Twenty-Five Cohorts of Major Depressive Disorder in China: Evidence for Reduced but not Enhanced Default Mode Network Functional Connectivity

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ABSTRACT

Background: Major Depressive Disorder (MDD) is common and disabling, but its neural pathophysiology remains unclear. Functional brain network studies in MDD have largely had limited statistical power and data analysis approaches have varied widely. The REST-meta-MDD Project of resting-state fMRI (R-fMRI) addresses these issues. **Methods:** The 25 research groups in China composing the REST-meta-MDD Project contributed R-fMRI data of 1,300 patients with MDD and 1,128 normal controls (NCs). The data were preprocessed locally with a standardized protocol prior to aggregated group analyses. We focused on functional connectivity (FC) within the default mode network (DMN), frequently reported to show increased FC in MDD. **Outcomes:** We found decreased instead of increased DMN FC in MDD compared to NCs. We found FC reduction only in recurrent MDD, not in first-episode drug-naïve MDD. Decreased DMN FC was associated with medication usage but not with MDD duration or severity. Exploratory analyses also revealed alterations of local intrinsic activity in MDD. **Interpretation:** We confirmed the key role of DMN in MDD but found reduced rather than increased FC within the DMN. Future studies should test whether decreased DMN FC mediates treatment response. The REST-meta-MDD model can be generalized to longitudinal MDD studies and to other psychiatric disorders. **Funding:** National Key R&D Program of China, National Natural Science Foundation of China and Chinese Academy of Sciences.

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 and results unlikely to reflect true effects.[2,3] An exception is the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium which has meta- and mega-analyzed data of thousands of structural MRI scans from MDD patients and healthy controls.[4,5] The ENIGMA-MDD working group found a 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 is comprised of regions that are most active during rest and which has been linked to rumination.[6] Most MDD studies have found increased DMN FC in MDD, although decreased or unchanged DMN FC have also been reported. As shown in the systematic review 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. For example, the first study focusing on the DMN in MDD reported increased DMN FC using independent component analysis (ICA).[7] However, other ICA

studies[8,9] reported both increased and decreased DMN FC in MDD. Using seed-based correlation, FC between the posterior cingulate cortex (PCC) and subgenual anterior cingulate cortex (sgACC) has been found to be increased[10] and decreased[11] in MDD.

These inconsistencies may be due to small sample size and limited statistical power[2] but data analysis flexibility may also contribute.[12] MDD studies have used different multiple comparison correction methods, most likely inadequate.[13] Data analysis flexibility also impedes large-scale meta-analysis. For example, a meta-analysis on DMN FC in MDD could only include seven studies because of seed variation across studies.[6] 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. Building on the R-fMRI data processing pipeline DPARSF,[14] we implemented a standardized preprocessing protocol at local sites with only final indices provided to the consortium. We have obtained R-fMRI indices (including FC matrices) corresponding to 1300 patients with MDD and 1128 normal controls (NCs) from 25 cohorts in China. To the best of our knowledge, the REST-meta-MDD is the largest R-fMRI database of MDD in the world. 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

Initial contributions were requested from researchers who used DPARSF (software developed by CGY and YFZ)[14] to process their MDD R-fMRI data. In the initial phase, 25 research groups from 17 hospitals in China agreed to share the final R-fMRI indices from patients with MDD and matched normal controls (please see Supplementary Table S2 for data composition; henceforth “site” refers to each cohort for convenience). All contributed data were from studies approved by local Institutional Review Boards. Data submitted to the consortium were fully deidentified and anonymized.

2.2. Phenotypic Data

Consortium members met on March 25th, 2017 to establish the collaboration; all agreed to include diagnosis, age at scan, sex and education in the “base” phenotypic protocol. Measures of first-episode or medication status, illness duration, treatment responsiveness, family history, Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) were also provided if they had been collected systematically.

2.3. Individual-Level Image Processing

Individual-level imaging processing was performed at each site using the standardized DPARSF processing parameters on individual R-fMRI data and 3D T1-weighted images. Neuroimaging analysts from each site took a two-day onsite DPARSF training course on May 13-14, 2017 at the Institute of Psychology, Chinese Academy of Sciences to harmonize data

analyses.

