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Abnormal resting-state functional connectivity in subregions of amygdala in adults and adolescents with major depressive disorder

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Abstract

Background The different symptoms of major depressive disorder (MDD) in adolescents compared to adults suggested there may be differences in the pathophysiology between adolescents and adults with MDD. However, despite the amygdala being considered critical in the pathophysiology, there was limited knowledge about the commonalities and differences in the resting-state functional connectivity (rsFC) of amygdala subregions in MDD patients of different age groups.

Methods In the current study, 65 adolescents (46 with MDD and 19 controls) and 91 adults (35 with MDD and 56 controls) were included. A seed-based functional connectivity analysis was performed for each of the amygdala subregions. A 2 × 2 ANOVA was used to analyze the main effect of age, diagnosis, and their interaction on the rsFC of each subregion.

Results A significant main effect of age was revealed in the rsFC of bilateral centromedial (CM) subregions and right laterobasal (LB) subregion with several brain regions in the limbic system and frontoparietal network. The significant main effect of diagnosis showed MDD patients of different ages showed higher connectivity than controls between the right LB and left middle frontal gyrus (MFG).

Conclusions The rsFC of specific amygdala subregions with brain regions in the limbic system and frontoparietal network is affected by age, indicating a distinct amygdala connectivity profile in adolescents. The decreased rsFC between the right LB and the left MFG in adolescents and adults with MDD could serve as a diagnostic biomarker and a target of nonpharmacological treatment for MDD.

Keywords Adolescents, Major depressive disorder, Resting-state functional connectivity, Amygdala subregions

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Introduction

Major depressive disorder (MDD) in adolescents represents a significant public health concern due to its widespread prevalence, heightened risk of suicide, and the complexities associated with diagnosis and treatment, particularly exacerbated during the COVID-19 pandemic [1, 2]. In the United States, the lifetime prevalence of MDD among adolescents is reported to be 11.0%, with severe cases accounting for 3.0% [3]. A meta-analysis involving 29,626 cases revealed a pooled prevalence of depressive symptoms among Chinese adolescents at 19.85% [4], highlighting a concerning statistic for the healthcare system. Research indicates that adolescents with MDD exhibit symptoms akin to those found in adult MDD, such as persistent sadness. However, distinct differences in symptomatology have also been identified, suggesting both shared mechanisms and unique aspects of MDD in adolescents compared to adults [5]. Therefore, investigations into the neural underpinnings of MDD in adolescents are crucial for gaining a comprehensive understanding of this disorder.

The amygdala, known for its role in emotional reactivity and regulation, is a pivotal area extensively studied in the context of depression [6, 7]. Resting-state functional connectivity (rsFC), a widely employed method for investigating the organization of brain networks and their alterations in various neurological and psychiatric disorders [8, 9], has revealed abnormalities in amygdala rsFC in MDD. For instance, studies have identified disrupted rsFC between the amygdala and prefrontal regions in adults with MDD [10–12]. Research on adults with MDD has demonstrated that reduced rsFC strengths between the amygdala and regions such as the orbitofrontal cortex and temporal lobes correlated with increased severity of self-reported depression and longer illness duration [10]. Conversely, increased amygdala-pons rsFC has been observed in adults with MDD, with rsFC strength significantly correlating with illness duration [13]. In our previous research, we observed decreased rsFC in specific amygdala subregions among individuals vulnerable to MDD [14]. Together, these findings underscore the potential significance of amygdala rsFC in the pathological mechanisms underlying MDD in adults.

In terms of adolescents, evidence indicates significant changes in amygdala-cortical resting-state functional connectivity (rsFC) from childhood to young adulthood in typically developing populations [15]. These findings suggest that deviations in this connectivity profile could contribute to abnormal rsFC patterns observed in adolescent MDD. Previous studies have reported increased rsFC between the amygdala and the occipitoparietal cortex, as well as the posterior cingulate cortex (PCC)/precuneus, along with decreased rsFC between the amygdala and the hippocampal/parahippocampal regions in adolescents with MDD [16–18]. Additionally, in adolescent females, rsFC among the amygdala, striatum, and prefrontal cortex (PFC) has been linked to depression symptoms [19]. These findings collectively suggest that adolescents with MDD exhibit disruptions in amygdala rsFC profiles similar to those observed in adult patients. However, developmental factors may contribute to differences in the rsFC abnormalities between adolescent and adult MDD.

To explore these differences, Tang et al. (2018) conducted voxel-wise meta-analyses separately for abnormal amygdala rsFC in adolescent and adult groups, followed by a quantitative comparison between the two groups. Their findings indicated that adolescent-specific amygdala rsFC abnormalities predominantly affect regions within cognitive control networks and the default mode network, whereas adult-specific abnormalities are more prominent within the affective network [20]. Nonetheless, this meta-analysis did not report on commonalities in amygdala rsFC abnormalities across MDD patients compared to healthy controls (HC). Therefore, direct comparisons of amygdala rsFC between depressive adults, depressive adolescents, and their respective controls are still needed to elucidate commonalities and differences in these connectivity patterns and their implications for symptomatology.

