Received: 4 August 2020 | Revised: 29 January 2021 | Accepted: 17 February 2021

DOI: 10.1002/hbm.25391

RESEARCH ARTICLE

WILEY

Eight-week antidepressant treatment reduces functional connectivity in first-episode drug-naïve patients with major depressive disorder

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Funding information
National Key R&D Program of China, Grant/Award Number: 2017YFC1309902; Beijing Municipal Science and Technology Project, Grant/Award Number: Z171100000117016; Beijing Nova Program of Science and Technology, Grant/Award Number: Z191100001119104; Capital Medical Development Research Fund, Grant/Award Number: 2016-1-4111; The 13th Five-year Informatization Plan of Chinese Academy of Sciences, Grant/Award Number: XXH13505; Key Research Program of the Chinese Academy of Sciences, Grant/Award Number: ZDBS-SSW-JSC006; National Key Technology R&D Program, Grant/Award Number: 2015BAI13B01; National Natural Science

Abstract

Previous neuroimaging studies have revealed abnormal functional connectivity of brain networks in patients with major depressive disorder (MDD), but findings have been inconsistent. A recent big-data study found abnormal intrinsic functional connectivity within the default mode network in patients with recurrent MDD but not in first-episode drug-naïve patients with MDD. This study also provided evidence for reduced default mode network functional connectivity in medicated MDD patients, raising the question of whether previously observed abnormalities may be attributable to antidepressant effects. The present study (ClinicalTrials.gov identifier: NCT03294525) aimed to disentangle the effects of antidepressant treatment from the pathophysiology of MDD and test the medication normalization hypothesis. Forty-one first-episode drug-naïve MDD patients were administrated antidepressant medication (escitalopram or duloxetine) for 8 weeks, with resting-state functional connectivity compared between posttreatment and baseline. To assess the replicability of the big-data finding, we also conducted a cross-sectional comparison of resting-state functional connectivity between the MDD patients and 92 matched healthy controls. Both Network-Based Statistic analyses and large-scale network

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Foundation of China, Grant/Award Numbers: 81630031, 81671774

analyses revealed intrinsic functional connectivity decreases in extensive brain networks after treatment, indicating considerable antidepressant effects. Neither Network-Based Statistic analyses nor large-scale network analyses detected significant functional connectivity differences between treatment-naïve patients and healthy controls. In short, antidepressant effects are widespread across most brain networks and need to be accounted for when considering functional connectivity abnormalities in MDD.

KEYWORDS
antidepressants, brain network, functional connectivity, major depressive disorder, resting-state fMRI

1 | INTRODUCTION

Major depressive disorder (MDD) is a highly recurrent disease and a leading cause of disability (Ferrari et al., 2013). Several neuroimaging studies have associated MDD with abnormalities of large-scale brain network functional connectivity (FC), relative to healthy controls (HCs; Alexopoulos et al., 2012; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). Antidepressant medications, as the first-line treatment for adult patients with MDD, are associated with substantial enduring effects on brain network FC (Abdallah et al., 2017; Clark & Beck, 2010; Klaassens, van Gerven, Klaassen, van der Grond, & Rombouts, 2018; McCabe & Mishor, 2011). As antidepressant effects on brain networks appear to be the reverse of the network abnormalities often observed in MDD, some researchers have proposed the hypothesis that the underlying mechanism of antidepressants is to normalize brain alterations related to MDD pathogenesis (Andreescu et al., 2013; Fitzgerald, Laird, Maller, & Daskalakis, 2008). Meta-analyses of early neuroimaging studies on MDD showed that the regions in which activation was decreased in MDD patients overlapped with those in which activation increased following treatment, suggesting a normalization effect of antidepressants (Delaveau et al., 2011; Fitzgerald et al., 2008). This hypothesis is not well supported, since some recent neuroimaging studies have revealed antidepressant effects on brain networks that were not associated with MDD-related network abnormalities (Fu et al., 2015; Gudayol-Ferre, Pero-Cebollero, Gonzalez-Garrido, & Guardia-Olmos, 2015). Resting-state fMRI was used to explore the effects of antidepressant treatment on intrinsic FC of different brain networks in patients with MDD (Abdallah et al., 2017; Fu et al., 2015; Li et al., 2013; Qin et al., 2015; Tian et al., 2020). Fu et al. (2015) identified several independent components of the default mode network (DMN), and the comparison revealed both increased and decreased FC to the DMN in MDD patients after antidepressant treatment. Li et al. (2013) decomposed the DMN into two subnetworks using independent component analysis and explored antidepressant effects on FC of the subnetworks. They found that abnormal FC for MDD patients disappeared after treatment in the posterior DMN, but persisted in the anterior DMN. Qin et al. (2015) used a classification method which could discriminate MDD patients and HCs based on FC of the DMN, affective and sensorimotor networks, and found that 30% of the discriminative connections were normalized after antidepressant treatment (Qin et al., 2015). As the evidence for the normalization hypothesis is contradictory, it's important to test the normalization effect in a longitudinal medication study. Notably, a critical premise for the medication normalization hypothesis is that mood disorders such as MDD are associated with neural abnormalities.

The past decade has seen a surge of resting-state fMRI research exploring the FC correlates of MDD. However, results have been inconsistent: hyper-connectivity and hypo-connectivity of many brain networks have been reported (Kaiser et al., 2015; Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015). A key cause of these inconsistencies is the small sample size of most studies (Button et al., 2013). Another causal driver is the heterogeneity of patients both across and within studies (Davey, Harrison, Yucel, & Allen, 2012; Sheline, Price, Yan, & Mintun, 2010; van Tol et al., 2014). With respect to the course of the disease, patients can be divided into those with first-episode MDD and those with recurrent MDD. Critically, patients with recurrent MDD are more likely to have received antidepressant treatment and cognitive therapy, which could change the brain network FC of MDD patients (Abdallah et al., 2017; Clark & Beck, 2010; McCabe & Mishor, 2011) and also affect that of healthy individuals (van Wingen et al., 2014). One longitudinal study administered the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine to healthy volunteers, and explored how 2-week antidepressant intake altered the intrinsic FC of task-negative and -positive networks with a seed-based approach (van Wingen et al., 2014). They found that the antidepressant decreased FC within the DMN and within the task-positive network. By focusing on the intrinsic FC of several striatal regions, An et al. (2019) showed that 2-week striatal-cortical FC change induced by an antidepressant was associated with later depressive improvement in MDD patients (An et al., 2019). Therefore, the observed brain network difference between MDD patients and healthy controls cannot be simply regarded as reflecting the inherent neuropathology of MDD, and antidepressant effects should be considered.

