

Original Article

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

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Abstract

Background. The age-related heterogeneity in major depressive disorder (MDD) has received significant attention. However, the neural mechanisms underlying such heterogeneity still need further investigation. This study aimed to explore the common and distinct functional brain abnormalities across different age groups of MDD patients from a large-sample, multi-center analysis.

Methods. The analyzed sample consisted of a total of 1238 individuals including 617 MDD patients (108 adolescents, 12–17 years old; 411 early-middle adults, 18–54 years old; and 98 late adults, >= 55 years old) and 621 demographically matched healthy controls (60 adolescents, 449 early-middle adults, and 112 late adults). MDD-related abnormalities in brain functional connectivity (FC) patterns were investigated in each age group separately and using the whole pooled sample, respectively.

Results. We found shared FC reductions among the sensorimotor, visual, and auditory networks across all three age groups of MDD patients. Furthermore, adolescent patients uniquely exhibited increased sensorimotor-subcortical FC; early-middle adult patients uniquely exhibited decreased visual-subcortical FC; and late adult patients uniquely exhibited wide FC reductions within the subcortical, default-mode, cingulo-opercular, and attention networks. Analysis of covariance models using the whole pooled sample further revealed: (1) significant main effects of age group on FCs within most brain networks, suggesting that they are decreased with aging; and (2) a significant age group × MDD diagnosis interaction on FC within the default-mode network, which may be reflective of an accelerated aging-related decline in default-mode FCs.

Conclusions. To summarize, these findings may deepen our understanding of the age-related biological and clinical heterogeneity in MDD.

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders and a leading cause of disability worldwide (Hasin *et al.*, 2018; Iancu, Wong, Rhebergen, van Balkom, & Batelaan, 2020; Lu *et al.*, 2021). Neuroimaging studies using resting-state functional magnetic resonance imaging (rs-fMRI) have documented that MDD is associated with altered intrinsic functional connectivity (FC) in large-scale brain networks. For instance, abnormal FC patterns within high-order neural networks such as the default-mode network in MDD patients have been frequently reported (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Luo *et al.*, 2021; Yan *et al.*, 2019). In other studies, it was found that MDD is related to decreased FCs within the sensorimotor, visual, and auditory networks (Javaheripour *et al.*, 2021; Lu *et al.*, 2020; Luo *et al.*, 2021). These findings have significantly advanced our knowledge about neural mechanisms underlying MDD.

The clinical and biological heterogeneity in MDD has received significant attention in recent years (Nguyen et al., 2022; Pine, 2019). Age is one of the most notable contributing factors to such heterogeneity, and there have been ample studies reporting that MDD patients in different age groups differ in depressive symptomatology, risk factors, and responses to treatment (Rep et al., 2022; Schaakxs et al., 2018; Wagner et al., 2020). For example, it was found that vegetative symptoms such as appetite change and insomnia are more common in adolescent MDD than adult MDD (Rice et al., 2019). Beside that, MDD in late adulthood is considered to be more characterized by somatic symptoms and cognitive impairments (Hegeman, Kok, van der Mast, & Giltay, 2012; Thomas et al., 2009). Potential differences in MDDs between different age stages have been also indicated by past neuroimaging studies from the perspectives of brain development and aging. To be specific, FC between the sensorimotor and subcortical regions as well as volumes of several subcortical structures such as putamen have been found to be reduced with increasing age during adolescence (Sanders et al., 2023; Supekar, Musen, & Menon, 2009; Whittle et al., 2014). These age-related brain changes were found to be attenuated in adolescents with MDD, which were thought to be reflective of delayed brain maturation (Jiao et al., 2011; Straub et al., 2019; Whittle et al., 2014). In contrast to adolescent MDD, most studies conducted in older patients suggested an accelerated brain aging process in patients with MDD (Ballester et al., 2021; Han et al., 2021; Jha, Chin Fatt, Minhajuddin, Mayes, & Trivedi, 2023). Together, these findings support the possibility that mechanisms of MDD are associated with age, which might be instructive for personalizing the treatment strategies for MDD patients (Wagner et al., 2020).

To test the hypothesis that MDD-related brain dysfunctions are age-associated, several studies have been performed to compare the abnormal brain FC patterns between different age groups of MDD patients. Especially, it was suggested that unique abnormal FC patterns may present in pre-adult and elderly patients with MDD when compared to the early-and-middle adult patients (Hu et al., 2019; Saberi, Mohammadi, Zarei, Eickhoff, & Tahmasian, 2022; Tang et al., 2018). As an example, abnormal FC patterns involving the insula, the amygdala, and the default-mode cortices have been found to differ between adolescents and adults with MDD (Hu et al., 2019; Tang et al., 2018). Furthermore, it was suggested that unique profiles of FC abnormalities may exist in patients with 'late-life depression', which can be defined as MDD occurring over the age of 50 or 55 no matter whether the illness started in early or later life (Saberi et al., 2022; Tan et al., 2023; Yang et al., 2022). Nevertheless, these studies are limited in several ways. First, many studies have compared FC patterns between adolescents and adults (Tang et al., 2018), or between young adults and older adults (Ye et al., 2017). However, little has been conducted to simultaneously compare MDD patients among adolescents, adults, and elderly patients. Second, some of the existing studies have reported heterogeneous and even conflicting results. For example, both decreased (Wu et al., 2011) and increased (Eyre et al., 2016) FCs between the posterior cingulate cortex and the anterior cingulate cortex have been reported in elderly patients with MDD than healthy controls (HCs). One possible reason for such inconsistency may be due to relatively small sample sizes (<60 per group) and potentially differing experimental settings in these published studies (Chen, Lu, & Yan, 2018).

To address the above limitations, the current study aimed to investigate the common and distinct features of functional brain network abnormalities across adolescents, adults, and elderly patients with MDD from a large-sample ($n > 1200$) analysis. All imaging data were preprocessed using the same standardized protocol, to minimize the potential biases and obtain as reliable results as possible. Using one of the largest and most well-powered rs-fMRI samples of MDD patients to our knowledge, we hope to gain insights into the functional disruptions among different age groups of MDD patients, facilitating future studies on the age-related heterogeneity in MDD.

Materials and methods

Subjects

The final analyzed sample in the current study consisted of 1238 participants (617 MDD patients and 621 HCs, 12–82 years old) of 350 men and 888 women recruited from 15 study sites across China. Such a sample was drawn from two sources: a publicly available multisite dataset from the REST-meta-MDD consortium (<http://rfmri.org/REST-meta-MDD>) (Deng et al., 2022; Ding et al., 2021; Liu et al., 2021; Long et al., 2020; Yan et al., 2019; Yang et al., 2021) and a local dataset from the First Affiliated Hospital of Chongqing Medical University in China. The sample size for each site can be found in online Supplementary Table S1. All patients were diagnosed with MDD (without comorbidity of other psychiatric disorders) based on the Structured Clinical Interview for DSM-5 (SCID) and had a total score ≥ 8 on the 17-item Hamilton Depression Rating Scale (HAM-D-17). Following some previous studies (Long et al., 2020; Yan et al., 2019; Yang et al., 2021), exclusion criteria include incomplete demographic information, poor imaging quality, and sites with less than 10 participants. In addition, a part of the participants was randomly excluded to ensure that demographics and MDD patients' depressive severity were matched between different age groups (see SI Methods for details). The respective local ethics committees have approved all contributing studies, and written informed consent has been obtained from all participants or their guardians at the local institutions.

All participants were categorized into three age groups: adolescents (108 MDD patients and 60 HCs, 12–17 years old), early-middle adults (411 MDD patients and 449 HCs, 18–54 years old), and late adults (98 MDD patients and 112 HCs, ≥ 55 years old), following the criterion in some recent studies (Cuijpers et al., 2020; Findling et al., 2022). The average age, sex ratio, and head motion were matched between the MDD patients and HCs in each age group; besides, the sex ratio, head motion, and depressive severity (measured by the HAM-D total score) were matched between different age groups of MDD patients. More details about the demographic characteristics of each group of participants can be found in Table 1.