Moreover, according to previous studies, the amygdala can be subdivided into six functional subregions, including the centromedial (CM), laterobasal (LB), and superficial (SF) areas [21]. The CM is considered crucial for motor behavior and response preparation, while the LB plays a role in associative learning, such as reward-related learning and integration of environmental information with self-relevant cognition [22, 23]. Animal research has demonstrated the involvement of both CM and LB in emotional learning and processing [23, 24], whereas the SF is associated with basic emotions and social information processing, essential for human survival and social interactions [25]. Altered connectivity in LB and CM has been observed in various mental disorders, including depression, panic disorder, bipolar disorder, and post-traumatic stress disorder [21, 26–28]. However, there is limited understanding of how age influences the rsFC of amygdala subregions with cortical regions in these disorders. In the present research, we compared the rsFC of the amygdala in adolescents with MDD, adolescent HCs, adults with MDD, and adult HCs, to investigate the neurobiological profile in depressed patients of different ages and the influence of developmental phase on the etiology of MDD. Instead of evaluating the amygdala as a whole, we focused on the aforementioned six subregions. Based on the existing evidence mentioned above, we hypothesized that (1) age will significantly affect the rsFC of amygdala subregions; (2) patients with MDD, both adults

and adolescents, will share common abnormal connectivity between amygdala and prefrontal regions; (3) association may be found between abnormal rsFC and specific domains of MDD symptoms.

Methods

Participants

The recruitment of the current study was from March 2019 to March 2022. Both adolescent and adult participants with MDD were recruited in the outpatient clinic of Beijing Anding Hospital from March 2019 to March 2022. Adolescent HCs were volunteers from the local middle schools and the adult HCs were recruited via internet advertisements. A total of 74 adolescents (53 MDD, 21 HCs) and 93 adults (36 MDD, 57 HCs) completed the study, number of participants excluded in each step was shown in Fig. 1. The age range for adolescent groups was set at 12–17 years old, while the adult groups were at least 25 years old and the onset of MDD must be later than 18 years of age; the gender of the participants were not limited. We used Mini International Neuropsychiatric Interview (M.I.N.I. 7.0.2, Chinese Mandarin version) as a diagnostic tool and all MDD patients met the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnostic criteria for major depressive disorder. All participants were medication-naïve. Hamilton Depression Rating Scale (HAMD-17) was used to evaluate the severity of different dimensions of depression. Controls were also assessed using M.I.N.I. to exclude all kinds of mental disorders. All participants were right-handed Han Chinese and individuals with neurological diseases or other medical conditions not suitable for functional magnetic resonance imaging (fMRI) scanning were excluded. After the preprocessing of fMRI data, 2 adolescent controls, 7 adolescents with MDD, 1 adult control, and 1 adult with MDD were excluded due to large head movement (>3 standard deviations). At last, 65 adolescents (46 MDD, 19 HCs) and 91 adults (35 MDD, 56 HCs) were included in the final analysis.

fMRI data

Imaging acquisition

Participants completed the fMRI scanning using a 3.0 T Siemens Magnetom Prisma scanner. A total of 200 volumes of fMRI images were acquired with an echo-planar imaging sequence using the following parameters: repetition time (TR)=2000 ms, echo time (TE)=30 ms, field of view (FoV)=200×200 mm^2, flip angel=90°, number of slices=33, matrix=64×64, slice thickness=3.5 mm, slice spacing=0.7 mm. Sagittal T1-weighed structural images with 192 slices were acquired using the following parameters: TR=2530 ms, TE=1.85ms, FoV=256×256 mm^2, matrix=256×256, flip angel=9°, slice thickness=1 mm. Participants were instructed to close their eyes and rest during fMRI scanning. The scanning took approximately 20 min.

Functional image processing

fMRI data was preprocessed and calculated using the DPABI toolbox ver. 4.2_190919 (http://rfmri.org/dpabi) and Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm) run under MATLAB R2014b (MathWorks Inc., Natick, MA, USA) respectively. Preprocessing of data included the following steps: removal of the first 5 time points; slice time correction; reorienting functional images according to T1 images; segmentation of T1 images; nuisance covariates regression with Friston 24-parameter model of head motion, signals of white matter and cerebrospinal fluid (the mean components of signals was extracted), linear and quadratic trends as regressors; normalization using T1 images unified segmentation with a voxel size of 2×2×2 mm^2; spatial smoothing with a full width at half maximum Gaussian kernel of 4×4×4 mm^2 and temporal band-pass filtering (0.01–0.1 Hz). The mean volume-based framewise displacement (FD) of each group was defined as the head motion parameter.

Resting-state functional connectivity analysis

The amygdala was divided into six subregions (i.e., bilateral CM, LB, and SF) based on previous published research by Amunts et al. [29] and Zhang et al. [14]. and saved as masks separately. The amygdala subregion masks were set as regions of interest (ROIs) for rsFC analysis. The functional connectivity analyses were conducted by using the DPABI toolbox (ver. 4.2_190919). In brief, the mean time series of each ROI (i.e., the seed time series) was calculated by averaging the time series of every voxel within the corresponding masks, which we had extracted. The Pearson's correlation coefficients between the mean time series of each ROI and the time series of each voxel within the whole brain were later calculated to obtain rsFC maps for each of the six amygdala subregions. We also used the entire left and right amygdala as seed regions for control analysis. To improve the normality of the correlation coefficients, the Fisher r-to-z transformation was performed, then the z maps were entered into the later second-level analysis.

