The Effects of Antidepressant Treatment on Resting-State Functional Brain Networks in Patients With Major Depressive Disorder

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Abstract: Although most knowledge regarding antidepressant effects is at the receptor level, the neurophysiological correlates of these neurochemical changes remain poorly understood. Such an understanding could benefit from elucidation of antidepressant effects at the level of neural circuits, which would be crucial in identifying biomarkers for monitoring treatment efficacy of antidepressants. In this study, we recruited 20 first-episode drug-naive major depressive disorder (MDD) patients and performed resting-state functional magnetic resonance imaging (MRI) scans before and after 8 weeks of treatment with a selective serotonin reuptake inhibitor—escitalopram. Twenty healthy controls (HCs) were also scanned twice with an 8-week interval. Whole-brain connectivity was analyzed using a graph-theory approach—functional connectivity strength (FCS). The analysis of covariance of FCS was used to determine treatment-related changes. We observed significant

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group-by-time interaction on FCS in the bilateral dorsomedial prefrontal cortex and bilateral hippocampi. Post hoc analyses revealed that the FCS values in the bilateral dorsomedial prefrontal cortex were significantly higher in the MDD patients compared to HCs at baseline and were significantly reduced after treatment; conversely, the FCS values in the bilateral hippocampi were significantly lower in the patients at baseline and were significantly increased after treatment. Importantly, FCS reduction in the dorsomedial prefrontal cortex was significantly correlated with symptomatic improvement. Together, these findings provided evidence that this commonly used antidepressant can selectively modulate the intrinsic network connectivity associated with the medial prefrontal-limbic system, thus significantly adding to our understanding of antidepressant effects at a circuit level and suggesting potential imaging-based biomarkers for treatment evaluation in MDD. *Hum Brain Mapp 00:000–000, 2014.*

Key words: depression; antidepressant; resting-state fMRI; graph theory; connectomics

INTRODUCTION

Major depressive disorder (MDD) has a high lifetime prevalence of up to 20% [Kessler et al., 2005] and constitutes a leading cause of worldwide disability [Whiteford et al., 2013]. Antidepressant drugs are commonly used treatments for MDD. While most antidepressants are known to work by inhibiting the uptake of monoamines, thereby increasing their synaptic availability, the particular mechanisms by which the neurochemical changes induced by antidepressants could translate into clinically meaningful effects are still poorly understood. Such a translational understanding may benefit from elucidation of the effects of antidepressants at the level of neural circuits [Harmer et al., 2009].

MDD has been typically associated with excessive processing of negative emotion and self-related information, and an inability to regulate emotions [Gotlib et al., 2004; Hamilton and Gotlib, 2008; Northoff, 2007]. Functional imaging provides a means for elucidating the brain circuit dysfunction underlying MDD and possible changes associated with successful treatment. Congruent with these behavioral disturbances, studies have shown altered blood flow metabolism or blood oxygen level dependent activation in MDD patients—most commonly in the lateral- and medial-prefrontal cortex (mPFC), and the limbic structures (i.e., amygdala and hippocampus), both in response to negative stimuli [Anand et al., 2005a; Mayberg et al., 1999] and at rest [Drevets, 2000; Kennedy et al., 2001]. Further, studies [Anand et al., 2005b; Kennedy et al., 2001] have reported that antidepressant drugs, particularly the selective serotonin reuptake inhibitors [SSRIs]), act by selectively modulating the emotion-induced activation in the mPFC and limbic regions. However, it is important to note that most of these studies examined the antidepressant effects on the local regional brain activity, while how antidepressants act at a connectivity or circuit level are rarely explored. This topic is of particular interest in light of growing understanding that MDD is not only associated with abnormalities of a single or independent brain region, but also with systems-level dysfunction affecting discrete but functionally integrated neural circuits [Gong and He, 2014; Lui et al., 2011; Tao et al., 2013; Zhang et al., 2011].

Resting-state functional magnetic resonance imaging (R-fMRI), which measures ongoing spontaneous brain activity [Biswal et al., 1995; Fox and Raichle, 2007], has emerged as a powerful tool to map intrinsic typical [He et al., 2009] and atypical [Buckner et al., 2009; Woodward et al., 2012] brain connectivity and networks. Studies using R-fMRI have shown that in MDD, resting-state functional connectivity (RSFC) is altered in multiple brain regions such as the mPFC [Sheline et al., 2010], cingulate cortex [Anand et al., 2005a; Lui et al., 2011], amygdala [Anand et al., 2005a; Lui et al., 2011], thalamus [Anand et al., 2005a; Lui et al., 2011], and hippocampus [Cao et al., 2012]. To our knowledge, only one study has been reported on the antidepressant effects on the RSFC in MDD. This trial demonstrated that 6 weeks of sertraline treatment normalized reduced RSFC between the dorsal anterior cingulate cortex and several limbic regions in MDD patients [Anand et al., 2005b]. However, that study used a seed-based analysis only examining the connectivity between several predefined regions—a potentially biased approach that is based on priori assumptions. Another approach examining functional connectivity—independent component analysis (ICA)—is suitable for analyzing functional associations within or between brain subnetworks. Studies using ICA have demonstrated disrupted functional connectivity within/between default-mode, salience, and central executive networks [Greicius et al., 2007; Manoliu et al., 2014; Veer et al., 2010] in MDD patients. However, the ICA approach is only capable of examining abnormalities in brain connectivity associated with specific functional subnetworks. Given the complex etiology and symptomatology of MDD, and the widespread abnormalities in brain connectivity reported in this condition, we propose that it would be of great interest to examine antidepressant effects on brain connectivity within a whole-brain range as an important step in unraveling antidepressant mechanisms at the level of neural circuits.