Data preprocessing and quality control

All participants underwent rs-fMRI and T1-weighted structural scans at each site. The scanning parameters for each site can be found in online Supplementary Table S1. Data were preprocessed using the DPARSF software (Yan, Wang, Zuo, & Zang, 2016) with the standardized protocol provided by the REST-meta-MDD project, as described in several previously published studies (Long et al., 2020; Yan et al., 2019; Yang et al., 2021; Zhang et al., 2021). A Chinese adolescent brain template (<https://github.com/>

Table 1. Demographic and clinical characteristics in the three age groups of participants

	MDD patients (N = 617)	HCs (N = 621)	MDD-HCs comparison
Adolescents (12–17 years old)			
No. of participants	108	60	
Age (years, mean \pm s.d.)	14.80 \pm 1.27	14.70 \pm 1.69	$t = 0.385, p = 0.701$
Sex (male/female)	28/80	15/45	$\chi^2 = 0.017, p = 0.895$
Mean FD (mm, mean \pm s.d.)	0.07 \pm 0.03	0.07 \pm 0.03	$t = -0.181, p = 0.856$
FEDN/non-FEDN/unknown	62/46/0	/	/
Illness duration (month, mean \pm s.d.) ^a	15.79 \pm 16.07	/	/
HAMD-17 total score (mean \pm s.d.)	19.31 \pm 5.16	/	/
Early-middle adults (18–54 years old)			
No. of participants	411	449	
Age (years, mean \pm s.d.)	32.14 \pm 9.83	31.62 \pm 10.72	$t = 0.742, p = 0.858$
Sex (male/female)	122/289	126/323	$\chi^2 = 0.275, p = 0.600$
Mean FD (mm, mean \pm s.d.)	0.07 \pm 0.03	0.07 \pm 0.04	$t = -1.555, p = 0.121$
FEDN/non-FEDN/ unknown	93/193/125	/	/
Illness duration (month, mean \pm s.d.) ^a	35.81 \pm 56.93	/	/
HAMD-17 total score (mean \pm s.d.)	20.04 \pm 4.14	/	/
Late adults (>= 55 years old)			
No. of participants	98	112	
Age (years, mean \pm s.d.)	61.33 \pm 5.81	61.91 \pm 5.31	$t = -0.761, p = 0.448$
Sex (male/female)	23/75	36/76	$\chi^2 = 1.946, p = 0.163$
Mean FD (mm, mean \pm s.d.)	0.07 \pm 0.04	0.08 \pm 0.03	$t = -1.555, p = 0.121$
FEDN/non-FEDN/ unknown	32/37/29	/	/
Illness duration (month, mean \pm s.d.) ^a	73.72 \pm 98.27	/	/
HAMD-17 total score (mean \pm s.d.)	20.13 \pm 8.29	/	/

^aData on illness duration was only available for 107 adolescent patients, 371 early-middle adult patients, and 66 late adult patients, respectively. FD, framewise-displacement; FEDN, first-episode, drug-naïve; HAMD, Hamilton Depression Rating Scale; HC, healthy controls; SD, standard deviation.

zuoxinian/CCS/tree/master/H3/GrowthCharts/Templates/IPCAS/BrainTemplate) was used for image normalization for participants who were under 18 years of age (Dong et al., 2020; Zhang et al., 2021). Subjects with poor image quality or excessive head motion as determined by mean framewise-displacement (FD) >0.2 mm were excluded from the analyses. See SI Methods for more details.

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

Nodes and edges between them (connections) make up a topological network. In the current study, the preprocessed images were parcellated into 264 nodes across the brain based on the 264 regions of interest (ROIs) in a validated and widely-used Power functional atlas (Liang et al., 2020; Long et al., 2023; Power et al., 2011). Edge-based FCs between brain nodes were defined by the z-transformed Pearson correlation coefficients between average time courses of each possible pair of nodes ($264 \times 263 / 2 = 34\,716$ edges in total) (Yan et al., 2019; Yang et al., 2021). To investigate FCs at the level of large-scale brain networks, all nodes were further 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 (see online

Supplementary Figure S1) (Cole et al., 2013; Feng et al., 2020; Mohr et al., 2016; Niu et al., 2022). The network-level FC strengths were calculated by averaging the z-transformed FC values across all involved edges within a specific network or between a specific pair of networks (Javaheripour et al., 2021; Li et al., 2021). Since 10 networks were defined, this resulted in a total of 10 within-network and 45 between-network averaged FC values.

Separate comparisons in each age group

The edge-based and network-level FCs were firstly compared between the MDD patients and HCs in each age group separately (e.g. adolescent patients v. adolescent controls) (Fig. 1). Edge-based FCs were compared by the network-based statistics (NBS) approach (Zalesky, Fornito, & Bullmore, 2010). Here, NBS analyses with t tests were conducted, with sex, age, head motion as measured by mean FD, and site added as covariates. Note here, the sites were added as covariates (as dummy variables) to control possible influences of different data scanning parameters across different sites. Permutation with 5000 iterations was employed and the results were considered significant at edge $p < 0.001$ and cluster $p < 0.05$ after NBS correction for multiple comparisons (Chopra et al., 2021; Li et al., 2021; Tsurugizawa

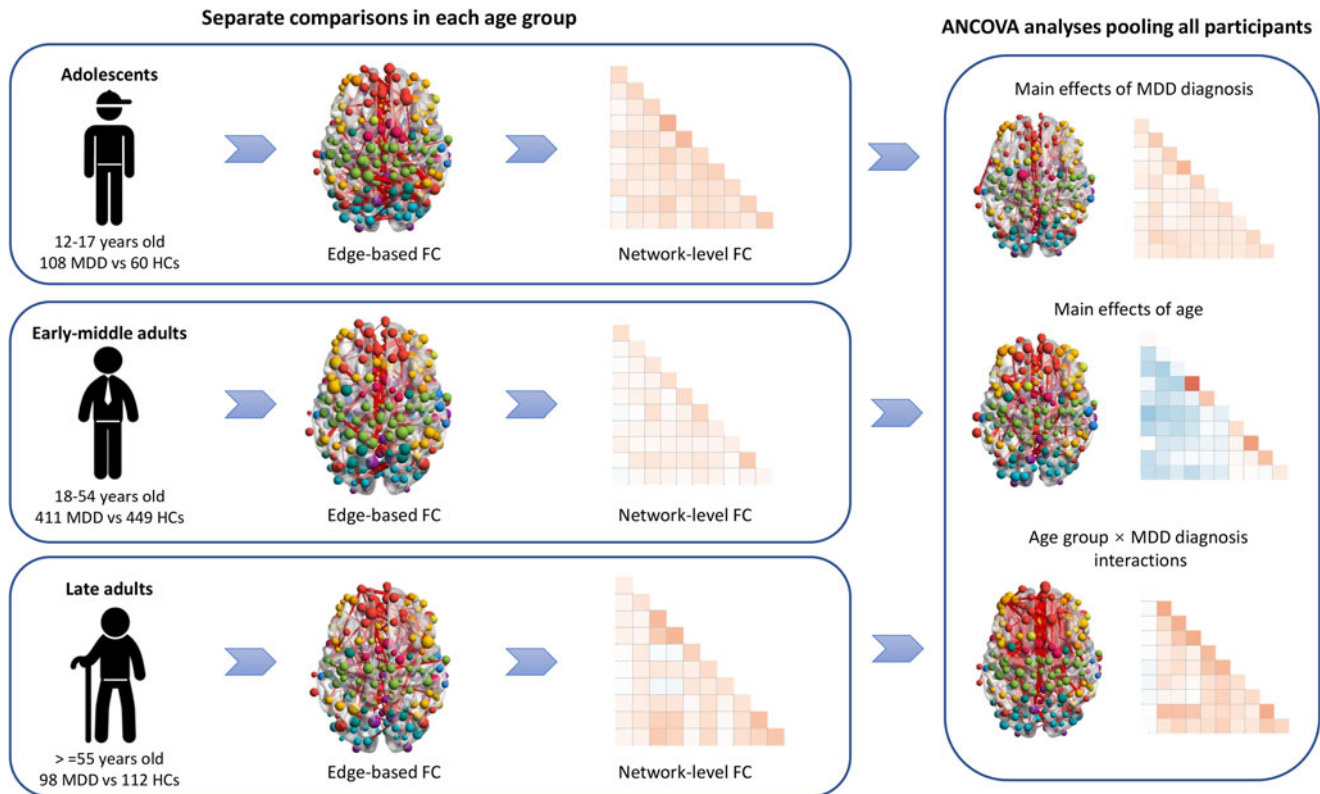


Figure 1. A summary of the main analyzing steps in the present study. ANCOVA, analysis of covariance; FC, functional connectivity; HCs, healthy controls; MDD, major depressive disorder.