Statistical analysis

We used SPSS software (version 26.0, IBM Corp., Armonk, NY, USA) to compare the age, sex distribution, HAMD-17 scores, and head motions between MDD and controls within two age groups, separately. Descriptive statistics, independent *t*-test, Mann-Whitney test, and Chi-square test were used to determine the differences of characteristics mentioned above. We used a regression

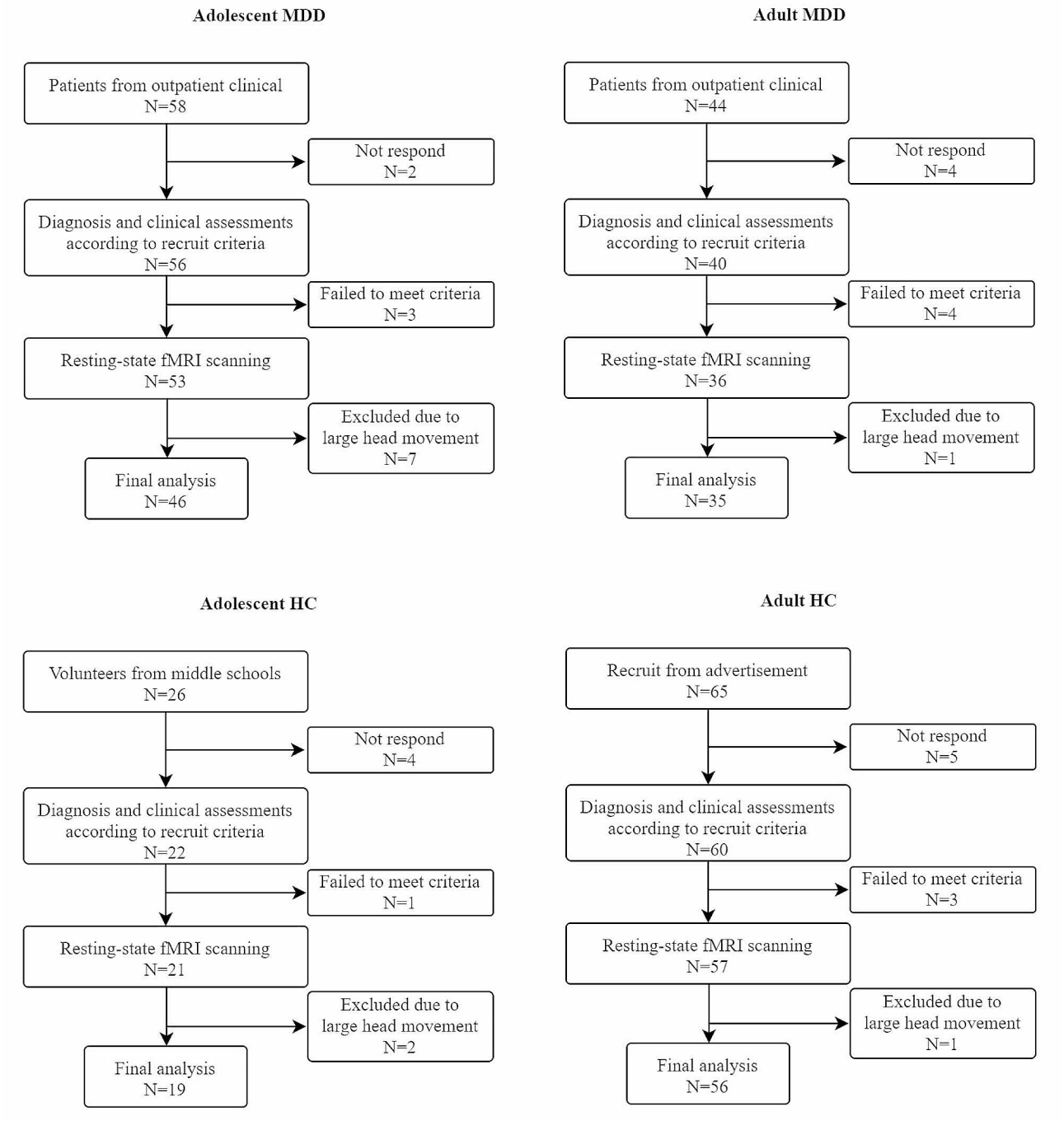

Fig. 1 Flowchart for recruitment and exclusion of each group

model to investigate if rsFC could be the predictor of HAMD-17 scores, sex and head motion were set as covariates.

The effects of diagnosis, age, and their interaction on rsFC were studied by 2×2 ANOVA using SPM12 with sex and head motion as covariates. All statistical maps were thresholded at voxel-wise of $P<0.001$ and in conjunction with a cluster-wise family-wise error (FWE) $P<0.05$ to correct for multiple comparisons. Significant regions in the whole brain were determined using the Gaussian random field (GRF) method with a voxel-level threshold of $P<0.001$ and a cluster-level family-wise error (FWE) $P<0.05$ to correct for multiple comparisons.

Table 1 Demographics of participants

	Adolescents		Adults		*P*
	MDD	HC	MDD	HC	
Age (median, range)	15.0 (12–17)	14.0 (12–17)	29.0 (25–46)	28.0 (25–47)	0.489/0.257[b]
Sex (male/female)	10/36	10/9	11/24	24/32	0.05
Education level[a]	12/34	14/5	7/20/8	6/24/26	0.771/0.067[c]
HAMD-17					
Anxiety/somatization	5.85 ± 2.05	-	4.63 ± 1.78	-	0.006
Weight change	0.39 ± 0.80	-	0.63 ± 0.88	-	0.209
Cognitive disturbance	4.96 ± 2.11	-	3.94 ± 1.61	-	0.020
Retardation	12.02 ± 4.60	-	6.86 ± 1.44	-	0.000
Sleep disturbance	2.57 ± 1.91	-	2.94 ± 1.51	-	0.338
Total score	21.33 ± 5.10	-	21.49 ± 3.57	-	0.875
FD power (mean ± std, mm)	0.15 ± 0.08	0.17 ± 0.06	0.14 ± 0.06	0.13 ± 0.05	0.115

