**Common and distinct functional brain network abnormalities in adolescent, early-middle adult, and late adult major depressive disorders**

***Supplemental Information***

## SI Methods

### Sample composition

The studied sample in the current study was drawn from two sources: a publicly available multisite dataset from the REST-meta-MDD consortium (http://rfmri.org/REST-meta-MDD) [1–3] and a local dataset from the First Affiliated Hospital of Chongqing Medical University in China. In the original sample, there were a total of 1300 major depressive (MDD) patients and 1128 healthy controls (HCs) from 25 study sites in the REST-meta-MDD dataset, as well as 161 MDD patients and 77 HCs from a single site in the local Chongqing dataset. We used the following exclusion criteria to select samples for the first round: (1) subjects without complete demographic information on sex or age were firstly excluded; (2) for MDD patients, those patients who had a total score < 8 on the 17-item Hamilton Depression Rating Scale (HAMD) or those without available information on the HAMD scores were excluded, for the purpose of excluding the patients who were in clinical remission at the time of functional magnetic resonance imaging (rs-fMRI) scanning; (3) subjects with a repetition time (TR) ≠ 2 seconds for their rs-fMRI scans were excluded, to minimize the potential bias caused by varied scanning parameters and temporal resolution of rs-fMRI signals across different sites; (4) subjects with poor imaging data or bad spatial normalization were excluded, as detected by careful visual inspections; (5) subjects with excessive head motion as defined by average framewise displacement (FD) > 0.2 mm, or who did not have full coverage of all 264 regions of interests (ROIs) in the Power atlas [4] were excluded. These steps resulted in a total of 928 MDD patients and 898 HCs from 18 sites left after the first-round selection.

All participants were categorized into three age groups strictly following the criterion in some recent studies [5, 6]: adolescents (12-17 years old), early-middle adults (18-54 years old), and late adults (>= 55 years old). However, after the first-round sample selection, it was found that several key demographics (e.g., sex ratio) and MDD patients’ depressive severity (as measured by the HAMD total scores) were not matched between different age groups. For example, the sex ratios were not well matched between the three age groups of MDD patients (27.1% males in adolescents, 37.0% males in early-middle-adults, and 23.0% males in late adults; *p* < 0.05 when applying the Chi-square test); the average HAMD score was significantly higher in the early-middle-adults (22.33 ± 5.85) group of MDD patients when compared with the adolescents (18.99 ± 5.97) and late-adults (20.20 ± 8.23) groups (analysis of variance with Bonferroni post-hoc comparisons, Bonferroni *p* < 0.05). To minimize possible confounding effects of these factors, we further randomly excluded part of the participants to ensure that these demographical factors and the average HAMD scores were matched between different age groups. For example, among the early-middle adult patients with MDD who were males and had a total HAMD score >= 27, part of the participants was selected using the random number method and then excluded from the analyses. Referring to prior research [1, 3], we finally removed the sites with fewer than 10 participants left after all the above steps, to overcome possible random play of chance on the estimation of any effects. The resulting final sample consisted of 617 MDD patients and 621 HCs from 15 sites, where the key demographic and clinical characteristics were well-matched between different age groups (see details in **Table 1** and **Supplemental Table S1**).

### Data preprocessing and quality control

All participants underwent rs-fMRI and high-resolution T1-weighted structural scans at each site. For those 14 sites from the REST-meta-MDD dataset, the key scanning parameters of each site were shown in **Supplemental Table S1**, and more details can be found online at: http://rfmri.org/REST-meta-MDD. For the local Chongqing dataset, the data was scanned with the following parameters: T1-weighted structural images were obtained using a 3D-MPRAGE sequence with a repetition time (TR) = 2000 ms, echo time (TE) = 2.56 ms, inversion time (TI) = 900 ms, flip angle = 9°, matrix size = 256×256, the field of view (FOV) = 256 × 256 mm2, slice thickness = 1 mm, slices per slab = 192, and voxel size = 1 × 1 × 1 mm3; rs-fMRI scans were obtained with TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm2, number of slices = 36, the reconstructed voxel size = 3.4 × 3.4 × 3 mm3, the layer thickness = 3.0 mm, and the total of volumes = 240.

