Sub-Hubs of Baseline Functional Brain Networks Are Related to Early Improvement Following Two-Week Pharmacological Therapy for Major Depressive Disorder

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Abstract: Accumulating evidence suggests that early improvement after two-week antidepressant treatment is predictive of later outcomes of patients with major depressive disorder (MDD); however, whether this early improvement is associated with baseline neural architecture remains largely unknown. Utilizing resting-state functional MRI data and graph-based network approaches, this study calculated voxel-wise degree centrality maps for 24 MDD patients at baseline and linked them with changes in the Hamilton Rating Scale for Depression (HAMD) scores after two weeks of medication. Six clusters exhibited significant correlations of their baseline degree centrality with treatment-induced HAMD changes for the patients, which were mainly categorized into the posterior default-mode network (i.e., the left precuneus, supramarginal gyrus, middle temporal gyrus, and right angular gyrus) and frontal regions. Receiver operating characteristic curve and logistic regression analyses convergently revealed excellent performance of these regions in discriminating the early improvement status

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for the patients, especially the angular gyrus (sensitivity and specificity of 100%). Moreover, the angular gyrus was identified as the optimal regressor as determined by stepwise regression. Interestingly, these regions possessed higher centrality than others in the brain ($P < 10^{-3}$) although they were not the most highly connected hubs. Finally, we demonstrate a high reproducibility of our findings across several factors (e.g., threshold choice, anatomical distance, and temporal cutting) in our analyses. Together, these preliminary exploratory analyses demonstrate the potential of neuroimaging-based network analysis in predicting the early therapeutic improvement of MDD patients and have important implications in guiding earlier personalized therapeutic regimens for possible treatment-refractory depression. *Hum Brain Mapp* 36:2915–2927, 2015. © 2015 Wiley Periodicals, Inc.

Key words: depression; early improvement; centrality; treatment; default-mode; fMRI

INTRODUCTION

Major depressive disorder (MDD) is a chronic, recurrent illness associated with significant suffering, high morbidity and mortality rates, and psychosocial functional impairments [Cassano and Fava, 2002]. In spite of considerable development in the pharmacological treatment of depressive disorders, clinical studies have reported high rates of nonremission even after several courses of standard antidepressant treatments [Rush et al., 2006; Souery et al., 1999]. This high rate of nonremission may be related to the treatment guidelines suggesting that the therapeutic regimen should be changed if there has not been a partial response after 4–6 weeks [American Psychiatric Association, 2013; National Institute for Health and Clinical Excellence, 2011].

Increasing studies have documented that whether patients with MDD exhibit early improvement after two-week antidepressant treatment [typically defined as a $> 20\%$ reduction in the 17-item Hamilton Rating Scale for Depression (HAM-D)] is predictive of later treatment outcome [Kim et al., 2011; Nierenberg et al., 1995; Stassen et al., 2007; Szegedi et al., 2003]. Specifically, a meta-analysis including 6,562 patients with MDD shows that early improvement within the first 2 weeks of antidepressant treatment predicts stable response and remission with high negative predictive values [Szegedi et al., 2009]. This suggests that a lack of early improvement signifies little chance of stable response or stable remission, indicative of potential refractory major depression. Moreover, patients with MDD who fail to show early improvement in response to an initial antidepressant treatment are demonstrated to benefit from timely switching of treatment strategies and, therefore, improved final outcome [Nakajima et al., 2011; Rush et al., 2006]. These studies collectively highlight two weeks as a crucial time frame in the process of antidepressant treatment where the clinical response of the patients is crucial to foreknow the final therapeutic outcomes; and meanwhile, lead us to raise another fundamental question of whether early improvement can be predicted at baseline to help timely screening of potential treatment-refractory depression for earlier customized treatment.