The complicated composition of patients in the literature makes meta-analyses difficult, as pathophysiological effects are commonly mixed with episode and medication effects. Using meta-analysis on resting-state functional connectivity, Kaiser et al. (2015) reported MDD patients demonstrated hyper-connectivity within the DMN, hypo-connectivity between the DMN and ventral attentional network (VAN), and hypo-connectivity within the frontoparietal network (FPN; Kaiser et al., 2015). However, although the authors conducted supplementary analyses on the effects of medication on FC, the limited data reported prevented investigation of this confound in depth. Recent studies revealed hypo-connectivity within the DMN in patients with first-episode drug-naïve (FEDN) MDD (Wang, Yu, Wu, Wu, & Wang, 2019), and in unremitted MDD patients (Goldstein-Piekarski et al., 2018). By meta-analyzing brain structural and functional studies on FEDN MDD patients, Wang, Zhao, et al. (2017) and Wang, Han, Nguyen, Guo, & Guo (2017) showed a complex pattern of neural abnormality in these modalities in patients (Wang, Han, et al., 2017; Wang, Zhao, et al., 2017).

Accordingly, we initiated the REST-meta-MDD Project to address the limited statistical power and clinical heterogeneity pervasive in the field (Yan et al., 2019). Our group aggregated resting-state fMRI data from over 1,000 MDD patients and compared intrinsic FC within the DMN and between several large-scale networks. The result showed that FC abnormalities of the DMN were not present in FEDN MDD patients (Yan et al., 2019). However, reduced FC of visual and somatosensory network, dorsal attentional network (DAN), and DMN was found in the entire sample of MDD patients relative to HCs. The FC reduction mainly occurred in patients with recurrent MDD, many of whom had a history of medication treatment. Further, the reduction was not associated with illness duration but with medication treatment status. Thus, this big-data study did not support the medication normalization hypothesis (Yan et al., 2019); whether the observed FC reduction was caused by antidepressant treatment would require a longitudinal study.

The current study aimed to directly explore this issue using a medication follow-up design in MDD patients by comparing post-treatment and baseline data. We administered treatment for 8 weeks with a selective serotonin reuptake inhibitor (SSRI) or SNRI to FEDN MDD. Large-scale brain network FC was compared between post-treatment and baseline, to examine the effects of antidepressant treatment in MDD. A group of matched healthy controls (HCs) was also recruited and compared to pre-treatment patients. According to the controversial medication normalization hypothesis, the pre-treatment patients should differ from the HCs in intrinsic network FC, some of which would return to normal levels after treatment.

2 | METHODS AND MATERIALS

2.1 | Participants

Sixty-three right-handed, first-episode drug-naïve patients with MDD recruited from the Outpatient Department of Peking University Sixth Hospital were assessed for eligibility. Diagnoses were confirmed on the basis of the Mini International Neuropsychiatric Interview (Sheehan et al., 1998) by experienced psychiatrists. Depressive symptom was assessed by experienced independent evaluators using the 17-item Hamilton Rating Scale for Depression (HRSD). Inclusion required scoring 17 or above on the 17-item HRSD, and being in a first episode of depression. None had comorbid intellectual disability, any other Axis I disorder or Axis II personality disorder, bipolar disorder, or comorbid lifetime or current diagnosis of psychotic disorder. Patients with alcohol dependence, substance dependence, or suffering from severe and unstable physical disease, and women in pregnancy or breast-feeding were also excluded. We then made sure that the recruited patients suffered from MDD for <2 years or did not have chronic depression. The absence of comorbidities further ensured that the MDD patients had not received other types of psychotropic treatment or medication. In our study, one SSRI (escitalopram) and one SNRI (duloxetine) were selected for investigation, because both SSRIs and SNRIs are the first-line treatments for adult patients with MDD based on national guidelines for the Prevention and Treatment of Major Depressive Disorder in China (Li & Ma, 2015). Fifty-nine eligible patients were assigned to escitalopram treatment (n = 23) or duloxetine treatment (n = 36), based on investigators' clinical practice. Of these 59 patients, 10 discontinued treatment due to poor efficacy or intolerable adverse effects, and eight patients declined follow-up scans. After their exclusion, 41 patients remained in the longitudinal study.

The 41 longitudinal patients (21 females; mean age = 30.5 years, range 19 to 55) completed 8-week medication treatment, and received clinical assessment and resting-state fMRI scans at baseline and posttreatment. Sixteen took the SSRI escitalopram, while the other 25 took the SNRI duloxetine. The mean initial doses of escitalopram and duloxetine were 10 mg/day (SD = 0) and 52.9 mg/day (SD = 13.1), respectively. Dose titration was completed within 2 weeks based on patient response. At the end of treatment, the mean doses of escitalopram and duloxetine were 17.3 mg/day (SD = 3.2) and 62.9 mg/day (SD = 7.2), respectively. In addition, 92 healthy participants (58 females; mean age = 30.3 years, range 19 to 58) with matched age and educational level to the patients with MDD, and without a personal or a positive family history for any mental illness were recruited from the community and universities near the hospital. The HCs were scanned once. The study was approved by the independent Ethics Committee of Peking University Sixth Hospital, and written informed consent was obtained from all participants before data collection.

2.2 | Data acquisition

Brain imaging was performed on a 3 T Siemens Trio scanner in the 306th Hospital of the People's Liberation Army of China. For resting-state scanning, this present study employed eyes-closed rather than eyes-open, since eyes-closed is the easiest way to enter resting state and can increase compliance in patients. Participants were instructed

to remain still in the scanner and keep their eyes closed, and not to think about anything in particular (e.g., counting) or fall asleep. Although individuals in the eyes-closed condition are more likely to have drowsiness and fall asleep (Allen, Damaraju, Eichele, Wu, & Calhoun, 2018), none of the subjects included in this study fell asleep during scanning, as self-reported by them after scanning. The resting-state scanning run lasted for 7 min during which 210 functional images were collected. Functional images were acquired using the T2-weighted gradient-echo echo-planar imaging (EPI) sequence with parameters: flip angle, 90°; repetition time (TR), 2000 ms; echo time (TE), 30 ms; matrix, 64 × 64; field of view, 210 × 210 mm^2; slice thickness/gap, 4.0 mm/0.8 mm; 30 interleaved axial slices covering the whole brain. After the resting-state scan, structural images were also collected for each subject, to facilitate spatial normalization. Structural images were acquired using the T1-weighted magnetization-prepared rapidly acquired gradient-echo (MPRAGE) sequence with parameters: flip angle, 9°; TR, 2300 ms; TE, 3.01 ms; matrix, 256 × 256; spatial resolution, 1 × 1 × 1 mm; thickness, 1 mm; 176 sagittal slices.