2.3.1. DMN FC Analyses

After preprocessing (described in Supplementary Methods), time-series for the Dosenbach 160 functional regions-of-interest (ROIs)[15] were extracted. To validate the primary analyses, time series for Zalesky's random 980 parcellations and the automated anatomical labeling (AAL) atlas were also extracted. For each atlas, we defined the DMN ROIs as those which overlapped with the DMN delineated by Yeo et al.[16] The average FC (Fisher's r-to-z transformed Pearson's correlation coefficient between time-series of all pairs of ROIs) within the DMN ROIs was taken to represent DMN within-network FC and contrasted between MDD patients and controls. In supplementary analyses, we also compared DMN ROIs connection by connection to identify which pair of DMN ROIs contributed the most.

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

Beyond hypothesis-driven analysis of DMN FC, we also explored local abnormalities in MDD with voxel-wise amplitude of low frequency fluctuations (ALFF), fractional ALFF (fALFF), regional homogeneity (ReHo), degree centrality (DC), and voxel-mirrored homotopic connectivity (VMHC).[17] These metrics are detailed in Supplementary Methods.

2.4. Group-Level Image Processing

After individual-level imaging processing performed locally at each site, individual-level imaging metrics (i.e., the ROI time-series and R-fMRI indices) together with phenotypic data

were uploaded to the data center at the Institute of Psychology, Chinese Academy of Sciences through the R-fMRI Maps Project (http://rfmri.org/maps) platform.

2.4.1. Sample Selection

From 1300 MDDs and 1128 NCs, we selected 848 MDDs and 794 NCs from 17 sites for group 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 S1.

2.4.2. Statistical Analyses

We used the Linear Mixed Model (LMM) to compare MDDs with NCs while allowing the effect to vary across sites. LMM extents linear regression models to data that are collected and summarized in groups.[18] LMM describes the relationship between a response variable (here DMN FC or other brain indices) 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). 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.

2.4.3. Subgroup Analyses

We also examined sub-group effects: several sites reported whether patients with MDD were in their first episode (and drug-naïve) or recurrent. We compared first episode drug-naïve (FEDN) MDD patients with corresponding NCs (232 FEDN MDDs vs. 394 NCs from 5 sites, each site with more than 10 subjects per group) with the same LMM model. We also compared recurrent MDD patients with corresponding NCs (189 recurrent MDD vs. 427 NCs from 6 sites). To directly compare FEDN MDD patients with recurrent MDD patients (119 FEDN MDDs vs. 72 recurrent MDDs from 2 sites), we replaced Diagnosis with FEDN or recurrent status in the same LMM model.

3. RESULTS

3.1. Sample Composition

Twenty-five research groups from 17 hospitals contributed 25 previously collected datasets of 2428 individuals (1300 MDDs and 1128 NCs) (Figure 1 and Supplementary Tables S2 and S3). On average, each site contributed 52·4 ± 52·4 MDDs (range 13-282) and 45·1 ± 46·9 NCs (range 6-251). The majority of MDD patients were females (826 females vs. 474 males), as is typical in MDD studies. There were 562 first episode MDDs, including 318 FEDN MDD and 160 currently on antidepressant treatment (medication status was unavailable for 84 first episode MDDs). Of 282 with recurrent MDD, 121 were being treated with antidepressants and 76 were not (medication status was unavailable for 85 recurrent MDD). Episodicity (first or recurrent) and medication status were unavailable for 456 MDD patients.

3.2. Decreased DMN Functional Connectivity in Patients with MDD

By overlapping the Dosenbach 160 functional ROIs[15] 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, Figure 2A). On subgroup analyses, FEDN MDDs did not differ significantly from NCs (T = -0·914, P = 0·361, Figure 2B), while DMN FC was significantly decreased in patients with recurrent MDD vs. NCs (T = -3·737, P = 0·0002, Figure 2C). We directly compared FEDN MDDs with recurrent MDDs (T = 2·676, P = 0·008, Figure 2D); the significantly lower DMN FC in recurrent MDD patients suggests they were the major contributor to decreased DMN FC in MDD.

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

We found that recurrent MDDs but not FEDN MDDs demonstrated reduced DMN FC. This could reflect illness duration or medication history. We first tested the effect of illness duration in FEDN MDDs (restricted to those with information on illness duration) 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; unbalanced sample because sites with <10 subjects/group were excluded) in DMN FC (T = 1·140, P = 0·257, 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 (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, Figure 3C). However, we were unable to examine treatment duration, as only binary information on medication status was provided.