Table 2 Main Effect of Age on the rsFC of amygdala subregions

ROI	Target region	BA area	MNI coordinate	Cluster size	Cluster-level P_{FWE}	F	Z
Left CM	Left hippocampus	-	-26, -10, -10	141	0.021	30.66	5.14
	Right amygdala	BA34	24, -6, -12	178	0.007	55.85	6.78
Right CM	Left middle frontal gyrus	BA6	-36, 6, 54	200	0.004	26.60	4.80
	Left superior parietal gyrus	BA7	-26, -76, 46	224	0.002	17.28	3.87
Right LB	Right medial orbitofrontal cortex	BA11	14, 54, -6	167	0.010	40.95	5.89

Abbreviations: ROI: regions of interest; BA: Brodmann Area; MNI: Montreal Neurosciences Institute; FWE: family-wise error; L: left; R: right.

Results

Demographic of participants

46 adolescents with MDD, 19 adolescent HCs, 35 adults with MDD, and 56 adult HCs were included in the final analysis. In each of the age groups, there were no significant differences in age, sex distribution, education level, or head motion between MDD patients and controls (Ps > 0.05). Two sample *t*-tests revealed that there was no significant difference in the total HAMD-17 score between adolescents and adults with MDD ($P > 0.05$). Details of demographics are shown in Table 1.

[a]: The education level of adolescent participants was divided into two categories: junior high school/senior high school; education of adult groups was divided into three categories: junior and senior high school/bachelor's degree/master's degree and above. [b]: *P*value of Mann-Whitney test in adolescent groups/*P*value of Mann-Whitney test in adult groups. [c]: *P*value of Chi-square test in adolescent groups/*P*value of Chi-square test in adult groups.

Difference in symptomatology between adolescents and adults with MDD

The five main dimensions of HAMD-17 were calculated to determine the difference between adolescents and adults with MDD. The results of two sample t-test discovered that adolescents with MDD suffered from more severe symptoms in anxiety/somatization (t = -2.798, $P = 0.006$), cognitive disturbance (t = -2.798, $P = 0.006$) and retardation (t = -6.398, $P = 0.000$), while weight change (t = 1.266, $P = 0.209$) and sleep disturbance (t = 0.964, $P = 0.338$) shown no significant difference (Table 1).

Main effect of age on the rsFC of amygdala subregions

A significant main effect of age on the rsFC was found in several specific amygdala subregions (Table 2; Fig. 2). Specifically, in both MDD patients and healthy controls, the rsFC between the left CM and left hippocampus as well as the right amygdala in adolescents were significantly higher than that in adults. The rsFC between the right CM and left middle frontal gyrus (MFG) as well as the left superior parietal gyrus (SPG) in adolescents were also significantly higher than that in adults regardless of their diagnosis. However, the rsFC between the right LB and the medial orbital part of the right superior frontal gyrus (mOFC) was significantly higher in adults than in adolescents.

Main Effect of Diagnosis on the rsFC of amygdala subregions

A significant main effect of diagnosis was revealed on the rsFC between the right LB and the left MFG (cluster size: 126; Brodmann Area: BA46; MNI coordinate: -42, 52, 8; cluster-level $P_{FWE} = 0.036$, F = 16.56, Z = 3.79), indicating that both adolescents and adults with MDD showed lower connectivity than healthy controls (Fig. 3)

