Twenty-Five Cohorts of Major Depressive Disorder in China: Evidence for Reduced Default Mode Network Functional Connectivity in Recurrent Depressive Patients

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KEY POINTS

Question: Given that the functional connectivity within the default mode network in major depressive disorder patients was frequently reported abnormal but with contradicting directions in previous small sample size studies, how does this property alter and what's the direction in sufficient powered depressed patients?

Findings: By creating the REST-meta-MDD consortium that included brain imaging of 1,300 depressed patients and 1,128 normal controls from 25 research groups in China, We found decreased instead of increased default mode network functional connectivity in depressed patients, but only in recurrent not in first-episode drug-naïve patients. Decreased default mode network functional connectivity was associated with current medication treatment but not with disease duration.

Meaning: These findings suggest that default mode network functional connectivity remains a prime target for understanding the pathophysiology of depression, with particular relevance to revealing mechanisms of effective treatments, as the greater the medication benefit, the more default mode network functional connectivity was reduced.

ABSTRACT

Importance: Major depressive disorder is common and disabling, but its neural pathophysiology remains unclear. Functional brain network studies in major depressive disorder have largely had limited statistical power and widely varying data analysis approaches, obviating consensus on how functional brain networks are altered in major depressive disorder, even for the most frequently studied default mode network.

Objective: To determine whether the functional connectivity within the default mode network is increased or decreased in major depressive disorder in a sufficiently powered sample.

Design: We created the REST-meta-MDD consortium comprising 25 Chinese depression cohorts contributing resting-state fMRI data from up to 1,300 patients with major depressive disorder and 1,128 normal controls. Data were preprocessed locally with a standardized protocol prior to aggregated group analyses (May, 2017).

Setting: Multicenter.

Participants: We selected 848 patients with major depressive disorder (534 females; age 34.3±11.5) and 794 normal controls (467 females; age 34.4±13.0) from 17 sites for statistical analyses. Exclusion criteria included incomplete information, poor spatial normalization, inadequate coverage, excessive head motion and sites with fewer than 10 subjects in either group.

Main Outcomes and Measures: Functional connectivity within the default mode network, frequently reported increased in major depressive disorder.

Results: We found decreased instead of increased functional connectivity within the default network (T=-3.762, P=0.0002, Cohen's d=-0.186). Default mode network functional

connectivity was only reduced in recurrent patients (T=-3.737, P=0.0002, d=-0.326), not in first-episode drug-naïve patients (T=-0.914, P=0.361, d=-0.076). Decreased functional connectivity was associated with medication usage (T=-2.629, P=0.009, d=-0.362) but not with illness duration (T=1.140, P=0.257, d=0.214). Connectivity was also positively related to symptom severity but only in recurrent patients (T=2.167, P=0.032, r=0.194). Exploratory analyses also revealed alterations of local intrinsic activity in MDD.

Conclusions and Relevance: We confirmed the key role of functional connectivity within the default network in major depressive disorder but found reduced rather than increased functional connectivity. Future studies should test whether such decreases mediate treatment response. This manuscript announces the publicly available resting-state fMRI indices of the REST-meta-MDD consortium shared via the R-fMRI Maps Project. The REST-meta-MDD model can be generalized to longitudinal depression studies and to other psychiatric disorders.

1. INTRODUCTION

Major Depressive Disorder (MDD) is the second leading-cause of disability world-wide, with point prevalence exceeding 4%.[1] The pathophysiology of MDD remains unknown despite intensive efforts, including neuroimaging studies. However, the small sample size of most MDD neuroimaging studies entails low sensitivity and reliability.[2,3] An exception is the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium which meta- and mega-analyzed thousands of structural MRI scans from MDD patients and healthy controls.[4,5] The ENIGMA-MDD working group found a slight albeit robust reduction in hippocampal volume[4] and cortical thinning in medial orbitofrontal cortex.[5] However, this approach does not consider communication among brain regions, i.e., functional brain networks.

Imbalanced communications among functional brain networks have been reported in MDD using resting-state functional connectivity (FC), which detects synchronized activity among anatomically distinct networks. MDD studies have focused on the default mode network (DMN), which has been linked to rumination.[6] The first study focusing on the DMN in MDD reported increased DMN FC.[7] However, similar studies[8,9] found both increased and decreased DMN FC in MDD. Meta-analyses have revealed increased DMN FC in MDD, although based on few studies.[6,10] As summarized in Supplementary Table S1, of 38 studies examining DMN FC alterations in MDD, 18 found increases, eight decreases, seven both increases and decreases, and five no significant changes. As shown in Supplementary Figure S1, a voxel-wise meta-analysis of 32 studies revealed increased orbitofrontal DMN FC

and decreased FC between dorsomedial prefrontal cortex (dmPFC) and posterior DMN in MDD. Such complex results may have contributed to prior inconsistent reports.

Inconsistencies may reflect limited statistical power[2] from small samples but data analysis flexibility may also contribute.[11] MDD studies have used diverse multiple comparison correction methods, most likely inadequate.[12] Data analysis flexibility also impedes large-scale meta-analysis.[6,10] Moreover, clinical characteristics such as number and type of episodes, medication status and illness duration vary across studies, further contributing to heterogeneous results.

To address limited statistical power and analytic heterogeneity, we initiated the REST-meta-MDD Project. We implemented a standardized preprocessing protocol on DPARSF[13] at local sites with only final indices provided to the consortium. We obtained R-fMRI indices (including FC matrices) corresponding to 1300 patients with MDD and 1128 normal controls (NCs) from 25 cohorts in China. To our knowledge, REST-meta-MDD is the largest MDD R-fMRI database (see Supplementary Table S2). We used linear mixed models to identify abnormal FC patterns associated with DMN across cohorts, and investigated whether episode type, medication status, illness severity and illness duration contribute to abnormalities.