3.5. Association of DMN Functional Connectivity with Symptom Severity

The association between DMN FC and HAMD scores was tested on 689 MDD patients from 14 sites and was not significant (T = 1·346, P = 0·179).

3.6. Verification of Reproducibility

We tested several alternative analysis strategies to verify the reproducibility of our results (Table 1). 1) Beyond functional atlas (Dosenbach 160 functional ROIs), we applied a structural atlas, i.e., AAL parcellation, analyzing DMN FC within 18 AAL ROIs. Conclusions remained unchanged. 2) We also tested finer-grade parcellations, e.g., Zalesky's random 980 parcellation (with 211 DMN ROIs). This also confirmed our results. 3) Beyond using LMM to summarize the diagnosis effect across sites, we also used meta-analysis to re-analyze our data. We calculated T values within each site, converted them into Hedge's *g*, and used a random effect meta-model to test the difference (using R package "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). 4) We also tested

whether using global signal regression (GSR) mattered. With GSR, we found similar results except the difference between FEDN MDDs and recurrent MDDs became non-significant (T = 0·974, P = 0·331) and the medication effect became a trend (T = -1·891, P = 0·060). 5) For head motion control, although we already used the Friston-24 model at the individual level and a motion covariate at the group level for the primary analyses, we also used scrubbing (removing time points with framewise displacement (FD)[19] > 0·2mm) to verify results. All results remained the same under this aggressive head motion control strategy.

3.7. Exploratory Findings of Local Abnormalities in MDD Patients

Although the main scope of the current study was to investigate DMN FC in MDD, we also performed exploratory analyses searching for local abnormalities to demonstrate the potential of this project's shared voxel-wise R-fMRI metric maps. Since ReHo demonstrated the highest test-retest reliability among the commonly used R-fMRI indices,[17] we present ReHo abnormalities in MDD and include the results of other indices in Supplementary Results. We applied the LMM model to each voxel, and then used Gaussian random field (GRF) theory correction to correct for multiple comparisons across voxels. To avoid unacceptable family-wise error rates, we set a strict threshold for GRF correction for each tail, with voxel p < 0·0005 (Z > 3·29) and cluster p < 0·025. This setup achieves a two-tailed voxel p < 0·001 and cluster p < 0·05 and maintains the family-wise error rate under 5%.[3,13] When we compared all 848 MDDs with 794 NCs, left dorsolateral prefrontal cortex (DLPFC) showed increased ReHo in MDD, while bilateral primary motor cortex showed decreased ReHo (Figure 4A). Interestingly, left DLPFC only showed significantly increased ReHo in FEDN MDDs (Figure

4B) but not in recurrent MDD (Figure 4C). By contrast, bilateral primary motor cortex only showed significantly decreased ReHo in recurrent MDDs (Figure 4C) but not in FEDN MDDs (Figure 4B). However, FEDN MDDs and recurrent MDDs did not differ significantly in ReHo when directly compared.

4. DISCUSSION

We have 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 the unprecedentedly large sample provided by the REST-meta-MDD Project we found decreased instead of increased FC within the DMN in MDDs compared with NCs. However, this effect was not significant in FEDN MDDs, but only in recurrent MDDs. Patients with recurrent MDD even demonstrated decreased DMN FC when directly compared to FEDN MDD. Furthermore, we revealed that the decreased DMN FC in recurrent MDD was associated with medication usage rather than illness duration or severity. Exploratory analysis of local abnormalities demonstrated increased ReHo in left DLPFC in FEDN MDD, and decreased ReHo in bilateral primary motor cortex in recurrent MDD.

Our primary results contradict a substantial number of previous studies which reported increased DMN FC in MDD (i.e., 18 of 38 studies in Supplementary Table S1). Several factors may account for this discrepancy. 1) Prior studies have also reported decreased DMN FC in MDD (see Supplementary Table S1), in line with our findings. A possible reason of the inconsistent findings of previous studies is the heterogeneity of analysis strategies. In the

current study, we applied a standardized analysis protocol to all sites, thus removing variations in analysis method. 2) 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 contribute to the discrepancy in DMN FC findings, as east Asians have a lower lifetime prevalence of MDD,[1] have more somatic symptoms and fewer psychological symptoms in MDDs,[20] and even have different risk genes for MDD.[21] 3) The measure of overall DMN FC (averaged across all pairs of within-DMN connections) might be over-simplified and insensitive to possibly pair-wise increase of DMN FC in MDDs. However, we tested pair-wise within-DMN connections in supplementary analyses (see Supplementary Results and Supplementary Figure S2) but did not find even a single pair of significantly increased within-DMN connection in MDDs. Large sample studies across ethnicities will be needed to clarify the pattern of DMN FC in MDD.