2.3 | Data pre-processing

Brain imaging data were preprocessed with the Data Processing Assistant for Resting-State fMRI (DPARSF; http://rfmri.org/DPARSF; Yan & Zang, 2010), which is based on MATLAB, SPM12 (http://www.fil.ion.ucl.ac.uk/spm), and DPABI (Yan, Wang, Zuo, & Zang, 2016). The first 10 functional images were removed to allow for signal stabilization. The remaining functional images were corrected for slice acquisition timing difference and head motion. Then nuisance signals were regressed out, including white matter signal, cerebrospinal fluid signal, linear trend, and the signal associated with the 24 Friston head-motion parameters. Derived functional images were coregistered with the corresponding structural images which were segmented and normalized to Montreal Neurological Institute (MNI) space using DARTEL. The functional images were then normalized to MNI space with warped parameters, and resampled to 3 mm cubic voxels. The normalized functional images were then bandpass filtered (0.01–0.1 Hz). Participants with maximum head motion larger than 3 mm in displacement or 3° in rotation were excluded from further analyses, as well as those with mean frame-wise displacement (FD) larger than 0.2 mm. Overall, one MDD patient and seven HCs were excluded. For the remaining 40 MDD and 85 HCs, head motion indicated by mean FD did not differ significantly between baseline and posttreatment in patients with MDD ($p > .05$; mean FD = 0.103 ± 0.036 for baseline, mean FD = 0.095 ± 0.035 for posttreatment), or between patients with MDD and HCs (all $p > .05$; mean FD = 0.103 ± 0.038 for HCs).

2.4 | Edge-based functional connectivity comparison

To examine the effects of antidepressant treatment on brain networks, we first compared edge-based FC between baseline and posttreatment in MDD, using the Network-Based Statistic (NBS; https://www.nitrc.org/projects/nbs) approach. NBS can provide more statistical power than mass-univariate analysis (Zalesky, Fornito, & Bullmore, 2010). To examine whether degree of improvement in clinical symptoms was directly related to the effects of antidepressant treatment on FC, we further analyzed the relationship between symptom improvement and FC change from baseline to posttreatment in MDD. Degree of symptom improvement was indexed by reducing rate of HRSD score as: ΔHRSD = (HRSD-baseline − HRSD-posttreatment)/HRSD-baseline × 100%. To identify abnormalities of MDD and confirm our previous findings, we also conducted between-group contrasts to compare FC between treatment-naïve patients with MDD and HCs, and between patients with MDD after treatment and HCs.

The Dosenbach atlas, which defines 160 ROIs (or nodes) distributed across the brain, was used (Dosenbach et al., 2010). Each node was a sphere with a radius of 5 mm. Since the cerebellum was not completely covered in all scans, we excluded it from analyses. After deleting 18 ROIs in the cerebellum, 142 ROIs remained. For each ROI, BOLD signals were extracted and averaged across all voxels in the ROI. Edge-based functional connectivity (FC) for any pair of two ROIs was computed as the Pearson's correlation coefficient of the BOLD signals, which was then transformed to z-scores using Fisher's r-to-z formula.

For the 10,011 pairs of ROIs (142 × 141/2), NBS analyses with *T* tests were conducted to compare FC for the above contrasts (for the between-group contrasts, sex, age, and head motion were added in the linear model as covariates), respectively. As to the NBS approach, a cluster (or subnetwork) is defined by interconnectedness of suprathreshold edges in topological space. The primary threshold was set at $p < .0005$ (one-tailed, the same below unless otherwise stated) in T-tests for every edge, as a strict threshold can decrease the family-wise error rate. As primary thresholding identified several clusters, the number of suprathreshold edges was counted for each cluster observed. Permutation with 10,000 iterations was employed to generate distributions of suprathreshold edge numbers in a cluster (the one with most suprathreshold edges) under the null hypothesis. For each permutation of the baseline versus posttreatment contrast in MDD, the two levels of time condition were randomly exchanged with each subject as a block. For each permutation of examining the linear effect of ΔHRSD on FC change, the ΔHRSD was randomly reassigned to the MDD. For each permutation of the between-group contrasts, group membership (MDD vs. HCs) was randomly exchanged, with group size unchanged. The significance level for each observed cluster found in the actual contrasts was determined by contrasting its suprathreshold edge number with the null distribution of edge numbers derived from 10,000 permutation. Two directions of the contrasts in NBS analyses were tested separately, and one-tailed p value was derived so that $p < .025$ was taken as significant.

To better describe significant clusters obtained in the NBS-based contrast, we also classified suprathreshold edges by their membership in the networks defined by Yeo et al. (2011). Since the limbic network

contained few ROIs, we used the subcortical network instead. The seven networks are the visual network (VN, 22 ROIs located in the occipital lobe and posterior fusiform gyrus), somatosensory-motor network (SMN, 29 ROIs located in the precentral and postcentral gyrus and auditory cortex), dorsal attention network (DAN, 14 ROIs located in the temporo-occipital cortex, angular gyrus, superior parietal lobule, and premotor cortex), ventral attention network (VAN, 16 ROIs located in the supramarginal gyrus, insula, middle frontal gyrus, supplementary motor area), subcortical network (SCN, seven ROIs located in the putamen and thalamus), frontoparietal network (FPN, 21 ROIs located in the superior parietal lobule, precuneus, lateral frontal cortex, and dorsal cingulate cortex), and default mode network (DMN, 33 ROIs located in the inferior parietal lobule, posterior cingulate cortex, lateral temporal cortex, and ventral and medial prefrontal cortex). We counted the number of edges falling into each of the seven within-network classes and 21 between-network classes.

2.5 | Large-scale network FC comparison

Beyond NBS analysis, we also validated our results by analyzing large-scale within- and between-network FC. Within- and between-network FC were calculated by averaging the FC z-scores across all involved edges. Since we defined seven networks, this resulted in seven within-network averaged FC values and 21 between-network averaged FC values. The effects of antidepressant treatment on large-scale network FC were examined by comparing large-scale network FC between posttreatment and baseline in the MDD patients, with paired-sample *T* tests. The association of symptom improvement and FC change was examined by correlating ΔHRSD with FC change from baseline to posttreatment. We then compared large-scale network FC between baseline of patients with MDD and HCs, and between the posttreatment scan for patients and the HCs, respectively, using two-sample *T* tests with sex, age, and head motion (mean FD) as covariates. False discovery rate (FDR) was employed to correct for multiple comparisons across seven within-network and 21 between-network FC values (corrected to $p < .025$).

3 | RESULTS

3.1 | Demographic information

After 8 weeks of antidepressant treatment, the MDD patients showed improvement in clinical symptoms, as revealed by substantial reduction in HRSD score ($t = 26.7$, $p < .001$; Table 1; Table S1 for SSRI and SNRI separately). Of the 41 patients who completed the 8 weeks of treatment and provided longitudinal scans, 36 achieved clinical remission (i.e., HRSD score at eighth week ≤ 7). It should be noted that the rate of remission would be largely inflated by discounting the dropout patients who were less likely to remit. The patients with MDD and HCs did not differ significantly in sex, age, and education level (all $p > .05$; Table 1).

