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ORIGINAL RESEARCH

# Disruption of Multimodal Brain Networks and Structural-Functional Coupling in Adolescents with Major Depressive Disorder

Yunhan Wang[1], Jinxue Wei[2], Yushun Yan[2], Min Wang[2], Huanhuan Fan[2], Yue Du[2], Xiao Yang[2], Xiaohong Ma[2], Xiaojuan Ma[1]

[1]Department of Ultrasound, West China Hospital, Sichuan University, Chengdu, People's Republic of China; [2]Mental Health Center and Institute of Psychiatry, West China Hospital, Sichuan University, Chengdu, People's Republic of China

Correspondence: Xiaojuan Ma, Email xiaojuanma@126.com



**Background:** Adolescent MDD has become a significant public health issue, yet its underlying mechanisms remain unclear. Multimodal brain imaging techniques offer a powerful method for exploring complex mental disorders. However, evidence focusing on the multimodal brain networks and structural-functional coupling in adolescent depression is still limited.

**Methods:** Participants with major depressive disorder (MDD) were Han Chinese individuals aged 13 to 18 who had been unmedicated for at least two weeks. We conducted multimodal MRI acquisitions, including structural MRI (sMRI), resting-state functional MRI (rsfMRI), and Diffusion Tensor Imaging (DTI). The cortex was parceled into 360 regions using the HCP-MMP atlas. Functional connectivity and deterministic structural connectivity matrices were constructed, and structural-functional coupling coefficients were calculated. Differences in connectivity and coupling coefficients between the MDD and healthy controls (HCs) groups were identified.

**Results:** A total of 25 adolescents with MDD (mean age: 15.68 years, standard deviation [SD]: 1.18; Female: 21 (84.00%)) and 27 hCs (mean age: 14.30 years, standard deviation [SD]: 1.51; Female: 13 (48.15%)) were included in the analysis. There were 9 structural connections and 122 functional connections that differed between the two groups, involving multiple cortical regions. Additionally, we identified structural-functional coupling differences in three brain areas, specifically the posterior cingulate cortex and the ventral visual cortex.

**Conclusion:** Adolescent MDD involves disruptions in brain structural networks, functional networks, and structural-functional coupling. These differing indicators may serve as potential biomarkers for adolescent MDD.

**Keywords:** major depressive disorder, adolescents, structural-functional coupling, brain network, magnetic resonance imaging

## Introduction

The incidence of Major Depressive Disorder (MDD) among adolescents is increasingly gaining attention. A meta-analysis revealed that the prevalence of worsening depressive symptoms among adolescents increased from 24% (95% CI: 0.19–0.28) during the period from 2001 to 2010 to 37% (95% CI: 0.32–0.42) during the period from 2011 to 2020.[1] According to the 2019 Global Burden of Disease report, disability-adjusted life years attributed to MDD rank fourth among individuals aged 10 to 24.[2] Adolescent MDD significantly impacts the physical and mental health of teenagers. Although numerous therapeutic strategies have been developed for MDD, their efficacy in treating adolescent MDD remains limited and constrained.[3–8] This limitation is partly attributed to an incomplete understanding of the pathophysiological mechanisms underlying adolescent MDD, hindering the development of effective clinical interventions.

As a non-invasive diagnostic technique, magnetic resonance imaging (MRI) plays a crucial role in the early diagnosis, investigation of pathological mechanisms, and evaluation of treatment efficacy in mental disorders. The human brain is viewed as a complex network in both structure and function, facilitating the effective segregation and integration of biological information. Abnormal structural connectivity between the rostral anterior cingulate cortex and the amygdala

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was found to precede the initial onset of MDD in adolescent females, as evidenced by comparing this group to healthy controls, highlighting a group difference based on structural connections.[9] Another study identified significant differences in the average functional connectivity within the left and right caudal cingulate gyrus and the tongue and larynx region of the postcentral gyrus between adolescents with MDD and healthy controls, suggesting a link to observed sleep disturbances and working memory deficits in the MDD group.[10] However, structural connectivity and functional connectivity within the brain, although representing distinct types of information, are inherently interconnected. Research has demonstrated a correlation between structural and functional networks.[11] It has been observed that functional connections can exist between brain regions devoid of direct structural links; conversely, regions interconnected by structural pathways often exhibit robust functional connectivity.[11,12] Furthermore, it has been established that structural connectivity can predict functional patterns, and a single structural link may correspond to multiple functional connectivity modalities.[13–15]