We found decreased DMN FC only in recurrent MDD patients. In a large-scale MDD structural abnormality study, the ENIGMA MDD working group[4] found a robust reduction in hippocampal volume only in recurrent MDD patients and not in first episode MDD patients. The hippocampus is a key DMN structure, thus this large-sample anatomic finding partly supports our functional findings of reduced DMN FC in recurrent MDDs. We initially considered that our findings in recurrent MDD might reflect illness duration. However, direct comparisons did not reveal any effects of illness duration, whether in all MDDs or only in FEDN MDD. In an early study of MDD and DMN FC, Greicius et al.[7] reported that DMN FC (especially at sgACC) was positively correlated with the length of current depressive episode.

However, later studies that directly tested the relationship between MDD illness duration and DMN FC found no significant correlations. For example, Guo et al.[9] found no significant correlation between illness duration and DMN FC (indexed by network homogeneity). Studies have also found no significant correlation between illness duration and DMN homotopic connectivity,[22] DMN FC variability[23] as well as DMN deactivation.[24] Taking these results together, we conclude that illness duration appears to have minimal effect on DMN FC. However, our comparison of illness duration was cross-sectional; future longitudinal studies are needed to confirm how DMN FC changes over the life course.

Another factor potentially contributing to decreased DMN FC in recurrent MDD patients is antidepressant medication usage in a large proportion of patients. We directly tested this possibility by comparing first episode MDDs on medication to FEDN MDDs and found medication usage indeed was associated with decreased DMN FC in medication-treated MDD patients. This result is supported by previous studies exploring the effect of antidepressants on DMN FC in MDD,[25] dysthymia,[26] and in healthy individuals.[27] Li et al. found 12 weeks of antidepressant treatment (with either paroxetine, venlafaxine, duloxetine or citalopram) reduced posterior DMN FC in MDD patients.[25] Posner et al. found 10 weeks of duloxetine treatment reduced DMN FC in patients with dysthymic disorder.[26] In healthy individuals, van Wingen et al. found 2 weeks of duloxetine administration significantly reduced DMN FC and improved mood.[27] The current finding of medication-associated reduction in DMN FC further supports those prior results and suggests a possible mechanism of antidepressant medications is to alleviate depressive symptoms in MDD by reducing DMN

FC. Again, this effect was observed in a cross-sectional sample, so it has to be confirmed by longitudinal medication follow-up designs.

To expand our investigation beyond DMN and partly overcome the dependence of previous analysis on a priori information (ROI specification), we further conducted exploratory analyses with local R-fMRI metrics and found some substantial alterations in MDD patients. For example, we found significantly increased ReHo in DLPFC and decreased ReHo in the primary motor area in MDDs compared with NCs. Further comparisons showed that the increase in DLPFC ReHo was attributable to abnormalities in FEDN MDDs while the decrease in primary motor area ReHo was attributable to recurrent MDD (see Figure 4). Our results are in line with several previous studies.[28,29] Specifically, a previous meta-analysis[29] of ReHo studies reported decreased ReHo in motor areas in MDDs, which is consistent with our current finding. However, that meta-analysis reported increased ReHo in medial prefrontal cortex, instead of DLPFC as we found. Recently, Jia et al.[30] directly compared classical coordinate-based meta-analysis and direct aggregated analysis with multi-site datasets and found that results from classical coordinate-based meta-analysis are less reliable than direct analysis on aggregated large samples. Thus, the discrepancy between our results and previous meta-analysis calls for further studies on local R-fMRI abnormalities in MDD. Besides, results from other metrics also highlight MDDs' local impairments (see Supplementary Results, Supplementary Figures S2~S5), which may shed light on future studies to identify local targets for neuromodulation of MDD.