3.2 | Edge-based functional connectivity

We first examined the effect of 8-week antidepressant treatment on edges in the MDD patients. Since the patients with MDD assigned to SSRI did not differ from those assigned to SNRI in terms of FC change after treatment in NBS analysis (max suprathreshold edge number = 2, $p = .550$), we merged these patients in the following analyses. NBS analysis revealed a significant cluster ($p < .001$) consisting of 68 ROIs and 107 edges with decreased FC after treatment (Figure 1). The suprathreshold edges with decreased FC involved all the networks, suggesting extensive impact of antidepressant treatment on brain networks (Figure 2a and Table S2). More affected edges were connected to ROIs in the VN and DAN, and fewer in the FPN and DMN. Separate NBS analyses on SSRI ($n = 16$) and SNRI ($n = 24$) also revealed similar 8-week medication effects associated with FC reduction (see Section S1). In addition, the finding of decreased FC after antidepressant treatment was replicated using the atlas developed by Craddock et al., which divided the brain into 200 regions (Craddock, James, Holtzheimer 3rd, Hu, & Mayberg, 2012; see Section S2).

We then examined whether the FC decrease after treatment was associated with symptom improvement. Due to large variation of reduction in HRSD score and small number of unremitted patients with MDD, the factor of symptom improvement was regarded as a

TABLE 1 Demographic and clinical information

	MDD ($n = 40$)	HCs ($n = 85$)	t/x^2	p (two-tailed)
Sex (M/F)	19/21	31/54	1.379	.240
Age (years)	30.23 (8.21)	29.54 (9.04)	0.406	.685
Education (years)	13.90 (3.03)	14.69 (2.21)	1.658	.100
HRSD baseline	24.43 (4.19)	NA	NA	NA
HRSD 8th week	4.88 (3.58)	NA	NA	NA

Note: Values shown are mean (count number for sex), statistics, and p value of two-sample *T* tests comparing MDD patients and HCs (Chi-square test for sex). Standard deviations are shown in parentheses. The participants only included those entering into fMRI statistical analyses, with one MDD and six HCs being excluded due to large head motion during scanning.
Abbreviations: F, female; HCs, healthy controls; HRSD, 17-item Hamilton Rating Scale for Depression; M, male; MDD, major depressive disorder; NA, not applicable.

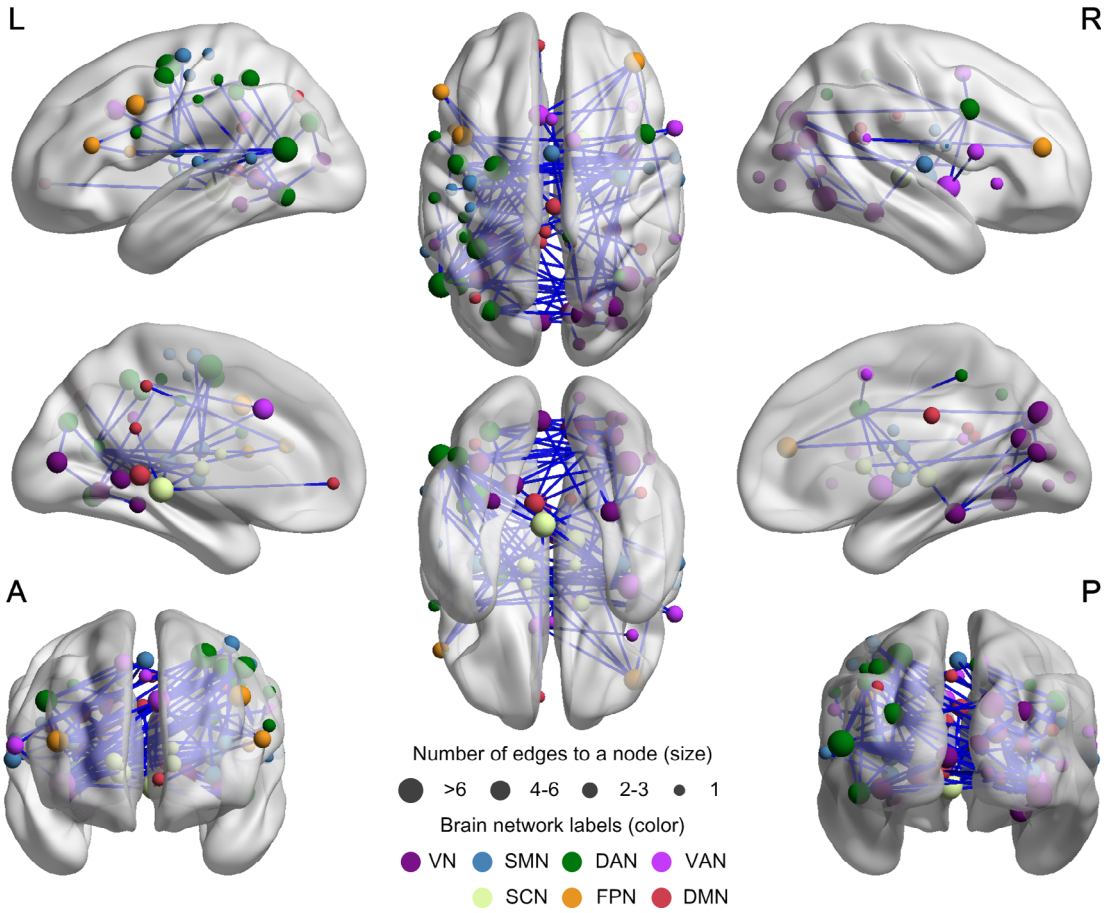

FIGURE 1 Eight-week antidepressant treatment decreases edge-based FC in MDD patients (n = 40). The brain maps show the affected edges (lines) and their connecting nodes (spheres) from several perspectives. The size of a node indicates how many affected edges are connected to this sphere. Bigger nodes have more affected edges than smaller ones. The color of a node indicates which network it belongs to. The color of edges (blue) indicates that the FC is decreased in MDD patients after treatment. A, anterior; DAN, dorsal attention network; DMN, default mode network; FC, functional connectivity; FPN, frontoparietal network; L, left; P, posterior; R, right; SCN, subcortical network; SMN, somatosensory network; VAN, ventral attention network; VN, visual network