Here, we used R-fMRI to examine the effect of 8 weeks of treatment with the most selective SSRI—escitalopram—

on whole-brain functional connectivity in a well-defined first-episode, drug-naive, and non-comorbid population with MDD. The functional connectivity analysis was undertaken using a data-driven graph theoretical approach—whole-brain functional connectivity strength (FCS) mapping [Buckner et al., 2009; Liang et al., 2013; Tomasi and Volkow, 2010]. Several studies have demonstrated that the FCS metric is closely associated with physiological measures such as regional cerebral blood flow [Liang et al., 2013] and glucose metabolism [Tomasi et al., 2013]. Notably, such an FCS approach has been used to explore the brain mechanisms associated with childhood maltreatment in MDD patients [Wang et al., 2014] and to assess the effect of electroconvulsive therapy on brain activity in MDD [Perrin et al., 2012]. In this study, we hypothesized that escitalopram would modulate the FCS in specific brain sites within the mPFC and limbic system. These treatment-affected areas are especially important for emotional processing and regulation, as well as self-reflection, which are typically disturbed in MDD [Disner et al., 2011]. This hypothesis is of particular interest with respect to SSRI treatment, given the phenomenon of dense serotonergic innervation in the mPFC and limbic systems [Lanzenberger et al., 2012].

METHODS

Subjects

Thirty-six first-episode drug-naive MDD patients from psychiatric outpatient clinics, and 32 age- and gender-matched healthy controls (HCs) from the local community were recruited. The diagnosis of MDD was confirmed by two trained psychiatrists using the Mini-International Neuropsychiatric Interview [Sheehan et al., 1998], a structured clinical interview developed to determine DSM-IV diagnoses. The inclusion criteria for MDD patients were: a current acute episode of depression; severe as defined by a score of at least 24 on the 17-item Hamilton Rating Scale for Depression (HRSD) [Hamilton, 1967]; and length of current depressive episode $\geq$1 months but $\leq$24 months. Exclusion criteria for MDD patients were: a concurrent comorbid Axis I disorder; an Axis II personality disorder; intellectual disabilities; and any previous or current use of psychotropic medications. The HCs were required to have no lifetime psychiatric disorder, no history of psychiatric disorder in their first-degree relatives, and no history of use of psychotropic medications. All HCs had a HRSD score less than 7. An additional questionnaire was implemented to ensure that all HCs had no recent experiences that might affect the mood, such as exams, unemployment, and family bereavement, within 6 months before and during the study. Other exclusion criteria for both the MDD and HC groups were: age under 18 or above 60, unstable medical condition, neurological illness, substance dependence or abuse, acutely suicidal, and any contraindication to MRI scans. The study was approved by the local Institutional Review Boards. Voluntary written informed consent was obtained from all subjects before participating in this study. No patients being involuntarily detained in hospital were included.

Escitalopram Administration

Depending on the judgment of the attending physician and the patient's consent, patients received treatment with escitalopram following the baseline MRI scan. Symptoms were assessed using the HRSD and the Hamilton Anxiety Scale (HAM-A) [Maier et al., 1988]. During the study period of 8 weeks, the dose of escitalopram for each individual was determined by the clinical judgment of the attending physician, based on illness symptoms of the patient and medication side effects. Of the initial 36 patients, one patient had excessive head movement during scanning; seven patients needed to have a change of medications due to a poor response to escitalopram; three patients discontinued medication due to serious adverse reactions ($n = 2$) or undisclosed reason ($n = 1$); and five patients refused to participate in the second scan. Those 16 patients were therefore excluded; the remaining 20 patients completed the second scan. For the 20 patients who completed the study, the dose of escitalopram was gradually increased to 10–20 mg/day within 7 days and continued at this dose until finishing the study 8 weeks later. The final doses of escitalopram were 20 mg/day ($n = 15$), 15 mg/day ($n = 4$), and 10 mg/day ($n = 1$). The average dose ($\pm$SD) of escitalopram at the time of the second scans was 18.5 ± 2.9 mg. No systematic psychological intervention such as cognitive behavior therapy was performed during the study period. All subjects adhered to treatment as confirmed by measuring escitalopram plasma concentration on the day of the second scan. Twenty matched HCs were rescanned 8 weeks later after their baseline scans. These 20 MDD patients and 20 HCs constituted the final sample. Of these 20 patients, 14 were included in a prior report [Wang et al., 2013] on the escitalopram effect on brain regional activities, distinct from this study of the antidepressant effect on whole-brain functional connectivity. Moreover, that study [Wang et al., 2013] used an independent sample of 14 HCs that were scanned only once.