Study limitations include that all research participants are Chinese, thus generalization to other populations is unknown. In the next step, we will expand the REST-meta-MDD Project to include cross-ethnicity samples by inviting international MDD researchers to join. With cross-ethnicity/culture samples, we could identify ethnicity/culture-general and ethnicity/culture-specific abnormal brain patterns in MDD. Another limitation is that our retrospective cross-sectional sample cannot directly address longitudinal effects, such as response to treatment. We plan to encourage the REST-meta-MDD consortium to perform coordinated prospective longitudinal studies. We only examined medication treatment as a binary variable; future studies should quantify cumulative doses and include non-pharmacologic treatments. Finally, our findings also require independent replication.[12] To improve transparency and reproducibility, we have openly shared the analysis code 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 substantial data will allow replication, secondary analyses and discovery efforts.

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. The current findings suggest that the DMN should remain a prime target for further MDD research, especially to determine whether reducing DMN FC mediates symptomatic improvement.

DATA SHARING STATEMENT

Immediately upon publication, the aggregated data of this study (deidentified 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.

DECLARATION OF INTERESTS

All the authors declare no competing financial interests.

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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)		AAL atlas (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*	*T*	*P*	*Z*	*P*	*T*	*P*	*T*	*P*
All MDDs vs. NCs (848 vs. 794)	-3·762	0·0002	-2·869	0·004	-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	-0·623	0·489	-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	-3·669	0·0003	-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	3·084	0·002	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	0·750	0·455	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	0·544	0·587	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	-2·695	0·008	-2·293	0·023	-2·568	0·010	-1·891	0·060	-2·504	0·013
Correlation with HAMD (*N* = 689)	1·346	0·179	0·978	0·329	0·898	0·370	0·759	0·448	0·091	0·928	1·530	0·126

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

FIGURE LEGENDS

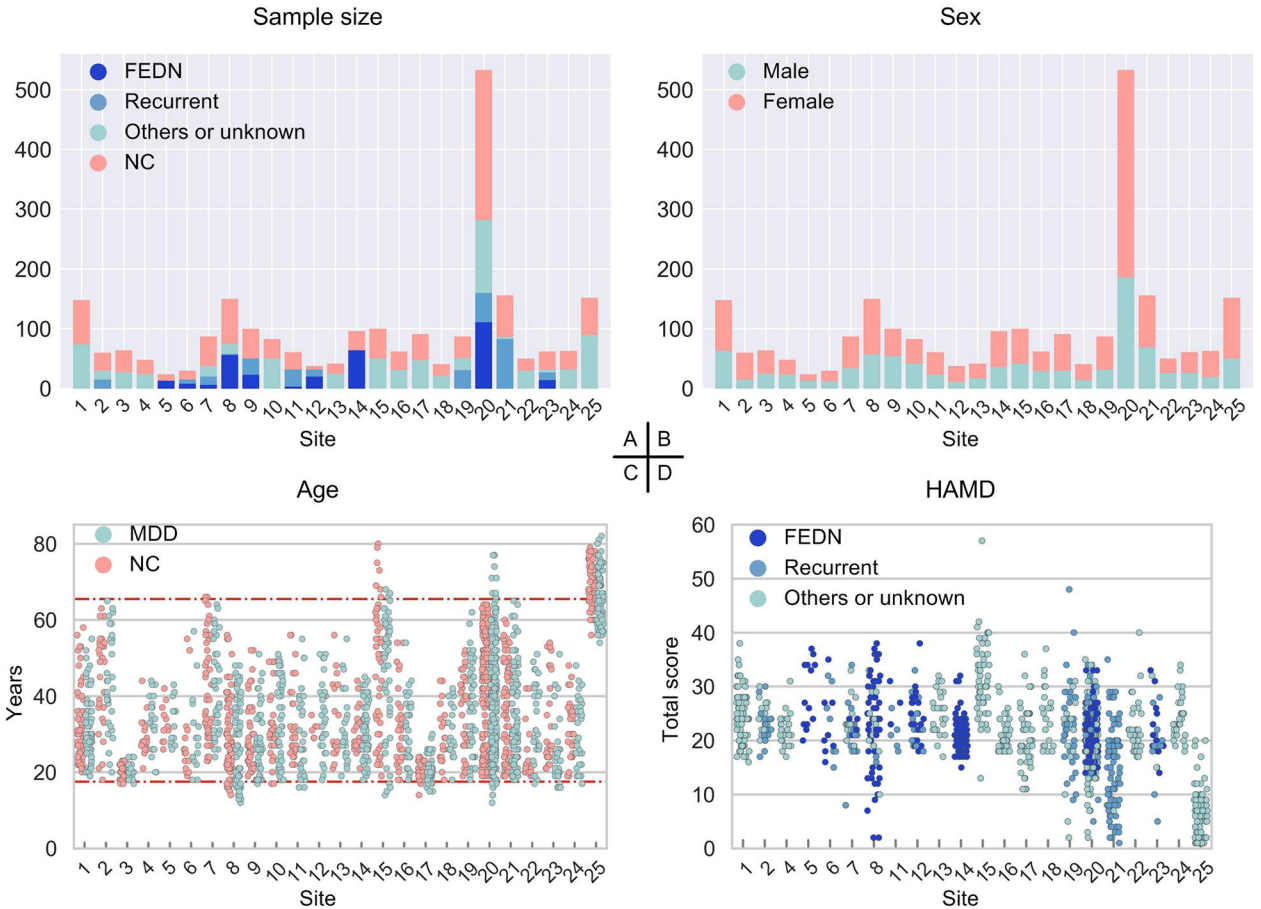
Figure 1. REST-meta-MDD sample characteristics. (A) Total number of participants per group for each contributing site. The MDD patients were subdivided into first-episode drug-naïve (FEDN), recurrent and others/unknown types. (B) Number of male subjects and female subjects for each site irrespective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