Therefore, researchers have proposed that multimodal structural-functional coupling may offer a more persuasive explanation of the mechanisms underlying complex mental disorders than unimodal approaches.[11,16] A study found that the structural-functional coupling within different cerebral hemispheres is significantly reduced in the MDD group, correlating with the severity of depressive symptoms.[17] Further findings suggest that structural-functional coupling of patients with MDD increases, correlating with improvements in executive functions.[18] Structural-functional coupling particularly in the regions involving the default mode network, visual network, and insula was increased in MDD.[19] Although the majority of research focuses on adult MDD, studies on structural-functional coupling in adolescent MDD are notably scarce. Nonetheless, investigating the pathogenesis of adolescent MDD through connectomics has shown considerable promise for enhancing clinical applications.

Therefore, we conducted a small-sample, cross-sectional study to explore potential disruptions in structural networks, functional networks, and structural-functional coupling in adolescent MDD.

# Methods

## Participants

Individuals participating in the study were enrolled at West China Hospital. The MDD sample consisted of Han Chinese aged less than 18, who had not used antidepressants, antipsychotics, or benzodiazepines for a minimum of two weeks prior to joining the study. Diagnoses of MDD were conducted by licensed psychiatric professionals with advanced degrees in psychiatry, following DSM-5 standards. Exclusion criteria included the presence of organic brain diseases or psychiatric conditions like schizophrenia, bipolar disorder, or substance use disorder. Healthy controls (HCs), displaying proper social functionality and lacking any psychiatric familial history, were drawn from the local population. This study was approved by the ethics committee of West China Hospital, Sichuan University and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their legal guardians. Data collection was conducted in dedicated research offices.

## Clinical Assessments

The Hamilton Depression Rating Scale (HDRS) was employed to assess the severity of depressive symptoms.[20] The HDRS is rated by observers and includes 17 components, resulting in a possible total score between 0 and 52. A higher score on the HDRS reflects greater depressive severity. The scale is organized into several categories: obstruction, cognitive, sleep disturbance, anxiety, and weight change. Additionally, the Hamilton Anxiety Rating Scale (HARS) was used to assess levels of anxiety.[21] This observer-rated instrument comprising 14 items, allowing for a total score range of 0 to 56. Increased scores denote more pronounced anxiety symptoms. The HARS is divided into two main factors: psychic anxiety and somatic anxiety.

## Neuroimage Acquisition and Preprocessing

Multimodal magnetic resonance imaging was conducted using a Philips 3T scanner (Philips, Amsterdam, the Netherlands) equipped with an eight-channel phased-array head coil. During the scanning process, participants were advised to stay motionless and alert with their eyes closed.

T1-weighted structural imaging was acquired as follows: echo time, 3.88 ms; repetition time, 8.4 ms; flip angle, 7°; acquisition matrix, 256 × 256; field of view: 240×240 mm²; slice thickness, 1mm; voxel size, 1 × 1×1 mm³; number of slices, 188. T1-weighted MRI was segmented into gray matter, white matter, and cerebrospinal fluid using tissue probability maps.

Rest-state functional imaging was acquired with following parameters: echo time: 30ms; repetition time, 2000 ms; flip angle, 90°; acquisition matrix, 64 × 64; field of view, 240×240 mm²; slice thickness, 4 mm; voxel size, 3.75×3.75 × 4 mm³; number of slices: 38; number of time points: 240. Preprocessing procedure was conducted based on the DPABI toolbox within SPM12.[22] Default pipeline was implemented as follows: (1) remove the first 10 time points; (2) slice timing correction; (3) head-motion realignment; (4) co-register the functional image and the segmented T1 structural image; (5) regress out the covariates; (6) resample at 3 $mm^3$ isotropic and normalize to the standard MNI152 space using group DARTEL template; (7) filtering (0.01~0.1Hz).

