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A preliminary study of the dysregulation of the resting networks in first-episode medication-naive adolescent depression

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ABSTRACT

Recent developments in depression studies have heightened the need for investigating adolescent major depressive disorder (MDD). Many previous neuroimaging studies used task designs and found consistent results in the dysfunction of brain regions in depressed adolescent patients. In this study, we aimed to evaluate the topological properties of brain functional networks of adolescents with MDD from an integrated view. Using resting state functional magnetic resonance imaging (fMRI), graph theory was applied to construct the resting networks in 16 first-episode and unmedicated adolescents with MDD and 16 healthy controls (HC). Our results showed that the topological properties of depressed adolescents' networks were significantly disrupted compared with HC. Dysregulation of brain regions were found in the anterior cingulate cortex, dorsolateral, medial and inferior prefrontal cortex, insula, amygdala, and the temporal cortices. Furthermore, the connectivity degree of amygdala related functional connection was positively correlated with the duration of depression. Detection and estimation of these functional impairments may advance our current understanding of the pathophysiological mechanism of adolescent MDD.

Major depressive disorder (MDD) consists of periods of decreased mood, low self-esteem, and withdrawal from pleasurable activities [12]. With this mental disorder, suicidal risk is high in children and teenagers [6]. Previous studies used different experimental designs to investigate differing aspects of adult depression [12,13], and several brain regions showed abnormal neural activities, including the prefrontal cortex, anterior cingulated cortex (ACC), insula, amygdala, basal ganglia and the temporal regions [12]. Recently, researchers have shown an increased interest in studying the neural substrates of adolescent depression [7,33,34]. These studies pointed out that adolescent MDD studies may lead to more significant understanding of the development of natural models for depression in adults [7,32,34]. However, the exact mechanisms underlying adolescent depression are not fully understood.

A recent advance that offers better understating of adolescent MDD focused on spontaneous modulations in the blood oxygen level-dependent (BOLD) signal that occur during resting conditions [7,23]. This so-called resting state functional connectivity networks are posited to provide insight into the intrinsic functional architecture of the brain [14,15,29]. Most studies focus on a local subsystem in the brain networks of adolescents with depression. For example, Cullen et al. analyzed functional connectivity using seeds in the subgenual ACC and found decreased functional connectivity in subgenual ACC-based neural networks in adolescents with MDD in comparison to healthy participants [7]. Based on these inherent features, current findings were still insufficient in making inferences regarding resting-state abnormalities in adolescents with MDD. Far too little attention has been paid to evaluate the functional connectivity as well as the temporal and spatial patterns of interactions between brain regions on a whole brain scale.

In this study, we aimed to investigate the organizational patterns of dysfunctional resting networks in adolescents with MDD, combining both spatial and temporal information from an integrative systems perspective. In the current study, we used graph theory analysis (GTA), which has become a powerful tool to investigate complex brain networks [1,2,20,21]. While a graph represents the functional connection between brain regions, we would explore abnormal topological properties in the brains of adolescents with MDD. To identify the relationship between dysregulation of brain connections and symptom severity, correlation analyses were performed between the resting-state functional connectivity intensity and individual duration of this illness across all subjects.

Sixteen first-episode and drug-naïve adolescents with MDD (right-handed, age 17.1 ± 1.3 years) were recruited from the Men-

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Table 1
Demographic and clinical characteristics of MDD patients and healthy controls.

Characteristic	MDD patients ($n = 16$)		Healthy controls ($n = 16$)		Analysis
	Mean	SD	Mean	SD	p-Value
Age (years)	17.1	1.3	17.3	1.5	>0.05
Gender (male/female)	8/8	–	8/8	–	
Education (years)	9.1	1.8	10.3	1.5	>0.05
Duration of illness (days)	150.6	46.3	–	–	
HDRS scores	21.7	2.4	3.2	1.0	<0.05*

MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale.
* p-Value was obtained by an independent-sample t-test.

tal Health Center, the First Affiliated Hospital of Medical College, Xi'an Jiaotong University, and sixteen age-, education- and gender-matched HC (right-handed, age 17.3 ± 1.5 years) were recruited from the local community (Table 1). The protocol was approved by the Ethical Committee of the Xi'an Jiaotong University. After the study had been explained, all participants gave written informed consent.