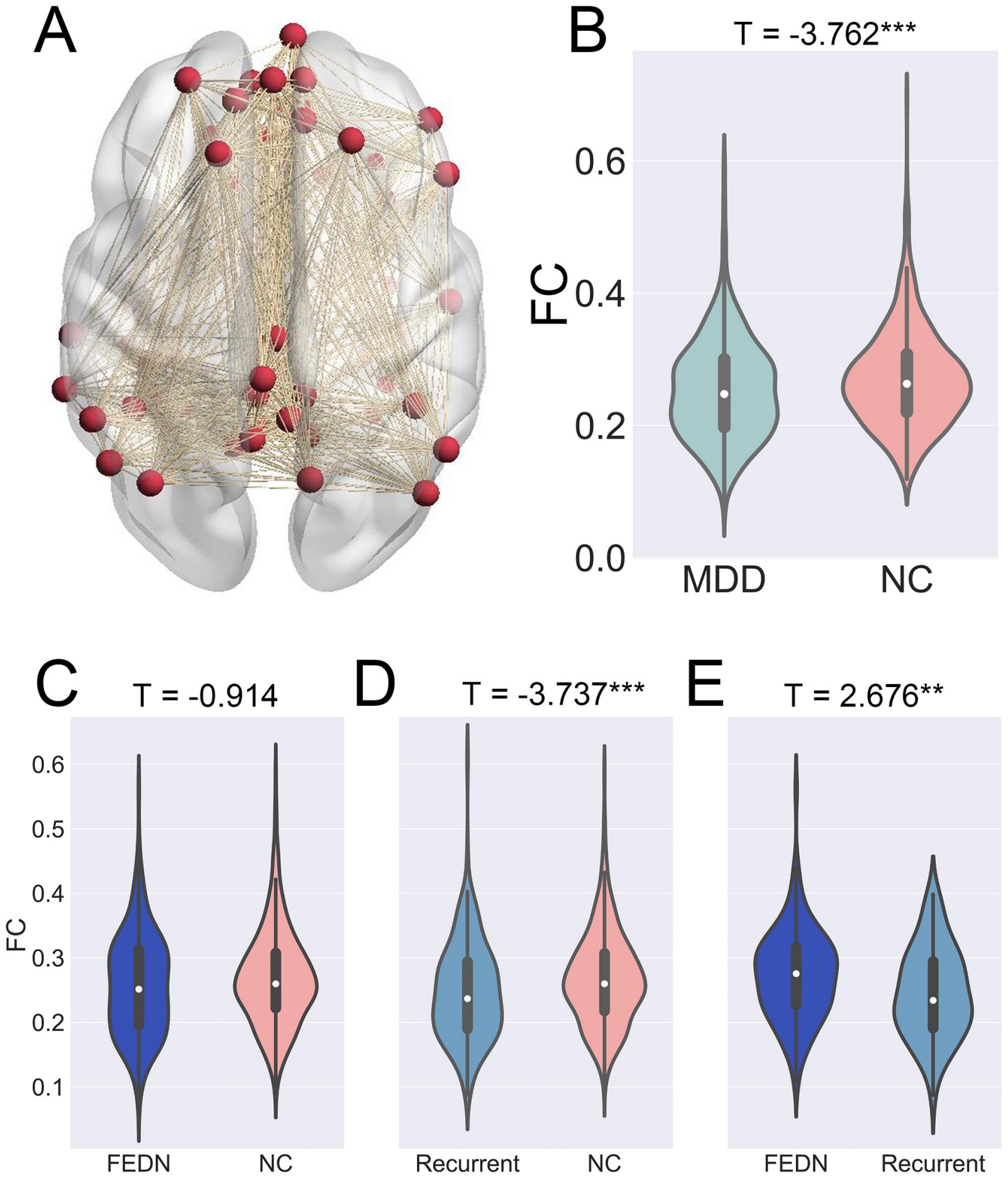
Figure 2. Decreased DMN functional connectivity in MDD patients. Mean DMN within-network FC was averaged across 33*32/2 = 528 connections as showed in A. The violin figures show the distribution of mean DMN within-network FC between MDD group and NC group (B), between first episode drug naïve (FEDN) 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. **, $p < 0{\cdot}01$; ***, $p < 0{\cdot}001$.