MRI Data Acquisition

Images were acquired with a 3.0-T MRI system (Siemens Magnetom Trio; Erlangen, Germany). The resting-state functional images were obtained using echo-planar imaging sequence (repetition time [TR] s/echo time [TE] ms, 2/30; 90° flip angle; matrix, 64×64; thickness/gap, 4.0 mm/0.8 mm; 30 slices). The acquisition time was 7 min. The anatomic images were then obtained by using a T1-weighted magnetization-prepared rapidly acquired gradient-echo sequence (TR s/TE ms, 2.3/3.01; matrix, 256×256; 9° flip angle). The participants were instructed to

keep their eyes closed without falling asleep and to move as little as possible. As assessed by a questionnaire, no subjects reported falling asleep during the scanning or being discomforted during or after the procedure.

Data Analysis

Image preprocessing

Image preprocessing was performed using SPM8 (www.fil.ion.ucl.ac.uk/spm) and DPARSF [Yan and Zang, 2010]. The preprocessing procedures were performed including slice timing, head-motion correction, and normalization to Montreal Neurological Institute (MNI) space. All data used in this study satisfied the criteria of spatial movement in any direction <1.5 mm or degree. Subjects demonstrated no significant group differences in head-motion parameters. Further, the linear detrend and band-pass filtering (0.01–0.08 Hz) was performed to reduce the effects of low-frequency drift and high-frequency noise. Subsequently, several nuisance signals including head motion, global mean, and signals from the cerebrospinal fluid and white matter were regressed from the data.

Whole-brain functional connectivity

Whole-brain functional connectivity analysis was performed as follows. We first computed Pearson's correlations between the time series of all pairs of voxels, constructing a whole-brain connectivity matrix for each participant. This computation was constrained within a gray matter (GM) mask that was generated by setting a threshold of 0.2 on the mean map of all GM maps involving all subjects. To improve normality, we then transformed individual correlation matrices to a *z*-score matrix using a Fisher *r*-to-*z* transformation. For a given voxel, FCS was computed as the sum of the connections (*z*-values) between a given voxel and all other voxels. Considering the ambiguous interpretation of negative correlations with removal of the global signal, we conservatively restricted our analysis to positive correlations above a threshold of $r = 0.2$. Such a threshold was chosen to eliminate the voxels with weak correlations attributable to signal noise. The FCS maps were further smoothed with a 6-mm Gaussian kernel and normalized to standard *z*-scores. Such a FCS metric is also referred to as the "degree centrality" of weighted networks in terms of graph theory [Buckner et al., 2009; Liang et al., 2013; Wang et al., 2014].

Statistical analysis

A two-way analysis of covariance (ANCOVA) and post hoc analyses were performed to determine the group × time interaction, main effects of group (MDD and HC groups) and time (weeks 8 and 0) on FCS, with age and gender as covariates. We restricted the ANCOVA within a mask that excluded the voxels showing significant FCS changes in the HC group over time. This mask was determined by performing a paired *t*-test on FCS maps of the HC group between weeks 0 and 8, with a threshold of uncorrected $P < 0.05$. The result for ANCOVA was thresholded at $P < 0.01$ with a cluster size of 32 voxels, corresponding to a corrected $P < 0.05$. The cluster size was determined by Monte Carlo simulations [Ledberg et al., 1998] using the REST AlphaSim utility [Song et al., 2011].

To examine the detailed RSFC alterations, we performed seed-based connectivity analyses, using the clusters showing significant group × time interaction effects on FCS as the seeds (See Supporting Information for details). The ANCOVA and post hoc analyses were performed on the RSFC maps for each seed. The significant level was set at $P < 0.05$ with a cluster size of 74 voxels, corresponding to a corrected $P < 0.05$. The analysis mask was generated by selecting the voxels that showing significant positive RSFC in any of the four groups. The voxels showing significant time differences in the HC group were excluded, in the same way as the FCS analyses.

Then, we performed correlation analyses between the mean changes (week 8 minus baseline) in symptom scores (e.g., total HRSD and its factors except for weight loss, as well as total HAM-A) and brain measurements (i.e., FCS and seed-based RSFC) in the areas showing significant group × time interaction, with age and gender as covariates. A threshold of $P = 0.05/6$ (0.008) was required for significance. (See Supporting Information for the computation of the HRSD factors). To examine the relationships between the medication dosage and functional connectivity, we additionally performed correlational analyses between the dosage of escitalopram for each patient (as indexed by average daily dose and total dose during the study period of 8 weeks) and the changes in brain connectivity measurements (i.e., FCS and seed-based RSFC) in the areas showing significant group × time interaction. An uncorrected threshold of $P < 0.05$ was used to determine the significance level.

Validation: Reproducibility

Considering that several methodological issues (e.g., connectivity threshold, head motion, and removal of global signal) may influence the results, we conducted the following procedures.

Correlation thresholds

We used a single correlation coefficient threshold of 0.2 to eliminate weak correlations possibly arising from noise signal during the FCS analysis. To determine whether the main results depended on the choices of correlation thresholds, we recomputed the FCS maps using other two different correlation thresholds (i.e., 0.1 and 0.3) and then reperformed statistical analysis, respectively.