2. MATERIALS AND METHODS

2.1. Contributions

Contributions were requested from users of DPARSF, a MATLAB- and SPM-based R-fMRI preprocessing pipeline[13]. Twenty-five research groups from 17 hospitals in China agreed to share final R-fMRI indices from patients with MDD and matched normal controls (see Supplementary Table S3 for data composition; henceforth "site" refers to each cohort for convenience) from studies approved by local Institutional Review Boards. Data submitted to the consortium were fully deidentified and anonymized. See Supplementary Methods for subject privacy protections.

2.2. Phenotypic Data

Consortium members met on March 25th, 2017 to establish the collaboration; all agreed to provide diagnosis, age at scan, sex and education. When collected systematically, measures of first-episode or recurrent MDD (if a patient's prior and current episode were diagnosed as MDD based on ICD10 or DSM-4), medication status, illness duration, 17-item Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) were also provided.

2.3. Individual-Level Image Processing

Neuroimaging analysts from each site took a two-day DPARSF training course on May 13-14, 2017 at the Institute of Psychology, Chinese Academy of Sciences to harmonize analyses of individual R-fMRI data and 3D T1-weighted images.

2.3.1. Preprocessing

As detailed in Supplementary Methods, preprocessing included slice timing correction, realignment, segmentation, nuisance regression, spatial normalization and temporal filtering, while adapting to local data acquisition parameters. We did not include global signal regression in primary analyses, but did in supplementary analyses. We also confirmed results using head motion scrubbing.

2.3.2. DMN FC Analyses

After preprocessing, time-series for the Dosenbach 160 functional regions-of-interest (ROIs)[14] were extracted as were Zalesky's random 980 parcellations[15] for comparison. For each, we defined DMN ROIs as those overlapping with the DMN delineated by Yeo et al.[16] The average FC (Fisher's r-to-z transformed Pearson's correlation between time-series of all ROI pairs) within DMN ROIs was defined as DMN within-network FC for patient-control contrasts. Supplementary analyses contrasted DMN ROIs connection-by-connection.

2.3.3. Exploratory Analyses of R-fMRI Metrics for Local Abnormalities

We explored local abnormalities in MDD with voxel-wise amplitude of low frequency fluctuations (ALFF), fractional ALFF, regional homogeneity (ReHo), degree centrality, and voxel-mirrored homotopic connectivity[17] as detailed in Supplementary Methods.

2.4. Group-Level Image Processing

Individual-level imaging metrics (i.e., ROI time-series and R-fMRI indices) and phenotypic data were uploaded through the platform of the R-fMRI Maps Project (http://rfmri.org/maps) at

the Institute of Psychology, Chinese Academy of Sciences.

2.4.1. Sample Selection

From 1300 MDDs and 1128 NCs, we selected 848 MDDs and 794 NCs from 17 sites for statistical analyses. Exclusion criteria (e.g., incomplete information, bad spatial normalization, bad coverage, excessive head motion and sites with fewer than 10 subjects in either group) and final inclusions are provided in Supplementary Methods and Supplementary Figure S2.

2.4.2. Statistical Analyses

We used the Linear Mixed Model (LMM) to compare MDDs with NCs while allowing site-varying effects. LMM describes the relationship between a response variable (e.g., DMN FC) and independent variables (here diagnosis and covariates of age, sex, education, and head motion), with coefficients that can vary with respect to grouping variables (here site)[18]. We utilized MATLAB's command fitlme (https://www.mathworks.com/help/stats/fitlme.html) to test the model:

y ~ 1 + Diagnosis + Age + Sex + Education + Motion + (1 | Site) + (Diagnosis | Site)

which yields T and P values for the fixed effect of Diagnosis. Cohen's d effect size was computed as $d = \frac{T(n_1 + n_2)}{\sqrt{df}\sqrt{n_1 n_2}}$.[19]

2.4.3. Subgroup Analyses

Several sites reported whether patients with MDD were in their first episode (and drug-naïve)

or recurrent. We compared 232 first episode drug-naïve (FEDN) MDD patients with 394 corresponding NCs from 5 sites. We also compared 189 recurrent MDD patients with 427 corresponding NCs from 6 sites. To directly compare 119 FEDN MDD patients with 72 recurrent MDD patients from 2 sites, we replaced Diagnosis with FEDN or recurrent status in the LMM model.

2.4.4. Analyses of Effects of Illness Duration, Medication, and Symptom Severity

As the distribution of illness duration was skewed (most were brief), we contrasted the terciles with longest and shortest illness durations instead of Diagnosis in the LMM model. To test medication effects, we replaced Diagnosis with medication (on/off) in the LMM model. Finally, to test symptom severity effects, we replaced Diagnosis with the 17-item HAMD total score regressor in the LMM model.

3. RESULTS

3.1. Sample Composition

Twenty-five research groups from 17 hospitals contributed 25 previously collected 2428 datasets (1300 MDDs and 1128 NCs) (Figure 1 and Supplementary Tables S3-5). On average, each site contributed 52.0±52.4 MDDs (range 13-282) and 45.1±46.9 NCs (range 6-251). Most MDD patients were female (826 vs. 474 males), as expected. The 562 patients with first episode MDD included 318 FEDN MDD and 160 scanned while receiving antidepressants (medication status unavailable for 84). Of 282 with recurrent MDD, 121 were scanned while receiving antidepressants and 76 were not being treated with medication

(medication status unavailable for 85). Episodicity (first or recurrent) and medication status were unavailable for 456 patients.

