

Affective network and default mode network in depressive adolescents with disruptive behaviors

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Aim: Disruptive behaviors are thought to affect the progress of major depressive disorder (MDD) in adolescents. In resting-state functional connectivity (RSFC) studies of MDD, the affective network (limbic network) and the default mode network (DMN) have garnered a great deal of interest. We aimed to investigate RSFC in a sample of treatment-naïve adolescents with MDD and disruptive behaviors.

Methods: Twenty-two adolescents with MDD and disruptive behaviors (_{disrup-}MDD) and 20 age- and sex-matched healthy control (HC) participants underwent resting-state functional magnetic resonance imaging (fMRI). We used a seed-based correlation approach concerning two brain circuits including the affective network and the DMN, with two seed regions including the bilateral amygdala for the limbic network and the bilateral posterior cingulate cortex (PCC) for the DMN. We also observed a correlation between RSFC and severity of depressive symptoms and disruptive behaviors.

Results: The _{disrup-}MDD participants showed lower RSFC from the amygdala to the orbitofrontal cortex and parahippocampal gyrus compared to HC participants. Depression scores in _{disrup-}MDD participants were negatively correlated with RSFC from the amygdala to the right orbitofrontal cortex. The _{disrup-}MDD participants had higher PCC RSFC compared to HC participants in a cluster that included the left precentral gyrus, left insula, and left parietal lobe. Disruptive behavior scores in _{disrup-}MDD patients were positively correlated with RSFC from the PCC to the left insular cortex.

Conclusion: Depressive mood might be correlated with the affective network, and disruptive behavior might be correlated with the DMN in adolescent depression.

Keywords: resting-state functional connectivity, major depressive disorder, disruptive behaviors, limbic network, default mode network

Introduction

Major depressive disorder and disruptive behavior in adolescence

Major depressive disorder (MDD) is a common psychiatric disorder in adolescence, with a prevalence rate higher than 4%.¹ Compared to classical depressive features, including low self-esteem, excessive guilt, suicidal behaviors or thoughts, sleep and appetite disturbance, and agitation in adults, adolescent depression tends to be more complex, presenting with comorbidities (anxiety disorder, alcohol and substance use, conduct disorder, or oppositional defiant disorder [ODD]).² Among various comorbidities, ODD might be one of the strongest comorbid conditions that affects the progress of adolescent depressive symptoms.² Moreover, it has been suggested that the irritable sub-component of ODD shares a genetic association with major depression and increases the risk of depression.³ The clinical symptoms of ODD or conduct disorder have also been frequently observed in adolescents with attention-deficit hyperactivity

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disorder (ADHD). Therefore, many clinicians are interested in differentiating MDD from ADHD when they observe disruptive behaviors and irritability in adolescents.⁴

It has been suggested that adolescents with MDD and disruptive behavior differ from those with MDD and no disruptive behavior symptoms. Children with MDD comorbid with conduct disorders were more frequently comorbid with substance use disorder and showed greater irritability and worse outcomes.⁵ The difference in severity of emotional symptoms related to depression between adolescents with MDD comorbid with and without conduct disorder remain controversial. Ezpeleta et al⁵ reported the accentuation of emotional symptoms and functional impairment in the comorbid condition. In contrast, Simic and Fombonne⁶ reported fewer emotional symptoms in the comorbid condition.

Resting-state functional connectivity for depression and disruptive behaviors

Neuroimaging techniques representing brain circuit-human behavior relationships can provide potential biological markers of mental disorders.⁷ Of existing neuroimaging techniques, resting-state functional connectivity (RSFC) indicates information about intrinsic connectivity within brain networks without the need for specific challenges or task stimulations.⁸ Moreover, because it enables a focus on brain regions of interest (ROI), including the amygdala, striatum, prefrontal cortex, and insula, which have been demonstrated to be candidate regions in previous studies with other modalities,^{9,10} RSFC studies provide an understanding of the pathophysiologic brain processing associated with behaviorally and emotionally labile adolescents.¹¹