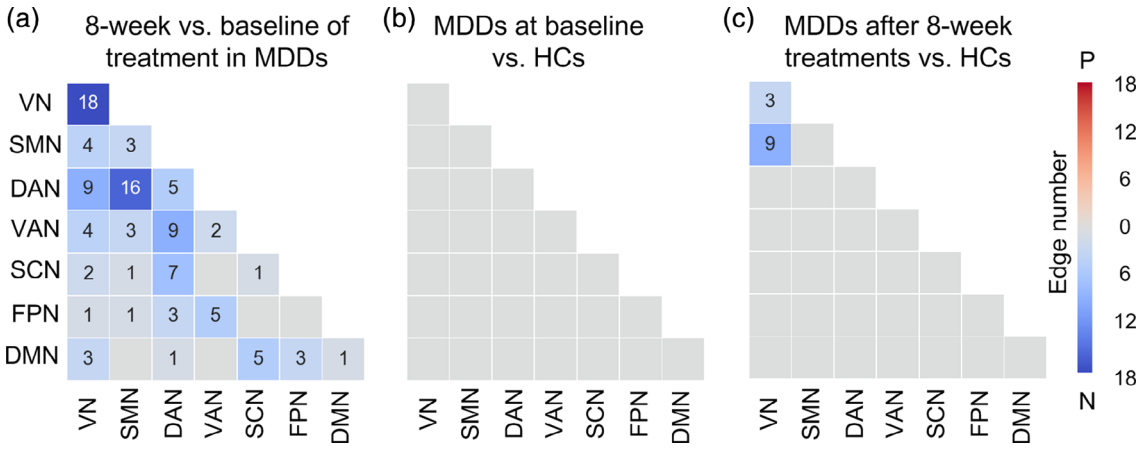

FIGURE 2 Antidepressant effect and group difference in edge-based FC. Heatmaps show the number of significant edges for each pair of networks for each of the three contrasts: (a) 8-week versus baseline of treatment in MDD (n = 40); (b) MDD at baseline versus HCs (n = 40 vs. n = 85); (c) MDD after treatment versus HCs (n = 40 vs. n = 85). HCs, healthy controls; MDD, patients with major depressive disorder. For network abbreviation, please refer to the legend of Figure 1

continuous variable indexed by reducing rate of the HRSD score. NBS analysis showed a marginally significant cluster (p = .050) consisting of 13 ROIs and 14 edges with negative correlation between FC change (baseline minus posttreatment) and ΔHRSD. The negative correlation indicated that the MDD patients who responded better showed less FC decrease after treatment. The cluster included connections of regions in the VN to regions in the SMN, FPN, and DMN, which did not overlap with connections showing FC reduction after treatment. No significant cluster with positive correlation was observed (max suprathreshold edge number = 1, p = .688).

NBS analysis of the MDD patients at baseline versus HCs did not reveal any significant cluster (max suprathreshold edge number = 1, p = .560). NBS analysis of the MDD patients after treatment versus HCs revealed a cluster at trend level (p = .076) consisting of 12 ROIs and 12 edges with decreased FC in MDD patients. This cluster is presented to illustrate the FC change after treatment, although it did not reach p < .025 significance in permutation test. The suprathreshold edges of this cluster with decreased FC in the MDD patients after treatment as compared to HCs involved connections of regions in the VN to regions in the VN and SMN (Figure 2c and Table S3), and partially (3/12 edges) overlapped with the edges showing FC reduction after treatment.

3.3 | Large-scale network functional connectivity

In the validation analysis of antidepressant effects, we found that MDD patients demonstrated decreased within-network FC of the VN, SMN, DAN, VAN, and SCN after 8 weeks of treatment (Figure 3 and Table 2). In addition, they also demonstrated decreased between-

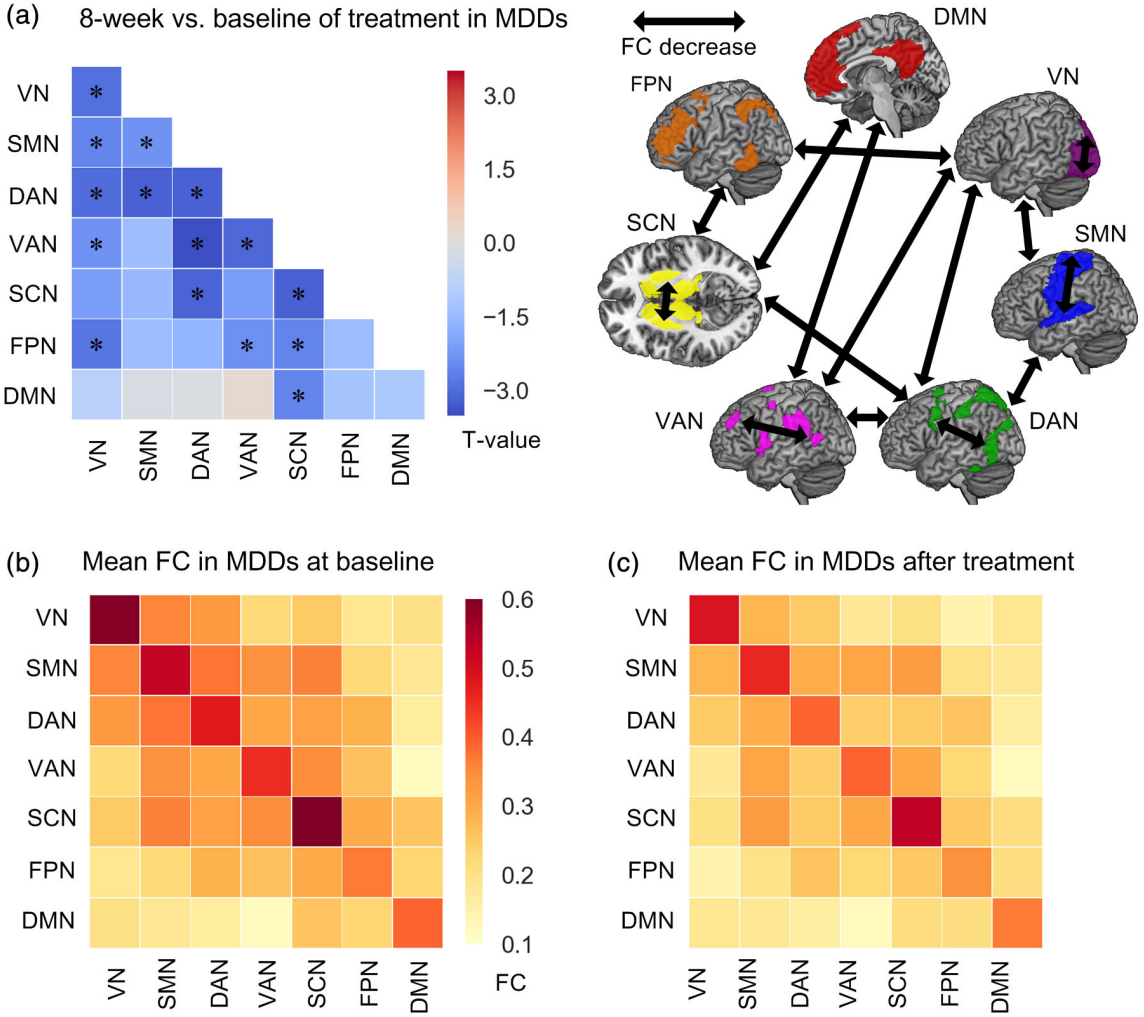

FIGURE 3 Eight-week antidepressant treatment decreases large-scale network FC in MDD patients (n = 40). (a) The upper-left heatmap shows the T values of paired-sample T tests on FC for each pair of networks between 8-week treatment and baseline. For T value color bar, blue indicates FC decrease while red indicates FC increase after treatment. The schematic diagram on the upper-right panel shows the network connections with significant FC decrease for the seven networks after treatment. The bottom heatmaps show the mean FC for each pair of networks in MDD patients (b) at baseline and (c) after treatment. The color bar indicates FC value. FC, functional connectivity; MDD, patients with major depressive disorder. For network abbreviations, please refer to the legend of Figure 1. *FDR-corrected p < .05 (two-tailed)