& Yoshimaru, 2021). The network-level FC values were compared by analysis of covariance (ANCOVA) covarying for sex, age, head motion as well as site, and the results were considered significant at $p < 0.05$ after false discovery rate (FDR) correction (Li et al., 2021; Sun et al., 2022). The results were visualized partly using the Brainnet Viewer toolbox (Xia, Wang, & He, 2013).

Analyses using the whole pooled sample

Data of all participants were then pooled and analyzed for direct investigations on the effects of age groups and MDD diagnosis, as well as their interactions (Fig. 1). A two-by-three ANCOVA statistical model was used to analyze both the edge-based and network-level FCs, with MDD diagnosis (MDD v. HCs), age group (adolescents v. early-middle adults v. late adults) and MDD diagnosis \times age group interaction as variables of interest, as well as sex, head motion and site as covariates. For edge-based FCs, such analyses were performed based on the NBS approach (5000 iterations), and the results were considered significant at edge $p < 0.001$ and cluster $p < 0.05$ after NBS corrections. For network-level FCs, the results were considered significant when $p < 0.05$ after FDR corrections across the multiple network-level FC values. When significant main effects of age group were found, the Bonferroni post-hoc pairwise comparisons were further adopted between different age groups and the differences were considered significant at Bonferroni $p < 0.05$.

Associations with clinical variables

Several post-hoc analyses were performed to explore possible associations between the observed significant brain network

alterations (edge-level and network-level) and clinical characteristics in MDD patients. Firstly, the brain network alterations were correlated with HAM-D-17 total score/illness duration using partial correlations adjusted for sex, age, head motion, and site effects. Secondly, the brain network alterations were compared between the first-episode, drug-naïve (FEDN) and non-FEDN patients by ANCOVA adjusted for the same above covariates. These investigations were performed both in each age group separately and in all MDD patients. For edge-level FCs, average FC values were firstly calculated across all the edges with significant alterations before being fed into the analyses. The results were considered significant at FDR-corrected $p < 0.05$. See SI Methods for more details.

Results

Separate comparisons in each age group

In all three age groups, the MDD patients showed significant alterations in both edge-based and network-level FCs when compared to age-matched HCs. The significant alterations in edge-based FCs (corrected $p < 0.05$) were shown in Fig. 2. For better visualization, we counted and presented both the raw number and normalized proportion (obtained by dividing the raw number by the maximum possible number) of edges falling into each of the within-network and between-network classes. The significant alterations in network-level FCs (corrected $p < 0.05$) were shown in Fig. 3.

Results on the edge-based FCs and network-level FCs were generally in agreement with each other, consistently suggesting significantly altered FC patterns (most of which are hypo-connected

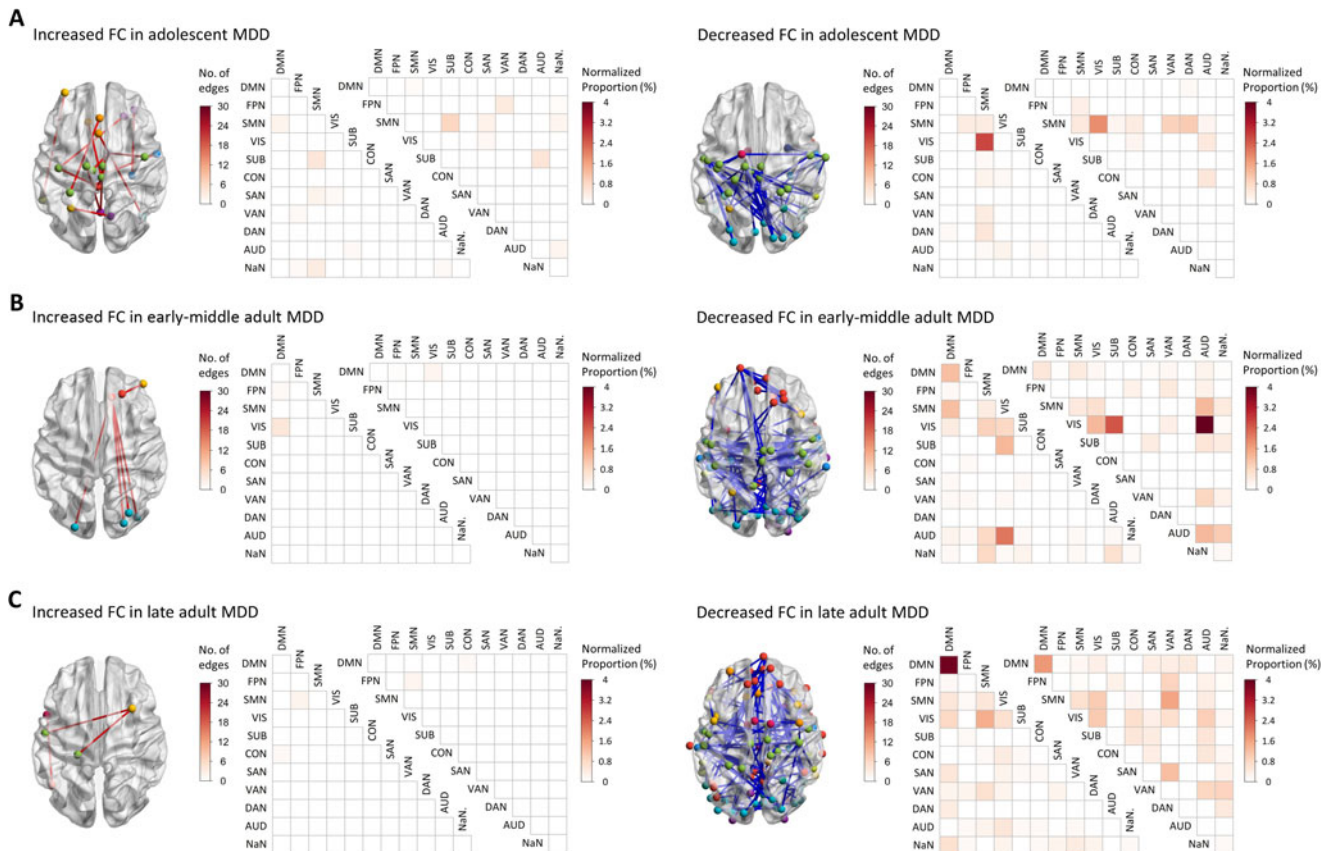


Figure 2. Results of the separate comparisons on edge-based FCs in each age group. (A) Results in the adolescents. (B) Results in the early-middle adults. (C) Results in the late adults. The edges with significantly increased or decreased FCs in MDD patients (corrected $p < 0.05$) were presented separately. AUD, auditory network; CON, cinguloopercular network; DAN, dorsal network; DMN, default-mode network; FC, functional connectivity; FPN, frontoparietal network; MDD, major depressive disorder; SAN, salience network; SMN, sensorimotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network.

edges) in all age groups of MDD patients. Specifically, the results suggested similar widespread decreases in FCs, which involved the sensorimotor, visual, and auditory networks, in all age groups of MDD patients. Several age group-specific alterations were also observed, including increased sensorimotor-subcortical FC in adolescent patients, decreased visual-subcortical FC in early-middle adult patients, as well as decreased subcortical-, cinguloopercular-, default-mode-, and attention-involved FCs in late adult patients (Figs 2, 3).

Pooled analyses on network-level FCs

Results of the ANCOVA model on network-level FCs when pooling the data of all participants were shown in Fig. 4. Firstly, the ANCOVA model revealed significant main effects of age group (corrected $p < 0.05$) in a considerable proportion of within-network and between-network FC values (Fig. 4A). The post-hoc comparisons indicated that such effects were mainly driven by significant reductions of FCs in the late adult patients with MDD when compared to the adolescent and early-middle adult patients (Fig. 4B). Such results, therefore, may indicate an aging-related decline in brain-wide FCs which involved multiple brain systems.