Diffusion Tensor Imaging (DTI) was acquired with the following parameters: echo time: 91 ms; repetition time: 10295 ms; slice thickness: 2 mm; acquisition matrix: 128 × 128; field of view: 128×128 mm²; voxel size: 2 × 2 × 2 mm³; number of averages: 2; b-value: 1000 s/mm²; diffusion directions: 32; number of slices: 75. DTI was preprocessed using the PANDA toolbox based on the FSL software as follows:[23,24] (1) brain mask estimation; (2) non-brain spaces removal; (3) eddy-current effect correction; (4) fractional anisotropy (FA) calculation.

## Brain Networks Construction and Structural-Functional Coupling

Regions of interest (ROIs) were defined utilizing the Human Connectome Project's multi-modal parcellation (HCP-MMP), which divided cerebral cortex into 360 regions.[25] For filtered functional MRI, DPABI toolbox was used to extract the time series of the average blood oxygen level dependent (BOLD) signal for each ROI of each subject. Pearson correlation coefficients of BOLD signals between two regions were calculated to construct individual functional network. For DTI, deterministic fiber tracking technique was used to construct individual white matter structural connectivity networks. Tracking stops when the FA value falls below 0.2 or when the fiber bundle deviation angle exceeds 45°.

The coupling between structural connectivity (SC) and functional connectivity (FC) was estimated using a technique described in earlier research. For each specific brain region, its regional connectivity was represented by a column in either a structural or functional connectivity matrix, indicating the links from one node to all others within the participant's network. Subsequently, Pearson's correlation coefficients were transformed using the Fisher Z method, comparing columns from the functional matrix with corresponding non-zero elements in the white matter connectivity matrix. Regions missing over 50% of their data were omitted from further analysis. This process yielded a series of metrics that captured the SC-FC interactions for each brain region across participants.

## Statistical Analysis

Continuous variables were presented as mean accompanied [standard deviation (SD)], and categorical variables were denoted by count [percentage]. Between-group deviations of general characteristics were detected utilizing two-sample *t* test for continuous variables and chi-squared test for categorical variables. The difference of FA and FN connectivity between MDD and HC was compared using permutation test for analysis of variance, whereas difference of SC-FC coupling was compared using linear model. Due to differences in the general characteristics of the sample in this study, we included age, sex, and education as covariates in subsequent analyses. P-value less than 0.05 after false discovery rate (FDR) correction was considered significantly different.

# Results

## General Characteristics of Samples

The study included 25 participants diagnosed with MDD and 27 hCs (see Table 1). The MDD group had a mean age of 15.7 years (SD = 1.18), which was significantly higher than the HC group's mean age of 14.3 years (SD = 1.51) ($t = 3.69$, $P < 0.001$). The proportion of females was higher in the MDD group (84.0%) compared to the HC group (48.1%), and this difference was also statistically significant ($\chi^2 = 5.87$, $P = 0.015$). Participants with MDD had a significantly lower

**Table 1** General Characteristics of Samples

| | Major Depressive Disorder (N = 25) | Health Controls (N = 27) | Statistics | P value |
|---|---|---|---|---|
| **Age, year** | 15.7 (1.18) | 14.3 (1.51) | t = 3.6892 | 0.0005674 |
| **Sex, female** | 21 (84.0%) | 13 (48.1%) | $\chi^2$ = 5.8729 | 0.01538 |
| **Education, year** | 10.0 (1.71) | 8.73 (1.80) | t = 2.583 | 0.01283 |
| **Age of Onset, year** | 14.4 (1.45) | / | / | / |
| **First Onset, yes** | 17 (68.0%) | / | / | / |
| **Duration, month** | 7.65 (6.36) | / | / | / |
| **Suicide Attempt, yes%** | 24 (96.0%) | / | / | / |
| **Suicide Behavior, yes%** | 12 (48.0%) | / | / | / |
| **HAMD** | 17.1 (5.44) | / | / | / |
| **HAMA** | 11.5 (6.56) | / | / | / |

level of education (mean = 10.0 years, SD = 1.71) compared to the HCs (mean = 8.73 years, SD = 1.80) (p = 0.01283). Within the MDD group, the mean age of onset was 14.4 years (SD = 1.45), with 68.0% experiencing their first onset. The average illness duration was 7.65 months (SD = 3.66). A majority (96.0%) of the MDD group reported a history of suicide attempts, and 48.0% reported engaging in suicidal behavior. The mean HAMD score for the MDD group was 17.1 (SD = 5.44), while the mean HAMA score was 11.5 (SD = 5.66).

