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Resting-state functional connectivity in medication-naïve adolescents with major depressive disorder

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ABSTRACT

Adolescence is a vulnerable period for major depressive disorder (MDD). The aim of our study was to investigate resting-state functional connectivity (RSFC) in first-episode, medication-naïve adolescent MDD patients. Twenty-three drug-naïve adolescents diagnosed with first-episode MDD and 27 healthy participants were enrolled. Seed-to-voxel RSFC analyses were performed. The frontolimbic circuit regions of interest included the amygdala, anterior cingulate cortex, insula, and hippocampus. A correlation analysis between the RSFC and Children's Depression Inventory, Hamilton depression rating scale, and duration of episodes was performed. The adolescents with MDD exhibited the following characteristics: a lower RSFC between the right amygdala and right superior frontal gyrus; a lower RSFC between the right hippocampus and clusters including the right insula and right middle frontal gyrus; a higher RSFC between the left insula and clusters including the bilateral middle frontal gyrus, right superior frontal gyrus, and right frontal pole; and a higher RSFC between the left dorsal anterior cingulate cortex and a cluster including the left insula. Medication-naïve adolescents with depression display lower connectivity of several brain regions implicated in processing, regulation, and memory of emotions. Higher connectivity was observed in brain regions that potentially explain rumination, impaired concentration, and physiological arousal.

1. Introduction

Major depressive disorder (MDD)[1] is a common mental health disorder that has a prevalence of 4–5%. Adolescence is a vulnerable period for the development of MDD. Significant brain maturation takes place during adolescence (Ho et al., 2015) and the developing brain experiences a period of overproduction and pruning of synapses and excessive signaling (Andersen, 2003). These maturation events accompany changes in the trajectory of synaptic development, programming of neurotrophic factor levels, connectivity between brain regions, rates of myelination, and increased expression of glucocorticoid receptors. Periods of vulnerability to MDD likely occur during this developmental period (Andersen and Teicher, 2008), which might result in an increased susceptibility to depression. Therefore, investigating the neurobiological mechanisms underlying adolescent MDD is critical for elucidating the etiology of depression and for the development of effective treatment options.

The brain is considered to be a dynamic organization of functional networks of interconnected areas (Bressler, 1995). Increasingly, resting-state functional magnetic resonance imaging (RS-fMRI) is used to explore the neurobiological mechanisms that underlie MDD. RS-fMRI may also be used in clinical settings to provide diagnostic and prognostic information about neurological and psychiatric diseases (Lee et al., 2013). RS-fMRI enables researchers to investigate functional connections by focusing on spontaneous fluctuations in brain activity without using externally controlled task paradigms (Fox and Raichle, 2007). In addition to the altered functional connectivity found in several task-related fMRI studies, findings from RS-fMRI studies further support the

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[1] MDD: major depressive disorder; ACC: anterior cingulate cortex; Rs-fMRI: resting-state functional magnetic resonance imaging; RSFC: resting-state functional connectivity; HDRS: Hamilton Depression Rating scale; CDI: Children's Depression Inventory; DOE: duration of episode; ROI: region of interest; dACC: dorsal anterior cingulate cortex; sgACC: subgenual ACC; MNI: Montreal Neurological Institute; HCs: Healthy controls; FIQ: Full-scale Intelligence Quotient; SFG: superior frontal gyrus; MFG: middle frontal gyrus; BA: Brodmann's area; PFC: prefrontal cortex.

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idea that dysfunctional interactions are a core feature of depressive symptomatology.

During MDD, aberrant activity occurs in the frontolimbic circuit, which is involved in emotion processing (Mayberg, 1997). The frontolimbic circuit consists of several key regions, including the prefrontal cortex, anterior cingulate cortex (ACC), amygdala, and hippocampus (Anand et al., 2009; Seminowicz et al., 2004). In addition, the insula is extensively connected to the frontolimbic circuit and may also be a component of this circuit (Guo et al., 2015b). Studies involving adult patients with depression have demonstrated that resting-state functional alterations are mainly observed in the frontolimbic circuit (Guo et al., 2015b; Zhong et al., 2016). The frontolimbic circuit plays an important role in regulating mood and affect, and MDD is a disorder that involves frontolimbic circuit dysregulation (Zhong et al., 2016). Regions in the frontolimbic circuit located in the dorsal part of the brain, which includes the neocortical and superior limbic elements, regulate attention and cognitive features of depression, while regions located in the ventral part of the brain, composed of the limbic, paralimbic, and subcortical regions, mediate the vegetative and somatic aspects of the illness (Wang et al., 2012).

Neurobiological studies on adolescent MDD are lacking, and most studies have investigated MDD in adults. MDD in adolescents has been associated with dysregulation of frontal-limbic neural circuits including the ACC, dorsolateral, medial, and inferior prefrontal cortex, insula, the temporal cortex, and amygdala (Jin et al., 2011); Most adolescent depression studies have mainly focused on the ACC and amygdala, according to findings from adult patients (Chattopadhyay et al., 2017; Connolly et al., 2017). In one such study, Connolly et al. (2013) examined resting-state functional connectivity (RSFC) of the subgenual ACC by comparing 23 adolescents with MDD and 36 age- and sex-matched control subjects. Compared with controls, the MDD group exhibited an increased connectivity between the subgenual ACC and the insula, and between the subgenual ACC and the amygdala. The amygdala has also been shown to be a central brain region in MDD. Tang et al. (2018) performed a voxel-wise meta-analyses of abnormal amygdala RSFC data from eight studies conducted with adolescents. Adolescent patients with MDD demonstrated decreased amygdala RSFC within the cognitive control network and imbalanced amygdala RSFC within the default mode network, which manifested as hyperconnectivity in the right precuneus and hypoconnectivity in the right inferior temporal gyrus (Tang et al., 2018).