The ANCOVA model also revealed significant main effects of MDD diagnosis (corrected $p < 0.05$) in FCs between the visual and sensorimotor networks, as well as between the visual and auditory networks (Fig. 4C). From the interaction plots, it can

be seen that these FC values were consistently lower in MDD patients than HCs in all age groups (Fig. 4C). Thus, it might be concluded that the visual-sensorimotor and visual-auditory FCs are decreased in MDD patients independent of the age group.

Additionally, a significant age group \times MDD diagnosis interaction was found on FC within the default-mode network (corrected $p < 0.05$); the interaction plots showed that the within-default-mode FCs were increased in adolescent patients, but decreased in early-middle adult and late adult patients with MDD in trends when compared to the HCs in each age groups (Fig. 4D).

Pooled analyses on edge-level FCs

Similar to the result on network-level FCs, the ANCOVA model indicated significant main effects of age group in a considerable proportion of the edges across the whole brain (corrected $p < 0.05$, see online Supplementary Figure S2). However, no significant main effects of MDD diagnosis or significant age group \times MDD diagnosis interactions were found on the edge-level FCs (corrected $p > 0.05$).

Associations with clinical measures

No significant correlations were found between the brain network alterations and HAM-D-17 total score/illness duration in MDD

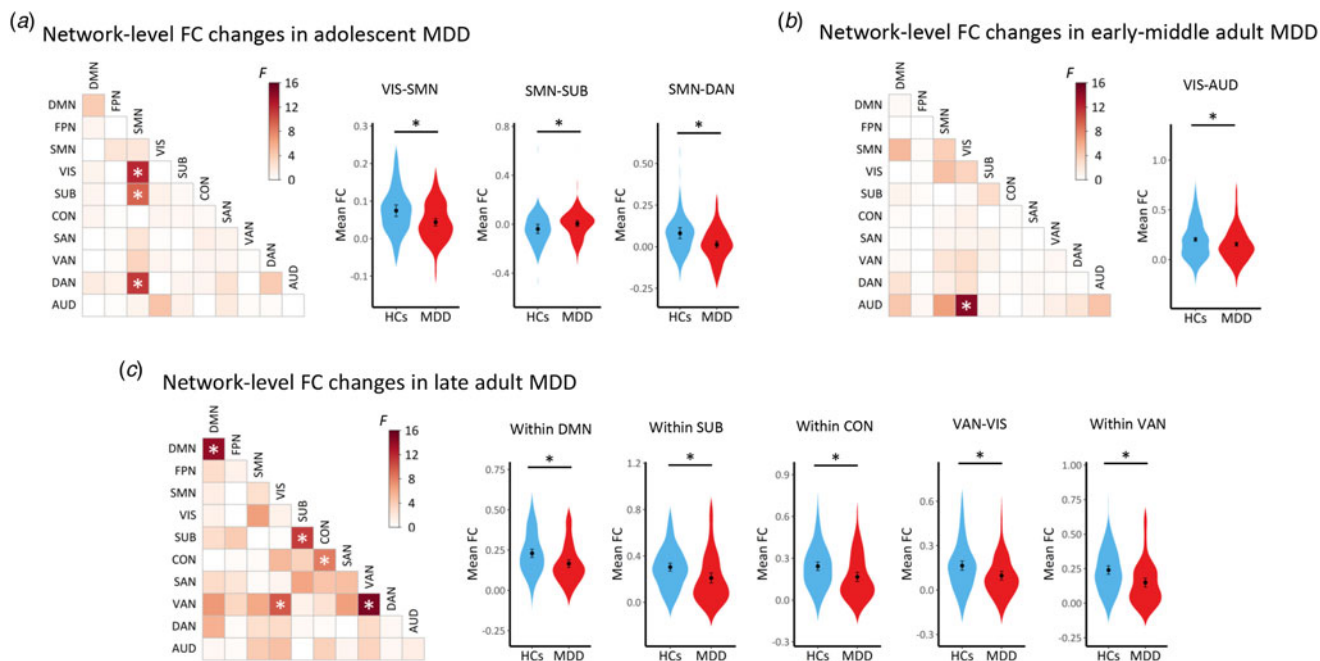


Figure 3. Results of the separate comparisons on network-level FCs in each age group. (A) Results in the adolescents. (B) Results in the early-middle adults. (C) Results in the late adults. The “*” indicates a significant difference (corrected $p < 0.05$) between the patients and HCs. Mean values of the network-level FCs showing significant differences were also presented on the right sides. AUD, auditory network; CON, cinguloopercular network; DAN, dorsal attention network; DMN, default-mode network; FC, functional connectivity; FPN, frontoparietal network; MDD, major depressive disorder; SAN, salience network; SMN, sensorimotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network.

patients (all corrected $p > 0.05$). No significant differences in the brain network alterations were found between the FEDN and non-FEDN MDD patients, either (all corrected $p > 0.05$).

Discussion

In the present study, we investigated the functional brain network abnormalities in MDD patients across three major age groups

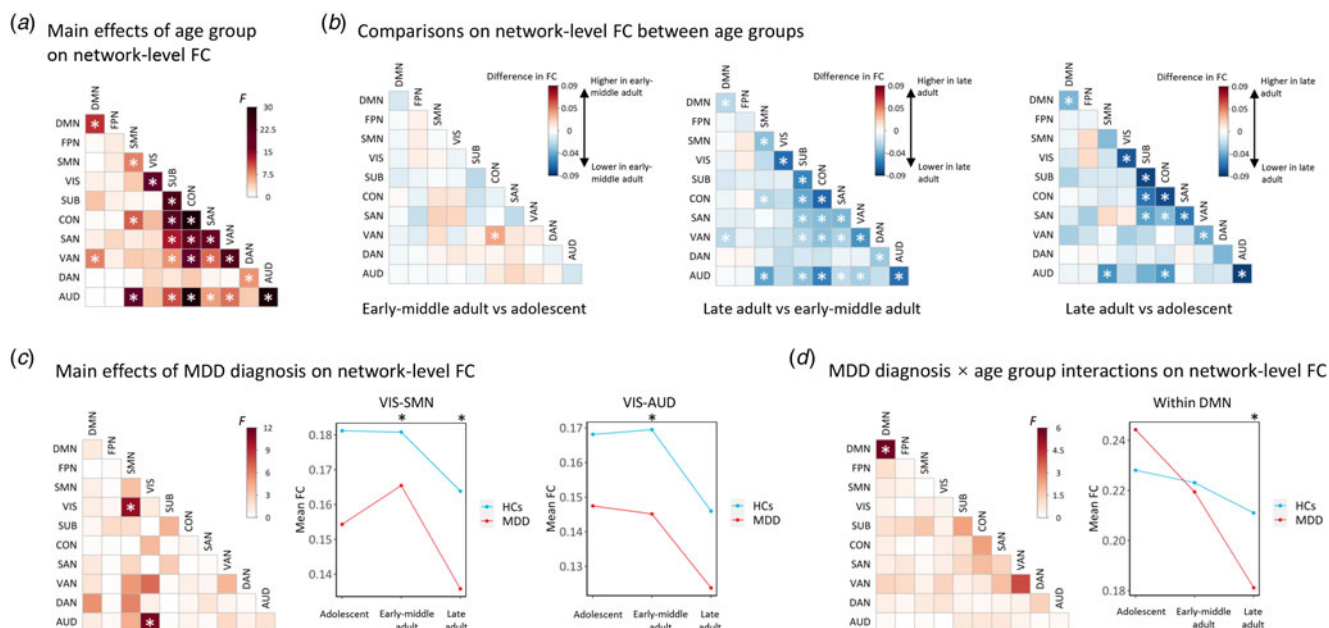


Figure 4. Results of the ANCOVA models pooling all participants on network-level FCs. (A) Results on main effects of age group. (B) Results on post-hoc comparisons between different age groups. (C) Results on main effects of MDD diagnosis. (D) Results on age group \times MDD diagnosis interactions. The “*” indicates significant effects with corrected $p < 0.05$. For network-level FCs showing significant main effects of MDD diagnosis, or significant age group \times MDD diagnosis interactions, the interaction plots were also presented on the right sides. AUD, auditory network; CON, cinguloopercular network; DAN, dorsal attention network; DMN, default-mode network; FPN, frontoparietal network; HCs, healthy controls; MDD, major depressive disorder; SAN, salience network; SMN, sensorimotor network; SUB, subcortical network; VAN, ventral attention network; VIS, visual network.

using a large, multi-site sample. Overall, we found that there are both shared and distinct abnormal FC patterns across different age groups of patients. These findings might provide valuable information for improving our insight into the age-related heterogeneity in MDD from a perspective of brain dysfunctions.