Clinical assessment was conducted by two experienced psychiatrists based on the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria. Inclusion criteria for all patients were that (1) they met the MDD in DSM-IV criteria (2) 17-item Hamilton Depression Rating Scale (HDRS) scores were 18 or greater (3) they were drug-naïve and (4) were having their first episode of depression. Exclusion criteria included the presence of (1) other Axis I psychiatric disorders and symptoms, (2) a history of brain disorder or neurological disorders, (3) pregnancy or any physical illness as assessed by personal history and laboratory analysis, and (4) the inability to undergo an MRI. Healthy control subjects met the exclusion criteria above and had no psychiatric illness history or any family history of major psychiatric diseases in their first-degree relatives. Subjects were instructed to keep their eyes closed, not to think about anything, and to stay awake during all scans. After scanning, all subjects reported that they all stayed awake during the scans.

All examinations were performed on a 1.5 T system (Philips Gyroscan Intera, Netherlands) using a standard quadrature head coil. The MRI transverse T2 FLAIR was scanned (TR = 6000 ms, TE = 110 ms, IR = 2000 ms, NSA = 1, TSE factors = 25, FOV = 256 mm, slice = 27, slice thickness = 5 mm, gab = 0 mm, scan time = 2 min and 42 s). During the resting state fMRI sequence, subjects were asked to keep their eyes closed, and remain motionless. We used a gradient echo planar sequence to acquire functional images. The parameters were as follows: TR = 3000 ms, TE = 50 ms, flip angle = 90°, FOV = 256 mm × 256 mm, matrix = 64 × 64, Slices = 27, slice thickness = 5 mm, gap = 0 mm, NSA = 1, Dynamic scans = 150. Each fMRI scan lasted 7 min and 39 s.

To minimize movement artifacts, individuals with an estimated maximum displacement in any direction larger than 1 mm or head rotation larger than 1° were discarded from the study. No data were excluded under this criterion. Image preprocessing was carried out using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). All resting functional images were processed using the following steps: (1) compensation of systematic, slice-dependent time shifts, (2) elimination of systematic odd–even slice intensity differences due to interleaved acquisition, (3) rigid body correction for geometrical displacements caused by head movement, (4) coregistration with the Montreal Neurological Institute (MNI) echoplanar imaging (EPI) template image, (5) bandpass (0.01–0.1 Hz) to reduce the effects of low-frequency drift and high-frequency noise, and (6) linear regression for head motion, the signal averaged over the lateral ventricles, and the signal averaged over a region centered in white matter.

GTA defined a graph as a set of nodes and edges. In this study, we used the anatomically labeled (AAL) template image used previously by Tzourio-Mazoyer et al. [28], which has been utilized in several previous GTA studies [20,22,30]. As can be seen from Table 2 [23], the AAL template divided the whole brain into 90 regions of interest (ROIs), and each of the ROI was considered as a node in our

Table 2
90 ROIs from the AAL template image.

Region	Abbreviation	Region	Abbreviation
Superior frontal gyrus, dorsolateral	SFGdor	Median- and para-cingulate gyrus	DCG
Superior frontal gyrus, orbital	ORBsup	Superior temporal gyrus	STG
Superior frontal gyrus, medial	SFGmed	Superior temporal gyrus, temporal pole	TOPsup
Superior frontal gyrus, medial orbital	ORBsupmed	Middle temporal gyrus	MTG
Middle frontal gyrus	MFG	Middle temporal gyrus, temporal pole	TOPmid
Middle frontal gyrus, orbital	ORBmid	Inferior temporal gyrus	ITG
Inferior frontal gyrus, opercular	IFGoperc	Heschl gyrus	HES
Inferior frontal gyrus, triangular	IFGtriang	Hippocampus	HIP
Inferior frontal gyrus, orbital	ORBinf	Parahippocampal gyrus	PHG
Gyrus rectus	REC	Amygdala	AMYG
Anterior cingulate gyrus	ACC	Insula	ANG
Olfactory cortex	OLF	Thalamus	THA
Superior parietal gyrus	SPL	Caudate nucleus	CAU
Paracentral lobule	PCL	Lenticular nucleus, putamen	PUT
Postcentral gyrus	PoCG	Lenticular nucleus, pallidum	PAL
Inferior parietal gyrus	IPL	Calcarine fissure and surrounding cortex	CAL
Supramarginal gyrus	SMG	Cuneus	CUN
Angular gyrus	ANG	Lingual gyrus	LING
Precuneus	PCUN	Superior occipital gyrus	SOG
Posterior cingulate gyrus	PCC	Middle occipital gyrus	MOG
Precentral gyrus	PreCG	Inferior occipital gyrus	IOG
Supplementary motor area	SMA	Fusiform gyrus	FFG
Rolandic operculum	ROL		