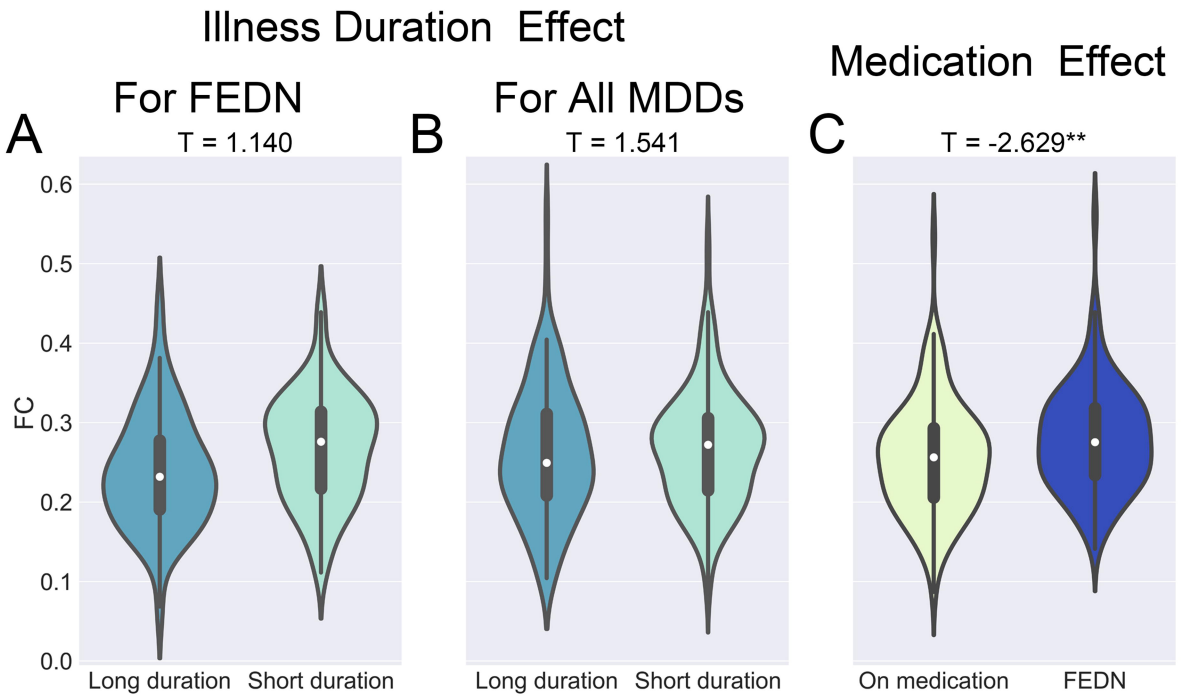
Figure 3. The effects of illness duration and medication on decreased DMN functional connectivity in MDD patients. The violin figures show the distribution of mean DMN within-network FC for first episode drug naïve (FEDN) MDDs with long vs. short illness duration (A), for pooled MDDs with long vs. short 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. **, $p < 0{\cdot}01$.

