS to DLPFC consisting of 37.5 min (3000 pulses; 30-s duty cycle, 4 s on, 26 s off) of 10-Hz excitatory TMS daily for 25 days (Monday–Friday for a 5 week period) | 17 MDD, 3/14 M/F, 42.3 ± 17.3 years 35 healthy controls, 12/23 M/F, 36 ± 16 years | MDD participants scanned before and after tx. Controls scanned once | Seed-based; Seeds= left DLPFC and subgenual cingulated cortex and targets in the CEN and DMN | 360 s, TR=2000 ms | Before tx, FC in MDD was ↑ within the DMN and ↓ within the CEN, and FC b/w these two networks was altered. TMS normalized MDD-related subgenual hyperconnectivity in the DMN but did not alter connectivity in the CEN. TMS also induced anticorrelated FC b/w the DLPFC and medial prefrontal DMN nodes. Baseline subgenual FC predicted clinical improvement | TMS selectively modulates FC both within and b/w the CEN and DMN, and modulation of subgenual cingulate FC may play an important mechanistic role in alleviating MDD |
| (Salomons et al., 2014) | 20 sessions (4 weeks/5 sessions/week) of open-label, add-on rTMS to the bilateral dmPFC. 120% resting motor threshold, 10 Hz, 5 s on, and 10 s off and for a mean of 6800 stimuli per session (34,000 stimuli per week) | 25 patients, 10/15 M/F, mean 42.6 years with either unipolar or bipolar illness ($n$=4; one type one, three type two) and a diagnosis of a major depressive episode resistant to ≥2 med trials or med intolerance | MDD participants scanned before and 1 week after tx | Seeds= DMPFC around the anterior midcingulate and the sgACC | Eyes closed, Time=600 s, TR=2000 ms | Patients with high baseline FC among cortical nodes involved in executive control and emotion regulation (dmPFC-sgACC and sgACC-dlPFC) experienced a greater reduction in symptoms following rTMS. Patients with low baseline cortico-thalamic (dmPFC-medial dorsal thalamus), cortico-striatal (dmPFC-putamen), and cortico-limbic (sgACC-amygdala and sgACC-hippocampus) | Positive outcomes were associated with the capacity for executive control over core emotional functions. Potential mechanism of action of rTMS to dmPFC is ↑ influence of cognitive control networks over thalamic and striatal regions, possibly linked with improved facilitation of goal-directed behavior |

**Table 2** (*continued*)

| Study | Tx modality | Sample characteristics | Study design | Analytic method | RS scan details* | Principle findings | Conclusions |
|---|---|---|---|---|---|---|---|
| | | | | | | FC also experienced a greater tx response. Clinical improvement associated with an ↑ in dmPFC-thalamus FC and a ↓ in sgACCcaudate FC. Improvement was also associated with ↓ in FC b/w dmPFC and insula, and b/w sgACC and a separate, more posterior region of midcingulate cortex | |

* Note: Scan parameters (i.e. eyes open or closed, scan length, and TR) are included when reported.

**Table 3**
Studies of ECT.

| Study | Tx modality | Sample characteristics | Study design | Analytic method | RS scan details | Principle findings | Conclusions |
|---|---|---|---|---|---|---|---|
| (Abbott et al., 2013) | Open-label ECT thrice weekly (11.17 ± 3.33 sessions in the series). Delivered a right unilateral ($n=10$) or bitemporal ECT($n=2$) stimulus delivery with a constant-current, brief pulse (0.50 ms) | 12 tx-resistant MDD with clinical indication for ECT, 4/8 M/F, 66.42 ± 9.78 years. 12 healthy controls, 4/8 M/F, 67.58 ± 8.89 years | MDD scanned before and at least 5 days after ECT (mean 21.13 ± 13.90 days after the last ECT tx). Controls scanned once | ICA comparing functional network connectivity: networks of interest include a_DM, SCC, DMPFC, p_DM, and r_DLPFC, l_DLPFC | Eyes open, Time=minimum of 316 s, TR=2000 ms | Remission associated with ECT reverses the FNC relationship from negative to positive b/w the p_DM and two other networks: the DMPFC and l_DLPFC. Relative to controls, the FNC b/w the p_DM areas and the DMPFC normalizes with ECT response. A direct comparison b/w ECT remitters and non-remitters showed the pattern of ↑ FNC b/w the p_DM and l_DLPFC following ECT to be specific to those who responded to the tx | The differences b/w ECT remitters and non-remitters suggest that this ↑ FC b/w p_DM areas and the l_DLPFC is a potential biomarker of recovery from MDD |

approach by looking at the entire topology of a network and measuring the number of shortest paths between all other points that pass through a given node (Barthélemy, 2004).