Resting-state functional MRI (R-fMRI) is a noninvasive neuroimaging technique that measures spontaneous brain activity [Biswal et al., 1995; Fox and Raichle, 2007]. R-fMRI does not require participants to engage in cognitive activities, therefore providing unique advantages for clinical studies [Kelly et al., 2012; Zhang and Raichle, 2010]. Particularly, this technique provides a promising tool to map intrinsic functional connectome of the human brain [Van Dijk et al., 2010; Wang et al., 2010], whose architectures are consistently reported to be disrupted in MDD [Greicius et al., 2007; Sheline et al., 2010; Zhang et al., 2011] and, more importantly, provide object biomarkers for the diagnosis of the disease [Zeng et al., 2012]. Furthermore, a growing body of evidence has shown that antidepressant drugs could significantly reverse MDD-related disruptions of network connectivity in healthy brains [McCabe et al., 2011; Scheidegger et al., 2012]. These findings collectively suggest that a network analysis of R-fMRI data is promising to address the issue of interest in the current study.

Here, utilizing a voxel-wise, whole-brain connectivity measure of degree centrality, we correlated baseline functional brain network architectures from 24 patients with MDD with their clinical responses after two-week antidepressant therapy. Furthermore, dichotomous discriminant analyses were used to test the potential of baseline brain organization to classify early improvement status for the patients. The reproducibility of our findings was finally examined over several possible confounding factors.

MATERIALS AND METHODS

Participants

A total of 28 patients with MDD were recruited in the current study from outpatients and inpatients of the Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China. The patients were screened from an ongoing follow-up project, which aims to systematically explore the relationships between baseline brain architectures and clinical outcomes of patients with MDD following antidepressant treatment by using multimodal

TABLE I. Demographics and clinical characteristics

	MDD (<i>n</i> = 24)
Gender (M/F)	10/14
Age (years)	41.04 ± 12.03 (24–64)
Education level (years)	10.78 ± 4.92 (6–19)
Handedness (R/L)	24/0
Disease duration (years)	4.25 ± 3.93 (0.1–13)
Age of onset (years)	36.92 ± 11.90 (20–58)
Number of episodes	1.63 ± 1.10 (1–5)
Duration of current episode (years)	1.53 ± 1.30 (0.1–4.5)
HAMD (baseline)	21.63 ± 2.86 (18–29)
HAMD (2 weeks)	12.29 ± 3.67 (7–20)
Rate of change in HAMD [(baseline – 2 weeks)/baseline]	0.42 ± 0.19 (0.06–0.68)

Data are presented as mean ± SD (min-max). MDD, major depressive disorder; HAMD, 17-item Hamilton Rating Scale for depression; M, male; F, female; R, right; L, left.

neuroimaging data. MDD was diagnosed according to the DSM-IV-TR criteria, using the Structured Clinical Interview for DSM-IV (SCID)-I. All patients were from 22- to 65-years old, right handed, free of psychotropic medications for at least 4 weeks before baseline MRI, and had a baseline mood Disorder Questionnaire (MDQ) score < 7. Exclusion criteria included (1) severe suicidal tendency; (2) pregnant or lactating women; (3) any physical diseases as assessed by personal history; (4) a history of organic brain disorder, neurological disorders, other psychiatric disorders, or cardiovascular diseases; or (5) a history of substance abuse including tobacco, alcohol, or other psychoactive substances. This study was approved by the Ethics Committee of the Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, and the Affiliated Hospital of Hangzhou Normal University. All participants gave written informed consent.

We evaluated their 17-item HAMD at baseline and after two weeks of treatment for each patient. Two patients were excluded because of baseline HAMD < 18. In addition, another two patients were also excluded due to incomplete spatial coverage of the brain or excessive head motion during MRI scan. Of the 24 remaining patients (10 males and 14 females), 16 received escitalopram (10 mg/day), 6 received agomelatine (20 mg/day), 1 received venlafaxine (75 mg/day), and 1 received mirtazapine (45 mg/day) and alprazolam (0.4 mg/day). More demographic and clinical characteristics of the patients are summarized in Table I.