Head motion

Several recent studies have reported influences of head motion on RSFC [Birn et al., 2006; Power et al., 2012; Van

TABLE I. Sample characteristics

	MDD patients baseline	Healthy controls baseline	MDD patients week 8	Healthy controls week 8	*P*
Gender (Male/Female)	9/11	9/11	9/11	9/11	>0.99[a]
Age (years)	34.6 ± 12.2	33.3 ± 10.3	34.7 ± 12.2	33.4 ± 10.3	0.72[a]
Handedness (Left/Right)	0/20	0/20	0/20	0/20	>0.99[a]
Education level (years)	12.9 ± 2.1	13.7 ± 3.1	12.9 ± 2.1	13.7 ± 3.2	0.35[a]
Length of depressive episode (months)	5.4 ± 6.3		7.4 ± 6.3		
Age of onset (years)	34.2 ± 12.2				
Total HDRS score	27.9 ± 4.0	0.9 ± 0.8	7.1 ± 4.5	0.9 ± 0.7	<0.0001[b]/0.84[c]
Anxiety	7.8 ± 1.8	0.5 ± 0.5	2.4 ± 2.0	0.5 ± 0.5	<0.0001[b]/1.00[c]
Weight loss	1.2 ± 0.7	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	<0.0001[b]
Cognitive disturbance	6.1 ± 2.6	0.1 ± 0.2	1.5 ± 1.2	0.1 ± 0.2	<0.0001[b]/1.00[c]
Retardation	9.1 ± 2.1	0.0 ± 0.0	3.0 ± 2.0	0.0 ± 0.0	<0.0001[b]
Sleep disturbance	3.7 ± 1.5	0.4 ± 0.5	0.6 ± 1.0	0.4 ± 0.5	<0.0001[b]/1.00[c]
Total HAM-A score	17.5 ± 4.6		6.8 ± 4.1		<0.0001[b]
Average dose of escitalopram (mg)			18.5 ± 2.9		

Unless otherwise indicated values shown are mean ± SD.
[a]Indicate the *P* values for the comparisons between the MDD patients at baseline and the healthy controls at baseline.
[b]Indicate the *P* values for the comparisons between the MDD patients at baseline and the patients after 8 weeks of treatment.
[c]Indicate the *P* values for the comparisons between the healthy controls at baseline and the healthy controls after 8 weeks.
The variables, gender, and handedness were analyzed using chi-square test, while other variables were analyzed using independent-sample *t*-test.

Dijk et al., 2012]. Although no significant differences were found in the maximum movements at each direction between any pairs of the groups, we conservatively evaluated the effects of head motion on our results using the "scrubbing" method [Power et al., 2012]. Briefly, we first calculated the frame-wise displacement between the neighboring volumes within each subject, and then scrubbed the volumes with a framewise displacement above 0.5 mm and their adjacent volumes for each subject. This procedure might reduce the bias on the R-fMRI signal induced by the head motion artifacts. Finally, we recalculated the FCS maps using the resultant scrubbed data and reperformed the statistical analysis.

Global signal regression

There is currently no consensus over whether whole brain signal should be removed in the preprocessing of the R-fMRI data. Some studies have suggested that the global signal is confounded with physiological noise [Birn et al., 2006] and should therefore be removed [Fox et al., 2009; Fransson, 2005], while other studies [Murphy et al., 2009; Weissenbacher et al., 2009] have suggested that the global signal regression (GSR) could introduce negative functional connectivity and thus alter intrinsic correlational structure of the brain. Of note, a recent study [Scholvinck et al., 2010] indicated that the global signal was associated with the neuronal signal and thus may be biologically meaningful. To examine whether the process of GSR affects our results, the data was reanalyzed without GSR.

Correlations covarying for baseline HRSD score

As depression severity may influence both neural and clinical response, we reperformed correlational analyses between changes in symptom scores and brain connectivity measurements (i.e., FCS and seed-based RSFC) in the areas showing significant group × time interaction covarying for baseline HRSD score in addition to age and gender.

RESULTS

Sample Characteristics

There were no significant differences between MDD patients and HCs in terms of age, gender, and education level (Table I). Symptom scores decreased significantly in patients after treatment ($P < 0.0001$) (Fig. 1, Table I). All patients showed a clinical response to escitalopram (Supporting Information Table I), defined as at least a 50% decrease from baseline HRSD score.

Functional Connectivity Strength

Main effects

The FCS patterns were remarkably similar across the MDD and HC groups (Supporting Information Fig. I). Regions with high FCS were mostly located in the default mode network (mainly involving the mPFC, posterior cingulate cortex, and inferior parietal lobule), lateral temporal

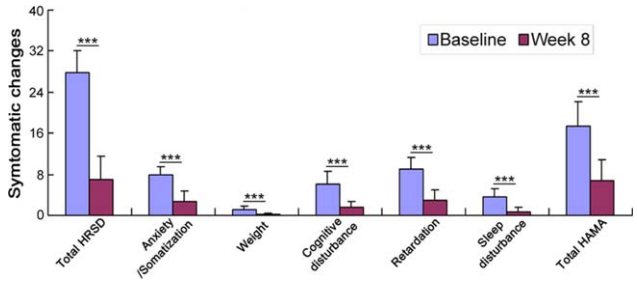

Figure 1.