To the best of our knowledge, very few studies on adolescent depression have focused the hippocampus and insula as seed regions, despite the knowledge that the hippocampus plays a key role in emotional memory and that there is a connection between the hippocampus, the frontolimbic system, and the insula. The hippocampus has also been implicated in emotional memory bias and rumination. Although previous adolescent depression studies have studied the frontolimbic circuit, the results have been inconsistent, with some studies reporting an increase in connectivity in this circuit and other reporting a decrease, and unclear findings on whether alterations in connectivity are correlated with symptom severity. These inconsistencies may be due to the heterogeneity of clinical populations, including large variations in exposure to antidepressants and clinical stages (Zhang et al., 2014). Some previous studies have involved patients who received different medications and experienced different numbers of episodes (Peters et al., 2016; Venta et al., 2018). Therefore, it is difficult to conclude whether the observed changes in RSFC are part of the primary pathogenesis of depression (Mayberg et al., 2000).

The aim of the present study was to investigate RSFC using RS-fMRI in adolescent patients with MDD and matched healthy controls (HCs). Based on previous findings (Anand et al., 2009; Guo et al., 2015a), we focused on the core regions of the frontolimbic circuit. Given the existing evidence, we hypothesized that functional alterations in these regions would be observed even in first-episode, drug-naïve adolescent patients with MDD. We further hypothesized that the strength of the abnormal connectivity would be correlated with clinical variables such as depression severity. To exclude the confounding effect of antidepressants and different clinical status, we only included first-episode, psychotropic drug-naïve adolescents with MDD.

2. Methods

2.1. Participants and clinical measures

Patients and HCs were only included in the study if they (1) were right-handed, (2) had no current or previous psychiatric disorder (for the MDD group: no other major psychiatric illnesses, including bipolar disorder), (3) had undergone a Full-scale Intelligence Quotient (FIQ) assessment using the Korean Wechsler Intelligence Scale and obtained an IQ score of 85 or above (patients with IQ score below 85 were excluded from the study to ensure that no participants had intellectual disabilities), (4) had no family history of psychotic or personality disorders, (5) had not previously experienced head trauma that resulted in loss of consciousness, (6) had no history of alcohol or substance abuse, (7) had not undergone or were not currently undergoing electroconvulsive therapy and were not taking psychotropic medications, and (8) had no neurological or chronic medical illnesses. Demographic data (e.g., age, sex, and years of education) were collected at baseline. After obtaining informed consent from all participants, they underwent a comprehensive diagnostic assessment. The Korean version of the investigator-rated Kiddies Schedule for Affective Disorders and Schizophrenia (K-SADS) Present and Lifetime Version was used to confirm the diagnosis of MDD in the MDD group (Kim et al., 2004). The K-SADS is a semi-structured interview used to diagnose mood disorders.

Depressed patients were prospectively recruited from the Child and Adolescent Psychiatry Clinic, Korea University Guro Hospital. Patients were between the ages of 13 and 18 years and were diagnosed with first episode MDD according to the Diagnosis and Statistical Manual of mental disorder-IV-Text Revision criteria. All patients were drug-naïve at the start of the study and had no history of alcohol and tobacco consumption, substance abuse, chronic systemic disorder, or neurological disorder. Depressive symptoms were scored using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960; Yi et al., 2005). Self-report measures, including the Children's Depression Inventory (CDI) (Cho and Lee, 1990; Kovacs, 1985) and the Korean version of the State and Trait Anxiety Inventory, were used to assess symptoms (Hahn et al., 1993; Spielberger et al., 1970) in the MDD group. In the MDD group, age of onset of depressive symptoms was confirmed by self-report, and the duration of the episode (DOE) was calculated.

Healthy volunteers matched for age, sex, and education years were prospectively recruited via advertisements placed in local middle and high school newspapers and served as control subjects. All HCs underwent neurological examination and a detailed interview to ensure that they had no neurological abnormalities, no history of neurological, psychiatric, or systemic disorders, and no history of alcohol or drug abuse.

All participants provided written informed consent, and their parents/legal guardians provided written informed consents after receiving a detailed description of the study. The study was approved by the Institutional Review Board of the Korea Medical University.

2.2. Functional MRI resting-state paradigm and image data acquisition

The participants were instructed to remain motionless, relax with their eyes closed without falling asleep, and not to think of anything specific during the MRI scanning. After the scanning session, participants were asked whether they fell asleep during the scan. Magnetic resonance images were acquired using a 3.0 Tesla Siemens MR scanner (MAGNETOM Skyra, SIEMENS Healthineers, Erlangen, Germany) at the Guro Hospital of Korea Medical University. A structural scan was acquired using a T1-weighted magnetization-prepared rapid gradient-

echo (MPRAGE) sequence (repetition time: 2300 ms; echo time: 2.32 ms; inversion time: 900 ms; flip angle: 8°; field of view: 230 mm; voxel size: 0.9 mm isotropic; 192 slices; and generalized autocalibrating partially parallel acquisitions acceleration factor: two along the phase-encoding direction; received bandwidth per pixel: 200 Hz/pixel; echo spacing: 7.1 ms). The RS-fMRI scan comprised 240 contiguous echo planar imaging whole-brain volumes (repetition time: 2000 ms; echo time: 3.0 ms; flip angle: 70°; field of view: 224 mm; voxel size: 2.0 mm isotropic; multi-slice mode; interleaved; simultaneous multi-slice (SMS) factor: three; with phase encoding shift factor: two; received bandwidth per pixel: 1786 Hz/pixel; echo spacing: 0.67 ms). The MR images were visually inspected for structural abnormalities and obvious artifacts from head motion or dental materials.