## Deviations of Structural Connectivity Between MDD and HC

Significant structural connectivity differences between MDD and HC are shown in Figure 1. Notably, altered connections were observed primarily in regions associated with auditory processing, the temporal lobe, and frontal regions ($P_{FDR} < 0.001$). Specifically, in the MDD group, there were disruptions in connectivity within the early auditory cortex (left PFcm and left RI), auditory association cortex (left STSdp and left STSvp), medial temporal regions (left Hipp and left PreS, right TF and right PeEc), opercular cortex (left 43 and left Pol2) and frontal cortex (right 111 and right 47m, right 47s and right 47L).

## Deviations of Functional Connectivity Between MDD and HC

Significant structural connectivity differences between MDD and HC are shown in Figure 2. The differential functional connectivity involved brain regions from various cortical areas across the whole brain, predominately posterior cingulate and dorsolateral prefrontal cortexes in left hemisphere, visual, superior and inferior parietal, posterior cingulate, anterior and medial prefrontal cortex in right hemisphere ($P_{FDR} < 0.001$).

## Deviations of Structural-Functional Coupling Between MDD and HC

Three brain regions demonstrated structural-functional coupling difference between adolescent MDD and HC. As shown in Figure 3, deviated regions were left 7m ($P_{FDR} = 0.045$) and right DVT ($P_{FDR} = 0.045$) in posterior cingulate cortex, and right VMV3 ($P_{FDR} = 0.034$) in ventral stream visual cortex.

# Discussion

In the current small-sample cross-sectional study, we discovered network-based deviations between adolescent MDD and HC. The structural network disruptions were limited to localized connection abnormalities, while the functional network disruptions involved changes in communication among widespread brain regions. In addition, we identified structural-