In RSFC studies of MDD, the affective network (limbic network) and the default mode network (DMN) have garnered a great deal of interest. The affective network includes the amygdala, orbitofrontal cortex (OFC), temporal cortex, pallidum, and insular cortex.¹² The role of the affective network is emotion regulation and processing.¹² In resting-state functional magnetic resonance imaging (fMRI) analysis of the amygdala seed, several studies have reported abnormalities within the affective network in patients with MDD.^{11,13,14} Luking et al¹³ have reported that RSFC from the amygdala to prefrontal regions and from the amygdala to the striatum in adolescents with MDD is decreased compared to that in healthy control (HC) participants. Pannekoek et al¹⁴ have reported that RSFC from the right amygdala to the left anterior cingulate cortex in adolescents with MDD is decreased compared to that in HC participants. Still, few studies on RSFC

in the affective network have been conducted in patients with conduct or ODD. The majority of functional neuroimaging studies in conduct disorder patients have involved event-related fMRI using emotion processing tasks.¹⁵ Bebko et al¹¹ have found that RSFC from the amygdala to the insula is negatively correlated with depressive symptoms and behavioral dysregulation symptom scores in adolescents with behavioral and emotional dysregulation.

The DMN includes the posterior cingulate cortex (PCC), precuneus, medial frontal cortex, ventral anterior cingulate cortex, and lateral and inferior parietal cortices.⁸ Interestingly, because the DMN is activated at rest and not during task stimulation, it is posited to be related to self-referential processing.¹⁶ Among components of the DMN, the PCC was the most consistently selected region in resting-state fMRI. The PCC is thought to be associated with the monitoring of internal and external environments.⁸ In a review of the DMN and patients with MDD, Nejad et al¹⁷ suggest that self-referential processing in patients with MDD is associated with increased RSFC in the DMN. In a study conducted in adolescents who had comorbid conduct disorder and substance use disorder,¹⁸ reduced activity was shown in several DMN regions thought to play a role in introspective processing and future thought.

The aim of this study

Based on previous studies, we sought to investigate RSFC in a sample of treatment-naïve adolescents with MDD and disruptive behaviors. We used a seed-based correlation approach concerning two brain circuits including the affective network and the DMN. In addition, we observed the correlation between RSFC and severity of depressive symptoms and disruptive behaviors.

Methods

Participants

A total of 35 adolescents with MDD and disruptive behaviors (_{disrup}-MDD) who visited the Department of Psychiatry at Chung-Ang University Hospital were screened. All patients were experiencing their first episode of depression and had no history of psychiatric treatment or medication. Inclusion criteria for _{disrup}-MDD were as follows: 1) right-handed adolescents aged 13–18 years; 2) demonstrating at least one disruptive behavior (consistent defiance of authoritative figures, inability to take responsibility for bad behavior, regular temper tantrums, vengeful behavior and resentment, aggressiveness toward people or animals, destroying property, stealing and lying, bullying, and constant rule breaking), in addition to meeting diagnostic criteria for MDD

according to the Diagnostic and Statistical Manual of Mental Disorders, text revision (DSM-IV-TR); and 3) a full-scale intelligence score (IQ) >80. Exclusion criteria for ^{disrup-}MDD were as follows: 1) primary DSM-IV-TR clinical diagnosis of another disorder, including ADHD, bipolar disorder, Tourette's syndrome, developmental disorder, anxiety disorder, or psychotic disorder; 2) general magnetic resonance imaging (MRI) contraindications including claustrophobia and previous metal insertion; and 3) substance abuse. HC participants had similar inclusion and exclusion criteria except for MDD and disruptive behavior conditions. This study was approved by the Chung-Ang University Hospital Institutional Review Board. Written, informed consent and assent were provided by adolescents and their parents.