2.3. Image preprocessing

The data were preprocessed and analyzed using MATLAB R2014b (MathWorks, Natick, MA, USA) and SPM12 (The Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/spm12). All functional images were slice-timing corrected and realigned to the first volume using a six-parameter rigid body transformation. The mean image generated was spatially normalized into standard stereotactic space, using the Montreal Neurological Institute (MNI) echo planar imaging (EPI) template. Computed transformation parameters were applied to all functional images, interpolated to isotropic voxels 2 mm in size, and the resulting images were smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel. Preprocessing procedures also included outlier detection using Artifact Detection Tools implemented in the CONN toolbox.

2.4. Functional connectivity analyses

Functional connectivity analyses were carried out using the CONN-fMRI Functional Connectivity toolbox v17 (Whitfield-Gabrieli and Nieto-Castanon, 2012; http://www.nitrc.org/projects/conn). Using the default preprocessing parameters, the possible confounding effects of head motion artifacts and cerebrospinal fluid and white matter blood oxygen-level dependent (BOLD) signals were defined and addressed. For denoising, signals from the white matter, cerebrospinal fluid, and motion parameters were regressed from the functional data and processed with a band-pass filter of 0.008–0.09 Hz. The band-pass filter was used to filter the signals to the range of interest to RS-fMRI and reduce noise due to physiological effects, such as respiration and pulsation, and noise due to scanner drift. Additional de-noising, including frame censoring, was applied using the image scrubbing ART method in the CONN toolbox with a frame-wise displacement threshold of 0.5, as well as linear de-trending.

Based on previous studies, the following seed regions of interest (ROIs) were selected: the amygdala (23, −5, −12; −23, −5, −12) (Anand et al., 2007), dorsal ACC (dACC) (5, 14, 42; −5, 14, 42), subgenual ACC (sgACC) (5, 25, −10; −5, 25, −10) (Zhou et al., 2016), anterior insula (36, 16, 2; −34, 14, 2), middle insula (38, 1, 6; −38, −1, 6), posterior insula (38, −10, 7; −38, −12, 7) (Taylor et al., 2009), and hippocampus (24, −18, −18; −24, −18, −18) (Tahmasian et al., 2013). The ROIs were 4 mm-radius spheres centered at the MNI coordinates that were defined using the Harvard-Oxford Subcortical Structural Probability Atlas in Functional Magnetic Resonance Imaging of the Brain Software Library.

The mean time series from each seed was used as a predictor in a multiple regression general linear model at each voxel. The toolbox created t-statistic volumes that were imported into SPM12 for whole-brain investigation of the between-group maps. An analysis of covariance controlling for IQ was performed. The threshold of voxel-wise $p < 0.001$ adjustment for multiple comparisons at the cluster level $p < 0.05$ was applied. False Discovery Rate correction was used for assessing statistical significance of the results.

2.5. Statistical analysis

SPSS version 23 was used for all statistical analyses (IBM Corp., Armonk, NY, USA). Means and standard deviations were calculated for the demographic and clinical data. The significance level for tests was established at $p \leq 0.05$. To test our hypothesis concerning an association between severity of depression and RSFC in the MDD group, we conducted a correlation analysis between the RSFC and the CDI scores, HDRS, scores, and DOE. During the analysis, clusters that showed altered RSFCs were considered to be new ROIs and were used to perform the ROI-to-ROI analysis in the MDD group. Subsequently, we generated the individual mean Z-scores of RSFCs from these ROIs using the CONN toolbox and computed Spearman's correlation coefficients between the FC and the CDI scores, HDRS scores, and DOE.

3. Results

3.1. Demographics and clinical characteristics

Of the 58 adolescents (30 patients with MDD, 28 HCs), two patients were excluded because their IQ was below 80, and two patients were excluded because their IQ was not measured. One control subject was excluded from the analysis due to structural abnormalities (i.e., focal cortical encephalomalacia). A further two patients were excluded from the analysis due to poor image quality resulting from excessive head movement (>0.5 mm) or the presence of dental materials. Another patient was excluded because his diagnosis was changed to bipolar disorder during the study period. Consequently, 50 participants were included in this study, including 23 treatment-naïve adolescents with MDD and 27 HCs.

The 23 adolescents in the MDD group all had HDRS scores that indicated that they were clinically depressed. All were treatment-naïve for pharmacotherapy and psychotherapy. There were no significant differences between the MDD and HC groups in terms of sex, age, or years of education. The MDD group scored significantly higher than the HC group on the CDI and HDRS and had significantly lower FIQ scores than HCs (Table 1).

3.2. Seed-based RSFC analyses: group comparisons

The RSFC between the right amygdala and a cluster that included the right superior frontal gyrus (SFG) was lower in the MDD group than

Table 1
Demographic comparison between patients with major depressive disorder and healthy control subjects.