TABLE 2 Decreased large-scale network FC after 8-week antidepressant treatment in MDD patients (n = 40)

	VN	SMN	DAN	VAN	SCN	FPN	DMN
VN	−2.93*						
SMN	−2.55*	−2.32*					
DAN	−2.98*	−3.17*	−3.17*				
VAN	−2.34*	−1.44	−3.44*	−3.04*			
SCN	−2.09	−1.52	−3.11*	−2.13	−3.15*		
FPN	−2.79*	−1.43	−1.60	−2.37*	−2.59*	−1.48	
DMN	−0.83	−0.11	−0.11	0.24	−2.55*	−1.25	−1.13

Note: T values of paired-sample T tests are shown.
Abbreviations: DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; VAN, ventral attention network; VN, visual network; SCN, subcortical network; SMN, somatosensory network.
*Significant after False Discovery Rate correction to $p < .05$ (two-tailed) among seven within-network and 21 between-network connections.

network FC for 10 pairs of networks after treatment, including VN-SMN, VN-DAN, VN-VAN, VN-FPN, SMN-DAN, DAN-VAN, DAN-SCN, VAN-FPN, SCN-FPN, and SCN-DMN (Figure 3 and Table 2). None of network FC values was increased after treatment. This finding reflected extensive network FC decrease in the MDD patients after 8-week of antidepressant treatment. In addition, although we did not observe significant correlations between network FC change (baseline minus posttreatment) with ΔHRSD after FDR correction, three pairs of networks with FC change showed a trend negative correlation with ΔHRSD ($p < .025$, uncorrected), including VN-SMN, VN-DAN, and VN-FPN, a subset of those with decreased FC after treatment.

For the comparison between the MDD patients at baseline and HCs, none of the within-network or between-network FC values differed significantly (Figure 4 and Table 3, upper panel). Network FC also did not differ significantly between MDD patients after treatment and HCs (Figure 4 and Table 3, bottom panel).

4 | DISCUSSION

The present study aimed to disentangle antidepressant effects from the effects of MDD pathophysiology, and to test the medication normalization hypothesis. We explored antidepressant effects by administering an SSRI or an SNRI for 8 weeks to FEDN MDD patients, and comparing their network FC before and after medication. Both NBS and large-scale network analyses revealed that antidepressants decreased intrinsic FC extensively, affecting almost all brain networks. We also explored the effect of MDD by comparing intrinsic FC between MDD patients before treatment and healthy controls, and did not detect significant differences in FC, thus failing to support the medication normalization hypothesis.

The opinion that large-scale functional networks in MDD patients are abnormal has been widely held (Alexopoulos et al., 2012; Kaiser et al., 2015). The pathophysiology of MDD remains largely unknown despite substantial neuroimaging research on MDD, which is complicated by tendencies of about half of patients to achieve temporary remission after several weeks of treatment (Gaynes et al., 2009; Holtzheimer & Mayberg, 2011). Notably, a large number of previous studies comparing MDD patients and HCs cannot determine whether observed differences in functional networks are caused by the disease itself or by antidepressant treatment. This is because some of the MDD patients included in those studies were taking or had ever taken antidepressant drugs. We found that antidepressant treatment substantially affected functional networks of MDD patients by decreasing intrinsic network FC. This was evidenced in both the NBS analysis and the large-scale network analysis of FC. This finding was in accord with previous research showing reduced subcortical–cortical FC in MDD patients after antidepressant treatment (McCabe & Mishor, 2011; van Wingen et al., 2014), and also with our recent finding that decreased DMN FC in MDD patients was associated with their medication use (Yan et al., 2019; also see Section S3 for correlation analyses of FC and depressive severity at baseline and at post-treatment). The antidepressant effect on intrinsic FC was observed in almost all the brain functional networks defined by Yeo et al. (2011) and in subcortical regions, indicating widespread effects on the brain. Due to the widespread effects induced by antidepressant action, brain functional network alteration, especially FC reduction, in MDD patients on medication or with history of medication use should be interpreted with extreme caution.

We found the DMN, VN, SMN, DAN, VAN, and SCN were all affected by treatment, consistent with our recent finding of intrinsic FC decrease involving the DMN, VN, SMN, and DAN in MDD patients (mainly those with recurrent MDD), compared to HCs (Yan et al., 2019). Brain regions of the VN and SMN support somatosensory, motor, auditory, and visual processing which are considered unimodal. Previous studies revealed that administration of SSRIs, such as citalopram or sertraline, to healthy volunteers decreased SMN FC (Klaassens et al., 2015; Klaassens et al., 2018). Regions of the DAN and VAN are spatially adjacent to regions of the VN and SMN in the brain (Yeo et al., 2011), and constitute the so-called "task-positive network" which routinely activates during goal-directed tasks (Fox, 2005). Neural activity in regions of these networks is thus externally directed, while activity in the DMN regions is internally directed

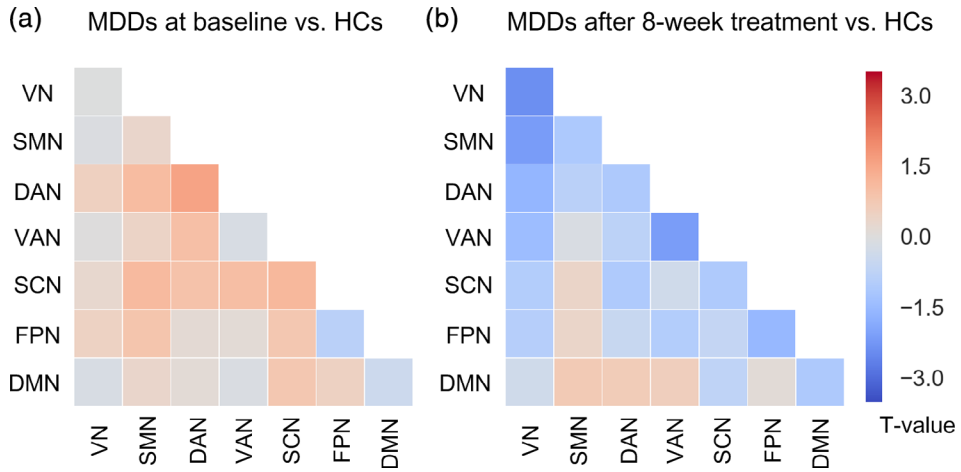

FIGURE 4 Indifference of large-scale network FC between MDD patients and healthy controls. The heatmaps show *T* values of two-sample *T* tests on FC (a) between MDD at baseline with HCs (n = 40 vs. n = 85), and (b) between MDD after treatment with HCs (n = 40 vs. n = 85), for all pairs of networks. For the *T* value color bar, blue indicates FC decrease while red indicates FC increase in MDD as compared to HCs. HCs, healthy controls; MDD, patients with major depressive disorder. For network abbreviations, please refer to the legend of Figure 1