### 3.2.3. *Independent component analysis*

Independent component analysis (ICA) is a data-driven approach that uses algorithms to examine whole datasets and identify statistically independent components (Lee et al., 2013). ICA does not require the *a priori* selection of a ROI seed region, but requires the researcher to distinguish noise from a true network.

## 3.3. *Resting-state fMRI and antidepressant medication response*

Tables 1–3 summarize the reviewed studies on the basis of treatment modality, sample characteristics, study design, analytic method, scan parameters, primary findings, and conclusions. Studies are divided on the basis of treatment modality to aid in the identification of common findings within each type of treatment, though it should be noted that studies of a given treatment modality often used different analytic methods, making direct comparisons of findings challenging.

Fifteen of the articles reviewed examined response to antidepressant medication, including open-label trials of specific medications (duloxetine, escitalopram, sertraline) antidepressants within a specific class (SSRI), or multiple classes (TCA's, SSRI's, SNRI's), some including augmentation with benzodiazapines (Alexopoulos et al., 2012; Anand et al., 2007; Guo et al., 2012a, 2012b, 2013a, 2013b; Kozel et al., 2011; Lai and Wu, 2012; Li et al., 2013; Lui et al., 2011; Ma et al., 2012; Posner et al., 2013; Wang et al., 2014; Wu et al., 2011; Yang et al., 2014). One RCT compared response to duloxetine versus placebo (Posner et al., 2013). Among studies comparing treatment resistant depression (TRD) and treatment sensitive depression (TSD), altered connectivity of the caudate with frontal regions was seen in both TRD and TSD (Ma et al., 2012). Wu et al. (2011) found decreased ReHo in prefrontal cortical regions and increased ReHo in the temporo-limbic regions in TRD relative to TSD. Guo et al. (2012b) found higher ALFF in the DMN in TRD patients relative to TSD patients, and Ma et al. (2012) found TRD to have increased connectivity of the middle temporal gyrus to parts of the DMN relative to TSD, and Lui et al. (2011) found decreased connectivity within thalamocortical circuits in TRD relative to TSD.

Cerebellar connectivity was also implicated in a number of studies comparing TRD and TSD; however results were inconsistent (Guo et al., 2012a, 2012b, 2013a; Wang et al., 2014). Guo et al. (2012b) used different analytic methods to determine the role of the cerebellum in MDD, and found that TRD was associated with increased ALFF in the cerebellum relative to TSD. However, Guo et al. (2012a) reported that TRD was characterized by

decreased Cohe-Reho in the cerebellum relative to TSD, whereas Guo et al. (2013a) found that TRD was characterized by decreased connectivity of the cerebellum with the DMN relative to TSD. Finally, Wang et al. (2014) reported that patients who did not respond to SSRI treatment within 2 weeks showed increased ALFF in the cerebellum.

Among studies comparing pre- and post-treatment scans, a number of studies found decreased activity (Lai and Wu, 2012; Wu et al., 2011) or connectivity (Alexopoulos et al., 2012; Lui et al., 2011) of frontal cortical brain regions. The CCN, composed of the dlPFC, ACC, and parts of the parietal lobe (Miller and Buschman, 2013) is another network important in the pathophysiology of MDD. Alexopoulos et al. (2012) found that lower CCN connectivity predicted poorer antidepressant outcomes in older adults, and Li et al. (2013) found that antidepressant medication normalized hyperconnectivity in the posterior DMN but not in the anterior DMN, possibly signaling the potential to relapse. Likewise, Posner et al. (2013) found that connectivity of the posterior cingulate cortex, part of the DMN, to the right lateral parietal cortex and right inferior temporal gyrus normalized after duloxetine therapy. Additionally, successful treatment of MDD with panic disorder with duloxetine resulted in increased ReHo in the right superior frontal cortex and right medial frontal cortex and decreased ReHo in the right superior temporal cortex (Lai and Wu, 2012). Kozel et al. (2011) reported that the more negative the correlation of the anterior cingulate cortex (ACC) with the subcallosal cortex (SCC), the better the treatment response, and Anand et al. (2007) found that 6 weeks of sertraline treatment resulted in increased connectivity between the ACC and limbic regions (thalamus, pallidostriatum, and amygdala). Likewise, Yang et al. (2014) found that open-label sertraline treatment resulted in increased FC between frontal and limbic brain regions, resulting in greater inhibitory control over emotion processing brain regions.