	MDD (n = 23)	HC (n = 27)	P value
Gender: Male/Female	9/14	5/22	0.110
Age (years)	15.4 (1.71)	15.9 (0.99)	0.230
Years of education (years)	9.9 (1.90)	10.0 (0.83)	0.767
FIQ	100.4 (12.31)	123.4 (12.69)	< 0.01
DOE (weeks)	3.39 (2.87)	N/A	< 0.01
HDRS score	20.6 (3.70)	0.1 (0.44)	< 0.01
CDI score	27.2 (8.76)	5.4 (4.57)	< 0.01
Comorbid disorders	4		
Obsessive–Compulsive disorder	2		
Social anxiety disorder	2		
Panic disorder	1		
Generalized anxiety disorder	2		
Bulimia nervosa	1		

MDD: patients with major depressive disorder, HC: healthy controls, FIQ: Full-scale intelligence quotient, DOE: Duration of episode, HDRS: Hamilton depression rating scale, CDI: Children's Depression Inventory. Each value is presented as mean (standard deviation).

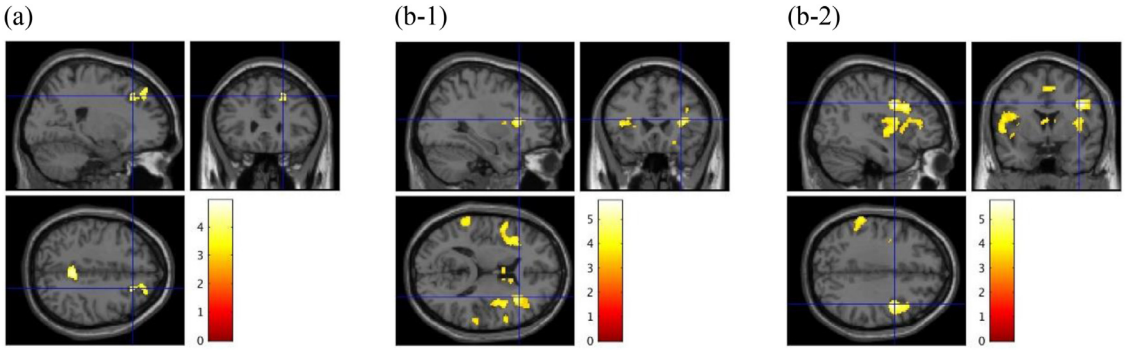

Fig. 1. Regions that showed decreased functional connectivity in the adolescent depression group. The results were obtained using a seed-based analysis method with the right amygdala (a) and right hippocampus (b-1, b-2) as seeds. The color scale indicates *t*-values. Red indicates a greater positive connectivity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Tables 2
Seed locations and regions showing between-group differences in resting state functional connectivity.

Seed	Regions	Peak (MNI) *x y z*	Number of voxels	*T* value	*p*-value (FDR-corrected)
HC > MDD					
Right amygdala	Right SFG	22, 28, 42	183	3.91	0.013
Right hippocampus	Right insula	32, 24, 14	604	5.09	0.000
	Right MFG	40, 04, 34	560	5.74	0.000
MDD > HC					
Left middle insula	Right MFG	42, 36, 22	673	5.32	0.000
	Left MFG	−34, 32, 24	665	4.87	0.000
	Left MFG	−46, 06, 32	342	5.51	0.003
	Right SFG, Right MFG	30, −02, 54	424	4.87	0.001
Left posterior insula	Right frontal pole	36, 44, 26	312	4.67	0.012
Left dorsal ACC	Left insula	−30, 16, −02	345	4.95	0.016

MDD: patients with major depressive disorder, HC: healthy controls, MNI: Montreal Neurological Institute, SFG: superior frontal gyrus, MFG: middle frontal gyrus, ACC: anterior cingulate cortex, FDR: false discovery rate.

that in the HC group. Additionally, the RSFC between the right hippocampus and a cluster that included the right insula cortex and right middle frontal gyrus (MFG) was lower in the MDD group compared to that in the HC group (Fig. 1, Table 2).

The MDD group displayed a higher left insula RSFC with a cluster that included the bilateral MFG, right SFG, and right frontal pole compared to the HC group. Furthermore, the RSFC between the left dACC and a cluster that included the left insula cortex was higher in the MDD group than that in the HC group (Fig. 2, Table 2).

3.3. Correlations between RSFC strength and clinical variables in the MDD group

No significant associations were found between the connectivity strength in regions that showed significant differences in RSFC and the scores on the depression rating scales (the CDI and HDRS) and DOE in the MDD group.

4. Discussion

This study compared RSFC in core regions of the frontolimbic circuit between a group of medication-naïve first-episode adolescent patients with MDD and a group of age- and sex-matched HCs. The main findings were that depressed adolescents had 1) a lower RSFC between the right amygdala and right SFG, 2) a lower RSFC between the right hippocampus and a cluster that included the right insula and right MFG, 3) a higher RSFC between the left insula and a cluster that included the bilateral MFG, right SFG, and right frontal pole, and 4) a higher RSFC between the left dACC and a cluster that included the left insula.