Measures

Both patients and HC participants were screened using the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version-Korean version (K-SADS-PL-K).¹⁹ Depressive symptoms, disruptive behaviors, clinical symptoms of ADHD, and anxiety were assessed with the Children's Depression Inventory (CDI),²⁰ the Rating Scale for Disruptive Behavior Disorder (DBDS),²¹ the Korean ADHD Rating Scale (K-ARS),²² and the Beck Anxiety Inventory,²³ respectively. Additionally, all adolescents were tested with the Korean version of the Wechsler Intelligence Scales for Children.²⁴ After screening and IQ assessment, a licensed child and adolescent psychiatrist confirmed diagnosis. Of the 35 patients screened, 13 adolescents were ruled out due to a diagnosis of ADHD (n=6), bipolar disorder (n=3), anxiety disorder (n=2), low IQ (n=1), or autism spectrum disorder (n=1). A final total of 22 adolescents with MDD and disruptive behaviors and 20 age- and sex-matched HC participants were included in data analyses.

Procedure

Brain imaging data analysis

We collected resting-state functional MRI (fMRI) data using a 3.0 Tesla TX MRI scanner (Philips, Eindhoven, the Netherlands). All images (230 volumes per participant) over 720 seconds were acquired with the following parameters: axially with an echo-planar imaging sequence, TR/TE=3,000/40 ms, 40 slices, 64×64 matrix, 90° flip angle, 230 mm field of view, and 3 mm section thickness without a gap. Data processing was carried out using the Data Processing Assistant for Resting-State fMRI (DPARSFA, <http://www.restfmri.net>) in Statistical Parameter Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) and the Resting-State fMRI Data

Analysis toolkit (REST, <http://resting-fmri.sourceforge.net>). The first ten volumes from each run were discarded due to signal equilibration. As the preprocessing steps, images were corrected for slice acquisition delay between slices and were realigned to the first image in order to correct head movement. All images were spatially normalized to the standard Montreal Neurological Institute (MNI) space, spatially smoothed with a 4 mm FWHM 3D Gaussian kernel to reduce spatial noise, and linearly de-trended and temporally filtered with a bandwidth of 0.01–0.08 Hz to reduce the effects of low-frequency drift and high-frequency noise, respectively. Finally, the first eigenvector of the time series in the white matter mask and the first eigenvector of the times series in the cerebrospinal fluid mask were removed using linear regression in order to reduce physiological and other sources of noise and head motion-related covariates.

In both participant groups, RSFC was calculated from blood-oxygenation level-dependent signal using a seed-based approach. The mean time series of an ROI was extracted by Wake Forest University PickAtlas software, version 2.4 (<http://fmri.wfubmc.edu/software/PickAtlas>; Wake Forest University School of Medicine Location, Winston-Salem, NC, USA),^{25,26} and ROIs were predefined by automated anatomical labeling equipped with PickAtlas. Based on previous studies,^{7,11} bilateral amygdala and posterior cingulate cortices were selected as seed ROIs representing the affective limbic network and DMN, respectively. Two functional connectivity maps were generated by calculating Pearson's correlation coefficients of the average time-course signal of each seed ROI to every other voxel. The resultant connectivity maps were converted to normally distributed z-scores using Fisher's z-transform.

Statistical analysis

Demographic and clinical characteristics were analyzed using chi-square tests and Mann–Whitney *U*-tests with significance set at $P < 0.05$. Based on previous studies,^{7,11} two seed regions including the bilateral amygdala (for the affective network) and the bilateral PCC (for the DMN) were selected. In the first-level analysis of the comparisons between ^{disrup-}MDD and control groups, seed-based FC analyses were performed using a two-sample *t*-test. In the second analysis, correlations between CDI scales (DBDS scales) and RSFC from the amygdala to the OFC and from the PCC to the insula were analyzed using regression. For multiple comparisons with >40 contiguous voxels in the cluster analysis, the resulting maps were set to a threshold of $P < 0.05$ for family-wise corrected type I error rate using Monte Carlo simulation (derived from an uncorrected $P < 0.001$ and 40 extended voxels).