The visual recognition circuit containing the lingual gyrus, middle occipital gyrus, fusiform gyrus and cuneus, was implicated in several of the reviewed articles (Guo et al., 2012b, 2013b; Wang et al., 2014). Guo et al. (2012a, 2012b) reported that the visual recognition circuit exhibited decreased ALFF in TRD than TSD. Similarly, Wang et al. (2014) reported increased ALFF in the lingual gyrus in SSRI early responders compared to early nonresponders, and Guo et al. (2013b) reported that the calcarine sulcus exhibited decreased connectivity to the middle occipital gyrus, cuneus, insula, opposite calcarine, and inferior temporal gyrus and increased connectivity to the vermis in TRD relative to TSD.

### 3.4. Resting-state fMRI and TMS response

Four of the reviewed articles examined response to TMS (Downar et al., 2014; Fox et al., 2012; Liston et al., 2014; Salomons et al., 2014), and results of these studies showed a relatively high degree of consistency with respect to SCC connectivity. Salomons et al. (2014) found that higher baseline SCC connectivity with the dorsomedial prefrontal cortex (dmPFC) and dorsolateral prefrontal cortex (dlPFC) predicted greater reductions in MDD symptoms after TMS; additionally, those patients with lower baseline cortico-thalamic (dmPFC-medial dorsal thalamus), cortico-striatal (dmPFC-putamen), and cortico-limbic (SCC-amygdala and SCC-hippocampus) connectivity showed better treatment response, leading the authors to propose that TMS functions to increase the influence of cognitive control networks over thalamic and striatal regions, facilitating goal-directed behaviors.

Liston et al. (2014) reported that pre-treatment SCC hyperconnectivity to the DMN and CCN predicted greater clinical improvement after TMS, though the same study also found that TMS normalized SCC hyperconnectivity in the DMN, but not the CCN, and induced anticorrelated connectivity between the VMPFC and medial prefrontal DMN nodes. Fox et al. (2012) found that the most effective TMS target sites in the dlPFC were the most anticorrelated with the SCC. Downar et al. (2014) reported (1) differences in connectivity between TMS responders and nonresponders in ventromedial prefrontal cortex (vmPFC) adjacent to the subgenual cortex, (2) that nonresponders demonstrated lower connectivity of the vmPFC to reward circuits, and (3) vmPFC connectivity with dorsolateral and dorsomedial prefrontal structures had an opposite pattern of lateralization in responders than nonresponders.

### 3.5. Resting-state fMRI and ECT response

Only one of the reviewed articles investigated response to ECT treatment (Abbott et al., 2013). This study found that response to ECT involved an increase in functional network connectivity between the posterior default mode and left dlPFC, whereas this change in connectivity was absent in participants who did not respond to treatment.

## 4. Discussion

The use of resting-state fMRI in the context of MDD treatment studies is increasing, with the ultimate goals of improved understanding of the effects of treatments on neural networks related to the pathophysiology of the disorder as well as the identification of biomarkers of MDD treatment response. Despite the variability across reviewed studies with respect to study designs and analytic methods, a number of consistencies emerged.

One pattern that emerged, particularly in studies examining response to antidepressant medication treatment, is that treatment response is associated with increased connectivity between frontal and limbic brain regions, possibly resulting in greater inhibitory control over neural circuits that process emotions (Alexopoulos et al., 2012; Lai and Wu, 2012; Lui et al., 2011; Wu et al., 2011; Yang et al., 2014). This mechanistic account of treatment effects is highly consistent with prevailing neural models of MDD that highlight decreased modulatory control of prefrontal brain regions on limbic brain regions, particularly in the context of emotion processing and emotion regulation (Johnstone et al., 2007; Joormann and Gotlib, 2010; Ray et al., 2005).

Another theme that emerged was that visual recognition circuits (i.e., containing the lingual gyrus, middle occipital gyrus, fusiform gyrus and cuneus) were implicated in several of the reviewed articles that compared TRD relative to TSD and in one study of early SSRI response (Guo et al., 2012b, 2013b; Wang et al., 2014). Although there is evidence of poor visual recall for social stimuli (e.g., facial identification and social scenes on standardized memory scales) in MDD that is related to cortical thickness and white matter volumes in the lateral surface of the right hemisphere (Peterson and Weissman, 2011), visual recognition circuits have not been a robust endophenotype in the MDD literature to date and thus this is a finding that warrants further research.