The amygdala is one component of the frontolimbic circuit that is involved in emotion generation and regulation. Increased amygdala activation in response to emotional stimuli has been associated with depression in both adults (Drevets, 2000) and adolescents (Hulvershorn et al., 2011). Previous studies that focused on the amygdala have consistently showed a decrease in amygdala-frontal connectivity in depression, which demonstrates the importance of the amygdala RSFC in adolescent depression. Treatment-naïve clinically depressed adolescents had a decreased right amygdala RSFC with left frontal cortical areas, including the ACC (Pannekoek et al., 2014). In another study, medication-naïve depressed adolescents showed a reduced RSFC between the amygdala and the dorsolateral and ventromedial prefrontal cortices (Connolly et al., 2017). The results of the present study are consistent with these previous findings. The SFG is composed of several subregions, including Brodmann areas 6, 8, 9, and 32 (Brodmann, 1909; Petrides and Pandya, 1999). The area of the SFG that showed a between-group difference in RSFC in this study corresponds to the anteromedial SFG (Brodmann area 8). The anteromedial SFG is anatomically and functionally connected to the cingulate cortex and involved in cognitive control, such as conflict monitoring, error detection, response selection, and attention control. The anteromedial SFG is part of the anterior sub-network of the default mode network (Li et al., 2013), which is involved in self-referential processing and emotion regulation through direct connectivity with the amygdala (Mulders et al., 2015). The involvement of the anteromedial SFG in the regulation of emotion, coupled with the observation of a reduced amygdala-anteromedial SFG connectivity in the present study, suggests abnormalities in the top-down cold system. The top-down cold system underlies cognitive processes that arise from frontal and prefrontal brain regions and emerge as proactive or reflective behaviors (Zhang, 2017). Taken together, these findings indicate that changes in the connectivity between the right amygdala and the right SFG may be specifically related to disruption in the network responsible for emotion

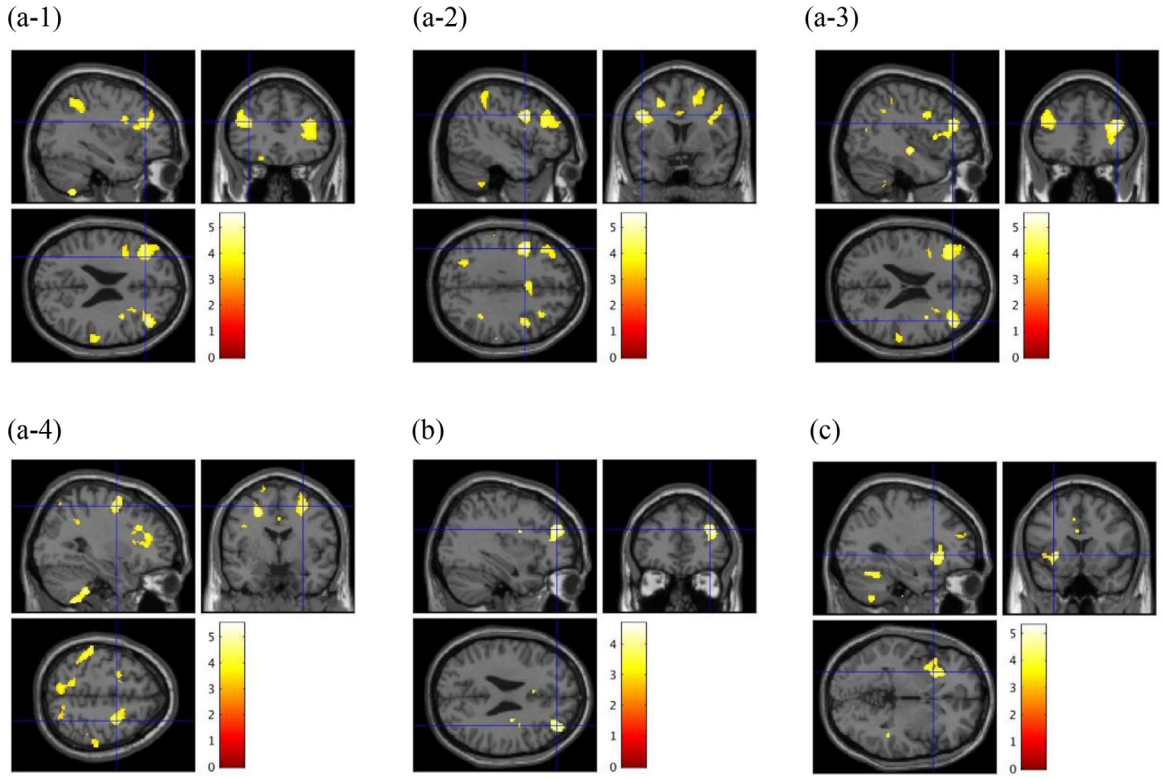

Fig. 2. Regions that showed increased functional connectivity in the adolescent depression group. The results were obtained using the seed-based analysis method with the left middle insula (a-1, a-2, a-3, a-4), left posterior insula (b), and left dorsal anterior cingulate cortex (c) as seeds. The color scale shows *t*-values. Yellow indicates a greater positive connectivity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

regulation in adolescent depression.

The hippocampus is also a key area in the limbic system, and is involved in memory formation and stress and emotion regulation (Eichenbaum, 2013). An abnormal prefrontal-hippocampus functional connectivity has reported in previous RSFC studies on adult depression (Cao et al., 2012; Tang et al., 2013). However, to the best of our knowledge, only one study focused on the hippocampus in adolescent depression; in that study, adolescent patients with MDD exhibited significantly decreased RSFC between the bilateral hippocampal and prefrontal cortex (PFC) regions (Geng et al., 2016). The insula, a key region involved in negative affective processing, has also been implicated in depression (Tao et al., 2013). Decreased RSFC between the hippocampus and insula has been reported in adult MDD (Peng et al., 2014). The right MFG is located in the dorsolateral PFC, an area primarily involved in cognition and executive function (Peng et al., 2012). Taken together, these results indicate that a lower right hippocampus-right insula/right MFG RSFC, which was also observed in the present study, may reflect an impaired cognitive control over negative emotions, ability to synthesize memories, decision making, and physiological perception observed in adolescent depression.