3.2. Decreased DMN Functional Connectivity in Patients with MDD

By overlapping the Dosenbach 160 ROIs[14] with the Yeo DMN,[16] we identified 33 DMN ROIs. Mean DMN within-network FC (averaged across 33*32/2=528 connections) was compared between 848 MDDs and 794 NCs (see Sample Selection in Supplementary Methods) with the LMM. MDD patients demonstrated significantly lower DMN within-network FC than NCs (T=-3.762, P=0.0002, d=-0.186, Figure 2A). On subgroup analyses, FEDN MDDs did not differ significantly from NCs (T=-0.914, P=0.361, d=-0.076, Figure 2B), while DMN FC was significantly decreased in patients with recurrent MDD vs. NCs (T=-3.737, P=0.0002, d=-0.326, Figure 2C). Significantly higher DMN FC in FEDN MDD patients directly compared to recurrent MDDs (T=2.676, P=0.008, d=0.400, Figure 2D) suggests the latter were the major contributors to decreased DMN FC in MDD.

3.3. Reduced DMN Functional Connectivity Was Not Associated with Illness Duration

Reduced DMN FC in recurrent MDD but not in FEDN MDD could reflect illness duration or medication history. We first tested the effect of illness duration in FEDN MDDs to reduce medication confounds. The tercile with longest illness duration (≥12 months, 70 MDDs from 2 sites) did not differ significantly from the tercile with shortest illness duration (≤3 months, 48 MDDs from the same 2 sites) in DMN FC (T=1.140, P=0.257, d=0.214, Figure 3A). Similarly, when exploring in the entire sample, the tercile with longest illness duration (≥24 months, 186

MDDs from 4 sites) did not differ significantly from the tercile with shortest illness duration (≤6 months, 112 MDDs from the same 4 sites): T=1.541, P=0.124, d=0.184 (Figure 3B).

3.4. Medication Effect and Reduced DMN Functional Connectivity in MDD Patients

To further examine medication treatment effects, we contrasted first episode MDDs on medication (115 MDDs from Site 20) with FEDN MDDs (97 MDDs from Site 20) and found significantly reduced DMN FC (T=-2.629, P=0.009, d=-0.362, Figure 3C). When directly comparing 102 first episode MDDs on medication with 266 NCs from 2 sites, we found a non-significant trend (T=-1.614, P=0.108, d=-0.188). While FEDN MDDs showed higher DMN FC than recurrent MDDs as shown in Section 3.2, 102 first-episode MDDs on medication and 57 recurrent MDDs from 2 sites did not differ significantly (T=0.548, P=0.585, d=-0.091). This suggests that medication treatment might account for our overall finding of reduced DMN FC in MDD. However, we could not address whether currently unmedicated recurrent MDDs had been previously treated with antidepressants. We were also unable to examine treatment duration, as medication status was binary.

3.5. Association of DMN Functional Connectivity with Symptom Severity

The association between DMN FC and HAMD scores was tested on 734 MDD patients (excluding remitted patients with HAMD scores below 7) from 15 sites and was not significant (T=1.591, P=0.112, r=0.059). The effect of symptom severity was not significant in FEDN MDDs (N=197, 3 sites; T=-0.158, P=0.874, r=-0.011), but significant in recurrent MDDs (N=126, 4 sites; T=2.167, P=0.032, r=0.194).

3.6. Reproducibility

We assessed reproducibility through several strategies (Table 1). 1) Using a finer-grade parcellation with 211 DMN ROIs confirmed our results, except that symptom severity in recurrent MDDs became insignificant (T=1.264, P=0.209, r=0.115). 2) Beyond LMM, we also performed meta-analyses: within-site T-values were converted into Hedge's *g*, and entered in a random effect meta-model (using R "metansue", https://www.metansue.com/). Results were almost the same, although the difference between FEDN MDDs and recurrent MDDs became a trend (Z=1.732, P=0.083, d=0.251), and symptom severity in recurrent MDDs became insignificant (Z=1.304, P=0.192, r=0.119). 3) We also tested whether global signal regression (GSR) mattered. With GSR, we found similar results except the difference between FEDN MDDs and recurrent MDDs became insignificant (T=0.974, P=0.331, d=0.145) and the medication effect became a trend (T=-1.891, P=0.060, d=-0.261), as did symptom severity in recurrent MDD (T=1.741, P=0.084, r=0.157). This overall confirmation is important since global signal has been viewed as reflecting spurious noise,[20] and its standard deviation differed significantly between MDDs and NCs (T=-2.662, P=0.008, d=-0.131). 4) For head motion control, despite already incorporating the Friston-24 model at the individual level and a motion covariate at the group level in primary analyses, we also used scrubbing (removing time points with framewise displacement >0.2mm[21] to verify results. All results remained the same using this aggressive head motion control strategy.

3.7. Exploratory Findings of Local Abnormalities in MDD Patients

Although we focused on DMN FC in MDD, we also performed exploratory analyses to illustrate the potential value of the shared voxel-wise R-fMRI metric maps to reveal local abnormalities. Please see Figure 4, Supplementary Results and Supplementary Figures S4-S7 for details.