The first important finding of this study is that all three age groups of MDD patients had similar decreased FCs involving the sensorimotor, visual, and auditory regions (Figs 2, 3), suggesting that MDD-related dysfunctions in these brain systems are common regardless of age stages. This was further supported by significant main effects of MDD diagnosis on the visual-sensorimotor and visual-auditory FCs in the ANCOVA analyses when pooling all participants (Fig. 4C). Multiple previous studies had observed decreased FCs within or between the sensory and motor networks in MDD (Chen *et al.*, 2021; Lu *et al.*, 2020; Zhuo *et al.*, 2017). In a recent mega-analysis including 606 MDD patients aged 18 to 65 years, it was also found that hypoconnectivities (relatively lower FCs than HCs) within the somatosensory motor network, as well as between the somatosensory motor and visual networks were two of the significant findings in such a sample (Javaheripour *et al.*, 2021). These alterations may be reflective of the impaired integration of sensory and motor processing that has been widely reported in MDD (Lu *et al.*, 2020; Ray, Bezmaternykh, Mel'nikov, Friston, & Das, 2021). Despite these findings, there is little knowledge about possible age effects on such MDD-related dysfunctions. To our knowledge, the present study might provide one of the first evidence that MDD-related reductions in sensory and motor FCs are shared across the lifespan from adolescence to late adulthood. Interestingly, in a recent meta-analysis on MDD-related brain structural changes, it was also shown that differences in the visual network are shared by both younger and older adults with MDD (Zhukovsky *et al.*, 2021), which may partly support our hypothesis from a brain structural perspective.

Beyond the commonly shared features, some unique abnormalities in brain FC patterns were observed in each age group of MDD (Figs 2, 3). In particular, an increased sensorimotor-subcortical FC was found in the adolescent patients. Past studies suggested that brain development during adolescence is characterized by age-related increases in FCs between the subcortical and higher-order cognitive networks, but declines in FCs between the subcortical and sensory/motor regions (Sanders *et al.*, 2023). Thus, one possible explanation for our results is that age-related decrease in sensory/motor-subcortical FCs is postponed in adolescent patients, which support the delayed brain maturation hypothesis for adolescent MDD (Straub *et al.*, 2019; Whittle *et al.*, 2014). From the structural perspective, past studies have also found delayed subcortical volumetric changes in adolescent MDD and they were associated with symptoms of insomnia (Blank *et al.*, 2022; Whittle *et al.*, 2014). Therefore, these unique changes may partly account for the unique symptom profiles in adolescent MDD such as more common insomnia and other vegetative symptoms (Rice *et al.*, 2019). Notably, the group of early-middle adult patients showed no similar increases in FCs between the sensory/motor and subcortical networks, but even a lower visual-subcortical FC than HCs. We therefore propose that MDD-related changes in some particular neural circuits, at least in the sensory/motor-subcortical connections, should be different between adolescent and early-middle adult stages.

As for late adult patients with MDD, it was observed that they uniquely exhibited wide FC reductions within multiple networks, especially within higher-order systems such as the default-mode,

cingulo-opercular, and attention networks (Figs 2, 3). Several published reports have suggested that normal aging in later adulthood is accompanied by decreases in FCs within most brain networks (Park *et al.*, 2017; Staffaroni *et al.*, 2018; Zonneveld *et al.*, 2019), which was also confirmed in our ANCOVA models (Figs 4A and 4B). Therefore, one possible explanation for our findings is that FCs within these networks may decrease more rapidly in the elderly MDD patient than in normal controls, which thus supports the hypothesis of an accelerated aging process in late adult MDD (Ballester *et al.*, 2022; Jha *et al.*, 2023; Tang *et al.*, 2022). Since the higher-order brain networks are known to be associated with advanced cognitive processes and cognitive changes in aging (Geerligs, Renken, Saliassi, Maurits, & Lorst, 2015; Hardcastle *et al.*, 2022; Hausman *et al.*, 2020), such changes can also partly explain why MDD in late adulthood is more characterized by cognitive declines (Thomas *et al.*, 2009). However, the observed larger-scale brain dysfunctions in older patients with MDD may be also partly due to potential influences of the longer average illness duration and longer exposure to antidepressant medication (Li *et al.*, 2021; Yan *et al.*, 2019). Nevertheless, we failed to detect any significant relationships between the illness duration and brain network changes, or any significant differences between the FEDN and non-FEDN patients to support this possibility.

In the pooled ANCOVA analyses, a significant age group \times MDD diagnosis interaction was found on FC within the default-mode network (Fig. 4D), a high-level brain system known to involve self-directed thoughts (Gandelman *et al.*, 2019; Guan *et al.*, 2022). In past studies, both decreased (Chen, Wang, Zhu, Tan, & Zhong, 2015; Jacob *et al.*, 2020; Yan *et al.*, 2019) and increased (Alexopoulos *et al.*, 2012; Scalabrini *et al.*, 2020) FCs within the default-mode network than HCs were ever reported in MDD. From the interaction plots (Fig. 4D), it can be seen that firstly, the FC within the default-mode network were decreased with increasing age in both MDD patients and HCs, but seemed to decrease more rapidly in the elderly patient than in elderly controls. Once again, this may support the hypothesis of an accelerated aging process in late adult MDD as mentioned earlier. Secondly, different age groups of MDD patients showed different trends of changes when compared to age-matched HCs: it was higher in adolescent patients (although not significant) but lower in early-middle-adult and late-adult patients. Thus, we propose that such heterogeneity may partly account for the inconsistencies in many previous studies, where MDD patients across different age stages were often estimated as a whole (Goldman *et al.*, 2022; Hu *et al.*, 2019). This may again highlight the importance of considering age-related heterogeneity in rs-fMRI studies on MDD.

Our study has several limitations to note. First, due to the variations in data management practices across different study centers in the REST-meta-MDD consortium, information on illness duration and medication status for each MDD patient was not available in a part of the patients; furthermore, the exact number of prior depression episodes and medication dosage were not available in most non-FEDN participants, which limited our power to further explore the effects of antidepressant medication in non-FEDN patients. Second, the current study was carried out based on cross-sectional datasets, while future studies using longitudinal data may provide more valuable information about the effects of aging on MDD-related brain dysfunctions. Third, the rs-fMRI data from different study sites were scanned with different machines and different scan parameters; although we have controlled the site effects in all analyses, the results may still be

partly influenced by them. Fourth, the depressive severity was assessed in all patients using the HAM-D, which may be not optimal for the adolescent patients. It might be more accurate to use those scales specifically developed for adolescents, such as the Children's Depression Inventory or Children's Depression Rating Scale-Revised (Stallwood et al., 2021) in the adolescent group. Finally, while conventional analyses of static FCs were performed in the present study, some other brain network measures such as the small-world metrics (Yang et al., 2021) and dynamic FCs (Long et al., 2020) may provide further important information and can be investigated in future research.

In conclusion, using a large multi-center dataset, this study explored the similar and different features of functional brain network abnormalities in MDD across different age groups. Our results suggested that decreased FCs among the sensory and motor networks may be common biomarkers for MDD shared across all adolescent, early-middle adult, and late adult patients. Some unique abnormalities in brain FC patterns were also observed in each age group of MDD, e.g. increased sensorimotor-subcortical FC in adolescent patients, decreased visual-subcortical FC in early-middle adult patients, as well as wide FC reductions within the subcortical, default-mode, cingulo-opercular, and attention networks in late adult patients. These findings may provide valuable information to expand our understanding of the age-related heterogeneity in MDD.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291723002234>.

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Competing interest. None.