Results

Demographic characteristics

There were no significant differences in sex, age, years of education, IQ, or Beck Anxiety Inventory score between disrup-MDD and HC (Table 1). However, the mean CDI score (MDD: mean \pm standard deviation, 39.5 ± 14.7 vs HC: 15.3 ± 8.1), DBDS score (MDD: 22.9 ± 11.5 vs HC: 5.1 ± 3.6), and K-ARS score (MDD: 11.3 ± 4.0 vs HC: 7.5 ± 3.8) in the disrup-MDD group were higher than those in the controls. There was significant correlation between DBDS score and CDI score ($r=0.44$, $P=0.04$) and K-ARS score ($r=0.49$, $P=0.02$) in the disrup-MDD group. However, there was no significant correlation between DBDS score and other clinical measurements in the disrup-MDD group.

RSFC analysis

Affective network

With respect to between-group analyses for the limbic network at baseline, the disrup-MDD participants showed lower amygdala RSFC compared to HC participants in a cluster that included the right subcallosal and right parahippocampal gyrus (Figure 1; Table 2). CDI score in disrup-MDD patients was negatively correlated with RSFC from the amygdala to the right OFC (101 voxels; Pearson $r=-0.63$, $P<0.001$). There was no significant association between CDI score in disrup-MDD patients and RSFC from the PCC to other brain regions.

Default mode network

With respect to between-group analyses for the DMN at baseline, the disrup-MDD participants showed higher PCC RSFC compared to HC participants in a cluster that included the left precentral gyrus (white matter), left insula (Brodmann's area [BA] 13), and left parietal lobe (white matter)

(Figure 2; Table 3). DBDS score in disrup-MDD patients was positively correlated with RSFC from the PCC to the left insular cortex (91 voxels; Pearson $r=0.71$, $P<0.001$). There was no significant association between DBDS score in disrup-MDD patients and RSFC from the PCC to other brain regions.

Discussion

The current study found that disrup-MDD participants show different RSFC in the affective network and DMN compared to HC participants. The disrup-MDD participants showed lower RSFC from the amygdala to the OFC and parahippocampal gyrus. Depression scores in disrup-MDD participants were negatively correlated with RSFC from the amygdala to the right OFC. The disrup-MDD participants also had higher PCC RSFC compared to HC participants in a cluster that included the left precentral gyrus, left insula, and left parietal lobe. Disruptive behavior score in disrup-MDD patients was positively correlated with RSFC from the PCC to the left insular cortex.

RSFC from the amygdala to the OFC and parahippocampal gyrus

Our current results are consistent with other RSFC studies showing lower RSFC in the affective network from the amygdala to the OFC and parahippocampal gyrus in adolescents with MDD.^{27–29} Lower RSFC between the amygdala and the OFC has also been reported in previous imaging studies, suggesting an inhibitory effect of the OFC.^{27,28} As part of the prefrontal cortex, the OFC is known to regulate negative emotion.³⁰ Disconnect between the amygdala and OFC might lead to a disruption of the OFC's ability to regulate emotion, especially negative emotions.^{27,28,30} Cullen et al²⁹ reported that adolescents with MDD show lower RSFC from the amygdala to the hippocampus, parahippocampus, and brain stem. This RSFC is negatively correlated with depression and dysphoric score. The amygdala is thought to be richly connected with the parahippocampal gyrus.^{31,32} Enhanced connectivity between the amygdala and hippocampus and parahippocampal gyrus might facilitate memory modulation.³³ The disconnect between the amygdala and parahippocampal gyrus might also be associated with depression, dysphoria, and lassitude.^{29,33} In contrast to RSFC, patients with MDD have also shown increased connectivity from the amygdala to the OFC in event-related fMRI studies involving memory of sad stimuli compared to that in HCs.³⁴ Taken together, these results indicate that the affective network in patients with MDD is underconnected during rest. However, compensatory processes to offset the hyperactivity