The subcallosal (or subgenual) cingulate cortex was implicated in studies of response to TMS and antidepressant medications (Downar et al., 2014; Fox et al., 2012; Kozel et al., 2011; Liston et al., 2014; Salomons et al., 2014). For example, Kozel et al. (2011) found that the connectivity of the SCC to the ACC was predictive of better antidepressants treatment outcomes whereas Liston and colleagues found that anticorrelations between the SCC and dlPFC was predictive of better TMS outcomes. These patterns are consistent with prior cross-sectional studies indicating hyperactivity of the SCC in MDD in a number of contexts (Berlim et al., 2014; Hamani et al., 2011), as well as evidence across studies that a variety of treatments exert their antidepressant effect via

decreasing SCC activity (see Hamani et al. (2011)for a review). Additionally, the SCC is a common target site in deep brain stimulation for MDD (Berlim et al., 2014), suggesting that normalized SCC activation and connectivity may be a common denominator across effective antidepressant treatments.

Other themes emerged, though not as consistently. Hyperconnectivity within the DMN and hyperconnectivity of the DMN to other structures in TRD compared to TSD were identified in two studies (Guo et al., 2012b; Ma et al., 2012), possibly suggesting that antidepressant medications are more effective for MDD patients with lower DMN connectivity. However, other studies suggest that antidepressant medications normalize the posterior portion of the DMN network (Li et al., 2013; Posner et al., 2013). Interestingly, the opposite trend was seen with TMS, where hyperconnectivity within the DMN predicted better treatment outcomes, as TMS effectively normalized hyperconnectivity between the SCC and the DMN (Liston et al., 2014). This suggests an explanation for why TMS may work as a second-line treatment for those who have not responded to antidepressant medications.

Alexopoulos et al. (2012) found that lower baseline connectivity within the CCN was correlated with worse medication treatment outcomes, and Wu et al. (2011) found increased activity in temporolimbic regions in TRD relative to TSD. The dlPFC acts in an inhibitory manner over limbic structures during emotional regulation (Ochsner and Gross, 2008; Siegle et al., 2006; Urry et al., 2006) and it is thus not surprising that CCN connectivity plays a critical role in antidepressant treatment response.

### 4.1. Conclusions, limitations, and future directions

The use of resting-state fMRI to study treatment response in MDD is becoming more common. However, the extant literature reviewed here illustrates an array of design strategies and analytic methods that, taken together, impede efforts to aggregate findings across studies. This point is illustrated by the fact that three studies analyzed the same dataset with different methods producing different results (Guo et al., 2012a, 2012b, 2013a), suggesting that results are critically dependent on analytic methods. The same may be said for different experimental designs as well. Finally, the array of different treatments examined, including various classes of antidepressant medications with different dosing strategies and treatment durations, TMS, and electroconvulsive therapy contribute to the heterogeneity of findings.

Despite such heterogeneity, a few common themes emerged: (1) associations between response to antidepressant medications and increased connectivity between frontal and limbic brain regions, possibly resulting in greater inhibitory control over neural circuits that process emotions; (2) the implication of visual recognition circuits in studies that compared treatment responsive and treatment sensitive patients; (3) response to TMS was consistently predicted by SCC connectivity; and (4) hyperconnectivity of the default mode network and hypoconnectivity of the cognitive control network predicted response to antidepressant treatment.

Limitations of the reviewed studies include the fact that there were no studies that addressed brain connectivity predictors of response to psychotherapy. Brain activation (rather than connectivity) predictors of response to antidepressant medication and psychotherapy are vastly divergent (Goldapple et al., 2004; Kennedy et al., 2007; Konarski et al., 2009). Comparisons across a range of treatment modalities are needed to determine whether biomarkers of response are specific to certain treatments. Additionally, studies predicting treatment response in pediatric or adolescent groups are needed to assess developmental profiles of connectivity predictors of treatment response. It is also well known that nonspecific treatment factors, such as therapeutic alliance and patient outcome expectancies, influence psychiatric treatment outcomes (Krupnick et al., 1996; Strupp and Hadley, 1979), and thus any systematic evaluation of predictors of antidepressant outcomes will need to consider such nonspecific factors. Finally, given that MDD most commonly presents as comorbid with other Axis I disorders (Kessler et al., 2003), studies including comorbid cases would increase the translational relevance of investigations of treatment response predictors.

Recommendations for future research include the standardization of data collection methods, including the length of resting-state scan, eyes-open versus eyes-closed, the creation of data repositories to aggregate data from different research groups, and consistent data analysis strategies. The creation of data repositories in particular will be critical to accrue larger sample sizes needed to robustly evaluate brain connectivity predictors of antidepressant treatment response.

In conclusion, this is the first systematic review of studies addressing linkages between resting state functional brain connectivity and response to antidepressant treatment. Future research with larger samples as well as consistent study designs and analytic strategies will increase the pace of discovery of brain-connectivity-based biomarkers of response to treatment in MDD.

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**Conflict of interest**

The authors of this manuscript do not have any conflicts of interests to disclose.

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