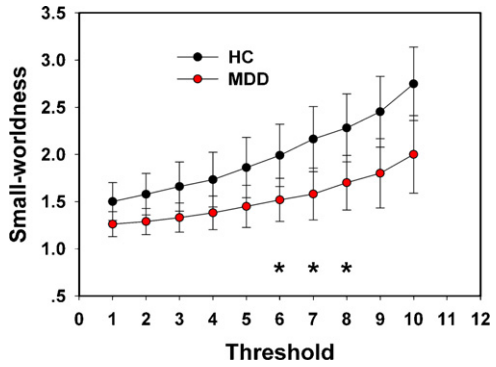

Fig. 1. Measures for small-world network properties between adolescent MDD and HC.

network analysis. We extracted the regional mean time series of each of the 90 ROIs, and partial correlation was used to construct undirected weighted networks. A brain functional connection could be represented as an undirected edge if the correlation coefficient between the two nodes achieved a correlation threshold T. The correlation coefficient between the two ROIs was chosen as the weights of the edges [30]. We thresholded each correlation matrix repeatedly at ten threshold values from 0.35 to 0.53 in 0.02 increments. The lower bound of T was set at 0.36 so that each network was fully connected with all of the nodes.

Several studies have demonstrated that the brain is organized as a small-world structure, which has a highly efficient neuronal architecture [2]. The clustering coefficient C, the mean minimum path length L and the degree are the key parameters of the small-world network. In graph theory, the degree of a node in the network is defined as the number of nodes across the brain that show strong correlation with the target node, and the C describes the proportion of possible connections that actually exist between the nearest neighbors of a node, and the L characterizes the average of the shortest path length over each possible pair of nodes [20]. The detailed descriptions of defining the equations of C and L are characterized in Watts and Strogatz [31]. If a network has a feature with a higher C than a similarly sized random graph and a small L, it is considered as a small-world network [2].

To test for the significant differences of the network parameters between the adolescent MDD group and HC group, a two-sample two-tailed t-test was performed. The false discovery rate (FDR) was used for multiple comparison corrections [5].

The networks of the two groups were created at different correlation thresholds T from 0.35 to 0.53 in 0.02 increments. Relative to the HC, the small-worldness was much lower in the adolescent MDD group over a wide range of thresholds. The most significant between-group difference of the small-world network properties was found at the threshold $T = 0.47$ ($p < 0.01$, FDR corrected, Fig. 1). Under this threshold, the small-worldness of the HC group was 2.13, and the adolescent MDD group was 1.57. The network patterns at threshold $T = 0.47$ for HCs' and adolescent MDDs' networks were shown as being typical in the following analysis.

By the definition of degree, the region that has a higher degree means that it has more functional connections with other brain regions in the network. Based on each region degree, a two-sample two-tailed t-test was performed to determine if the degree of the brain regions were significantly different between the HCs' and adolescent MDDs' resting networks at threshold $T = 0.47$ ($p < 0.05$, corrected). Compared with the HC group, connectivity strength was higher overall in several brain regions in the adolescent MDDs' resting networks, including the ACC, dorsolateral, medial and inferior prefrontal cortex (PFC), insula, amygdala, and the temporal cortices (Table 3). In this study, we also compared the degree difference at other threshold values ($T = 0.45$ and $T = 0.49$). Although the statistical significance of the degree difference changed quantitatively for different thresholds, no additional brain regions were found.

Table 3
Foci with significant differences in degree between HC and adolescent MDD.

Regions of interest		HC degree mean ± SD	MDD degree mean ± SD	p-Value
Frontal cortex				
SFGdor	L	40.7 ± 14.6	55.2 ± 16.4	0.45
	R	37.4 ± 17.1	57.1 ± 15.9	0.02
ORBsup	L	14.1 ± 9.1	38 ± 23.5	0.01
	R	15.9 ± 8.7	39.1 ± 13.7	0.0006
ORBinf	L	20.8 ± 11.9	46.8 ± 25.8	0.01
	R	25.1 ± 13.5	47.1 ± 21.9	0.02
ORBmid	L			
	R	16.4 ± 11.6	33.7 ± 20	0.03
SFGmed	L	29.1 ± 18.2	48.1 ± 17.9	0.02
	R	14.5 ± 52.9	52.3 ± 14.1	0.0006
MFGmed	L	16.1 ± 11.8	42 ± 18.8	0.004
	R	19.5 ± 18.6	41.3 ± 14.1	0.009
PreCG	L	39.7 ± 18.5	58.6 ± 9.1	0.02
	R	36.1 ± 18.1	59.7 ± 15.6	0.01
Limbic system				
ACC	L	21.4 ± 14.1	44.4 ± 21.7	0.02
	R	22.3 ± 11.7	49.8 ± 20.9	0.002
INS	L			
	R	16.1 ± 18.6	44 ± 22.8	0.01
AMYG	L	7.4 ± 13.2	24.8 ± 15.2	0.03
	R			
Temporal cortex				
STG	L			
	R	36.1 ± 19.4	58.4 ± 15.1	0.02
TPOsup	L	32.7 ± 20.6	56 ± 18.6	0.03
	R	31.8 ± 20.3	54.8 ± 16.7	0.03
MTG	L	39.1 ± 18.8	62.7 ± 18.6	0.02
	R	35.8 ± 22.1	57.9 ± 18.4	0.04