Symptomatic changes in MDD patients following treatment. After 8-weeks treatment, MDD patients showed significant decreases in symptom scores, including the total HRSD and its five factors, and the total HAM-A. The data were expressed as mean value + SD. ***$P < 0.0001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

cortex, sensorimotor and visual cortices. The FCS patterns were similar to those observed in previous studies [Buckner et al., 2009; Tomasi and Volkow, 2010; Wang et al., 2014]. We observed significant group main effect on FCS in the right medial frontal gyrus, right supplemental motor area and right parahippocampal gyrus (MDD > HC), left superior temporal gyrus, right angular gyrus, and occipital regions (MDD < HC) (Supporting Information Fig. II). No regions showed significant main effects of time.

Group × time interaction

Significant group × time interactions on FCS were observed in the bilateral dorsal mPFC (dmPFC) and the bilateral hippocampi (Fig. 2A, Supporting Information Table II). The FCS changes in the bilateral dmPFC showed a significant positive correlation with the symptomatic improvements as indicated by changes in total HRSD, using age and gender as covariates (Fig. 2B). This correlation remained significant after adding the baseline HRSD score as a covariate (Supporting Information Fig. III). Post hoc analysis revealed that the FCS in the bilateral dmPFC was significantly higher in the MDD patients compared to the HC group at baseline ($t_{38} = 4.11$, $P = 0.0002$) and

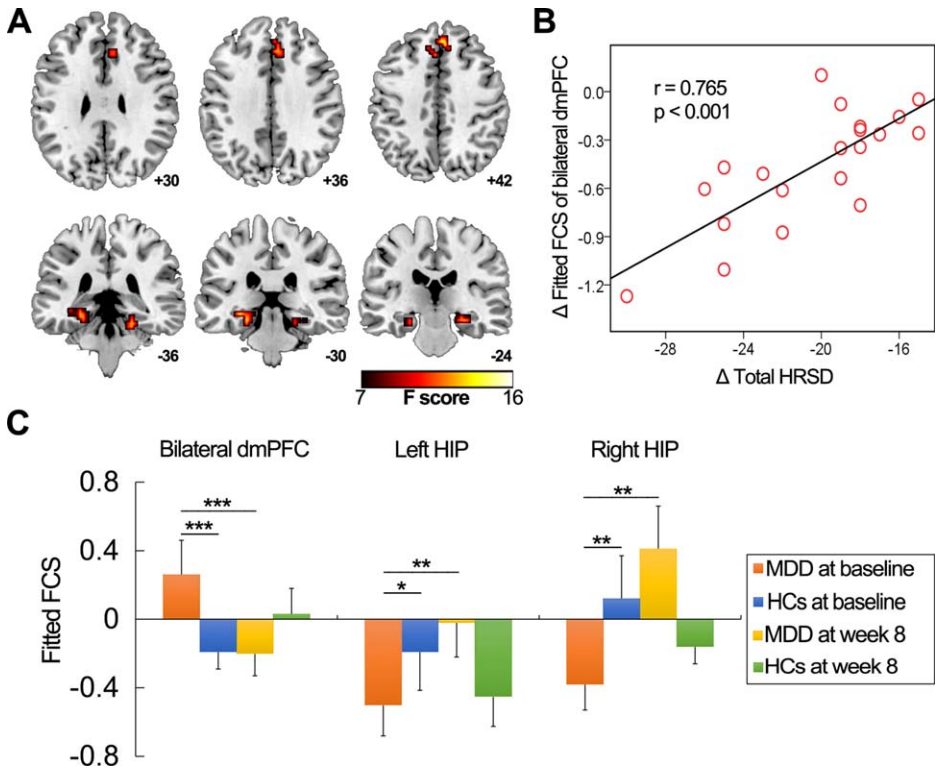

Figure 2.

Group × Time Interaction on FCS. **A**. Significant group × time interaction on FCS was observed in the bilateral dmPFC and bilateral hippocampus. This result was obtained by performing a 2×2 ANCOVA on the FCS maps of MDD patients at baseline and week 8 and HC subjects at baseline and week 8, with a threshold of corrected $P < 0.05$. **B**. The scatter map shows significant correlation between changes in FCS of the bilateral dmPFC and total HRSD scores. Δ = week 8—baseline. **C**. The bar maps present the between-groups and within-group differences in regions showing significant group × time interaction on FCS. The data were expressed as the mean value + SD. HIP, Hippocampus. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