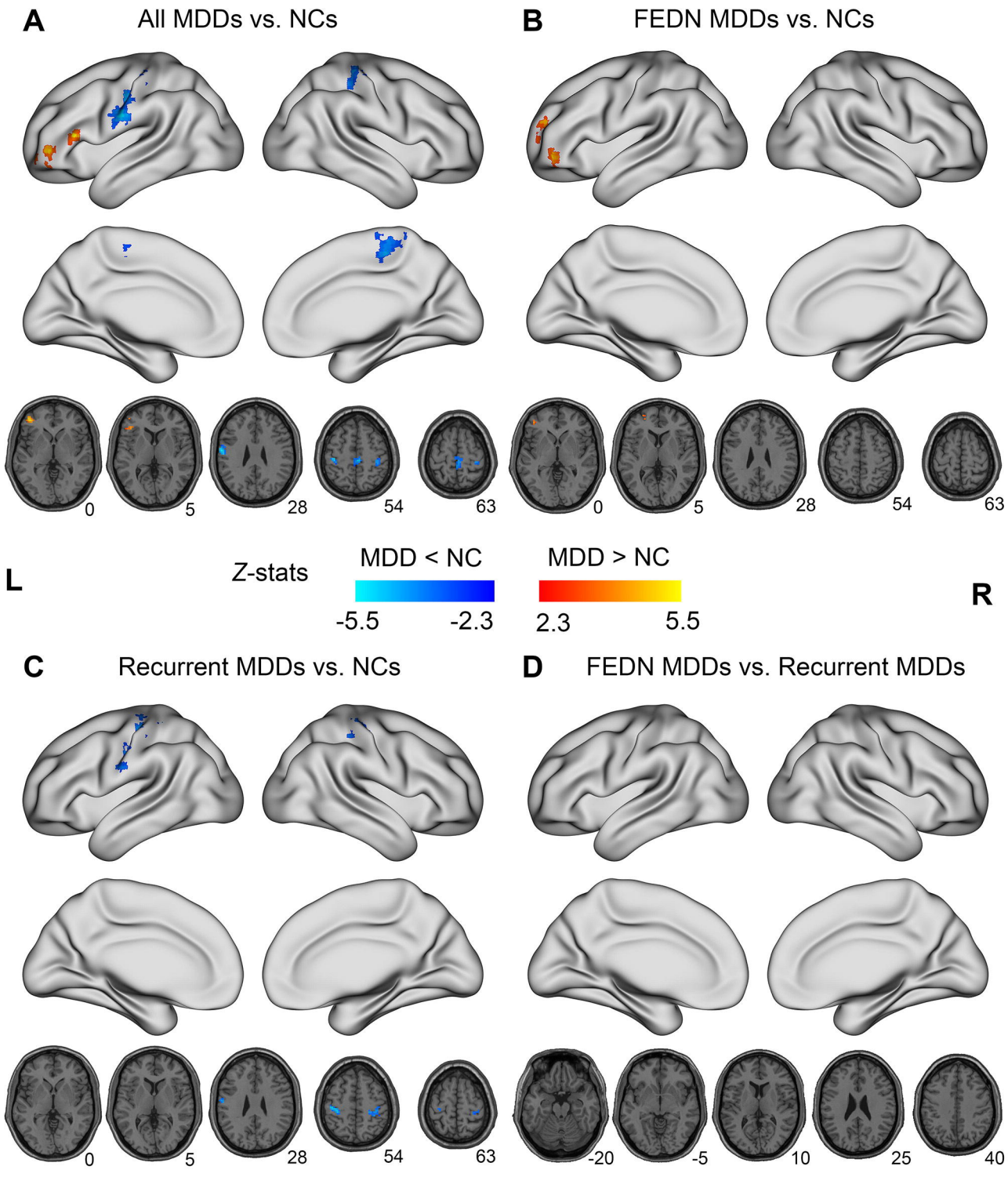
Figure 4. Regional homogeneity (ReHo) abnormalities in MDD patients. Significant group differences between (A) all individuals with MDD and NCs, (B) first episode drug naïve (FEDN) MDDs and NCs, (C) recurrent MDDs and NCs, (D) FEDN and recurrent MDDs were depicted. Gaussian random field (GRF) theory correction was employed to control family-wise error

rates (voxel-level $P < 0{\cdot}0005$; cluster-level $P < 0{\cdot}025$ for each tail, two-tailed). L, Left hemisphere; R, right hemisphere.


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