References

- Alexopoulos, G. S., Hoptman, M. J., Kanelopoulos, D., Murphy, C. F., Lim, K. O., & Gunning, F. M. (2012). Functional connectivity in the cognitive control network and the default mode network in late-life depression. *Journal of Affective Disorders*, 139(1), 56–65. <https://doi.org/10.1016/j.jad.2011.12.002>.
- Ballester, P. L., Romano, M. T., Azevedo Cardoso, T., Hassel, S., Strother, S. C., Kennedy, S. H., & Frey, B. N. (2022). Brain age in mood and psychotic disorders: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, 145(1), 42–55. <https://doi.org/10.1111/acps.13371>.
- Ballester, P. L., Suh, J. S., Nogovitsyn, N., Hassel, S., Strother, S. C., Arnott, S. R., ... Frey, B. N. (2021). Accelerated brain aging in major depressive disorder and antidepressant treatment response: A CAN-BIND report. *NeuroImage: Clinical*, 32, 102864. <https://doi.org/10.1016/j.nicl.2021.102864>.
- Blank, T. S., Meyer, B. M., Wieser, M., Rabl, U., Schögl, P., & Pezawas, L. (2022). Brain morphometry and connectivity differs between adolescent- and adult-onset major depressive disorder. *Depression and Anxiety*, 39(5), 387–396. <https://doi.org/10.1002/da.23254>.
- Chen, C., Liu, Z., Zuo, J., Xi, C., Long, Y., Li, M. D., ... Yang, J. (2021). Decreased cortical folding of the fusiform gyrus and its hypoconnectivity with sensorimotor areas in major depressive disorder. *Journal of Affective Disorders*, 295, 657–664. <https://doi.org/10.1016/j.jad.2021.08.148>.
- Chen, X., Lu, B., & Yan, C. G. (2018). Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. *Human Brain Mapping*, 39(1), 300–318. <https://doi.org/10.1002/hbm.23843>.
- Chen, Y., Wang, C., Zhu, X., Tan, Y., & Zhong, Y. (2015). Aberrant connectivity within the default mode network in first-episode, treatment-naïve major depressive disorder. *Journal of Affective Disorders*, 183, 49–56. <https://doi.org/10.1016/j.jad.2015.04.052>.
- Chopra, S., Francey, S. M., O'Donoghue, B., Sabarodin, K., Arnatkeviciute, A., Cropley, V., ... Fornito, A. (2021). Functional connectivity in antipsychotic-treated and antipsychotic-naïve patients with first-episode psychosis and low risk of self-harm or aggression. *JAMA Psychiatry*, 78(9), 994. <https://doi.org/10.1001/jamapsychiatry.2021.1422>.
- Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nature Neuroscience*, 16(9), 1348–1355. <https://doi.org/10.1038/nn.3470>.
- Cuijpers, P., Karyotaki, E., Eckshtain, D., Ng, M. Y., Corteselli, K. A., Noma, H., ... Weisz, J. R. (2020). Psychotherapy for depression across different age groups: A systematic review and meta-analysis. *JAMA Psychiatry*, 77(7), 694. <https://doi.org/10.1001/jamapsychiatry.2020.0164>.
- Deng, K., Yue, J., Xu, J., Ma, P., Chen, X., Li, L., ... Cheng, Y. (2022). Impaired robust interhemispheric function integration of depressive brain from REST-meta-MDD database in China. *Bipolar Disorders*, 24(4), 400–411. <https://doi.org/10.1111/bdi.13139>.
- Ding, Y.-D., Yang, R., Yan, C.-G., Chen, X., Bai, T.-J., Bo, Q.-J., ... Guo, W.-B. (2021). Disrupted hemispheric connectivity specialization in patients with major depressive disorder: Evidence from the REST-meta-MDD Project. *Journal of Affective Disorders*, 284, 217–228. <https://doi.org/10.1016/j.jad.2021.02.030>.
- Dong, H. M., Castellanos, F. X., Yang, N., Zhang, Z., Zhou, Q., He, Y., ... Zuo, X. N. (2020). Charting brain growth in tandem with brain templates at school age. *Science Bulletin*, 65(22), 1924–1934. <https://doi.org/10.1016/j.scib.2020.07.027>.
- Eyre, H. A., Yang, H., Leaver, A. M., van Dyk, K., Siddarth, P., Cyr, N. S., ... Lavretsky, H. (2016). Altered resting-state functional connectivity in late-life depression: A cross-sectional study. *Journal of Affective Disorders*, 189, 126–133. <https://doi.org/10.1016/j.jad.2015.09.011>.
- Feng, J., Chen, C., Cai, Y., Ye, Z., Feng, K., Liu, J., ... Xue, G. (2020). Partitioning heritability analyses unveil the genetic architecture of human brain multidimensional functional connectivity patterns. *Human Brain Mapping*, 41(12), 3305–3317. <https://doi.org/10.1002/hbm.25018>.
- Findling, R. L., DelBello, M. P., Zuddas, A., Emslie, G. J., Ettrup, A., Petersen, M. L., ... Rosen, M. (2022). Vortioxetine for major depressive disorder in adolescents: 12-week randomized, placebo-controlled, fluoxetine-referenced, fixed-dose study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 61(9), 1106–1118.e2. <https://doi.org/10.1016/j.jaac.2022.01.004>.
- Gandelman, J. A., Albert, K., Boyd, B. D., Park, J. W., Riddle, M., Woodward, N. D., ... Taylor, W. D. (2019). Intrinsic cognitive network connectivity is associated with clinical symptoms and cognition in late-life depression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 4(2), 160–170. <https://doi.org/10.1016/j.bpsc.2018.09.003>.
- Geerligs, L., Renken, R. J., Saliassi, E., Maurits, N. M., & Lorist, M. M. (2015). A brain-wide study of age-related changes in functional connectivity. *Cerebral Cortex*, 25(7), 1987–1999. <https://doi.org/10.1093/cercor/bhu012>.
- Goldman, D. A., Sankar, A., Rich, A., Kim, J. A., Pittman, B., Constable, R. T., ... Blumberg, H. P. (2022). A graph theory neuroimaging approach to distinguish the depression of bipolar disorder from major depressive disorder in adolescents and young adults. *Journal of Affective Disorders*, 319, 15–26. <https://doi.org/10.1016/j.jad.2022.09.016>.
- Guan, C., Amdanee, N., Liao, W., Zhou, C., Wu, X., Zhang, X., & Zhang, C. (2022). Altered intrinsic default mode network functional connectivity in patients with remitted geriatric depression and amnesic mild cognitive