Table 1 Demographic characteristics of the study participants

Characteristics	disrup-MDD (n=22)	HC (n=20)	Statistics
Sex (male/female)	14/8	14/6	$\chi^2=0.19$, $P=0.66$
Age (years)	$13.9 \pm 1.6^*$	14.5 ± 1.7	$z=1.16$, $P=0.22$
Years of education	6.0 ± 1.6	6.6 ± 1.7	$z=1.16$, $P=0.21$
IQ	96.2 ± 9.6	100.8 ± 9.4	$z=1.50$, $P=0.13$
CDI	40.0 ± 7.3	10.0 ± 5.1	$z=5.46$, $P<0.01$
DBDS	22.9 ± 11.4	5.1 ± 3.6	$z=4.98$, $P<0.01$
K-ARS	11.3 ± 4.0	7.5 ± 3.8	$z=3.15$, $P<0.01$
BAI	8.0 ± 4.1	4.3 ± 3.1	$z=1.01$, $P=0.30$

Notes: *Mean \pm standard deviation. $P<0.05$, statistically significant.

Abbreviations: disrup-MDD , adolescents with major depressive disorder and disruptive behaviors; HC, healthy controls; IQ, intelligence quotient; CDI, Children's Depression Inventory; DBDS, Rating Scale for Disruptive Behavior Disorder; K-ARS, Korean ADHD Rating Scale; BAI, Beck Anxiety Inventory.