Adolescents with MDD exhibited an increased RSFC between the left insula and a cluster including the PFC (MFG, SFG, and frontal pole) compared to the HCs. This altered insula-PFC connectivity could potentially affect the regulation of negative or arousing stimuli, given the insula's key role in emotional regulation, conscious arousal, and awareness (Critchley et al., 2004; Pavuluri and May 2015).

The insula is modulated through its reciprocal connections with the PFC and is involved in interoceptive awareness (Klumpp et al., 2012). It is considered to be a hub of the salience network (Seeley et al., 2007) and is thought to play a role in the integration of autonomic, visceral, and hedonic information (Sliz and Hayley, 2012). This could further suggest that negative interpretations of internal states driven by exaggerated insula responsiveness and inefficient PFC regulation could lead to impaired negative emotion control during adolescent MDD. According to a recent comparative meta-analysis study of amygdala RSFC in adolescents and adults with MDD, adolescent patients have strengthened amygdala RSFC with the bilateral insula relative to adult patients. This may indicate that adolescent patients have less disruptions of the bottom-up salience process than adults (Tang et al., 2018).

We observed a significantly increased RSFC between the left dACC and a cluster involving the left insula in adolescents with MDD compared to HCs. The ACC is important for emotional and cognitive information processing. Cognitive information is processed in the dorsal/caudal ACC while emotional information is processed in the rostral/ventral ACC (Bush et al., 2000; Davis et al., 2005). The dACC subregion of the ACC not only performs a specific cognitive function but is also part of a salience network that contributes to general brain functioning and is involved in cognitive and emotional information processing (To et al., 2017). A previous study found that treatment-naïve clinically depressed adolescents exhibited a decreased RSFC between the bilateral dACC and the right MFG, frontal pole, and inferior frontal gyrus (Pannekoek et al., 2014). Considering the importance of the ACC in emotion processing, the altered RSFC between the dACC and the insula might contribute to the disruption in circuits critical for emotional information processing.

4.1. Limitations and future directions

Several limitations of this study should be noted. By using a seed-based correlation instead of a data-driven approach, possible RSFC abnormalities in other resting-state networks might have been overlooked. It should be noted that we only investigated the functional connectivity between specific key regions of the frontolimbic circuit. Future studies involving other seed regions or networks are needed to clarify the role of other regions of the frontolimbic circuit in MDD. However, our study has several strengths. Our study involved clinically

depressed, treatment-naïve adolescents, which enabled us to exclude the confounding effect of antidepressants and different clinical status. Additionally, we investigated the frontolimbic circuit, which has been implicated in affective disorders, using a seed-based approach to ensure replicability. We also investigated functional connectivity in the insula, which has not been investigated in previous studies on adolescent depression. These results support the hypothesis that abnormalities in the frontolimbic circuit may be a characteristic feature of adolescent depression.

4.2. Conclusion

As hypothesized, we found changes in the RSFC of the frontolimbic circuit in clinically depressed adolescents. Adolescents with MDD, prior to exposure to medication, displayed a decreased connectivity between several brain regions involved in emotion processing and regulation and emotional memory. An increased connectivity was observed in brain regions known to be involved in rumination, impaired concentration, and physiological arousal. Taken together, our results provide insight into functional connectivity disturbances in depressed adolescents. Future studies are needed to confirm our findings and to further investigate other changes in the RSFC in adolescents with depression.

Disclosure of conflicts of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.04.008.