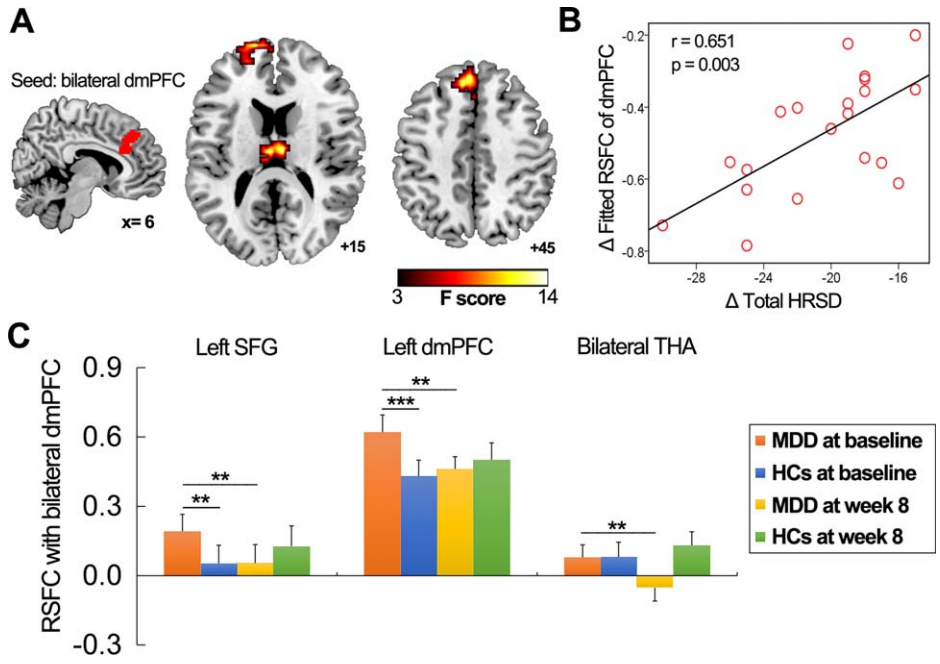

Figure 3.

Group × time interaction on the dmPFC-RSFC. **A**. The sagittal image shows the anatomical location of the bilateral dmPFC seed. The axial images show significant group × time interaction on the dmPFC-RSFC, which was observed in the left SFG, the left dmPFC, and the bilateral thalamus. This result was obtained by performing a 2×2 ANCOVA on the dmPFC-RSFC maps of MDD patients at baseline and week 8 and HC subjects at baseline and week 8, with a threshold of corrected $P < 0.05$. The numbers at the lower right corner of axial images refer to the MNI z-coordinates. **B**. The scatter map shows significant correlation in the changes between the dmPFC-RSFC with the left dmPFC and total HRSD scores. Δ = week 8—baseline. RSFC, resting state functional connectivity. **C**. The bar maps show the between-groups and within-group differences in regions showing significant group × time interaction on the dmPFC-RSFC. The data were expressed as the mean value + SD. THA, Thalamus. $^{**}P < 0.01$, $^{***}P < 0.001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

reduced significantly in patients following treatment ($t_{19} = -5.54$, $P < 0.0001$) (Fig. 2C). The FCS in the bilateral hippocampi was significantly lower (for the left hippocampus: $t_{38} = -2.03$, $P = 0.049$; for the right hippocampus: $t_{38} = -3.27$, $P = 0.003$) in the patients compared to the HC group at baseline and increased significantly in patients following treatment (for the left hippocampus: $t_{19} = 3.10$, $P = 0.006$; for the right hippocampus: $t_{19} = 2.90$, $P = 0.009$) (Fig. 2C). These results were largely preserved after accounting for the effects of correlation thresholds (Supporting Information Fig. IVA,B), head motion (Supporting Information Fig. IVC), and global signal removal (Supporting Information Fig. IVD). The regions (i.e., dmPFC and hippocampus) showing significant group × time interaction on FCS were selected as the seed regions for the subsequent RSFC analysis.

Seed-Based RSFC

The spatial patterns of the RSFCs for each seed region were similar across the MDD and HC groups (Supporting Information Fig. V). Regions showing significant group × time interaction on the dmPFC-RSFC were located in the left superior frontal gyrus (SFG), the left dmPFC, and the bilateral thalamus (Fig. 3A, Supporting Information Table III). The RSFC changes between the dmPFC seed and the left dmPFC showed significant positive correlation with the symptomatic improvements indicated by the changes in total HRSD, with age and gender as covariates (Fig. 3B). This correlation remained significant after adding the baseline HRSD score as a covariate (Supporting Information Fig. VI). Post hoc analysis revealed that the RSFCs between the dmPFC seed and the left SFG and the left dmPFC were significantly higher in the MDD patients compared to the HC group at baseline (for the left SFG: $t_{38} = 2.78$, $P = 0.008$; for the left dmPFC: $t_{38} = 4.13$, $P = 0.00019$) and reduced significantly in patients following treatment (for the left SFG: $t_{19} = -4.07$, $P = 0.001$; for the left dmPFC: $t_{19} = -3.98$, $P = 0.001$) (Fig. 3C). The RSFC between the dmPFC seed and the bilateral thalamus did not show any significant difference between the patients and HCs at baseline ($t_{38} = -0.07$, $P = 0.95$) but was found to be reduced significantly in patients following treatment ($t_{19} = -3.82$, $P = 0.001$) (Fig. 3C).