4. DISCUSSION

We created a model for building consortium and aggregate large-scale functional brain imaging data for depression, which can be generalized to other psychiatric disorders. Using an unprecedentedly large sample, we found decreased instead of increased FC within the DMN in MDDs compared with NCs. However, this effect was only significant in recurrent MDD whether vs. controls or patients with FEDN MDD. Furthermore, decreased DMN FC in recurrent MDD was associated with being scanned on medication rather than illness duration. DMN FC was also positively related to symptom severity but only in recurrent MDDs. Exploratory analyses revealed increased ReHo in left DLPFC in FEDN MDD, and decreased ReHo in bilateral primary motor cortex in recurrent MDD.

Our primary results contradict the prevailing notion that DMN FC is increased in MDD[6,10]. Several factors may account for this discrepancy. 1) Prior studies have also reported decreased DMN FC in MDD (see Supplementary Table S1). Our voxel-wise meta-analysis of 32 studies (Supplementary Figure S1) revealed both increases (orbitofrontal DMN FC) and decreases (dmPFC / posterior DMN FC) in MDD. 2) Prior inconsistent results may also reflect heterogeneous analysis strategies. We applied a standardized analysis protocol across sites,

removing analytic variations. 3) Average DMN FC might be insensitive to possible pair-wise increases in MDD DMN FC. However, pair-wise tests did not reveal even a single pair of significantly increased within-DMN connection in MDDs (see Supplementary Results and Supplementary Figure S3). Finally, most studies reporting increased DMN FC in MDDs were conducted in Caucasian samples, while our study was performed in purely Chinese population. Ethnic differences may have contributed, as east Asians report lower lifetime prevalence of MDD,[1] more somatic symptoms and fewer psychological symptoms,[22] and differ in MDD risk genes.[23] Large sample studies will be needed to clarify the pattern of DMN FC in MDD across ethnicities.

In subgroup analyses, we only found decreased DMN FC in recurrent MDD patients, with nearly twice the effect size of the whole-group (d=-0.326 vs. -0.186). Similarly, ENIGMA-MDD found a robust reduction in hippocampal volume (a key DMN node) only in recurrent MDD and not in first episode MDD[4]. Illness duration in recurrent MDD was significantly longer than in FEDN MDD ($Z=6.419$, $p<0.001$), but it was unrelated to DMN FC on direct comparisons. An early MDD study[7] found that DMN FC was positively correlated with current episode duration but this was not confirmed subsequently[9,24,25]. We conclude that illness duration is likely unrelated to DMN FC. However, longitudinal studies are needed to determine whether DMN FC changes over the course of depressive episodes.

Decreased DMN FC in recurrent MDD was associated with antidepressant medication treatment. We confirmed that first episode MDDs scanned while on medication had

decreased DMN FC than FEDN MDD. This result aligns with studies of antidepressants on DMN FC in MDD,[26] dysthymia,[27] and in healthy individuals.[28] In MDD, antidepressant treatment for 12 weeks reduced posterior DMN FC.[26] In patients with dysthymia, 10 weeks of duloxetine treatment reduced DMN FC.[27] In healthy individuals, duloxetine for 2 weeks reduced DMN FC and improved mood.[28] Our finding of medication-associated reduction in DMN FC suggests antidepressant medications may alleviate depressive symptoms by reducing DMN FC. This medication effect (effect size d=-0.362) might also underlie the contradiction between our finding of reduced DMN FC in MDD and prior meta-analyses. This cross-sectional effect has to be confirmed by longitudinal medication follow-up designs.

We did not find significant associations between DMN FC and symptom severity in all MDDs nor in FEDN MDDs. However, symptom severity was positively correlated with DMN FC in recurrent MDDs. Similarly, a prior report[29] found a positive correlation between DMN FC in a specific frontal subcircuit and illness severity in MDDs (half treated with medication). Our finding may reflect medication effects in recurrent MDD (the effect was stronger in recurrent MDDs on medication: N=40, 2 sites; T=3.268, P=0.003, r=0.489): the greater the medication benefit (indicated by lower HAMD score), the more DMN FC was reduced. Again, testing this hypothesis requires longitudinal follow-up of medication effects.

To extend beyond the DMN and a priori ROIs, we explored local R-fMRI metrics. Results included significantly increased ReHo in DLPFC and decreased ReHo in primary motor cortex in MDDs compared with NCs. The increase in DLPFC ReHo was attributable to

abnormalities in FEDN MDDs whereas decreased primary motor area ReHo was attributable to recurrent MDD (see Figure 4). Our results in motor cortex align with a previous meta-analysis[30] of ReHo studies. Analyses of other local metrics also revealed local functional abnormalities in MDD (see Supplementary Results, Supplementary Figures S4~S7), which could yield local neuromodulation targets for treating MDD if replicated independently.

Study limitations include an exclusively Chinese sample, with unknown generalization to other populations. In the future, we plan to invite international MDD researchers to join the REST-meta-MDD Project to identify ethnicity/culture-general and ethnicity/culture-specific abnormal brain patterns in MDD. Second, we could not address longitudinal effects, such as response to treatment. We plan to encourage the REST-meta-MDD consortium to perform coordinated prospective longitudinal studies. Third, medication treatment was binary; future studies should quantify cumulative doses and include non-pharmacologic treatments. Finally, our findings require independent replication.[11] To improve transparency and reproducibility, the analysis code has been openly shared at https://github.com/Chaogan-Yan/PaperScripts/tree/master/Yan_2018. Upon publication, the R-fMRI indices of the 1300 MDD patients and 1128 NCs will be openly shared through the R-fMRI Maps Project (LINK_TO_BE_ADDED). These data derivatives will allow replication, secondary analyses and discovery efforts while protecting participant privacy and confidentiality. Future independent efforts could examine other networks beyond DMN (e.g., salience network or executive control network), dynamic FC, MDD subtypes, and data mining

with machine learning algorithms.