References

Anand, A., Li, Y., Wang, Y., Gardner, K., Lowe, M.J., 2007. Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. J. Neuropsychiatry Clin. Neurosci. 19, 274–282.
Anand, A., Li, Y., Wang, Y., Lowe, M.J., Dzemidzic, M., 2009. Resting state corticolimbic connectivity abnormalities in unmedicated bipolar disorder and unipolar depression. Psychiatry Res. 171, 189–198.
Andersen, S.L., 2003. Trajectories of brain development: point of vulnerability or window of opportunity? Neurosci. Biobehav. Rev. 27, 3–18.
Andersen, S.L., Teicher, M.H., 2008. Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci. 31, 183–191.
Bressler, S.L., 1995. Large-scale cortical networks and cognition. Brain Res. Rev. 20, 288–304.
Brodmann, K., 1909. Vergleichende Lokalisationslehre Der großhirnrinde: in Ihren Prinzipien Dargestellt Auf Grund Des Zellenbaues. Johann Ambrosius Barth, Leipzig.
Bush, G., Luu, P., Posner, M.I., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends Cognit. Sci. 4, 215–222.
Cao, X., Liu, Z., Xu, C., Li, J., Gao, Q., Sun, N., Xu, Y., Ren, Y., Yang, C., Zhang, K., 2012. Disrupted resting-state functional connectivity of the hippocampus in medication-naive patients with major depressive disorder. J. Affect. Disord. 141, 194–203.
Chattopadhyay, S., Tait, R., Simas, T., van Nieuwenhuizen, A., Hagan, C.C., Holt, R.J., Graham, J., Sahakian, B.J., Wilkinson, P.O., Goodyer, I.M., Suckling, J., 2017. Cognitive behavioral therapy lowers elevated functional connectivity in depressed adolescents. EBioMedicine 17, 216–222.
Cho, S.C., Lee, Y.S., 1990. Development of the Korean form of the Kovacs' children's depression inventory. J. Korean Neuropsychiatr. Assoc. 29, 943–956.
Connolly, C.G., Ho, T.C., Blom, E.H., LeWinn, K.Z., Sacchet, M.D., Tymofiyeva, O., Simmons, A.N., Yang, T.T., 2017. Resting-state functional connectivity of the amygdala and longitudinal changes in depression severity in adolescent depression. J. Affect. Disord. 207, 86–94.
Connolly, C.G., Wu, J., Ho, T.C., Hoeft, F., Wolkowitz, O., Eisendrath, S., Frank, G., Hendren, R., Max, J.E., Paulus, M.P., Tapert, S.F., Banerjee, D., Simmons, A.N., Yang, T.T., 2013. Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. Biol. Psychiatry 74, 898–907.
Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7, 189–195.
Davis, K.D., Taylor, K.S., Hutchison, W.D., Dostrovsky, J.O., McAndrews, M.P., Richter, E.O., Lozano, A.M., 2005. Human anterior cingulate cortex neurons encode cognitive and emotional demands. J. Neurosci. 25, 8402–8406.
Drevets, W.C., 2000. Neuroimaging studies of mood disorders. Biol. Psychiatry 48, 813–829.
Eichenbaum, H., 2013. Hippocampus: remembering the choices. Neuron 77, 999–1001.
Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8, 700–711.
Geng, H., Wu, F., Kong, L., Tang, Y., Zhou, Q., Chang, M., Zhou, Y., Jiang, X., Li, S., Wang, F., 2016. Disrupted structural and functional connectivity in prefrontal-hippocampus circuitry in first-episode medication-naive adolescent depression. PLoS One 11, e0148345.
Guo, W., Liu, F., Liu, J., Yu, M., Zhang, Z., Liu, G., Xiao, C., Zhao, J., 2015a. Increased cerebellar-default-mode-network connectivity in drug-naive major depressive disorder at rest. Medicine 94, e560.
Guo, W., Liu, F., Xiao, C., Zhang, Z., Liu, J., Yu, M., Zhang, J., Zhao, J., 2015b. Decreased insular connectivity in drug-naive major depressive disorder at rest. J. Affect. Disord. 179, 31–37.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hahn, D.W., Lee, C.H., Tak, J., 1993. Korean standardization of Spielberger's state-trait anxiety inventory. In: Korean Psychological Association '93 Annual Meeting Collection of Dissertations 1993, pp. 505–512.
Ho, T.C., Connolly, C.G., Henje Blom, E., LeWinn, K.Z., Strigo, I.A., Paulus, M.P., Frank, G., Max, J.E., Wu, J., Chan, M., Tapert, S.F., Simmons, A.N., Yang, T.T., 2015. Emotion-dependent functional connectivity of the default mode network in adolescent depression. Biol. Psychiatry 78, 635–646.
Hulvershorn, L.A., Cullen, K., Anand, A., 2011. Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. Brain Imaging Behav. 5, 307–328.
Jin, C., Gao, C., Chen, C., Ma, S., Netra, R., Wang, Y., Zhang, M., Li, D., 2011. A preliminary study of the dysregulation of the resting networks in first-episode medication-naive adolescent depression. Neurosci. Lett. 503, 105–109.
Kim, Y.S., Cheon, K.A., Kim, B.N., Chang, S.A., Yoo, H.J., Kim, J.W., Cho, S.C., Seo, D.H., Bae, M.O., So, Y.K., Noh, J.S., Koh, Y.J., McBurnett, K., Leventhal, B., 2004. The reliability and validity of Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version- Korean version (K-SADS-PL-K). Yonsei Med. J. 45, 81–89.
Klumpp, H., Angstadt, M., Phan, K.L., 2012. Insula reactivity and connectivity to anterior cingulate cortex when processing threat in generalized social anxiety disorder. Biol. Psychol. 89, 273–276.
Kovacs, M., 1985. The Children's Depression, Inventory (CDI). Psychopharmacol. Bull. 21, 995–998.
Lee, M.H., Smyser, C.D., Shimony, J.S., 2013. Resting-state fMRI: a review of methods and clinical applications. AJNR Am. J. Neuroradiol. 34, 1866–1872.
Li, W., Qin, W., Liu, H., Fan, L., Wang, J., Jiang, T., Yu, C., 2013. Subregions of the human superior frontal gyrus and their connections. Neuroimage 78, 46–58.
Mayberg, H.S., 1997. Limbic-cortical dysregulation: a proposed model of depression. J. Neuropsychiatry Clin. Neurosci. 9, 471–481.
Mayberg, H.S., Brannan, S.K., Tekell, J.L., Silva, J.A., Mahurin, R.K., McGinnis, S., Jerabek, P.A., 2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol. Psychiatry 48, 830–843.
Mulders, P.C., van Eijndhoven, P.F., Schene, A.H., Beckmann, C.F., Tendolkar, I., 2015. Resting-state functional connectivity in major depressive disorder: a review. Neurosci. Biobehav. Rev. 56, 330–344.
Pannekoek, J.N., van der Werff, S.J., Meens, P.H., van den Bulk, B.G., Jolles, D.D., Veer, I.M., van Lang, N.D., Rombouts, S.A., van der Wee, N.J., Vermeiren, R.R., 2014. Aberrant resting-state functional connectivity in limbic and salience networks in treatment – naive clinically depressed adolescents. J. Child Psychol. Psychiatry 55, 1317–1327.
Pavuluri, M., May, A., 2015. I feel, therefore, I am: the insula and its role in human emotion, cognition and the sensory-motor system. AIMS Neurosci. 2, 18–27.
Peng, D., Shi, F., Shen, T., Peng, Z., Zhang, C., Liu, X., Qiu, M., Liu, J., Jiang, K., Fang, Y., Shen, D., 2014. Altered brain network modules induce helplessness in major depressive disorder. J. Affect. Disord. 168, 21–29.
Peng, H., Zheng, H., Li, L., Liu, J., Zhang, Y., Shan, B., Zhang, L., Yin, Y., Liu, J., Li, W., Zhou, J., Li, Z., Yang, H., Zhang, Z., 2012. High-frequency rTMS treatment increases white matter FA in the left middle frontal gyrus in young patients with treatment-resistant depression. J. Affect. Disord. 136, 249–257.
Peters, A.T., Burkhouse, K., Feldhaus, C.C., Langenecker, S.A., Jacobs, R.H., 2016. Aberrant resting-state functional connectivity in limbic and cognitive control networks relates to depressive rumination and mindfulness: a pilot study among adolescents with a history of depression. J. Affect. Disord. 200, 178–181.
Petrides, M., Pandya, D.N., 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur. J. Neurosci. 11, 1011–1036.
Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.
Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., Goldapple, K., Kennedy, S., Segal, Z., Rafi-Tari, S., 2004. Limbic-frontal circuitry in major depression: a path modeling metanalysis. Neuroimage 22, 409–418.