Data from 14 sites in the REST-meta-MDD consortium has been preprocessed using the DPARSF software [7, 8] with the standardized protocol provided by the REST-meta-MDD project. Details of the protocol can be found in some earlier publications [1, 2]. Briefly, it included removing the first 10 volumes for signal equilibrium, slice-timing correction, head motion realignment, brain tissue segmentation, spatial normalization, and temporal filtering (0.01-0.10Hz). To control for head motion and physiological noises, the Friston-24 head motion parameters, liner trend, as well as signals from the white matter and cerebrospinal fluid were regressed out as nuisance covariates.

Data from the local Chongqing dataset was preprocessed using the same above protocol. Especially, as suggested in recent studies [9, 10], for those participants who were under 18 years of age, we used a Chinese adolescent brain template (https://github.com/zuoxinian/CCS/tree/master/H3/GrowthCharts/Templates/IPCAS/BrainTemplate) instead of the default template for achieving more accurate image normalization.

Subjects with poor imaging data or bad spatial normalization were excluded, as detected by careful visual inspections after data preprocessing. The subjects with excessive head motion (average FD > 0.2 mm), or who did not have full coverage of all 264 ROIs in the Power atlas were also excluded from the analyses.

### Brain parcellation, edge-based FC and network-level FC

All nodes in the Power were assigned into 10 networks including the default-mode, frontoparietal, sensorimotor, visual, subcortical, cingulo-opercular, salience, ventral attention, dorsal attention, and auditory networks referring to previous work [11–14]. The network assignments were visualized in **Supplemental Figure 1** using the Brainnet Viewer toolbox [15].

### Associations with clinical variables

Among the MDD patients, there were a total of 187 first-episode, drug-naïve (FEDN) patients (62 adolescents, 93 early-middle adults, and 32 late adults) as well as 276 non-FEDN patients (46 adolescents, 193 early-middle adults, and 37 late adults) based on the records in the REST-meta-MDD and Chongqing datasets, while such information was unavailable for other patients. As shown in **Supplemental Table S2**, the age, sex ratio, and head motion were generally matched between the FEDN and non-FEDN patients in each age group. To explore the possible effects of medication, we performed post-hoc comparisons on all observed significant MDD-related brain network alterations between the FEDN and non-FEDN patients by ANCOVA adjusted for sex, age, head motion, and site effects. Such comparisons were performed both in each age group separately and in all MDD patients.

## SI Results

### Pooled analyses on edge-level FCs

The ANCOVA model indicated significant main effects of age group in a considerable proportion of the edges across the whole brain (corrected *p* < 0.05), which is shown in **Supplemental Figure S2**. Such results are in line with findings in the analyses on network-level FCs, possibly indicating an aging-related decline in brain-wide FCs which involved multiple brain systems.