In summary, based on the largest R-fMRI database of MDD, we confirmed the key role of the DMN in MDD, identifying a reduction of DMN FC in recurrent MDD patients. This reduction appears to reflect medication usage rather than illness duration. These findings suggest that the DMN should remain a prime target for further MDD research, especially to determine whether reducing DMN FC mediates symptomatic improvement.

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CONFLICTS OF INTEREST AND FINANCIAL DISCLOSURES

All the authors declare no competing financial interests.

ROLE OF THE FUNDERS/SPONSOR

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

DATA ACCESS, RESPONSIBILITY, AND ANALYSIS

Dr. Chao-Gan Yan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA SHARING STATEMENT

Immediately upon publication, this manuscript announces that the aggregated data of this study (deidentified anonymized R-fMRI indices of 1300 MDD patients and 1128 NCs) will be

made available through The R-fMRI Maps Project (http://rfmri.org/maps) to interested investigators. The investigators should sign a data access agreement and submit a data use proposal, which will be reviewed by the REST-meta-MDD consortium.

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TABLES

Table 1. Verification results of default mode network (DMN) within-network functional connectivity (FC) in MDD with multiple alternative analysis strategies. Linear Mixed Effect (LME) model or meta-analytic model was utilized on different parcellations in different statistical comparisons (the effects of age, sex, education level, head motion and scanning site were controlled).

	Dosenbach 160 functional ROIs (LME)		Zalesky random 980 parcellations (LME)		Dosenbach 160 functional ROIs (meta)		Dosenbach 160 functional ROIs (LME & GSR)		Dosenbach 160 functional ROIs (LME & Scrubbing)	
	T	*P*	*T*	*P*	*Z*	*P*	*T*	*P*	*T*	*P*
All MDDs vs. NCs (848 vs. 794)	-3.762	0.0002	-3.179	0.002	-4.057	0.00004	-4.373	0.0001	-3.818	0.0001
FEDN MDDs vs. NCs (232 vs. 394)	-0.914	0.361	-0.561	0.575	-0.658	0.511	-0.585	0.559	-0.990	0.322
Recurrent MDDs vs. NCs (189 vs. 427)	-3.737	0.0002	-3.356	0.0008	-3.702	0.0002	-4.382	0.0001	-3.836	0.0001
FEDN MDDs vs. Recurrent MDDs (119 vs. 72)	2.676	0.008	3.284	0.001	1.732	0.083	0.974	0.331	2.527	0.012
Long duration FEDN MDDs vs. Short duration FEDN MDDs (70 vs. 48)	1.140	0.257	1.116	0.267	1.089	0.276	0.522	0.603	1.169	0.245
Long duration MDDs vs. Short duration MDDs (186 vs. 112)	1.541	0.124	1.361	0.175	1.386	0.166	1.334	0.183	1.552	0.122

On medication vs. FEDN (115 vs. 97)	-2.629	0.009	-2.293	0.023	-2.568	0.010	-1.891	0.060	-2.504	0.013
Correlation with HAMD in all MDDs (*N* = 734)	1.591	0.112	1.181	0.238	0.754	0.451	0.448	0.654	1.765	0.078
Correlation with HAMD in FEDN MDDs (N = 197)	-0.158	0.874	0.540	0.590	-0.676	0.499	-0.163	0.871	-0.167	0.868
Correlation with HAMD in recurrent MDDs (N = 126)	2.167	0.032	1.264	0.209	1.304	0.192	1.741	0.084	2.446	0.016

Abbreviations: FEDN, First Episode Drug Naïve; LME, Linear Mixed Effect; global signal regression; DMN, Default Mode Network.