- impairment. *International Psychogeriatrics*, 34(8), 703–714. <https://doi.org/10.1017/S1041610221001174>.
- Han, L. K. M., Dinga, R., Hahn, T., Ching, C. R. K., Eyler, L. T., Aftanas, L., ... Schmaal, L. (2021). Brain aging in major depressive disorder: Results from the ENIGMA major depressive disorder working group. *Molecular Psychiatry*, 26(9), 5124–5139. <https://doi.org/10.1038/s41380-020-0754-0>.
- Hardcastle, C., Hausman, H. K., Kraft, J. N., Albizu, A., Evangelista, N. D., Boutzoukas, E. M., ... Woods, A. J. (2022). Higher-order resting state network association with the useful field of view task in older adults. *GeroScience*, 44(1), 131–145. <https://doi.org/10.1007/s11357-021-00441-y>.
- Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*, 75(4), 336. <https://doi.org/10.1001/jamapsychiatry.2017.4602>.
- Hausman, H. K., O'Shea, A., Kraft, J. N., Boutzoukas, E. M., Evangelista, N. D., Van Etten, E. J., ... Woods, A. J. (2020). The role of resting-state network functional connectivity in cognitive aging. *Frontiers in Aging Neuroscience*, 12, 177. <https://doi.org/10.3389/fnagi.2020.00177>.
- Hegeman, J. M., Kok, R. M., van der Mast, R. C., & Giltay, E. J. (2012). Phenomenology of depression in older compared with younger adults: Meta-analysis. *British Journal of Psychiatry*, 200(4), 275–281. <https://doi.org/10.1192/bjp.bp.111.095950>.
- Hu, L., Xiao, M., Ai, M., Wang, W., Chen, J., Tan, Z., ... Kuang, L. (2019). Disruption of resting-state functional connectivity of right posterior insula in adolescents and young adults with major depressive disorder. *Journal of Affective Disorders*, 257, 23–30. <https://doi.org/10.1016/j.jad.2019.06.057>.
- Iancu, S. C., Wong, Y. M., Rhebergen, D., van Balkom, A. J. L. M., & Batelaan, N. M. (2020). Long-term disability in major depressive disorder: A 6-year follow-up study. *Psychological Medicine*, 50(10), 1644–1652. <https://doi.org/10.1017/S0033291719001612>.
- Jacob, Y., Morris, L. S., Huang, K.-H., Schneider, M., Rutter, S., Verma, G., ... Balchandani, P. (2020). Neural correlates of rumination in major depressive disorder: A brain network analysis. *NeuroImage: Clinical*, 25, 102142. <https://doi.org/10.1016/j.nicl.2019.102142>.
- Javaheripour, N., Li, M., Chand, T., Kircher, T., Dannlowski, U., ... Wagner, G. (2021). Altered resting-state functional connectome in major depressive disorder: A mega-analysis from the PsyMRI consortium. *Translational Psychiatry*, 11(1), 511. <https://doi.org/10.1038/s41398-021-01619-w>.
- Jha, M. K., Chin Fatt, C., Minhajuddin, A., Mayes, T. L., & Trivedi, M. H. (2023). Accelerated brain aging in adults with major depressive disorder predicts poorer outcome with sertraline: Findings from the EMBARC study. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 8(4), 462–470. <https://doi.org/10.1016/j.bpsc.2022.09.006>.
- Jiao, Q., Ding, J., Lu, G., Su, L., Zhang, Z., Wang, Z., ... Liu, Y. (2011). Increased activity imbalance in fronto-subcortical circuits in adolescents with major depression. *PLoS One*, 6(9), e25159. <https://doi.org/10.1371/journal.pone.0025159>.
- Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder. *JAMA Psychiatry*, 72(6), 603. <https://doi.org/10.1001/jamapsychiatry.2015.0071>.
- Li, L., Su, Y. A., Wu, Y. K., Castellanos, F. X., Li, K., Li, J. T., ... Yan, C. G. (2021). Eight-week antidepressant treatment reduces functional connectivity in first-episode drug-naïve patients with major depressive disorder. *Human Brain Mapping*, 42(8), 2593–2605. <https://doi.org/10.1002/hbm.25391>.
- Liang, S., Deng, W., Li, X., Greenshaw, A. J., Wang, Q., Li, M., ... Li, T. (2020). Biotypes of major depressive disorder: Neuroimaging evidence from resting-state default mode network patterns. *NeuroImage: Clinical*, 28, 102514. <https://doi.org/10.1016/j.nicl.2020.102514>.
- Liu, P.-h., Li, Y., Zhang, A.-X., Sun, N., Li, G.-Z., Chen, X., ... Zhang, K.-R. (2021). Brain structural alterations in MDD patients with gastrointestinal symptoms: Evidence from the REST-meta-MDD project. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 111, 110386. <https://doi.org/10.1016/j.pnpb.2021.110386>.
- Long, Y., Cao, H., Yan, C., Chen, X., Li, L., Castellanos, F. X., ... Liu, Z. (2020). Altered resting-state dynamic functional brain networks in major depressive disorder: Findings from the REST-meta-MDD consortium. *NeuroImage: Clinical*, 26, 102163. <https://doi.org/10.1016/j.nicl.2020.102163>.
- Long, Y., Ouyang, X., Yan, C., Wu, Z., Huang, X., Pu, W., ... Palaniyappan, L. (2023). Evaluating test–retest reliability and sex-/age-related effects on temporal clustering coefficient of dynamic functional brain networks. *Human Brain Mapping*, 44(6), 2191–2208. <https://doi.org/10.1002/hbm.26202>.
- Lu, F., Cui, Q., Huang, X., Li, L., Duan, X., Chen, H., ... Chen, H. (2020). Anomalous intrinsic connectivity within and between visual and auditory networks in major depressive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 100, 109889. <https://doi.org/10.1016/j.pnpb.2020.109889>.
- Lu, J., Xu, X., Huang, Y., Li, T., Ma, C., Xu, G., ... Zhang, N. (2021). Prevalence of depressive disorders and treatment in China: A cross-sectional epidemiological study. *The Lancet Psychiatry*, 8(11), 981–990. [https://doi.org/10.1016/S2215-0366\(21\)00251-0](https://doi.org/10.1016/S2215-0366(21)00251-0).
- Luo, L., Wu, H., Xu, J., Chen, F., Wu, F., Wang, C., & Wang, J. (2021). Abnormal large-scale resting-state functional networks in drug-free major depressive disorder. *Brain Imaging and Behavior*, 15(1), 96–106. <https://doi.org/10.1007/s11682-019-00236-y>.
- Mohr, H., Wolfensteller, U., Betzel, R. F., Mišić, B., Sporns, O., Richiardi, J., & Ruge, H. (2016). Integration and segregation of large-scale brain networks during short-term task automatization. *Nature Communications*, 7(1), 13217. <https://doi.org/10.1038/ncomms13217>.
- Nguyen, T.-D., Harder, A., Xiong, Y., Kowalec, K., Hägg, S., Cai, N., ... Lu, Y. (2022). Genetic heterogeneity and subtypes of major depression. *Molecular Psychiatry*, 27(3), 1667–1675. <https://doi.org/10.1038/s41380-021-01413-6>.
- Niu, Y., Sun, J., Wang, B., Yang, Y., Wen, X., & Xiang, J. (2022). Trajectories of brain entropy across lifetime estimated by resting state functional magnetic resonance imaging. *Human Brain Mapping*, 43(14), 4359–4369. <https://doi.org/10.1002/hbm.25959>.
- Park, J. E., Jung, S. C., Ryu, K. H., Oh, J. Y., Kim, H. S., Choi, C. G., ... Shim, W. H. (2017). Differences in dynamic and static functional connectivity between young and elderly healthy adults. *Neuroradiology*, 59(8), 781–789. <https://doi.org/10.1007/s00234-017-1875-2>.
- Pine, D. S. (2019). Heterogeneity in major depressive disorder: Lessons from developmental research on irritability. *American Journal of Psychiatry*, 176(5), 331–332. <https://doi.org/10.1176/appi.ajp.2019.19020214>.
- Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., ... Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, 72(4), 665–678. <https://doi.org/10.1016/j.neuron.2011.09.006>.
- Ray, D., Bezmaternykh, D., Mel'nikov, M., Friston, K. J., & Das, M. (2021). Altered effective connectivity in sensorimotor cortices is a signature of severity and clinical course in depression. *Proceedings of the National Academy of Sciences*, 118(40), e2105730118. <https://doi.org/10.1073/pnas.2105730118>.
- Rep, C., Peyre, H., Sánchez-Rico, M., Blanco, C., Dosquet, M., Schuster, J.-P., ... Hoertel, N. (2022). Contributing factors to heterogeneity in the timing of the onset of major depressive episode: Results from a national study. *Journal of Affective Disorders*, 299, 585–595. <https://doi.org/10.1016/j.jad.2021.12.082>.
- Rice, F., Riglin, L., Lomax, T., Souter, E., Potter, R., Smith, D. J., ... Thapar, A. (2019). Adolescent and adult differences in major depression symptom profiles. *Journal of Affective Disorders*, 243, 175–181. <https://doi.org/10.1016/j.jad.2018.09.015>.
- Saberi, A., Mohammadi, E., Zarei, M., Eickhoff, S. B., & Tahmasian, M. (2022). Structural and functional neuroimaging of late-life depression: A coordinate-based meta-analysis. *Brain Imaging and Behavior*, 16(1), 518–531. <https://doi.org/10.1007/s11682-021-00494-9>.
- Sanders, A. F. P., Harms, M. P., Kandala, S., Marek, S., Somerville, L. H., Bookheimer, S. Y., ... Barch, D. M. (2023). Age-related differences in resting-state functional connectivity from childhood to adolescence. *Cerebral Cortex*, 33(11), 6928–6942. <https://doi.org/10.1093/cercor/bhad011>.
- Scalabrini, A., Vai, B., Poletti, S., Damiani, S., Mucci, C., Colombo, C., ... Northoff, G. (2020). All roads lead to the default-mode network—global source of DMN abnormalities in major depressive disorder. *Neuropsychopharmacology*, 45(12), 2058–2069. <https://doi.org/10.1038/s41386-020-0785-x>.