Data Acquisition

All MRI data were acquired at baseline using a 3.0 T MR scanner (GE Discovery MR750, GE Medical Systems, Milwaukee, WI) equipped with an eight-channel head coil array. During the scanning, all participants were asked to

lie quietly in the scanner with their eyes open and to try not to think of anything systematically. Functional images were obtained axially using a single-shot, gradient-recalled echo-planar imaging sequence parallel to the line of the anterior-posterior commissure. The acquisition parameters were as follows: repetition time (TR) = 2,000 ms; echo time (TE) = 40 ms; flip angle (FA) = 90°; field of view (FOV) = 220 × 220 mm²; matrix = 96 × 96; slice thickness = 3.2 mm; and no gap. A total of 184 volumes were acquired for each subject. High-resolution T1-weighted images were also acquired for spatial normalization with a three-dimensional spoiled gradient-recalled sequence: 176 axial slices; TR = 8.1 ms; TE = 1 ms; FA = 8°; FOV = 250 × 250 mm²; matrix = 250 × 250; slice thickness = 1.0 mm; and no gap.

Data Preprocessing

Data preprocessing was performed using spm12 (<http://spm12.u-bourgogne.fr/>) and GREYNA (<http://www.nitrc.org/projects/gretna/>) packages. After discarding the first five volumes, the functional images were corrected for intra-volume temporal offsets and inter-volume head motion. The corrected images were then spatially normalized into standard Montreal Neurological Institute space using the transformation derived from T1 segmentation and resampled to 3-mm isotropic voxels. Linear drifts were further removed from the resulting normalized images, which was followed by temporal band-pass filtering (0.01–0.1 Hz). Finally, several nuisance signals, including 24-parameter head motion profiles [Friston et al., 1996; Yan et al., 2013], white matter signal, and cerebrospinal fluid signals were regressed out from each voxel's time series to exclude non-neuronal sources. Notably, we did not perform spatial smoothing given the possible introduction of artifactual local correlations between voxels that were unrelated to their functional connectivity [Zuo et al., 2012].

Voxel-Wise Degree Centrality

Among numerous centrality measures, we chose degree centrality for its simplicity in understanding and performance. For a given node *i* in a binary graph, degree centrality is calculated as the number of edges connecting to it, while in a weighed graph, it is computed as the sum of weights over these edges. Compared with binary degree centrality, its weighted version provides a more precise centrality characterization of functional brain networks by taking connection weights into account [Cole et al., 2010]. Therefore, we calculated the voxel-wise weighted degree in the current study. Specifically, for each voxel, its time series was first extracted and then correlated against the time courses of all other voxels in a study-specific brain mask. The brain mask was obtained to include only voxels showing: (1) non-zero variance over time for all participants and (2) >20% gray matter tissue probability in terms

of the prior map provided in the spm12 package. The final mask includes a total of 48,949 voxels. Therefore, an array of 48,948 ($48,949 - 1$) correlation coefficients (and their corresponding P -values) was generated for each voxel that represents its functional connectivity profile over the entire brain. To exclude confounding effects of spurious non-significant correlations, we filtered and summed those elements whose P -values passed through a statistical threshold in the array [Zuo et al., 2012]. To correct for multiple comparisons, a rigorous Bonferroni method was used (that is, $P < 0.05/48,948$). After finishing these analyses for each voxel in the mask, a weighted centrality map was finally derived for each participant, with the value at a given voxel reflecting the extent to which the voxel functionally integrates with other voxels in the brain. Voxels with higher degree centrality are considered more important in maintaining network integrity and performance. Finally, all the resulting centrality maps were further spatially smoothed (a Gaussian kernel with a full-width at half maximum = 6 mm). Of note, all correlation computations and thresholding procedures were implemented voxel by voxel; therefore, we actually did not obtain individual voxel-wise whole-brain connectivity matrices because of storage load.