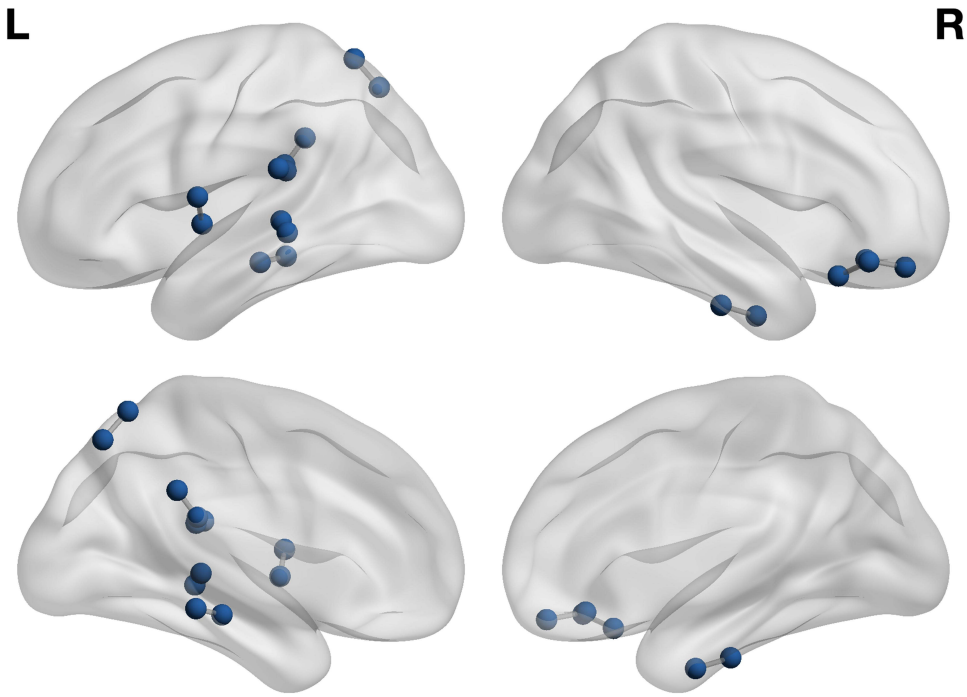


**Figure 1** Deviations of Structural Connectivity between MDD and HC.

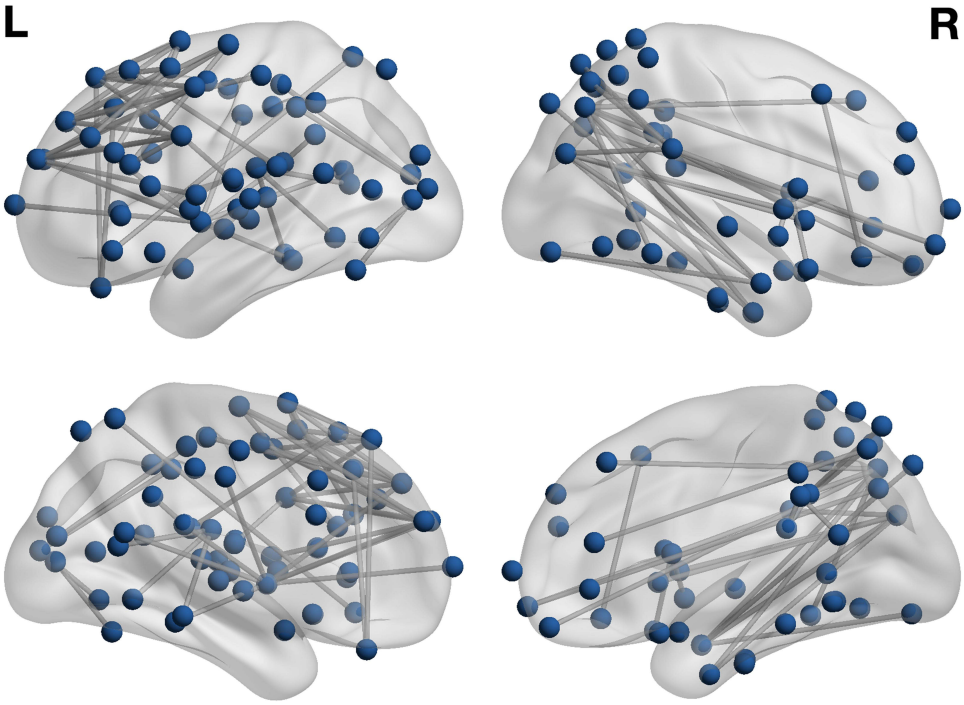


**Figure 2** Deviations of Functional Connectivity between MDD and HC.

functional coupling changes in three brain regions, suggesting that these regions may serve as central nodes in the pathophysiology of adolescent MDD.

The current study found significant alterations in the cingulate cortex in adolescent MDD. Cingulate cortex was serves as a central hub for integrating cognitive, emotional, and social information, and its impaired maturation was