**References**

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**Supplemental Table S1.** The sample sizes and key data scanning parameters of each site included in this study. HC, healthy controls; MDD, major depressive disorder; TE, echo time; TR, repetition time.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Site numbera | Affiliations | Samples | | Scanner | TR (ms) | TE (ms) | Flip angle (°) | Slice number | Time points |
|  | MDD patients | HCs |
| 1 | National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital) & Key Laboratory of Mental Health, Ministry of Health (Peking University) | 35 | 54 | Siemens 3T | 2000 | 30 | 90 | 30 | 210 |
| 2 | Department of Clinical Psychology, Suzhou Suzhou Psychiatric Hospital, The Affiliated Guangji Hospital of Soochow University | 25 | 22 | Philips 3T | 2000 | 30 | 90 | 37 | 200 |
| 3 | Sir Run Run Shaw Hospital, Zhejiang University School of Medicine | 26 | 35 | GE 3T | 2000 | 30 | 90 | 37 | 184 |
| 4 | Department of Psychiatry, First Affiliated Hospital, China Medical University | 31 | 42 | GE 3T | 2000 | 30 | 90 | 35 | 200 |
| 5 | Department of Psychosomatics and Psychiatry, Zhongda Hospital, School of Medicine, Southeast University | 20 | 34 | Siemens 3T | 2000 | 25 | 90 | 36 | 240 |
| 6 | Huaxi MR Research Center, West China Hospital of Sichuan University | 25 | 17 | GE 3T | 2000 | 30 | 90 | 30 | 200 |
| 7 | Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical Universit | 26 | 23 | GE 3T | 2000 | 40 | 90 | 33 | 240 |
| 8 | Department of Radiology, The First Affiliated Hospital, College of Medicine, Zhejiang University | 12 | 13 | Philips 3T | 2000 | 35 | 90 | 24 | 200 |
| 9 | Faculty of Psychology, Southwest University | 182 | 175 | Siemens 3T | 2000 | 30 | 90 | 32 | 242 |
| 10 | Beijing Anding Hospital, Capital Medical University | 45 | 48 | Siemens 3T | 2000 | 30 | 90 | 33 | 240 |
| 11 | The Institute of Mental Health, Second Xiangya Hospital of Central South University | 13 | 12 | Philips 3T | 2000 | 30 | 90 | 36 | 250 |
| 12 | Mental Health Center, West China Hospital, Sichuan University | 16 | 22 | Philips 3T | 2000 | 30 | 90 | 38 | 240 |
| 13 | First Affiliated Hospital of Kunming Medical University | 19 | 18 | GE 1.5T | 2000 | 40 | 90 | 24 | 160 |
| 14 | Department of Neurology, Affiliated ZhongDa Hospital of Southeast University | 28 | 37 | Siemens 3T | 2000 | 25 | 90 | 36 | 240 |
| 15 | Department of Psychiatry, The First Affiliated Hospital of Chongqing Medical University | 114 | 69 | Siemens 3T | 2000 | 30 | 90 | 36 | 240 |
| Total |  | 617 | 621 |  |  |  |  |  |  |

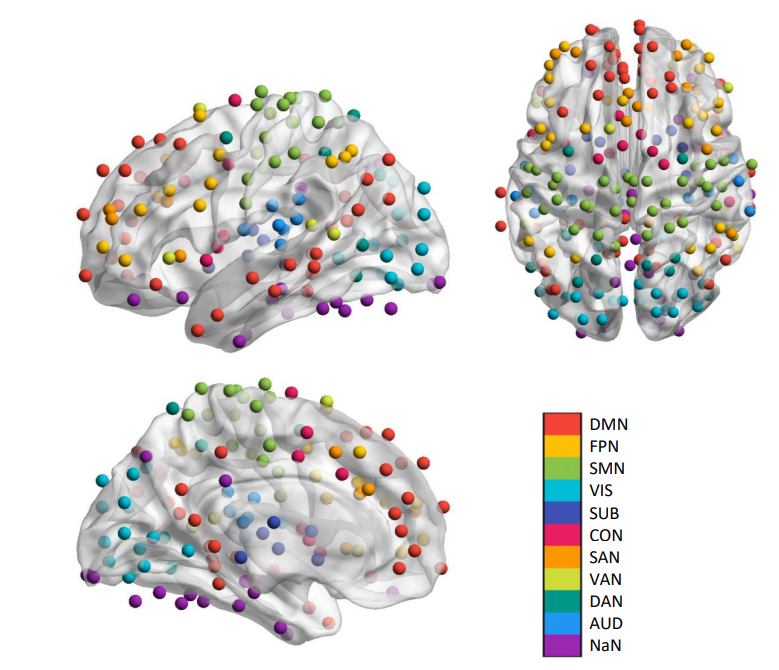
aThe sites 1-14 were drawn from data of the original 25 sites in the REST-meta-MDD project, whose details can be found at: <http://rfmri.org/REST-meta-MDD>. The site 15 was a local dataset from the Chongqing Medical University, China.