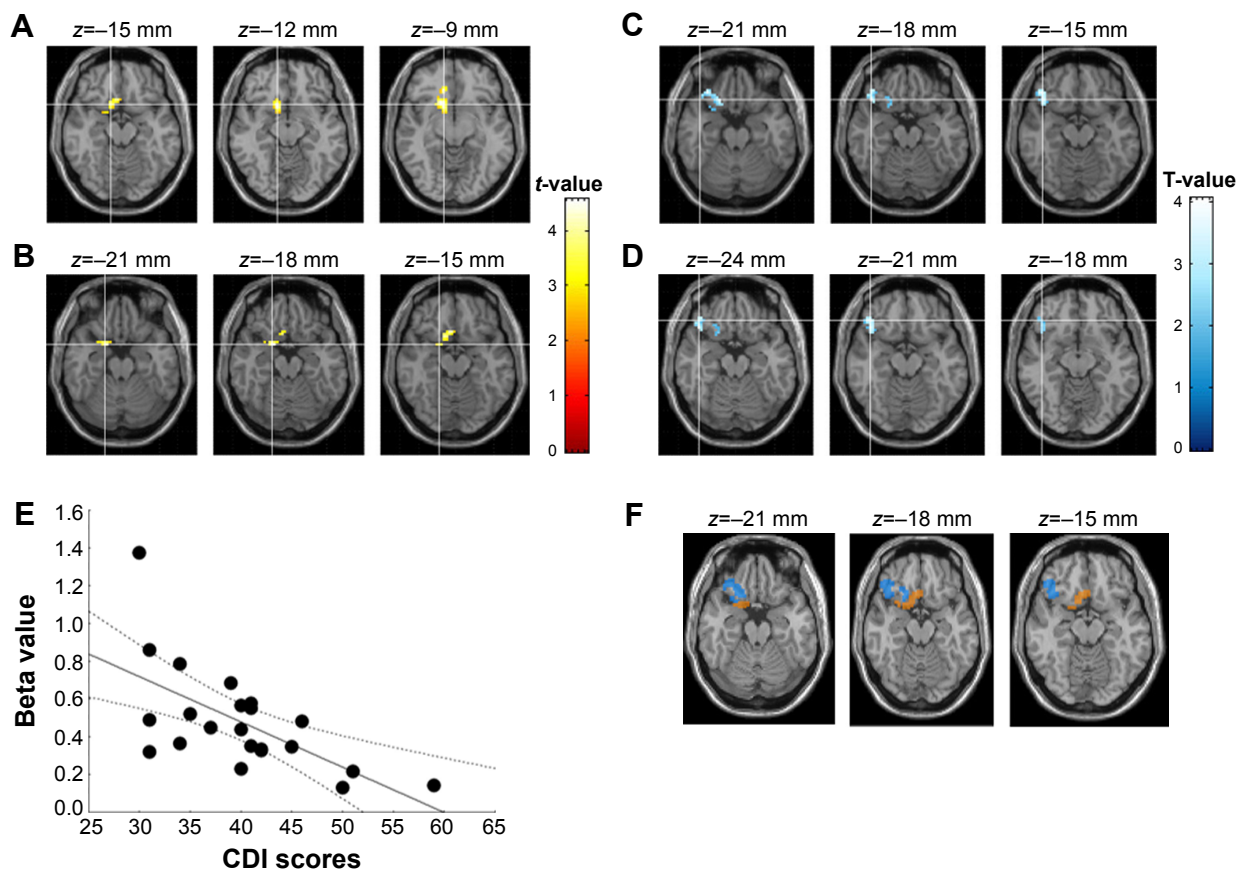


Figure 1 Affective network in depressive adolescents with disruptive behaviors.

Notes: (A) Lower functional connectivity from the amygdala to the subcallosal area in healthy control participants compared to depressive adolescents with disruptive behaviors (yellow). (B) Lower functional connectivity from the amygdala to the parahippocampal gyrus in healthy control participants compared to depressive adolescents with disruptive behaviors (yellow). (C and D) Amygdala-orbitofrontal cortex connectivity associated with Children Depression Inventory (CDI) score (blue). (E) Correlation between CDI score and beta value extracted from the amygdala-orbitofrontal cortex. (F) Overlap between figures A+B and C+D.

of the amygdala might also be triggered by the stimulation of negative emotional memories.³⁵

RSFC from the PCC to the left precentral gyrus, insula, and parietal lobe

Our current results show higher RSFC of the DMN from the PCC to the left precentral gyrus, left insula, and left

parietal lobe in ^{disrup-}MDD participants compared to HC participants. Increased RSFC in the DMN in patients with MDD has been reported in previous RSFC studies.^{17,36,37} Sheline et al³⁶ reported that patients with MDD exhibit increased RSFC from the bilateral dorsomedial prefrontal cortex to the anterior and posterior cingulate cortices and to the precuneus regions. Zhou et al³⁷ reported that patients with

Table 2 Limbic network resting-state connectivity

Regions	BA	k*	Talairach coordinates			T**	P _{uncorrected} ***
			x	y	z		
Amygdala seed connectivity							
(disrup- ^{MDD} < HC)							
Right subcallosal gyrus	47	99	15	15	-12	4.38	<0.001
Right parahippocampal gyrus	34	41	21	6	-18	4.56	<0.001
CDI scores associated with amygdala							
RSFC in ^{disrup-} MDD patients							
Right inferior frontal gyrus	47	101	45	33	-18	4.04	<0.001
Right inferior frontal gyrus			35	33	-21		

Notes: *k, cluster size in voxels. **T, t-test statistical value. ***P_{uncorrected}, uncorrected voxel-wise probability value. P<0.001, statistically significant.

Abbreviations: WM, white matter; BA, Brodmann's area; ^{disrup-}MDD, patients with major depression and disruptive behavior; HC, healthy controls; CDI, Kovacs' Children Depression Inventory; RSFC, resting-state functional connectivity.