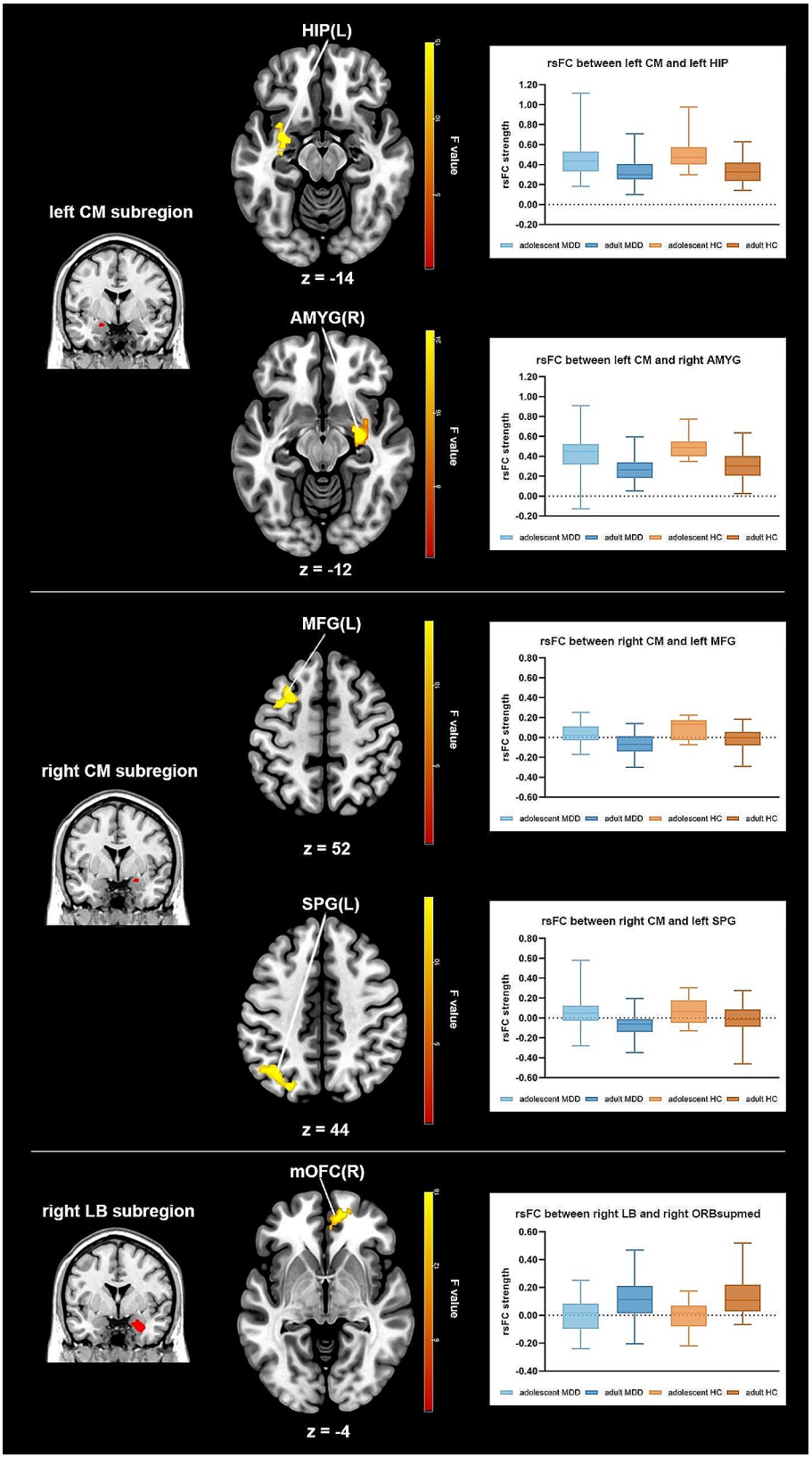

Fig. 2 The main effect of age on the rsFC of amygdala subregions. The left column showed the amygdala subregions with a significant main effect of age; the middle column showed the correspondent target regions; the right column showed the strength of rsFC within each group for each of the target regions. Abbreviations: CM: centromedial; LB: laterobasal; HIP: hippocampus; AMYG: amygdala; MFG: middle frontal gyrus; SPG: superior parietal gyrus; mOFC: medial orbitofrontal cortex

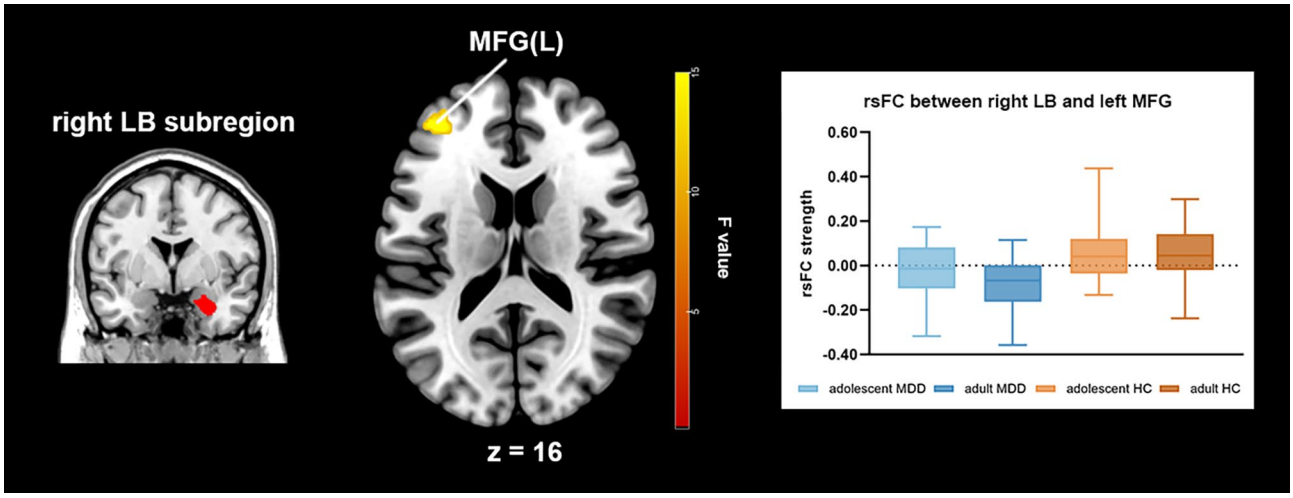

Fig. 3 The main effect of diagnosis on the rsFC of amygdala subregions. The left figure showed the amygdala subregion with a significant main effect of diagnosis; the middle figure showed the correspondent target region; the right figure exhibited the strength of rsFC within each group for the target region mentioned above. Abbreviations: LB: laterobasal; MFG: middle frontal gyrus

Interaction effect between age and diagnosis on the rsFC of amygdala subregions

No significant interaction effect between age and diagnosis on the rsFC was found in any of the amygdala subregions (voxel-level $P<0.001$, cluster-level $P_{FWE}<0.05$).