FIGURE LEGENDS

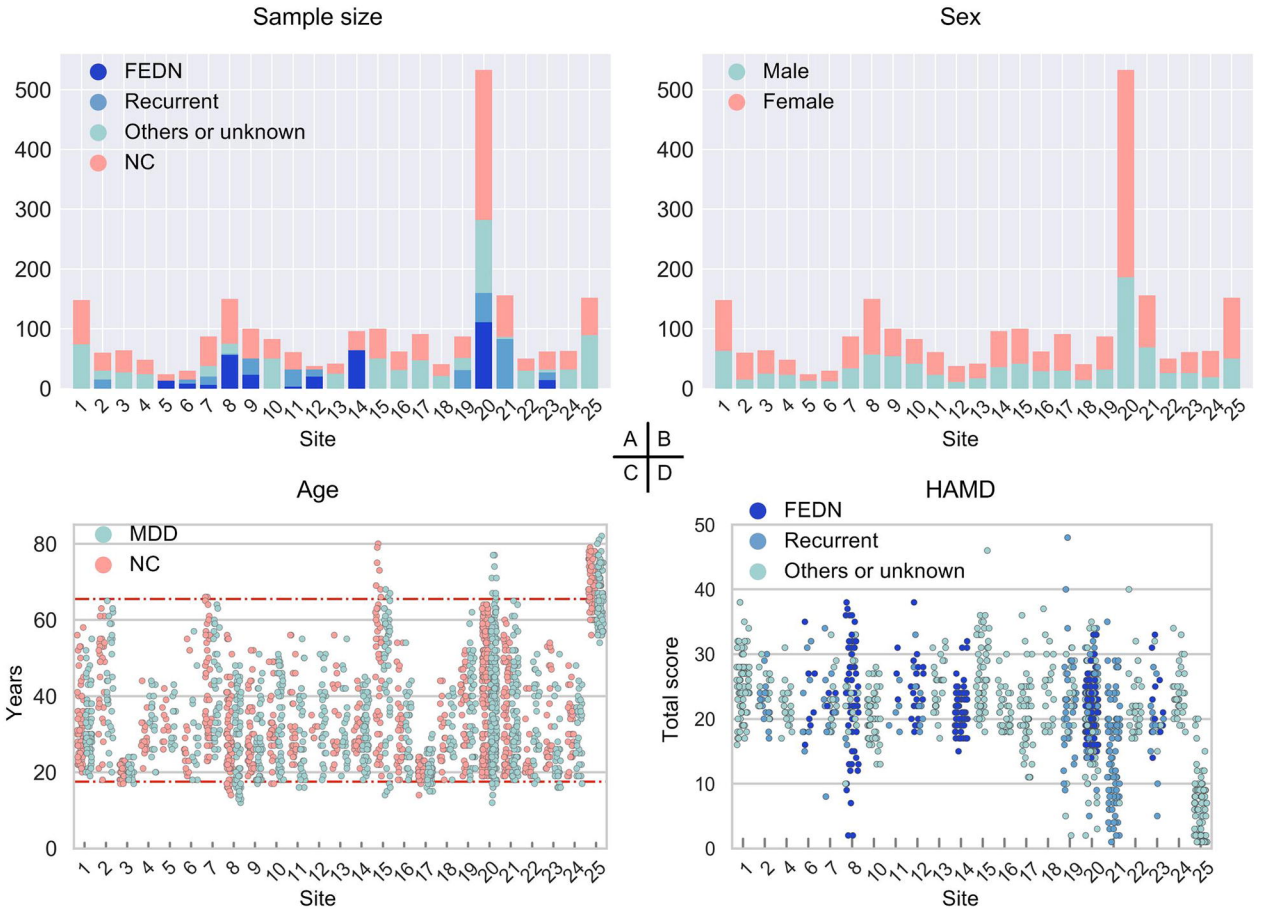
Figure 1. REST-meta-MDD sample characteristics. (A) Total number of participants per group for each contributing site. The MDD patients were subdivided into first-episode drug-naïve (FEDN), recurrent and others/unknown types. (B) Number of male subjects and female subjects for each site irrespective of diagnostic group. (C) Age (in years) for all individuals per site for the MDD group and NC group. The two horizontal lines represents ages 18 and 65, the age limits for participants chosen for imaging analysis. (D) The score of Hamilton Depression Rating Scale (HAMD) for the MDD patients. Of note, some sites did not provide HAMD information.

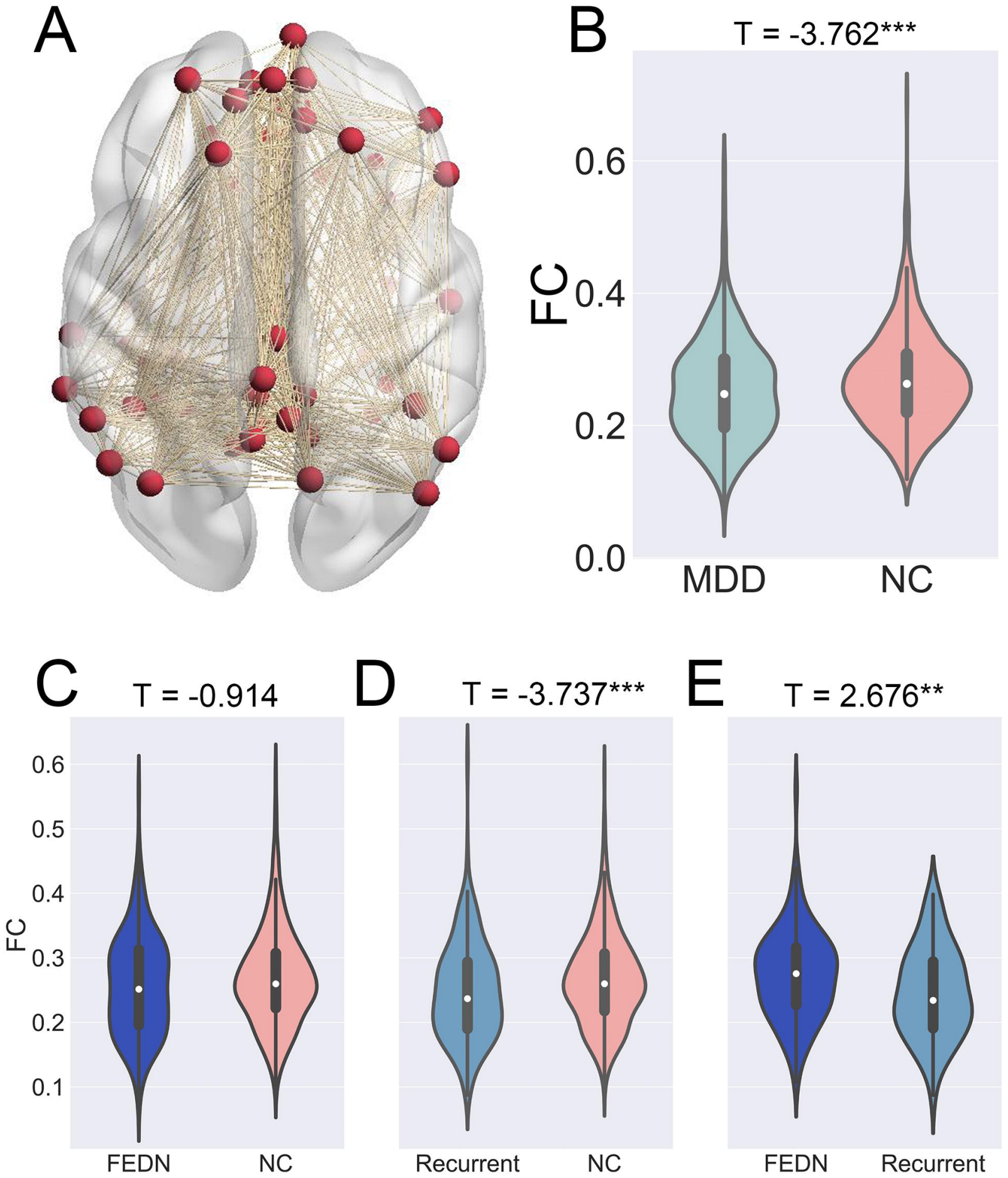
Figure 2. Decreased DMN functional connectivity in MDD patients. Mean DMN within-network FC was averaged across 33*32/2=528 connections as shown in A. The violin figures show the distribution of mean DMN within-network FC between MDD group and NC group (B), between first episode drug naïve (FEDN) MDD group and NC group (C), between recurrent MDD group and NC group (D), and between FEDN MDD group and recurrent MDD group (E). Of note, for each comparison, only sites with sample size larger than 10 in each group were included. The T values were the statistics for these comparisons in Linear Mixed Model analyses. **, $p < 0.01$; ***, $p < 0.001$.