- Schaakxs, R., Comijs, H. C., Lamers, F., Kok, R. M., Beekman, A. T. F., & Penninx, B. W. J. H. (2018). Associations between age and the course of major depressive disorder: A 2-year longitudinal cohort study. *The Lancet Psychiatry*, 5(7), 581–590. [https://doi.org/10.1016/S2215-0366\(18\)30166-4](https://doi.org/10.1016/S2215-0366(18)30166-4).
- Staffaroni, A. M., Brown, J. A., Casaletto, K. B., Elahi, F. M., Deng, J., Neuhaus, J., ... Kramer, J. H. (2018). The longitudinal trajectory of default mode network connectivity in healthy older adults varies as a function of age and is associated with changes in episodic memory and processing speed. *Journal of Neuroscience*, 38(11), 2809–2817. <https://doi.org/10.1523/JNEUROSCI.3067-17.2018>.
- Stallwood, E., Monsour, A., Rodrigues, C., Monga, S., Terwee, C., Offringa, M., & Butcher, N. J. (2021). Systematic review: The measurement properties of the children's depression rating scale—revised in adolescents with major depressive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 60(1), 119–133. <https://doi.org/10.1016/j.jaac.2020.10.009>.
- Straub, J., Brown, R., Malejko, K., Bonenberger, M., Grön, G., Plener, P. L., ... Ablner, B. (2019). Adolescent depression and brain development: Evidence from voxel-based morphometry. *Journal of Psychiatry and Neuroscience*, 44(4), 237–245. <https://doi.org/10.1503/jpn.170233>.
- Sun, J., Zhao, R., He, Z., Chang, M., Wang, F., Wei, W., ... Yang, X. (2022). Abnormal dynamic functional connectivity after sleep deprivation from temporal variability perspective. *Human Brain Mapping*, 43(12), 3824–3839.
- Supekar, K., Musen, M., & Menon, V. (2009). Development of large-scale functional brain networks in children. *PLoS Biology*, 7(7), e1000157. <https://doi.org/10.1371/journal.pbio.1000157>.
- Tan, W., Ouyang, X., Huang, D., Wu, Z., Liu, Z., He, Z., & Long, Y. (2023). Disrupted intrinsic functional brain network in patients with late-life depression: Evidence from a multi-site dataset. *Journal of Affective Disorders*, 323, 631–639. <https://doi.org/10.1016/j.jad.2022.12.019>.
- Tang, S., Lu, L., Zhang, L., Hu, X., Bu, X., Li, H., ... Huang, X. (2018). Abnormal amygdala resting-state functional connectivity in adults and adolescents with major depressive disorder: A comparative meta-analysis. *EBioMedicine*, 36, 436–445. <https://doi.org/10.1016/j.ebiom.2018.09.010>.
- Tang, S., Wu, Z., Cao, H., Chen, X., Wu, G., Tan, W., ... Liu, Z. (2022). Age-Related decrease in default-mode network functional connectivity is accelerated in patients with major depressive disorder. *Frontiers in Aging Neuroscience*, 13, 809853. <https://doi.org/10.3389/fnagi.2021.809853>.
- Thomas, A. J., Gallagher, P., Robinson, L. J., Porter, R. J., Young, A. H., Ferrier, I. N., & O'Brien, J. T. (2009). A comparison of neurocognitive impairment in younger and older adults with major depression. *Psychological Medicine*, 39(5), 725–733. <https://doi.org/10.1017/S0033291708004042>.
- Tsurugizawa, T., & Yoshimaru, D. (2021). Impact of anesthesia on static and dynamic functional connectivity in mice. *NeuroImage*, 241, 118413. <https://doi.org/10.1016/j.neuroimage.2021.118413>.
- Wagner, S., Wollschläger, D., Dreimüller, N., Engelmann, J., Herzog, D. P., Roll, S. C., ... Lieb, K. (2020). Effects of age on depressive symptomatology and response to antidepressant treatment in patients with major depressive disorder aged 18 to 65 years. *Comprehensive Psychiatry*, 99, 152170. <https://doi.org/10.1016/j.comppsy.2020.152170>.
- Whittle, S., Lichter, R., Dennison, M., Vijayakumar, N., Schwartz, O., Byrne, M. L., ... Allen, N. B. (2014). Structural brain development and depression onset during adolescence: A prospective longitudinal study. *American Journal of Psychiatry*, 171(5), 564–571. <https://doi.org/10.1176/appi.ajp.2013.13070920>.
- Wu, M., Andreescu, C., Butters, M. A., Tamburo, R., Reynolds, C. F., & Aizenstein, H. (2011). Default-mode network connectivity and white matter burden in late-life depression. *Psychiatry Research - Neuroimaging*, 194(1), 39–46. <https://doi.org/10.1016/j.psychres.2011.04.003>.
- Xia, M., Wang, J., & He, Y. (2013). BrainNet viewer: A network visualization tool for human brain connectomics. *PLoS One*, 8(7), e68910. <https://doi.org/10.1371/journal.pone.0068910>.
- Yan, C. G., Chen, X., Li, L., Castellanos, F. X., Bai, T. J., Bo, Q. J., ... Zang, Y. F. (2019). Reduced default mode network functional connectivity in patients with recurrent major depressive disorder. *Proceedings of the National Academy of Sciences of the United States of America*, 116(18), 9078–9083. <https://doi.org/10.1073/pnas.1900390116>.
- Yan, C. G., Wang, X. di, Zuo, X. N., & Zang, Y. F. (2016). DPABI: Data processing & analysis for (resting-state) brain imaging. *Neuroinformatics*, 14(3), 339–351. <https://doi.org/10.1007/s12021-016-9299-4>.
- Yang, H., Chen, X., Chen, Z. B., Li, L., Li, X. Y., Castellanos, F. X., ... Yan, C. G. (2021). Disrupted intrinsic functional brain topology in patients with major depressive disorder. *Molecular Psychiatry*, 26(12), 7363–7371. <https://doi.org/10.1038/s41380-021-01247-2>.
- Yang, M., Chen, B., Zhong, X., Zhou, H., Mai, N., Zhang, M., ... Ning, Y. (2022). Disrupted olfactory functional connectivity in patients with late-life depression. *Journal of Affective Disorders*, 306, 174–181. <https://doi.org/10.1016/j.jad.2022.03.014>.
- Ye, J., Shen, Z., Xu, X., Yang, S., Chen, W., Liu, X., ... Cheng, Y. (2017). Abnormal functional connectivity of the amygdala in first-episode and untreated adult major depressive disorder patients with different ages of onset. *NeuroReport*, 28(4), 214–221. <https://doi.org/10.1097/WNR.0000000000000733>.
- Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying differences in brain networks. *NeuroImage*, 53(4), 1197–1207. <https://doi.org/10.1016/j.neuroimage.2010.06.041>.
- Zhang, M., Palaniyappan, L., Deng, M., Zhang, W., Pan, Y., Fan, Z., ... Pu, W. (2021). Abnormal thalamocortical circuit in adolescents with early-onset schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 60(4), 479–489. <https://doi.org/10.1016/j.jaac.2020.07.903>.
- Zhukovsky, P., Anderson, J. A. E., Coughlan, G., Mulsant, B. H., Cipriani, A., & Voineskos, A. N. (2021). Coordinate-based network mapping of brain structure in major depressive disorder in younger and older adults: A systematic review and meta-analysis. *American Journal of Psychiatry*, 178(12), 1119–1128. <https://doi.org/10.1176/appi.ajp.2021.21010088>.
- Zhuo, C., Zhu, J., Wang, C., Qu, H., Ma, X., & Qin, W. (2017). Different spatial patterns of brain atrophy and global functional connectivity impairments in major depressive disorder. *Brain Imaging and Behavior*, 11(6), 1678–1689. <https://doi.org/10.1007/s11682-016-9645-z>.
- Zonneveld, H. I., Pruim, R. H. R., Bos, D., Vrooman, H. A., Muetzel, R. L., Hofman, A., ... Vernooij, M. W. (2019). Patterns of functional connectivity in an aging population: The Rotterdam study. *NeuroImage*, 189, 432–444. <https://doi.org/10.1016/j.neuroimage.2019.01.041>.