Association between rsFC and HAMD-17 scores

To study the association between functional connectivity and depressive symptoms, we used a regression model to investigate if rsFC between the right LB and left MFG, in which a significant main effect of diagnosis was found, could be the predictor of HAMD-17 scores using age (adolescents vs. adults) as the moderator variable. Sex and head motions were set as the covariates. Results showed that no significant main effect of rsFC strength or rsFC × age interaction was found ($P>0.05$)

Control analysis

We performed a control analysis using the left and right amygdala as seed regions. A significant main effect of diagnosis was discovered on the rsFC between the right amygdala and the left MFG (cluster size: 308; Brodmann Area: BA 46; MNI coordinate: -34, 52, 16; cluster-level $P_{FWE} < 0.001$, F=25.60, Z=4.71). We also found a significant effect of age on the rsFC between the left amygdala and both right (cluster size: 157; Brodmann Area: BA 34; MNI coordinate: 24, -6, -12; cluster-level $P_{FWE} = 0.014$, F=50.04, Z=6.46) and left (cluster size: 135; Brodmann Area: BA 34; MNI coordinate: -24, -6, -12; cluster-level $P_{FWE} = 0.026$, F=442.57, Z=6.00) clusters near amygdala, in which adolescents demonstrated a higher rsFC than adults (Fig. 4)

Supplementary analysis

To assess the reproducibility of our volume-based analysis findings using a surface-based cortical analysis, we employed the methods described by Alexander-Bloch et al [30]. First, we calculated the mean time series for each of the six amygdala subregions in each participant using the nilearn (version 0.10.1) module in Python (version 3.10.13). Subsequently, we computed the correlation between each of these time series and the time series of each vertex on FreeSurfer average surfacespace (fsaverage5), which enabled us to derive the corresponding surface-based functional connectivity for each subregion. Next, we conducted a spin permutation test to evaluate whether the group differences observed in the volume-based analysis remained statistically significant in the surface space. To accomplish this, we projected the mask of the clusters showing significant differences in the bilateral CM and the right LB subregions from the volume-based analysis onto the fsaverage5 space. We then compared the empirical ANOVA F-score with the results obtained from the permutation tests ($n=1000$). Notably, the F-distribution of the ANOVA tests demonstrated substantial distinctions between the empirical F-scores and the permutation results (Fig. 5), indicating that the significance of the clusters we observed in the volume-based analysis was reproducible in the surface space ($ps<0.001$).

Discussion

In the current study, we focused on the six subregions of the bilateral amygdala, and compared the functional connectivity of these six subregions with the whole brain across four participant groups - adolescents with MDD, adults with MDD, healthy adolescent controls, and

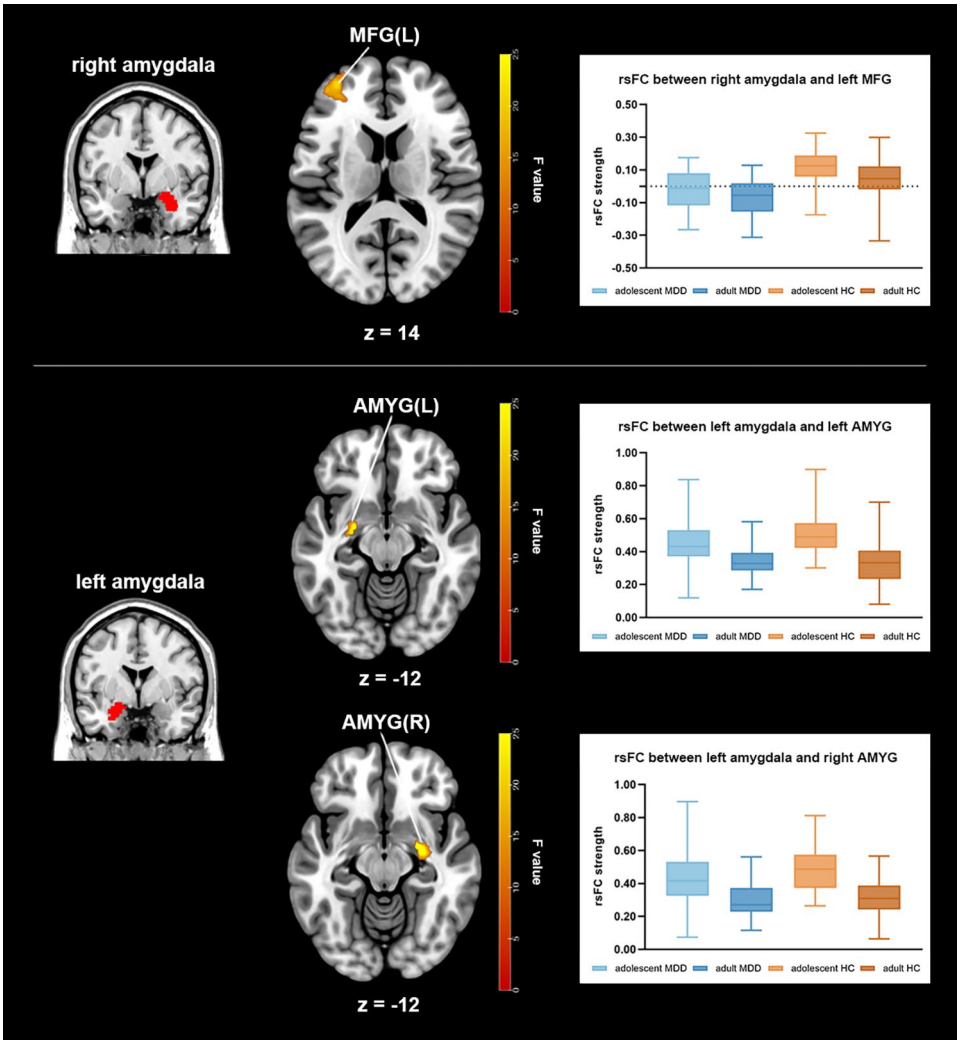

Fig. 4 Control analysis using bilateral amygdala as seed regions. The left column showed the locations of the seed regions; the middle column showed the correspondent target regions; the right column showed the strength of rsFC within each group for each of the target regions. Abbreviations: AMYG: amygdala; MFG: middle frontal gyrus