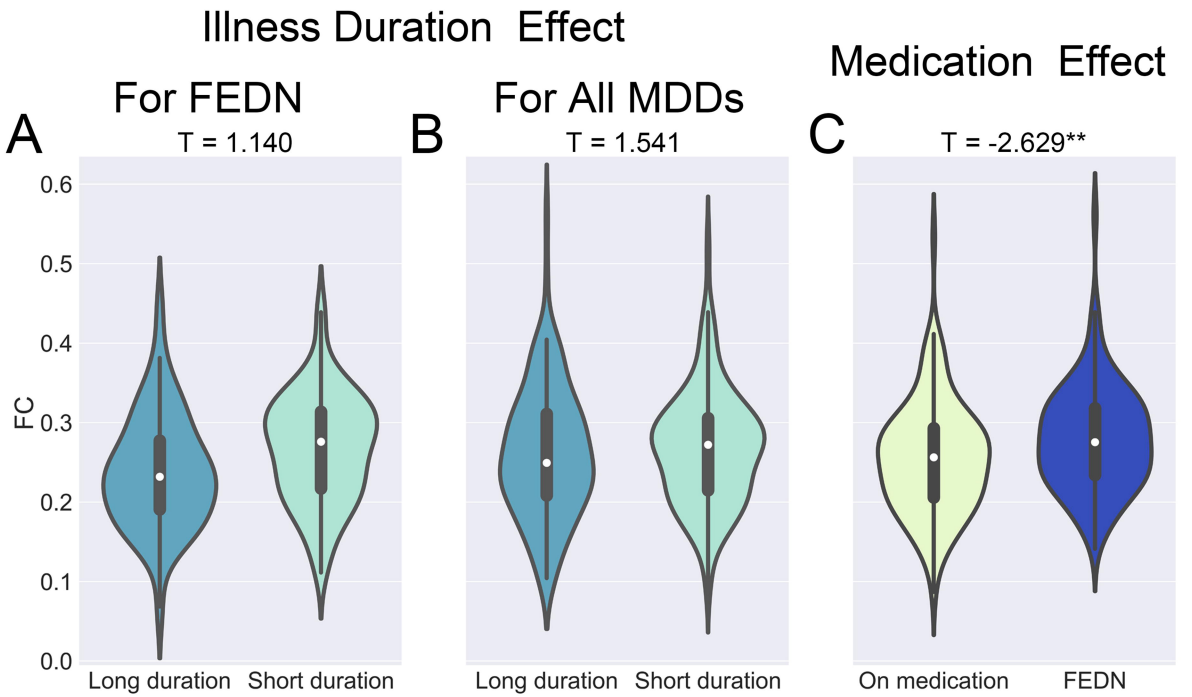
Figure 3. The effects of illness duration and medication on decreased DMN functional connectivity in MDD patients. The violin figures show the distribution of mean DMN within-network FC for first episode drug naïve (FEDN) MDDs with long vs. short illness duration (A), for pooled MDDs with long vs. short illness duration (B), and for first episode MDDs with vs. without medication usage (C). The T values are the statistics for these comparisons in Linear Mixed Model analyses. **, $p < 0.01$.