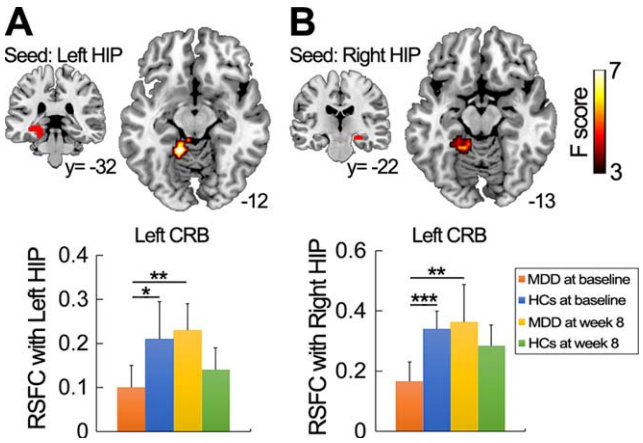

Figure 4.

Group × time interaction on the hippocampus-RSFC. **A**. The coronal image shows the anatomical location of the left hippocampus seed. The axial image shows significant group × time interaction on the RSFC between the left hippocampus and the left cerebellum after correction for multiple comparisons at $P < 0.05$. The number at the lower right corner of axial image refers to the MNI z-coordinate. **B**. The coronal image shows the anatomical location of the right hippocampus seed. The axial image shows significant group × time interaction on the RSFC between the right hippocampus seed and the left cerebellum, which could only be observed without correction for multiple comparisons. The bar maps below A and B show the between-groups and within-group differences in regions showing significant group × time interaction on the hippocampus-RSFC. The data were expressed as the mean value + SD. HIP, Hippocampus. CRB, Cerebellum. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

A significant group × time interaction effect on the RSFC between the left hippocampal seed and the left cerebellum was observed (Fig. 4A, Supporting Information Table III), with significant lower values in the MDD patients compared to the HC group at baseline ($t_{38} = -2.53$, $P = 0.016$) and significant increases in patients following treatment ($t_{19} = 3.88$, $P = 0.001$) (Fig. 4A). A significant group × time interaction effect on the RSFC between the right hippocampus seed and the left cerebellum could be only observed at an threshold of uncorrected $P < 0.05$ (Fig. 4B, Supporting Information Table III), with significant lower values in the patients compared to the HC group at baseline ($t_{38} = -4.10$, $P = 0.0002$) and significant increases in patients following treatment ($t_{19} = 2.95$, $P = 0.008$) (Fig. 4B).

Correlations Between the Medication Dosage and Brain Measurements

No significant correlations were found between the dosage of escitalopram and changes in brain measurements (i.e., FCS and seed-based RSFC) in the areas showing significant group × time interaction.

DISCUSSION

This study is the first, to our knowledge, to investigate the effect of an antidepressant on whole-brain functional connectivity (as indexed by FCS) in MDD. We observed a treatment-related change that was consistent with our initial hypothesis concerning the functional connectivity of the areas within the medial prefrontal-limbic network in MDD patients. We specifically found that 8 weeks of escitalopram had a normalizing effect on abnormally higher FCS in the bilateral dmPFC and abnormally lower FCS in the bilateral hippocampi.

The dmPFC is considered important in the treatment of mood disorders because of its extensive involvement in the processing of negative emotion and self-reflection [Lemogne et al., 2011]. Increased RSFC has been observed in MDD patients between the dmPFC and many areas across the cognitive control, default mode, and affective networks [Sheline et al., 2010]. The dmPFC is thus thought to constitute a converging node of depressive "hot wiring," and a modification in connectivity via this region has been hypothesized to represent a target for antidepressant treatment [Sheline et al., 2010]. In support of this proposal, healthy volunteers receiving citalopram showed reduced RSFC between the dmPFC and the hippocampus [McCabe et al., 2011]. Another study [Perrin et al., 2012] revealed that ECT treatment could dramatically downregulate the RSFC between the dmPFC and the DLPFC in patients with MDD, an executive component within the brain circuitry. In this study, we found that escitalopram could downregulate the abnormally higher FCS in the bilateral dmPFC. The dmPFC was then shown to have reduced positive RSFC with the left SFG, the left dmPFC, and the bilateral thalamus in MDD patients following treatment. The SFG and thalamus have been highlighted as important brain sites in MDD and possible mediators of antidepressant efficacy [Anand et al., 2005b; Greicius et al., 2007; Kennedy et al., 2001], in line with our findings. Distinct from the examination of local regional brain activities previously performed by our group [Wang et al., 2013], this study demonstrated—from a connectivity or circuitry perspective—that modulation of the dmPFC could simultaneously lead to a change in activity of some other regions within the brain circuitry of MDD. This indicates that the dmPFC may be an important target region for antidepressant treatment in MDD, thus providing direct evidence for that prior proposal [Sheline et al., 2010]. Significant correlations observed between the changes in FCS of the dmPFC, the dmPFC-RSFC with the left dmPFC, and symptomatic improvement suggest that the dmPFC connectivity may act as an objective indicator of the clinical response of MDD patients to SSRI treatment.