Correlation Between Baseline Degree Maps and Therapeutic Response

To identify brain regions that are significantly related to the clinical responses of the patients with MDD to drug treatment, a voxel-wise general linear model was implemented between baseline degree centrality maps and the rate of changes in the HAMD scores [defined as $(\text{HAMD}_{\text{baseline}} - \text{HAMD}_{\text{two-week}})/\text{HAMD}_{\text{baseline}}$]. Age and gender were added as covariates in the model. The AlphaSim procedure was used to account for multiple comparison issues by combining a height $P < 0.001$ and an extent $P < 0.05$ [Woo et al., 2014]. The survived regions were mapped onto the cortical surfaces using the BrainNet Viewer package [Xia et al., 2013].

Receiver Operating Characteristic Curve and Logistic Regression

To examine whether the baseline brain architecture might be sufficiently sensitive and specific to serve as a potential biomarker for differentiating early improvement, two analytical strategies were employed, receiver operating characteristic (ROC) curve and logistic regression. The ROC curves were plotted using the public MATLAB codes (<http://www.mathworks.cn/matlabcentral/fileexchange/19950-rocout=roc-varargin-;> Giuseppe Cardillo, Naples, Italy) and the logistic regression was performed using MATLAB functions (glmfit and glmval). All ROC and logistic regression analyses were done for each cluster whose baseline degree centrality was significantly related to the

clinical response of the patients with MDD to drug treatment. In the current study, our results were mainly reported based on the criterion of a $>20\%$ decrease in the HAMD score after treatment in defining early improvement.

To determine whether the discriminative performances could occur by chance, we employed a non-parametric permutation test. Briefly, an empirical distribution was obtained for the area under curve (AUC) derived from the ROC analysis and the determination coefficient (R^2) derived from the logistic regression analysis, respectively, by randomly reallocating all of the patients into two groups (improvers and non-improvers) and re-computing the AUC and R^2 based on the two randomized groups (10,000 permutations). The 95th percentile points of the empirical distributions were used as critical values to estimate statistics (P values), which indicate the deviation of the observed discriminative performances from those expected by chance.

Given the relatively small sample size in the current study, we further employed a bootstrap resample procedure to test the robustness of our discriminative results against small data fluctuations. The bootstrap procedure is a non-parametric technique that can be used to mimic random variations of the finite sample of subjects. Specifically, we generated 10,000 bootstrap samples by resampling without replacement from our 24 patients (19 subjects in each sample, i.e., 80% of all the patients). Of note, we ensured the same proportion (80%) for both improvers and non-improvers that were included in each bootstrap sample. Based on these bootstrap samples, the ROC and logistic regression analyses were then performed and the performances (i.e., AUC and R^2) were recorded. Again, the 95th percentile points of the resulting distributions were used as critical values to determine whether the observed discriminative performances fell within the 95% confidence interval of those derived from the bootstrap samples.

Modularity

To study the infrastructure among the identified clusters (see Results) that carried discriminative information for early improvement, we conducted a modularity analysis on their pairwise connectivity matrices. Two methods were used to derive these matrices for each patient, including a temporal correlation analysis by calculating pairwise Pearson correlation coefficients in their mean time series and a spatial correlation analysis by calculating pairwise Pearson correlation coefficients in their seed-based functional connectivity maps. These two sets of matrices were then separately averaged across participants after a fisher's r -to- z transformation, therefore outputting two group-level mean correlation matrices (one for temporal and the other for spatial). Finally, a spectral optimization algorithm [Newman, 2006] was implemented to divide the clusters into sub-communities within which

there is denser connectivity than that predicted by chance. The modularity analysis was performed using the Brain Connectivity Toolbox (BCT, <https://sites.google.com/site/bctnet/>).

Stepwise Regression

We identified six regions whose baseline centrality correlated with clinical responses of patients with MDD to two-week antidepressant therapy and could classify their early improvement status. The natural next question is to determine which region provides the strongest power in the classification from the clinical and economic views. To answer this question, we utilized a stepwise regression procedure that initially begins with no regressors in the model. This analysis was performed using a MATLAB function (stepwise).