TABLE 3 Large-scale network FC comparisons between HCs (n = 85) and MDD patients (n = 40) at baseline (upper) and posttreatment for 8 weeks (lower)

	VN	SMN	DAN	VAN	SCN	FPN	DMN
Baseline							
VN	−0.01						
SMN	−0.08	0.34					
DAN	0.54	1.07	1.58				
VAN	0.01	0.42	1.00	−0.15			
SCN	0.30	1.10	0.92	1.02	1.16		
FPN	0.49	0.86	0.18	0.14	0.80	−0.84	
DMN	−0.14	0.34	0.14	−0.10	0.81	0.51	−0.43
Posttreatment							
VN	−2.38*						
SMN	−2.14*	−1.10					
DAN	−1.59	−0.84	−1.07				
VAN	−1.43	−0.12	−0.79	−2.12*			
SCN	−0.97	0.40	−1.04	−0.34	−1.06		
FPN	−0.91	0.37	−0.53	−0.98	−0.61	−1.55	
DMN	−0.33	0.72	0.67	0.57	−0.71	0.13	−1.09

Note: T values of two-sample *T* tests are shown. The contrasts of MDD at baseline versus HCs (upper panel), and MDD after 8 weeks of treatment versus HCs (bottom panel) were conducted. For each contrast, neither within-network nor between-network FC differed significantly between groups after FDR correction. For network abbreviations, please refer to the legend of Table 1.
Abbreviations: HCs, healthy controls; MDD, major depressive disorder.
*p < .05 (two-tailed), uncorrected.

(Andrews-Hanna, Smallwood, & Spreng, 2014). The DMN regions are proposed to support mind wandering, mentalizing, and self-reflection (Andrews-Hanna et al., 2014), which are associated with the core symptom, rumination, of MDD. In the current study, the DMN was less affected (lower ratio of edges showing decreased FC, and fewer significant pairs of large-scale networks) than other networks. It could be that short-term antidepressant mainly reduces intrinsic FC of the externally directed networks, affecting the internally directed network less. The employment of an eyes-closed condition might also explain the lesser extent of effects on the DMN. Previous studies revealed higher test–retest reliability in an eyes-open condition than an eyes-closed condition for the FC measure related to the DMN (Patriat et al., 2013; Zou et al., 2015), and increased reliability when removing the impact of sleep (Wang, Han, et al., 2017). Lower reliability might thus result in lower significance levels of antidepressant effect on FC in the DMN, as compared to other networks. It is also possible that

the FC decrease in the DMN only happened to some of the patients (e.g., in nonremitters but not in remitted MDD patients) (Goldstein-Piekarski et al., 2018). We speculate that substantial antidepressant effect on the DMN may need longer treatment, and be achieved through connections with externally directed networks. Future long-term follow-up studies using both eyes-open and eyes-closed conditions are needed to address this issue.

We further compared MDD patients before treatment with HCs. The patients were suffering their first episode of MDD, had never been treated with antidepressants before this study, and had no psychiatric comorbidities. No significant difference was found in intrinsic network FC between these two groups before treatment (even when the threshold was lowered to $p < 0.1$, uncorrected), and this finding partly contradicts the traditional understanding that large-scale network dysfunction underlies core abnormalities of MDD. Regarding network dysfunctions in MDD, previous findings are inconsistent with each other (Kaiser et al., 2015; Mulders et al., 2015). By reviewing previous research on MDD, Mulders et al. (2015) showed inconsistent findings of within-FPN and FPN-DMN FC change in MDD. It is also possible that the potential effects of the brain's reactivity to the disease may make FC change (if any) difficult to observe. In addition, a recent big-data study by our group revealed that FEDN MDD patients did not show abnormalities in intrinsic FC for almost all brain networks (except within-VN; Yan et al., 2019). With respect to null findings in FEDN MDD patients, the present study is consistent with this big-data study. More importantly, as we mentioned above, MDD patients recruited in many previous studies have a history of antidepressant treatment, so that medication effects likely confound observed differences between patients and healthy individuals. The phenomenon of publication bias should also be considered. Studies reporting statistically significant results are more likely to be published than are negative studies, especially when sample sizes are small (Bakker, van Dijk, & Wicherts, 2012). Notably, the null findings were confined to intrinsic FC as revealed by the resting-state approach. Many previous studies have shown abnormalities of task-related activation and connectivity in FEDN MDD patients compared to HCs (Desseilles et al., 2011; Godlewska, Browning, Norbury, Cowen, & Harmer, 2016; Ho et al., 2015; Keren et al., 2018). Resting-state FC and task-related neural activity reflect different aspects of the brain, and normal levels of intrinsic FC in patients before treatment does not imply normal levels of activation and connectivity during tasks. Previous multimodal studies on MDD or antidepressant have observed dissociated effects across states (resting vs. task) or across modalities (functional vs. structural; Fu et al., 2015; Wang, Zhao, et al., 2017). Furthermore, together with our previous null results of large-sample FEDN MDD versus HCs (Yan et al., 2019), as we did not observe FC abnormality for the MDD patients, our findings lend no support for the normalization hypothesis in terms of intrinsic network FC.