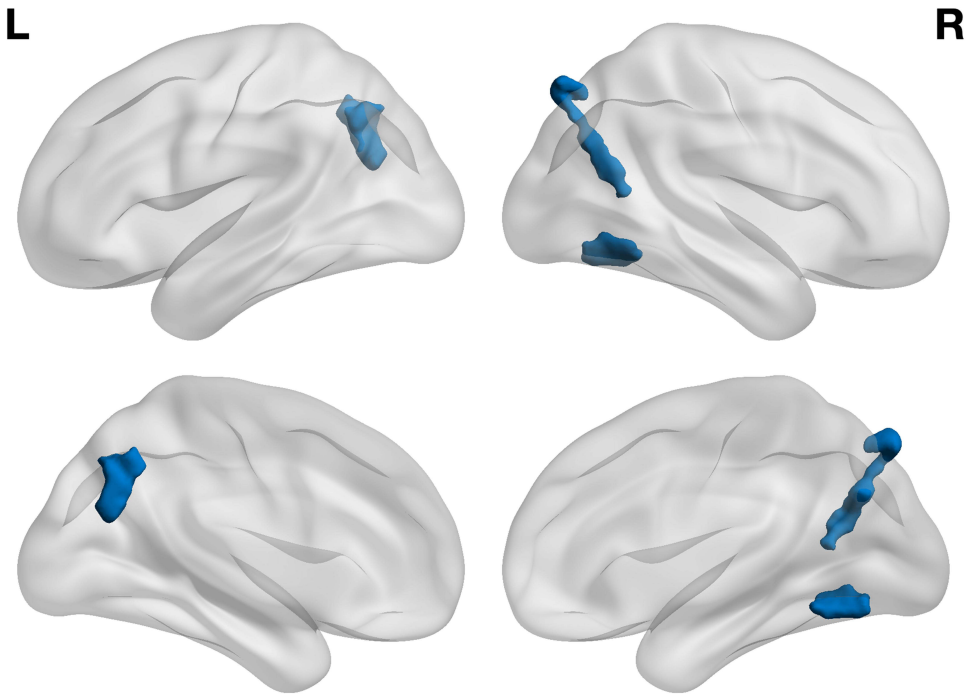


**Figure 3** Deviations of Structural-Functional Coupling between MDD and HC.

linked to the onset of adolescent MDD.[26] In multiple studies, adolescent MDD exhibited stronger functional connectivity between the anterior cingulate cortex and the amygdala,[27,28] while showing reduced connectivity between the anterior cingulate cortex and frontal cortical regions.[29,30] Dysregulated functional connectivity between the posterior cingulate cortex and the amygdala was associated with rumination,[31] while functional connectivity between the posterior cingulate cortex and cerebellum was associated with suicide in adolescent MDD.[32] The findings of this study aligned with these conclusions, indicating the significant importance of the cingulate cortex in adolescent MDD. The clinical implications of these findings suggest that alterations in the cingulate cortex connectivity could serve as potential biomarkers for the early detection and targeted treatment of adolescent MDD.

This study found significant differences in structural connectivity, functional connectivity, and structural-functional coupling in various prefrontal regions between adolescent MDD and HC. Previous studies demonstrated that resting-state functional connectivity using the dorsomedial prefrontal cortex as a seed was associated with the severity of depression and anhedonia in adolescent MDD.[33] Changes in functional connectivity using the dorsolateral prefrontal cortex as a seed were associated with adolescent MDD's response to antidepressants treatment.[34] Similar studies have also found changes in effective connectivity from the ventrolateral prefrontal cortex to the amygdala are associated with the diagnosis of adolescent MDD and post-treatment alterations.[35] The results of the current study supported these conclusions, suggesting that prefrontal cortex may serve as a potential biomarker for adolescent MDD. These findings highlighting the role of prefrontal cortex in the diagnosis and treatment of adolescent MDD. Understanding these connectivity patterns could facilitate the development of more precise diagnostic tools and personalized treatment strategies, potentially enhancing therapeutic outcomes for adolescents with MDD.

This study has certain limitations. First, the small sample size limits the generalizability of the conclusions. To address this, future studies will incorporate larger sample sizes and more comprehensive statistical evaluations to provide a more detailed exploration of the observed phenomena, helping to confirm the trends suggested by the current study and offering a more definitive understanding of the underlying mechanisms. Second, as a cross-sectional study, this research does not examine the longitudinal effects of these changes during adolescent development and the progression of MDD, which should be investigated in future longitudinal studies. Lastly, the use of non-parametric tests provides less statistical power than parametric tests. We acknowledge the potential impact of this limitation on the robustness of our findings and aim to apply more rigorous statistical approaches in future research to further validate our results.

## Conclusions

Adolescent MDD is characterized by disruptions in structural networks, functional networks, and the coupling between structure and function within the brain. The structural network disruptions involve localized connectivity changes in specific brain regions, while the functional network disruptions are characterized by widespread connectivity alterations across the entire brain. The disruptions in structural-functional coupling primarily involve the posterior cingulate and visual cortex. These distinct alterations could potentially serve as valuable biomarkers for identifying and understanding adolescent MDD.

## Data Sharing Statement

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

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## Disclosure

The authors report no conflicts of interest in this work.

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