Reproducibility

After a series of processing steps, six regions were revealed to exhibit significant correlations of their baseline degree centrality with clinical response of the patients with MDD to drug treatment. To validate the reproducibility of our correlation results, we conducted several complementary analyses as follows.

Threshold effect

We evaluated the effects of different significance thresholds in defining spurious correlations during the degree calculation (Bonferroni corrected $P < 0.01$, uncorrected $P < 0.0001$ and 0.0005).

Network member

Given the disagreements in treating negative correlations in the R-fMRI community, we separately considered positive, negative, and absolute correlations.

Network type

Although weighted analysis can characterize the brain architecture more accurately than the binary version, it may be sensitive to disturbances in the functional connectivity strength due to noise and, therefore lower reliability [Wang et al., 2011]. We also calculated the binary degree centrality in the current study.

Anatomical distance

Recent studies highlight the significance of the anatomical distance in shaping cortical connectivity patterns [Ercsey-Ravasz et al., 2013; Sepulcre et al., 2010]. Therefore, we further classified the connections into short-range and long-range connections (cut-off = 75 mm) [Achard et al., 2006; He et al., 2007].

Temporal cutting

To examine temporal test-retest reproducibility, we divided individual data sets into two parts (the first 90 volumes as sub-data1 and the last 89 volumes as sub-data2), based on which weighted degree centrality maps were separately obtained.

RESULTS

Demographics and Clinical Characteristics

Table I shows the demographic and clinical characteristics for the patients with MDD who were finally included in the current study. After two weeks of treatment, the HAMD scores significantly decreased for the patients ($P < 10^{-8}$, paired t -test).

Brain–Therapeutic Effect Relationship

Six clusters were identified showing significantly negative correlations in their baseline degree centrality with rate of changes in the HAMD scores after two weeks of antidepressant therapy ($P < 0.05$, corrected), including the left precuneus, supramarginal gyrus, and middle temporal gyrus as well as the right angular gyrus and two spatially discrete clusters in the right middle frontal gyrus (Fig. 1).

Specificity and Sensitivity of Baseline Centrality in Differentiating Early Improvement

Based on the criterion of a $>20\%$ decrease in the HAMD score after treatment to define early improvement, 19 out of 24 patients with MDD were early responders and 5 were non-early responders. The ROC analyses revealed that the mean degree of all the clusters exhibited excellent performance in classifying the early improvement status after two weeks of treatment (all AUC > 0.91) (Fig. 2). The AUCs were significantly higher than those expected by chance (all $P < 10^{-3}$, permutation test) but comparable with those derived from bootstrap samples (all $P > 0.05$) (Supporting Information Table I). Notably, the AUCs of the angular gyrus and two frontal clusters approached 1, with both a sensitivity and specificity of 100% in the classification using the cut-off values.

The logistic regression analyses also revealed high (all $R^2 > 0.59$), non-random (all $P < 0.002$, permutation test), and robust (all $P > 0.05$, bootstrap resample) discriminative power of these clusters in discriminating early improvement (Fig. 3 and Supporting Information Table II). Again, we noted that the angular gyrus and two frontal clusters accounted for more than 70% of the final rates of change in the HAMD scores and correctly classified all the patients with respect to their early improvement status.

All the results derived from both the ROC and logistic regression analyses were largely robust against different

Figure 1.

Regions whose baseline degree centrality showed significant correlations with clinical response of MDD patients to two-week medications.

criteria (25%: 18 responders and 6 non-responders; 30%: 17 responders and 7 non-responders) in defining early improvement (Supporting Information Tables I and II).