The hippocampus participates in emotional memory and affective regulation [Harmer and Cowen, 2013]. Deficits in these areas have been associated with MDD [Harmer and Cowen, 2013]. Neuroimaging studies have reported a volumetric decrease [Arnone et al., 2012] and reduced sadness-induced activation [Lee et al., 2008] in the hippocampus of MDD patients. However, much of the evidence highlighting the importance of modulating the hippocampus in the treatment of MDD has been derived from animal studies [Jun et al., 2012; Serafini, 2012]. It was found that antidepressant drugs may reverse both the impaired neuroplasticity and the neurogenesis modifications in the hippocampus, such as dendritic atrophy and loss of glial cells [Jun et al., 2012; Serafini, 2012]. In this study, we found that escitalopram has a normalizing effect on abnormally lower FCS in the bilateral hippocampi in MDD patients, which was accompanied by an increase in RSFC between the bilateral hippocampi and the left cerebellum. The cerebellum is thought to be involved in emotional and cognitive functions [Schmahmann and Caplan, 2006]. Altered RSFC between the hippocampus and cerebellum has been observed in MDD patients [Cao et al., 2012]. Our study confirmed that the abnormal RSFC between the left cerebellum and bilateral hippocampi could be reversed by antidepressant treatment. In combination with the current knowledge of physiological functions of the hippocampus [Harmer and Cowen, 2013], we propose that such reversal in the hippocampal connectivity may lead to a beneficial impact on emotional memory and affective regulation functions in MDD patients. This hypothesis should be further verified by combining imaging and neuropsychological data. Further studies of the means by which treatment-related imaging changes in the hippocampus could be linked with the neurohistological changes observed in animal studies would be beneficial.

The medication had no effect on FCS in the occipital and sensorimotor regions, despite abnormalities in these areas having been observed in MDD patients. This finding is not surprising as serotonergic projections are relatively weak in the occipital and sensorimotor regions, in contrast to the very strong projections in the mPFC and limbic neural system [Lanzenberger et al., 2012]. Thus, the treatment-affected regions in our study closely reflect the known pathways of the neurotransmitter system targeted by escitalopram, suggesting an area-specific effect of escitalopram.

Our results demonstrated treatment-related global functional connectivity changes in several brain regions, whereas such findings could not be detected by seed-based functional connectivity analyses and ICA. Seed-based functional connectivity analyses need to define prior "seed" regions according to specific hypothesis in MDD. ICA assumes that the brain is comprised of several independent components which are in charge of distinct brain functions. Therefore, ICA is capable to parcellate the brain into different subnetworks and further examines the functional connectivity within or between these subnetworks. Using ICA, several R-fMRI studies [Greicius et al., 2007; Veer et al., 2010; Zhu et al., 2012] have demonstrated altered brain activity in the posterior cingulate cortex/precuneus, ventral anterior cingulate cortex, thalamus, amygdala, insula, and lingual gyrus in MDD patients, findings inconsistent with our current results. These discrepancies of the abnormal regions between our study and previous ICA-based studies are partly explainable by the different analysis strategies used. In the framework of graph theory, the data-driven FCS analysis provides a whole-brain functional connectivity profile from a global network perspective. On the basis of the FCS, additional seed-based connectivity analyses revealed drug-affected RSFC between dmPFC and thalamus, and between hippocampus and cerebellum. These findings could not be identified by ICA, as these regions usually belong to different subnetworks based on previous ICA-based studies [Jafri et al., 2008; Veer et al., 2010].

We also observed a significant group main effect on FCS, primarily in the right medial frontal gyrus, right supplemental motor area, right parahippocampal gyrus, left superior temporal gyrus, right angular gyrus, and occipital regions. This result is consistent with a R-fMRI study that examined whole-brain nodal centrality in MDD and reported connectivity alterations similar to ours [Zhang et al., 2011].

Several issues need to be further addressed. First, we cannot clearly determine whether the FCS changes over time in the MDD patients were due to a pharmacological effect, state changes associated with the natural course of the illness, a placebo effect, or some combination of these possibilities. The ideal controls would be groups of untreated or placebo-treated patients. However, it is ethically questionable for patients experiencing severe depressive episodes to remain untreated or be given placebo for 8 weeks. Further recruitment of a group of patients with mild or moderate depressive episode and use of placebo for a shorter term (such as single use or continuous use for a few days) could be helpful to clarify any placebo effect. Further, similar studies of other antidepressant drugs or psychotherapy would help to clarify if the brain changes observed in this study are a general or specific action of antidepressant treatment. Additionally, some the patients initially recruited discontinued the escitalopram medication due to poor response and therefore withdrew from the study. Patients who completed the second fMRI scan were all responders to escitalopram treatment. Future studies should include responders and nonresponders in final scanning to also enable identification of markers of nonresponse to antidepressant treatment. Furthermore, the structural foundation underlying these treatment-related brain changes needs to be explored by a combined analysis of multimodal imaging data. Finally, the results of this study require replication in a larger sample.

In conclusion, this study demonstrated that successful antidepressant treatment with escitalopram was associated with a normalizing effect on functional connectivity (i.e., FCS and seed-based RSFC) in the dmPFC and the hippocampus of MDD patients. This study provides new insights into the antidepressant effects at the level of

neural circuits and suggests important biological pathways by which antidepressants may treat MDD. Future work should extend to other antidepressant treatments (both pharmacological and psychological) to determine both specific and common brain modulators of treatment efficacy.

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