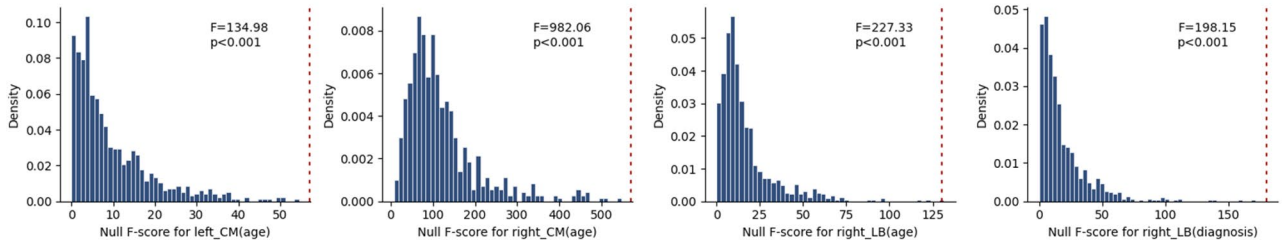

Fig. 5 Correspondence of voxel-based results and surface-based results. The four figures showed the F-distribution of ANOVA tests in the clusters in bilateral CM and the right LB subregions. The red dashed line indicates the empirical ANOVA F-score. Abbreviations: CM: centromedial amygdala; LB: laterobasal amygdala

healthy adult controls. Our findings revealed a significant main effect of age (i.e., adolescents vs. adults). Specifically, differences were observed in rsFC between the left CM and limbic regions (left hippocampus and right amygdala), between the right CM and regions within the fronto-parietal network (left MFG and left SPG), and between the right LB and the medial orbitofrontal cortex (mOFC).

Furthermore, a significant main effect of diagnosis (MDD vs. healthy controls) was identified in the rsFC

between the right LB amygdala and left MFG, indicating consistent alterations in MDD patients across age groups compared to healthy controls. Notably, no significant age × diagnosis interaction was found, suggesting that the observed abnormalities in rsFC were not specific to either adolescent or adult MDD populations

Compared to adults, adolescents with MDD exhibited more pronounced symptoms in anxiety/somatization, cognitive disturbance, and motor retardation. This is partially consistent with the report by Rice et al. [5]. , revealing the more common externalized and physical symptoms in adolescent MDD. However, no significant correlation was found between HAMD-17 scores and the right LB – left MFG connectivity despite the symptomatology differences we found between adult and adolescent patients, this discrepancy might be attributed to the HAMD-17 scale's broader assessment of depressive symptoms, potentially overlooking specific domains such as anxiety [31]. Future studies should consider employing more comprehensive and nuanced measures of symptomatology to elucidate these findings.

Age effects on rsFC of specific amygdala subregions

Developmental research indicates that both the volume of the amygdala and the rsFC of its subregions undergo changes with age, reflecting the structural and functional immaturity of the amygdala during adolescence [32, 33]. Specifically, one study observed a decrease in rsFC between the amygdala and the parahippocampal gyrus as individuals age, which aligns with our own findings [15]. However, the developmental trajectory of rsFC between amygdala subregions and hippocampus in humans remains relatively unexplored

Our study revealed that the left CM subregion exhibited stronger rsFC with the adjacent hippocampus and right amygdala. These findings may suggest more intense functional interaction within the limbic system in adolescents than in adults [34–36]. Additionally, we observed that adults displayed a negative rsFC between the right CM amygdala subregions and the left frontoparietal cortex, whereas adolescents exhibited a positive rsFC in this connection. The frontoparietal network was believed to be crucial in goal-oriented behavior, executive functions, and top-down cognitive control [37–39]. Previous cross-sectional studies have indicated a developmental shift from positive to negative rsFC in amygdala-prefrontal circuitry, reflecting neural maturation during adolescence and increased prefrontal cortex (PFC) regulation over the limbic system [40, 41]. Our findings are consistent with these observations, suggesting that the adult-specific top-down influence of the frontoparietal network on the amygdala is specific to certain subregions

Additionally, we found that adults had a stronger rsFC between the right LB and the right mOFC. Previous research has highlighted the critical role of the amygdala, particularly the LB, in anxiety and depression [42, 43], with the OFC receiving neural projections from various brain regions, including the amygdala [44, 45]. The OFC and the LB subregion were later found to be involved in emotion, motivation, and learning processes, especially the encoding of the association between cues and corresponding outcomes, and their interaction contributed to the updating and storing of Pavlovian contingencies [46, 47]. Therefore, our finding of a positive rsFC specifically in adults may indicate a more mature and refined predictive processing of outcomes, a capacity that adolescents may not yet fully develop, potentially contributing to their heightened symptoms of anxiety and somatization

Decreased rsFC of specific amygdala subregions across adolescent and adult MDD patients

In MDD patients, we found a decreased rsFC between the right LB and left MFG, a component of the dorsolateral prefrontal cortex. This finding aligns with our hypothesis and is consistent with prior research indicating reduced rsFC between the amygdala and prefrontal cortex in depressive patients [48–50]. Researchers have also pointed out that the decoupling within the cortical-limbic system could play a pivotal role in the pathology of MDD [51]. The amygdala and prefrontal cortex are typically interconnected during emotional processing, regulation, and social cognition [52]. Hence, the decreased connectivity between these regions in MDD participants could contribute to emotional dysregulation [53], as well as symptoms like impaired social cognition and negativity bias [50, 54]