Characteristics and Interregional Relationship for Regions With Discriminative Information Regarding Early Improvement

We compared the mean degree between regions with and without significant correlations with clinical responses of the patients with MDD to drug treatment. The mean degree centrality (across participants) was distributed heterogeneously over the cortical mantle with most highly connected regions predominantly located in the posterior parietal and occipital, medial/lateral prefrontal, and lateral temporal cortices (Fig. 4A). Histogram plots demonstrated a larger proportion of intermediate degree for regions showing significant correlations (Fig. 4B). Given the huge difference in the number of voxels between these two classes of regions (170 vs. 48,779 voxels), we performed the following statistical analysis. We first randomly selected 170 voxels from the

entire brain and calculated their mean degree. This procedure was implemented 10,000 times to generate an empirical null distribution, which was used to determine a P -value, indicating the deviation of a real observation from chance operations. Intriguingly, we found that the six aforementioned clusters tended to be more central (but not the most central) in the functional brain networks with respect to their centrality ($P < 10^{-3}$, Fig. 4C).

The temporal and spatial correlation matrices among the six clusters are shown in Figure 5. These clusters were similar to each other in both their temporal profiles and spatial connectivity patterns ($r = 0.414 \pm 0.117$ for temporal and 0.519 ± 0.115 for spatial correlation matrices). Moreover, both the temporal and spatial correlation matrices highly resemble each other ($r = 0.981$, $P < 10^{-3}$). Further modular analysis of these two matrices revealed a convergent finding that there was no modular architecture among the six clusters (modularity = 0.3, Z -score = 0.533 for temporal and modularity = 0.3, Z -score = 0.366 for spatial matrices), suggesting that these regions act homogeneously together.

Figure 2.

Performances of all the clusters in Figure 1 in classifying early improvements of the MDD patients after two-week medications using ROC curves. AUC, area under curve.

Figure 3.

Performances of all the clusters in Figure 1 in classifying early improvements of the MDD patients after two-week medications using logistic regression analysis.

Figure 4.

Mean degree centrality distribution (A), histogram of mean degree for regions with (purplish blue, as circled by black borders in A) or without (orange) significant correlations with clinical responses of MDD patients to two-week antidepressant therapy (B), and differences in the mean degree between these two classes of regions (C). See Results for a description of these findings.

The Best Regressor in Classifying Early Improvement

Using a stepwise regression model began with no regressors, we found that the final optimal model only contained the angular gyrus ($t = -5.434$, $P < 10^{-3}$), suggesting this region is a potential candidate for distinguishing early improvement of patients with MDD in the clinic.

Reproducibility of the Main Findings

To validate the reproducibility of our correlation findings over different choices of analytical strategies, we studied the effects of several factors, including the network type, network member, spatial distance, thresholding, and temporal cutting. We found that the observed brain-clinical correlations were highly reproducible and reliable (Supporting Information Table III), indicating the

Figure 5.

Temporal and spatial relationships among the clusters in Figure 1. See Results for a description of these findings.

credibility of our findings. Of note, with respect to the network member, the brain-clinical relationships were predominantly attributed to positive functional connectivity.

DISCUSSION

Using R-fMRI, we demonstrated that the baseline functional centralities of several highly connected parietal, frontal, and temporal regions were associated with the clinical responses of patients with MDD to two-week medications. Particularly, the angular gyrus exhibited the greatest discriminative power (sensitivity and specificity of 100%) and was identified as the sole regressor in the final optimal model. These findings indicate the potential for using an objective MRI marker to predict the outcome of pharmacological therapy in MDD.