In the current study, the correlation coefficient between the two regions was preserved as the weights of the edges in our graphs. To estimate the connection differences between the two groups, the intensity of the functional connectivity (connection weights) were compared (two-sample two-tailed t-test, $p < 0.05$, corrected). Many pairs of connections showed dysregulated functional connectivities, and furthermore, these connections also presented a positive correlation with the duration of this illness across all depressed individuals ($p < 0.05$), including the amygdala–temporal cortices, amygdala–precentral cortex, amygdala–postcentral cortex, PFC-inferior parietal lobe (IPL) and connections within the PFC (Fig. 2, red lines).

In this study, we applied the GTA method to characterize the functional connectivity of the resting networks of adolescents with MDD and HC from an integration point. Comparing the topological properties of functional brain networks between the two groups, disrupted small-world properties were found in the cortical networks in adolescents of the MDD group; the connectivity degree was significantly higher overall in several brain regions in adolescents with depression; interregional correlation strengths were prominently altered in amygdala-related and PFC-related connections in adolescents of the MDD group.

Many studies employing GTA have consistently demonstrated that the normal brain is organized as having a highly efficient neuronal architecture, which has small-world properties of clustered local connectivity with relatively few long-range connections mediating a short path length between any pair of neurons or brain regions in the network [16,30]. Compared with the HC, the small-world topological properties of resting networks in adolescents with MDD were significant decreased (Fig. 1). According to the definition of small-worldness, our findings revealed that the clustering coefficient and the mean minimum path length of the resting network were unfavorably influenced by depression. Bassett and