Our finding further demonstrated that alternation in connectivity is observed in patients with MDD regardless of age, consistent with recent meta-analytical findings. This meta-analysis indicated that the left MFG in MDD patients exhibits both altered rsFC and reduced gray matter density [55], suggesting that changes in this brain region might be rather stable and long-standing. Nevertheless, given the heterogeneity in previous research findings, future large-sample studies are warranted to elucidate the relationship between MFG and specific amygdala subregions in depressed patients

In brief, our findings indicated that reduced rsFC between the right amygdala LB subregion and the MFG in MDD was independent of the developmental stage, suggesting that this abnormality may manifest early in MDD and could potentially serve as a biomarker for the disorder. Moreover, considering the prefrontal cortex as a target in neuromodulation treatments for adult MDD [56–58], our findings support its potential as a target for non-pharmaceutical interventions in adolescents, potentially improving its modulation of amygdala function

No significant interaction effect on rsFC of amygdala subregion

No significant interaction between diagnosis and age was identified in the current study, suggesting that these two factors were relatively independent. Specifically, the abnormal functional connectivity profiles of amygdala subregions observed in participants with MDD were not influenced by their age. Likewise, the developmental characteristics of functional connectivity were not affected by the participants' diagnosis. The existing literature on the interaction between age and diagnosis remains limited and inconsistent. For instance, a recent large-scale multi-site study found a significant interaction between age and childhood maltreatment on cortical thickness, but did not find an interaction between age and depression diagnosis [59]. Another morphometric study revealed significant age-by-diagnosis interactions in specific brain regions such as lateral orbital frontal gyrus and insular subregions [60]

To date, no studies have investigated rsFC specifically in terms of the interaction between age and MDD diagnosis. In our study, we did not observe any significant interaction between age and diagnosis concerning amygdala subregions. However, the absence of significant findings does not rule out the possibility of detecting such interactions using other functional indices. Therefore, future research is required to examine this interaction. In any case, future studies should incorporate longitudinal research spanning various developmental stages to investigate the neural activity of individuals with and without MDD.

Limitations

The current study has the following limitations. Firstly, as an exploratory analysis, we did not apply Bonferroni correction for the number of amygdala subregions. However, we conducted a control analysis using the entire left and right amygdala as seed regions, which yielded consistent results. Additionally, we performed a supplementary analysis in the surface space, which further validated the reliability of our results. To bolster the robustness of our findings, future studies should consider increasing the sample size and conducting reproducibility research. What's more, anxiety symptoms were not assessed in the current study using anxiety specific questionnaire, and it is possible that some patients with MDD met the diagnosis of MDD with anxiety features in DSM-5. A previous study found that the rsFC between right CM/LB subregions and the right MFG were significantly declined in MDD patients with anxiety features compared to MDD patients without anxiety [21], suggesting that accompanied features may also contribute to the rsFC abnormality. Thus, the current findings might be influenced by symptomatologic heterogeneity in participants with MDD. Future studies should take the course and characteristics of disease into analysis, to further uncover the alternation of neural profile in MDD adolescents.

Conclusions

The current study found an age effect on the rsFC of specific amygdala subregions, indicated by the stronger rsFC of the left CM and the adjacent hippocampus and the right amygdala, weaker negative connectivity between the right CM and the left frontoparietal region, and weaker positive connectivity between the right LB and the medial orbital part of superior frontal cortex in the adolescents. More importantly, we found decreased rsFC between the right LB and the left MFG in both adolescent and adult MDD patients, indicating that this abnormality is independent of the development stage and could potentially serve as a biomarker for early diagnosis of MDD. The current study did not reveal any significant interaction effect between age and diagnosis, which warrants further investigation in future studies. Overall, these findings enhance our understanding of the developmental trajectory of rsFC in the amygdala subregions and how it influences the symptomatology of MDD.

Abbreviations

MDD	major depressive disorder
rsFC	resting-state functional connectivity
CM	centromedial. LB: laterobasal
MFG	middle frontal gyrus
PCC	post cingulate cortex
PFC	prefrontal cortex
HC	healthy controls
SF	superficial
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
HAMD-17	Hamilton Depression Rating Scale
fMRI	functional magnetic resonance imaging
TR	repetition time
TE	echo time
FoV	field of view
ROI	region of interest
SPG	superior parietal gyrus
mOFC	medial orbitofrontal cortex
HIP	hippocampus
AMYG	amygdala.
BA	Brodmann Area
MNI	Montreal Neurosciences Institute
FWE	family-wise error

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Author contributions

L. G. and R. L. analyzed the fMRI data and wrote the main manuscript text. C.W. and Q.F. offered support in the supplementary analysis. J. Z., Y. W., Y. F., and J. L. collected the data for the current study. All authors reviewed the manuscript.

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Data availability
The datasets analyzed during the current study are not publicly available due to the participants did not consent to the disclosure of the data to the public but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures in this study were conducted in accordance with the Declaration of Helsinki, and the current study was approved by the ethics committee of Beijing Anding Hospital, Capital Medical University. All adult participants signed informed consents during recruiting, and the informed consents of adolescent participants were signed by both the participants themselves and their legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors have declared that they have no competing or potential conflicts of interest.

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