We found that the left middle temporal gyrus, precuneus, supramarginal gyrus, and right angular gyrus exhibited significant correlations with clinical responses of MDD patients to medications and classified an early improvement status with high performances. All of these regions are key components of the default-mode network (DMN). The DMN is involved in a diverse array of functions, such as episodic memory, self-relevant mental processing, monitoring the external environment, remembering the past, and planning the future [Buckner et al., 2008]. Numerous studies have reported the wide involvement of the DMN in the pathophysiology of depression [Greicius et al., 2007; Korgaonkar et al., 2014; Sheline et al., 2010; Zhang et al., 2011]. Interestingly, we note that the identified regions were all in the posterior DMN. Although the DMN is routinely regarded as a homogenous network, increasing evidence demonstrates its functional heterogeneity, such as the strikingly different functional connectivity patterns between the anterior and posterior DMN [Uddin et al., 2009]. With respect to depression, the anterior and posterior DMN are also differentially involved in the disease. For example, compared with healthy controls, patients with MDD have lower negative responses in the anterior but higher responses in the posterior DMN during judgment of self-relatedness [Grimm et al., 2011]. Moreover, a recent study shows that antidepressant therapy selectively normalizes the functional abnormalities of the posterior rather than anterior DMN in patients with MDD [Li et al., 2013]. Consistent with this report, we showed that the baseline centrality of the posterior DMN could differentiate early improvement of antidepressant efficacy. Although the neural mechanism underlying this spatial dissociation of the DMN responds to antidepressant medication, our results, together with previous findings, propose that the posterior DMN is potential therapeutic target, on which direct or indirect operations could be executed to alleviate the disease severity via techniques, such as transcranial magnetic stimulation.

In addition to the posterior DMN regions, we also identified two frontal clusters of the right middle frontal gyrus

that exhibited significant correlations with clinical responses of patients with MDD to medications. MDD-related dysfunctions in frontal regions have been well documented in literature [Brzezicka, 2013; Rogers et al., 2004; Wang et al., 2012]. With respect to therapy, increasing studies have shown that frontal dysfunction is normalized after pharmacological treatment [Fales et al., 2009; Rosenblau et al., 2012; Wang et al., 2014]. Furthermore, the baseline activity of the frontal regions during an emotional task is predictive of the likelihood of improvement in patients with MDD [Lisiecka et al., 2011; Samson et al., 2011; Walsh et al., 2007]. Using R-fMRI, a more recent study shows that the intrinsic functional connectivity of multiple frontal regions (e.g., dorsolateral prefrontal cortex) predicts the treatment outcome in severe and treatment-resistant depression after electroconvulsive therapy [van Waarde et al., 2014]. Therefore, our results are consistent with these previous studies and highlight the frontal regions as common prognostic markers for both pharmacological and electroconvulsive therapies, although the similarities and differences of their therapeutic mechanisms need to be further studied.

An interesting finding in the current study is that the regions showing correlations with clinical responses of patients with MDD to medications tended to be highly connected hubs, which are consistently identified in the posterior cingulate and precuneus, lateral parietal, and medial/lateral prefrontal cortices in the literature [Buckner et al., 2009; Hagmann et al., 2008; Tomasi and Volkow, 2010; van den Heuvel and Sporns, 2013]. Hubs are critically important in maintaining the network integrity and overall information communication [Achard et al., 2006; He et al., 2009]. On the other hand, however, hubs are associated with a high rate of metabolism [Liang et al., 2013; Tomasi et al., 2013] and wiring cost [van den Heuvel et al., 2012], features rendering them points of vulnerability in brain disorders [Crossley et al., 2014]. More recently, Qin et al. demonstrate that hubs in the brain (e.g., middle frontal gyrus and middle temporal gyrus) carry important discriminative information in differentiating depressed patients from healthy controls [Qin et al., 2014]. Notably, compared with the most central hubs, the identified regions are within the second tier of hubs (i.e., sub-hubs). This is consistent with previous reports of disorder-specific patterns in hub degeneration [Crossley et al., 2014].

Among the six regions, the right angular exhibited the highest correlation with the clinical response to antidepressant therapy and the best performance in classifying the early improvement status. Stepwise regression also identified this region as the optimal regressor in the final model. This result is consistent with previous findings, demonstrating that the angular is associated with the severity of depressive symptoms, episode number, and illness duration [Guo et al., 2014; Liu et al., 2014]. In addition, treatment-resistant depression patients are reported to have significantly different cerebellar-angular functional

connectivity from treatment-sensitive depression patients [Guo et al., 2013]. Intriguingly, a recent study shows that the right angular gyrus is also predictable of long-term remission of patients with MDD [Korgaonkar et al., 2015]. Overall, these findings provide convincing evidence for the crucial role of the angular gyrus in the physiopathology of depression and propose the angular gyrus as an economic, reliable candidate prognostic biomarker to guide a customized personalized therapeutic regimen.