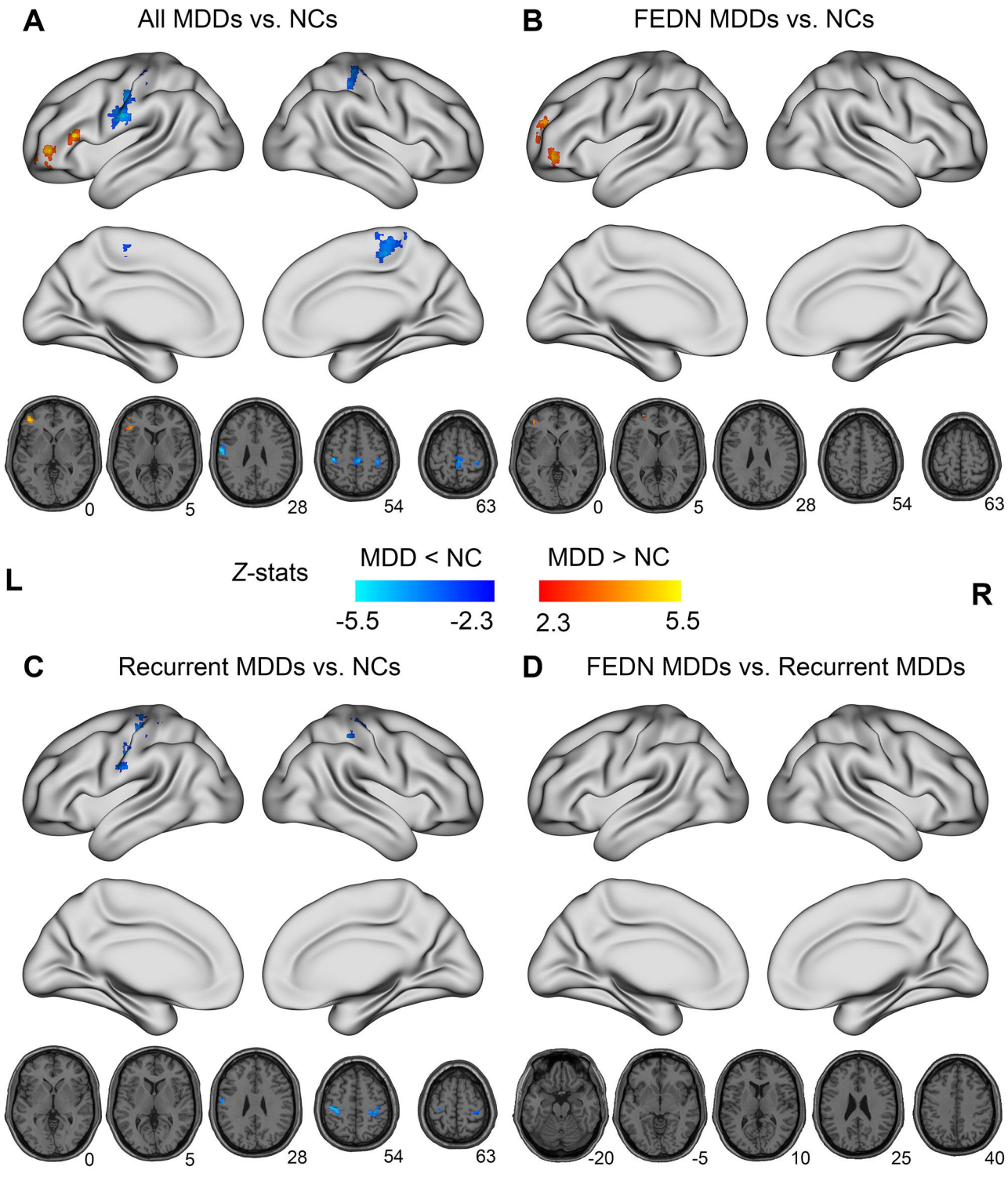
Figure 4. Regional homogeneity (ReHo) abnormalities in MDD patients. Significant group differences between (A) all individuals with MDD and NCs, (B) first episode drug naïve (FEDN)

MDDs and NCs, (C) recurrent MDDs and NCs, (D) FEDN and recurrent MDDs were depicted. Since ReHo demonstrated the highest test-retest reliability among commonly used R-fMRI indices,[17] we present ReHo abnormalities here and include other indices in Supplementary Figures S4-S7. In applying LMM voxel-wise, we used Gaussian random field theory to correct for multiple comparisons, with strict two-tailed thresholds (voxel $p<0.0005$ [$Z>3.29$] and cluster $p<0.025$), maintaining the family-wise error rate under 5%.[3,12] Comparing all 848 MDDs with 794 NCs, ReHo was increased in left dorsolateral prefrontal cortex (DLPFC) in MDD and decreased in bilateral primary motor cortex (A). Among subgroups, left DLPFC ReHo was significantly increased in FEDN MDDs (B) but not in recurrent MDD (C). By contrast, ReHo in bilateral primary motor cortex was only significantly decreased in recurrent MDDs (C) but not in FEDN MDDs (B). However, FEDN MDDs and recurrent MDDs did not differ significantly in ReHo when compared directly (D).


Sample size
FEDN
Recurrent
Others or unknown
NC
Site
Sex
Male
Female
Site
A
B
C
D
Age
MDD
NC
Years
Site
HAMD
FEDN
Recurrent
Others or unknown
Total score
Site


A
B
T = -3.762***
FC
0.6
0.4
0.2
0.0
MDD
NC
C
T = -0.914
FC
0.6
0.5
0.4
0.3
0.2
0.1
FEDN
NC
D
T = -3.737***
Recurrent
NC
E
T = 2.676**
FEDN
Recurrent


Illness Duration Effect
Medication Effect
For FEDN
For All MDDs
A
B
C
T = 1.140
T = 1.541
T = -2.629**
FC
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Long duration
Short duration
Long duration
Short duration
On medication
FEDN


A
All MDDs vs. NCs
B
FEDN MDDs vs. NCs
0
5
28
54
63
0
5
28
54
63
L
Z-stats
MDD < NC
-5.5
-2.3
MDD > NC
2.3
5.5
R
C
Recurrent MDDs vs. NCs
D
FEDN MDDs vs. Recurrent MDDs
0
5
28
54
63
-20
-5
10
25
40