**Supplemental Table S2** Comparisons ondemographic/clinical characteristics between the first-episode, drug-naïve (FEDN) and non-FEDN patients in each age group. FD, framewise-displacement; HAMD, Hamilton Depression Rating Scale; SD, standard deviation.

|  |  |  |  |
| --- | --- | --- | --- |
|  | FEDN patients (*N* = 187) | Non-FEDN patients (*N* =314) | Comparisons between patients and controls |
| **Adolescents (12-17 years old)** | | | |
| Number of participants | 62 | 46 |  |
| Age (years, mean ± SD) | 15.04 ± 1.15 | 14.46 ± 1.35 | *t* = 2.402, *p* = 0.018 |
| Sex (male/female) | 15/47 | 13/33 | *χ*2 = 0.227, *p* = 0.633 |
| Mean FD (mm, mean ± SD) | 0.07 ± 0.03 | 0.06 ± 0.03 | *t* = 1.045, *p* = 0.298 |
| Illness duration (month, mean ± SD)*a* | 15.11 ± 14.32 | 16.74 ± 18.33 | *t* = -0.517, *p* = 0.606 |
| HAMD-17 total score (mean ± SD) | 18.94 ± 4.76 | 19.80 ± 5.67 | *t* = -0.865, *p* = 0.389 |
| **Early-middle adults (18-54 years old)** | | | |
| Number of participants | 93 | 193 |  |
| Age (years, mean ± SD) | 33.06 ± 11.00 | 33.20 ± 9.74 | *t* = -0.103, *p* = 0.918 |
| Sex (male/female) | 24/69 | 63/130 | *χ*2 = 1.386, *p* = 0.239 |
| Mean FD (mm, mean ± SD) | 0.06 ± 0.03 | 0.07 ± 0.03 | *t* = -0.210, *p* = 0.834 |
| Illness duration (month, mean ± SD)*a* | 30.11 ± 44.53 | 49.78 ± 70.93 | *t* = -2.801, *p* = 0.005 |
| HAMD-17 total score (mean ± SD) | 19.53 ± 4.27 | 19.64 ± 4.35 | *t* = -0.212, *p* = 0.833 |
| **Late Adults (>= 55 years old)** | | | |
| Number of participants | 32 | 37 |  |
| Age (years, mean ± SD) | 59.44 ± 3.26 | 60.70 ± 5.77 | *t* = -1.139, *p* = 0.259 |
| Sex (male/female) | 7/25 | 12/25 | *χ*2 = 0.959, *p* = 0.328 |
| Mean FD (mm, mean ± SD) | 0.07 ± 0.03 | 0.08 ± 0.04 | *t* = -0.406, *p* = 0.686 |
| Illness duration (month, mean ± SD)*a* | 48.24 ± 71.74 | 100.17 ± 114.40 | *t* = -2.190, *p* = 0.033 |
| HAMD-17 total score (mean ± SD) | 26.69 ± 6.95 | 21.43 ± 4.89 | *t* = 3.579, *p* = 0.001 |

*a*Data on illness duration was only available for 107 adolescent (62 FEDN and 45 non-FEDN) patients, 273 early-middle adult (92 FEDN and 181 non-FEDN) patients, and 63 late adult (29 FEDN and 34 non-FEDN) patients, respectively.

**Supplemental Figure S1. Network assignments of the 264 regions of interest.** AUD, auditory network; CON, cinguloopercular network; DAN, dorsal attention network; DMN, default-mode network; FPN, frontoparietal network; SAN, salience network; SMN, sensorimotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network.



**Supplemental Figure S2. Significant main effects of age group on edge-level functional connectivity (FC) as detected in the pooled analyses.** All the edges showing significant main effects of age group (corrected *p* < 0.05) were presented, and the nodes from different networks were marked by different colors.AUD, auditory network; CON, cinguloopercular network; DAN, dorsal attention network; DMN, default-mode network; FPN, frontoparietal network; SAN, salience network; SMN, sensorimotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network.