In the current study, six clusters were identified whose baseline centralities significantly correlated with the clinical response of patients with MDD to medications. Given the fact that numerous preprocessing steps are implemented before network construction and that numerous choices exist in determining network analytical strategies, one could therefore question the reproducibility of these findings. To address this issue, we validated our finding over multiple factors as diverse as the thresholding choice, network type, network member, anatomical distance, and temporal cutting. Encouragingly, the results remained largely unchanged. Moreover, subsequent discriminative results were also robust against different criteria in defining early improvement. The high reproducibility of our findings indicate the feasibility in establishing reliable, neuroimaging-based biomarkers for clinical outcomes of therapy in depression, although independent studies are needed to further validate this.

This study has several limitations. First, the sample size was relatively small in the current study, which limits the statistical power in revealing subtle effects and challenges the generalizability of our findings. Therefore, this study should be considered a pilot study. Further studies with a larger sample size are expected in the future to test the reproducibility of the current findings. Second, the current exploratory study showed that baseline functional brain architecture was promising to predict clinical responses of patients with MDD following antidepressant medications. Further studies on this topic can benefit by optimizing the experimental design (e.g., including a test group), employing more sophisticated methods (e.g., supporting vector machine), or selectively focusing on specific brain structures or neural circuits (e.g., the DMN) that are related to MDD. Third, consistent with previous studies on antidepressant effectiveness and prediction [Korgaonkar et al., 2015; Li et al., 2013], the antidepressant drugs were heterogeneous among patients for the current dataset. This makes our research as clinically relevant as possible because different drug regimens reflect the natural treatment course of MDD. Although different drugs may trigger antidepressant responses in different ways [Gideons et al., 2014], it is notable that only baseline fMRI data were used in the current study, which were collected before and therefore independent of the heterogeneous treatment. Moreover, a previous large-sample study shows that there are subtle differences between antidepressant treatment modalities in individual onsets of early improvement [Stassen et al., 2007]. Nevertheless, further studies are required to determine drug- or

type-specific relationships between baseline brain organization and clinical outcomes of patients with MDD. Fourth, several previous studies have shown that degree centrality, used in the current study, is associated with a low-to-moderate test-retest reliability [Cao et al., 2014; Wang et al., 2011; Zuo and Xing, 2014]. In addition, there exist many other voxel-wise centrality [e.g., Joyce et al., 2010; Lohmann et al., 2010; Zuo et al., 2012] and local [e.g., Smith et al., 2014; Wink et al., 2012; Zang et al., 2007] metrics that capture different aspects of the human brain. For example, the regional homogeneity measure is highly test-retest reliable [Zuo et al., 2013] and biologically meaningful [Jiang et al., 2014] for studying local functional integration of the human brain. Therefore, future studies are warranted to integrate these metrics in revealing more sensitive and reliable biomarkers for early improvement of MDD by using more optimized analytical strategies and/or more advanced imaging protocols [Zuo and Xing, 2014]. For instance, using a recently developed multiband echo planar imaging protocol, a fair-to-good test-retest reliability is demonstrated for voxel-wise degree centrality of functional brain networks [Liao et al., 2013]. Fifth, this study demonstrates the promise of neuroimaging-based network analysis in predicting the early improvement of patients with MDD in response to antidepressant therapy. Apart from the short-term clinical outcome, another important clinical question is whether the long-term ultimate remission could be predicted, an interesting topic in the future. Finally, the current study only used a single measure derived from a single data modality to link baseline brain architecture with antidepressant effectiveness of pharmacological treatment for patients with MDD. Future studies using various imaging modalities and methodologies could collectively accelerate the painting of a comprehensive picture of neural biomarkers for the efficacy of treatments for depression, including pharmacological, psychological, and stimulation therapies.

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