Sliz, D., Hayley, S., 2012. Major depressive disorder and alterations in insular cortical activity: a review of current functional magnetic imaging research. Front. Hum. Neurosci. 6, 323.
Spielberger, C.D., Gorsuch, R., Lushene, R.E., 1970. Manual for the State-Trait Anxiety Inventory. Consulting Psychologist Press, Palo Alto, California.
Tahmasian, M., Knight, D.C., Manoliu, A., Schwerthoffer, D., Scherr, M., Meng, C., Shao, J., Peters, H., Doll, A., Khazaie, H., Drzezga, A., Bauml, J., Zimmer, C., Forstl, H., Wohlschlager, A.M., Riedl, V., Sorg, C., 2013. Aberrant intrinsic connectivity of hippocampus and amygdala overlap in the fronto-insular and dorsomedial-prefrontal cortex in major depressive disorder. Front. Hum. Neurosci. 7, 639.
Tang, S., Lu, L., Zhang, L., Hu, X., Bu, X., Li, H., Hu, X., Gao, Y., Zeng, Z., Gong, Q., 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.
Tang, Y., Kong, L., Wu, F., Womer, F., Jiang, W., Cao, Y., Ren, L., Wang, J., Fan, G., Blumberg, H.P., Xu, K., Wang, F., 2013. Decreased functional connectivity between the amygdala and the left ventral prefrontal cortex in treatment-naive patients with major depressive disorder: a resting-state functional magnetic resonance imaging study. Psychol. Med. 43, 1921–1927.
Tao, H., Guo, S., Ge, T., Kendrick, K.M., Xue, Z., Liu, Z., Feng, J., 2013. Depression uncouples brain hate circuit. Mol. Psychiatry 18, 101–111.
Taylor, K.S., Seminowicz, D.A., Davis, K.D., 2009. Two systems of resting state connectivity between the insula and cingulate cortex. Hum. Brain Mapp. 30, 2731–2745.
To, W.T., De Ridder, D., Menovsky, T., Hart, J., Vanneste, S., 2017. The role of the dorsal Anterior Cingulate Cortex (dACC) in a cognitive and emotional counting Stroop task: two cases. Restor. Neurol. Neurosci. 35, 333–345.
Venta, A., Sharp, C., Patriquin, M., Salas, R., Newlin, E., Curtis, K., Baldwin, P., Fowler, C., Frueh, B.C., 2018. Amygdala-frontal connectivity predicts internalizing symptom recovery among inpatient adolescents. J. Affect. Disord. 225, 453–459.
Wang, L., Hermens, D.F., Hickie, I.B., Lagopoulos, J., 2012. A systematic review of resting-state functional-MRI studies in major depression. J. Affect. Disord. 142, 6–12.
Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2, 125–141.
Yi, J.S., Bae, S.O., Ahn, Y.M., Park, B.-B., Noh, K.S., Shin, H.-K., Woo, H.W., Lee, H.S., Han, S.I., Kim, Y.S., 2005. Validity and reliability of the Korean version of the hamilton depression rating scale (K-HDRS). J. Korean Neuropsychiatr. Assoc. 44, 456–465.
Zhang, F., 2017. Resting-state functional connectivity abnormalities in adolescent depression. EBioMedicine 17, 20–21.
Zhang, X., Zhu, X., Wang, X., Zhu, X., Zhong, M., Yi, J., Rao, H., Yao, S., 2014. First-episode medication-naïve major depressive disorder is associated with altered resting brain function in the affective network. PLoS One 9, e85241.
Zhong, X., Pu, W., Yao, S., 2016. Functional alterations of fronto-limbic circuit and default mode network systems in first-episode, drug-naive patients with major depressive disorder: a meta-analysis of resting-state fMRI data. J. Affect. Disord. 206, 280–286.
Zhou, Y., Shi, L., Cui, X., Wang, S., Luo, X., 2016. Functional connectivity of the caudal anterior cingulate cortex is decreased in autism. PLoS One 11, e0151879.