The pharmacological mechanism of SSRI or SNRI is to increase serotonin content in the synaptic cleft. As a neurotransmitter, serotonin plays prominent roles in modulating neuronal connectivity. Serotonin has been shown to suppress the firing of dopamine neurons (Blier & El Mansari, 2013; Dremencov, El Mansari, & Blier, 2009), and dopamine depletion may decrease FC during resting state and a task (Cole et al., 2013; Nagano-Saito et al., 2008). These investigations may explain why all the brain networks affected by 8-week antidepressant treatment uniformly showed decreases (but no increase) in intrinsic FC. Since abnormalities in brain network connectivity were not present in patients with FEDN MDD, the antidepressant effect cannot be simply regarded as a normalization process. It is possible that a part of the decreased FC in extensive networks associated with the antidepressant treatment is a compensatory effect underlying remission of clinical symptoms in MDD patients. As revealed by previous studies, during a visual attention task, FEDN MDD patients showed abnormal activation and connectivity patterns of the visuo-attention system (VN and DAN here; Desseilles et al., 2009; Desseilles et al., 2011). In autobiographical memory tasks, MDD patients showed increased activation in medial prefrontal cortex and frontal operculum (VAN and DMN regions; Young, Bellgowan, Bodurka, & Drevets, 2013). The resting-state neural activity amplitude was increased for FEDN MDD patients in the bilateral supplementary motor area (SMN here; Wang, Zhao, et al., 2017). It is possible that the abnormalities of task-related activation and connectivity might be mitigated by decreased intrinsic connectivity after treatment. For example, brain activation has been shown to increase during rumination conditions when individuals repeatedly focus on distressing thoughts (Zhou et al., 2019), and weaker intrinsic connectivity between the DMN regions, induced by antidepressants, may mitigate rumination in MDD patients by cutting off repetition and spreading of rumination-related activation across the brain. Notably, the observed effects of antidepressants on FC was not merely constrained to the MDD patients without comorbidities examined in this study, as previous studies showed that antidepressants induced similar effects on the brain networks of healthy controls (Klaassens et al., 2015; Klaassens et al., 2018; van de Ven, Wingen, Kuypers, Ramaekers, & Formisano, 2013; van Wingen et al., 2014). Furthermore, as revealed by the negative correlation between intrinsic FC change and symptom improvement, the MDD patients who responded better showed less FC decrease after antidepressant treatment. The observed negative correlation may be affected by dose titration which was administered in an individualized way. It might be that patients whose clinical symptoms improved to a larger extent took smaller doses of medication (see Table S4 for weak evidence), showing less FC reduction after treatment. The extent of intrinsic FC change induced by antidepressant treatment was mainly driven by how the brain responded to treatment and by the dosage of treatment. For these reasons, it is difficult to unravel the nature of such negative correlation. More large-scale randomized trials are needed to unravel the intrinsic abnormalities associated with MDD (e.g., the EMBARC study [Trivedi et al., 2016], although they only have baseline fMRI data but no post-treatment fMRI data) and the mechanisms through which antidepressants induce remission of MDD.

As to the approach of data analysis, the present study differed from previous ones in that we examined antidepressant effects and MDD-related abnormalities on intrinsic FC across all pairs of brain regions and networks. Many early neuroimaging studies on these

issues mainly used seed-based FC analysis and focused on connections of one or more networks, especially the default mode network (Andreescu et al., 2013; Goldstein-Piekarski et al., 2018; Peng et al., 2015; Sheline et al., 2010; van Wingen et al., 2014). Hereby, we observed that most of the brain networks were affected by antidepressant treatment. In addition, compared with recent studies that used global measures based on FC (Abdallah et al., 2017; Tian et al., 2020; Wang et al., 2019), we combined NBS analyses and large-scale brain network analyses, which showed consistent results. Notably, the NBS approach can reveal a cluster (or subnetwork) of pairs of brain regions with abnormal FC rather than some isolated pairs, and provide more statistical power than mass-univariate analysis (Zalesky et al., 2010). It is more suitable for comparing FC across all pairs of regions due to extensive interconnection of the brain.

One major limitation of the present study concerns the two kinds of drugs administrated to the patients. Escitalopram selectively inhibits 5-HT reuptake, while duloxetine inhibits both 5-HT and norepinephrine reuptake. The present study could thus not determine whether the observed extensive FC decrease after treatment was due to SSRI or SNRI (see Section S1 for the separate analyses of their effects on FC). The observation of no significant difference between the MDD patients taking SSRI and those taking SNRI partly supports a more critical role for 5-HT reuptake inhibition. The second limitation is that we did not employ a randomized controlled trial design, which could be ethically challenging in practical treatment. Due to the personalized dose titration, antidepressant dosage from baseline to 8-week treatment differed among patients, and was partly dependent on their symptom improvement at an early stage of treatment (e.g., 2-week). The dose titration might thus affect the relationship between symptom improvement and FC change, but it is unlikely to affect the overall pattern of antidepressant-induced intrinsic FC change. Without a control group of MDD patients taking placebo, we cannot precisely quantify the effect of medication on brain network FC or exclude the effect of disease progression. The third limitation is the sample size of our study. Much larger sample size is needed for between-subject designs than within-subject designs to detect an effect (Fan et al., 2019). Thus, null results in comparing MDD patients before treatment and HCs could be due to this design difference. Notably, when loosening the threshold, we did not find any change in the comparison of MDD at baseline versus HCs, but did find some changes in the comparison of MDD posttreatment versus HCs. Finally, although we did not observe abnormalities of intrinsic FC in FEDN MDD patients, future multimodal studies combining resting state and tasks can unravel the neural abnormalities of MDD and the mechanisms through which antidepressant action remits MDD.

In conclusion, the current study revealed that after 8-week antidepressant treatment, intrinsic FC in patients with FEDN MDD was substantially decreased. The FC reduction involved extensive brain networks, mainly the externally directed networks. In accord with our previous study, in this study we did not observe abnormalities in intrinsic FC for patients with FEDN MDD compared to healthy controls. Taken together, the effects of antidepressants on extensive brain networks must be taken into account when interpreting FC alterations found in patients, especially for those who have ever taken medication, such as patients with recurrent MDD.

ACKNOWLEDGMENTS

This study was supported by the National Key R&D Program of China (2017YFC1309902), the National Natural Science Foundation of China (No. 81671774 and 81630031), Beijing Municipal Science and Technology Project (Z171100000117016), Beijing Nova Program of Science and Technology (Z191100001119104), Capital Medical Development Research Fund (2016-1-4111), National Key Technology R&D Program (2015BAI13B01), the 13th Five-year Informatization Plan (XXH13505) of Chinese Academy of Sciences, and the Key Research Program of the Chinese Academy of Sciences (ZDBS-SSW-JSC006).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Le Li, Yun-Ai Su, Tian-Mei Si, and Chao-Gan Yan designed this study. Yun-Ai Su, Yan-Kun Wu, Ke Li, and Ji-Tao Li acquired the data. Le Li, Yun-Ai Su, Tian-Mei Si, and Chao-Gan Yan analyzed and interpreted the data. Le Li, Yun-Ai Su, Francisco Xavier Castellanos, Tian-Mei Si, and Chao-Gan Yan drafted the manuscript. All the authors approved the manuscript.

DATA AVAILABILITY STATEMENT

MATLAB-based codes for the analysis are openly shared at GitHub (https://github.com/Chaogan-Yan/PaperScripts/tree/master/Li_2021_HBM). The data that support the findings of the present study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Li L, Su Y-A, Wu Y-K, et al. Eight-week antidepressant treatment reduces functional connectivity in first-episode drug-naïve patients with major depressive disorder. *Hum Brain Mapp*. 2021;42:2593–2605. https://doi.org/10.1002/hbm.25391