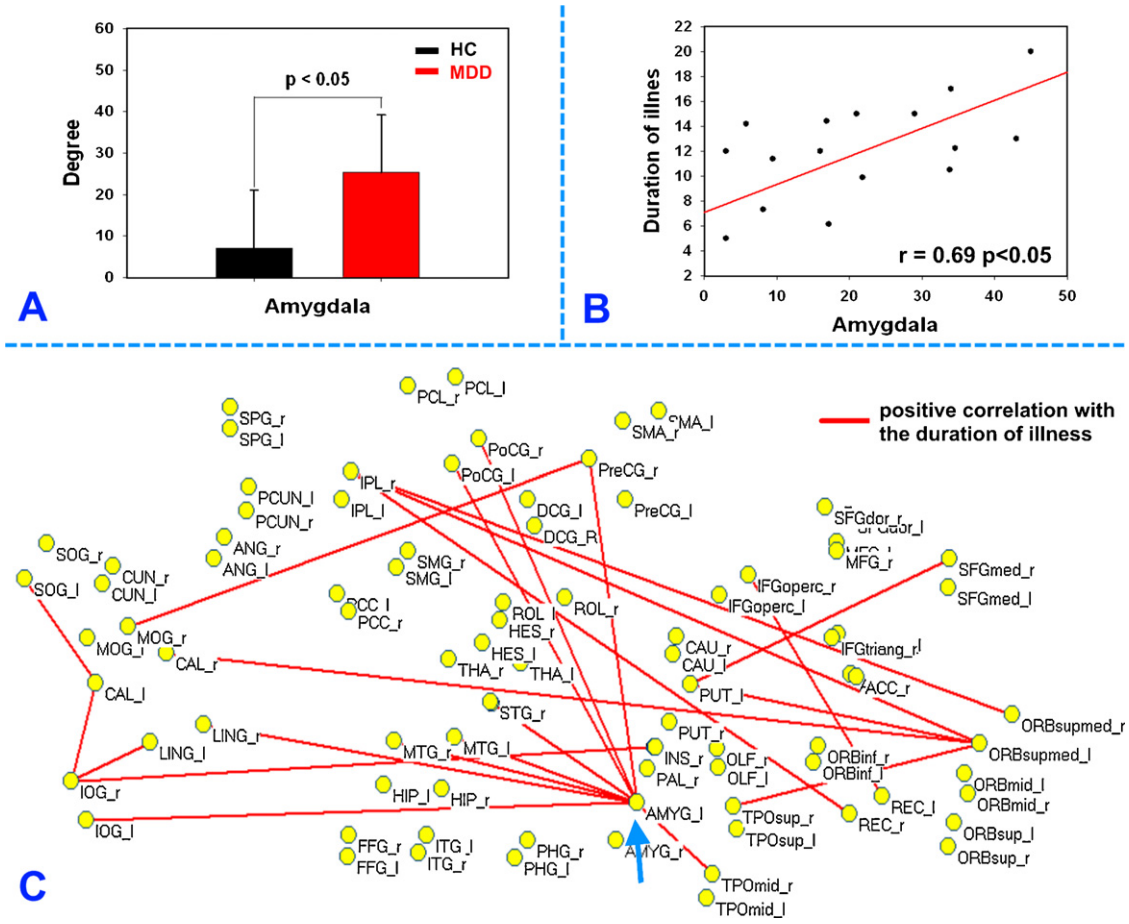

Fig. 2. Dysregulation of the AMYG in the networks of adolescent MDD. (A) The degree of AMYG differences between the two groups. (B) The correlation between the degree of the AMYG in the networks of adolescent MDD and individual duration of the illness across all patients. (C) Significant differences in the intensity of the functional connection between the two groups. Red lines indicate the increased intensity in adolescent MDD networks (MDD > HC), and the intensity of these connections also showed a positive correlation with the patients' duration of the illness.

Bullmore [3] and Liu et al. [22] suggested that high clustering coefficient and short path length could promote effective interactions between and across different cortical regions. Hence, the disrupted small-world networks may lead to impaired organization of brain networks for the information flow between connected brain regions in a slow and less efficient depressed brain. Several studies indicated that the information interactions within cortical networks were a basis of human cognitive processes [17,22,24,27]. As mentioned above, dysregulated resting network may be one reason that led to abnormal cognitive function in depressed patients.

MDD in adolescents is an increasingly important area in understanding the progression of adult MDD [7,33,34]. Pine et al. (1999) evaluated the relationship between subclinical depressive symptoms in adolescents and major depressive episodes in adulthood, and they pointed out that the symptoms of depression in adolescents could be early signs of adult depressive disorders [25]. Compared with HCs' resting networks, our results showed that the major component of the PFC has aberrant functional connectivity in adolescents with MDD group (Table 2). The abnormal activation of the PFC in depression was largely considered to be involved in the cognitive disorder [11,26]. Individuals with MDD have tendencies to focus on negative stimuli and themselves [19]. Lemogne et al. reviewed studies in self-referential processing in patients with major depression and provided an updated overview regarding the role of increased medial PFC activity during depressive self-focus [19]. According to our findings, the dysregulation functional connectivity in the regions of the PFC may lead to more focused attention on negative aspects of one's self in depressed adolescents.

The results of this study also showed a significantly higher degree of the amygdala in the networks of depressed patients than in the HC. Furthermore, the intensity of the amygdala related connections in adolescent MDDs' resting networks exhibited a positive correlation with symptom severity (Fig. 2). This indicated that depression may injure cortical networks in depressed adolescent patients and led to dysregulated functional connectivity in the amygdale-related brain networks. There were similarities between the findings in this study and those described by Drevets et al., who found increased glucose metabolism in the left amygdala at baseline in depressed patients and an elevation in neural activity was also positively correlated with depression severity [8]. Based on our present observations, depression may cause destructive functional changes in the amygdala that result in an abnormal hyperactive amygdale in depressed adolescents compared to healthy controls. Several previous studies have reported greater amygdala reactivity to negative emotion stimuli in patients with depression compared with controls [10,34]. We postulated that the abnormal interaction between the amygdala and other brain regions may possibly cause depressed adolescent patients had a abnormal responses to emotion-related cues in their daily life [13].

There exist limitations in the present study. First, several studies found dysfunction of the ACC and its related connections in the MDD. In our results, we only found prominent differences in the degree of ACC between MDD and HC, and we did not observe

any significant correlation between the symptom severity of MDD and the ACC-related connections. Different symptom profiles may result in different brain activation patterns, and different depression severity in study patients may have different results [4,9,18]. This may be the reason why we have different findings compared to previous studies. Second, the sample size used was fairly minute, which may have resulted in a non-significant correlation between the network parameters and the duration of the illness. A larger sample size is pertinent in future studies to be statistically significant in validating these results.

This paper describes a preliminary study on the dysfunctional brain networks for adolescents with MDD during the resting state. One of the more significant findings to emerge from this study was that the PFC and amygdala were dysregulated in depressed adolescents' resting networks, which may mediate the emotion processing in their daily lives. The current findings provided more evidence for our understanding of the pathophysiological mechanism of adolescent MDD.

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