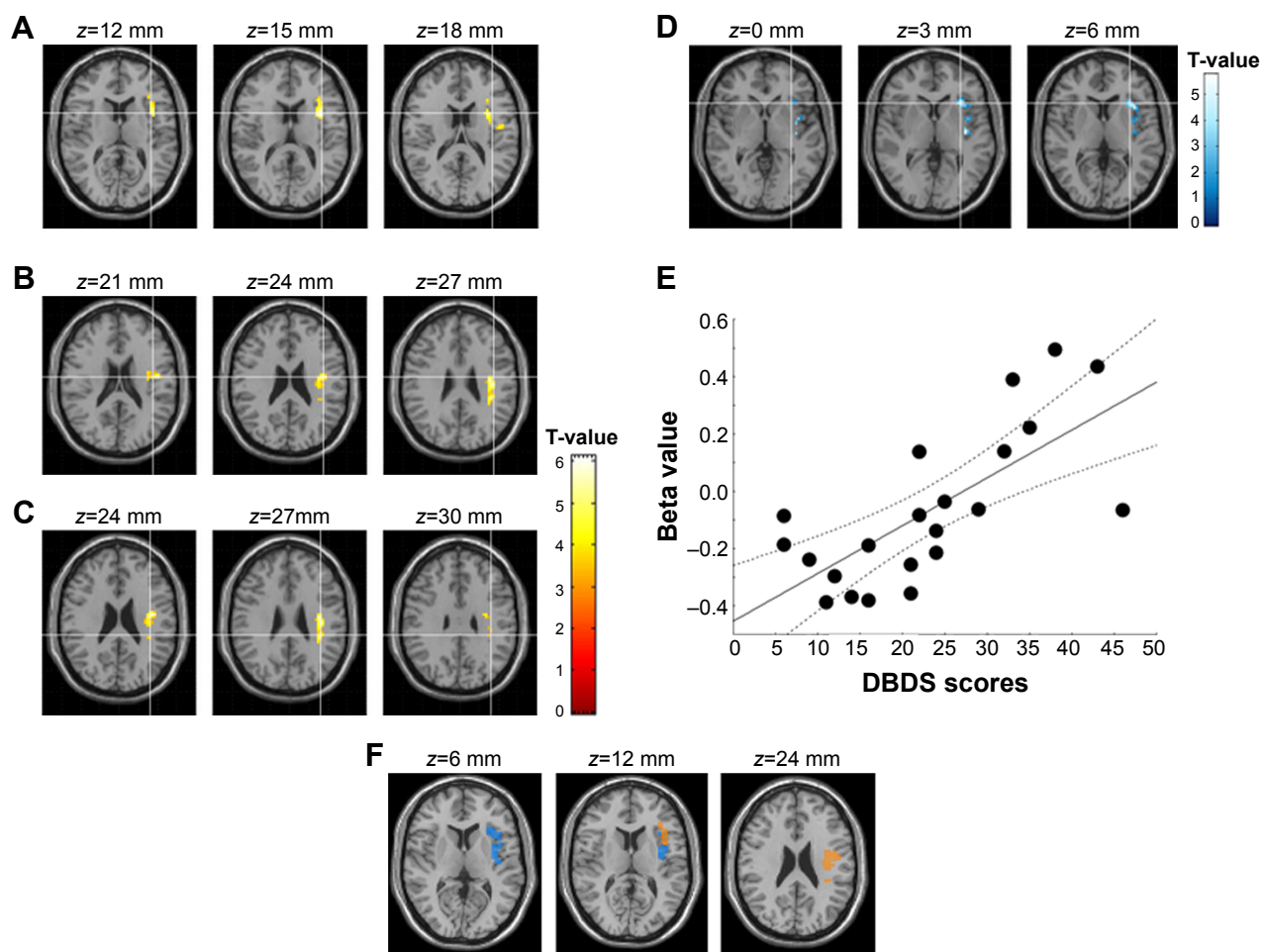


Figure 2 Default mode network in depressive adolescents with disruptive behaviors.

Notes: (A) Higher functional connectivity from the posterior cingulate cortex (PCC) to the insula in healthy control participants compared to depressive adolescents with disruptive behaviors (yellow). (B) Higher functional connectivity from the PCC to the left precentral gyrus in healthy control participants compared to depressive adolescents with disruptive behaviors (yellow). (C) Higher functional connectivity from the PCC to the left inferior parietal lobe in healthy control participants compared to depressive adolescents with disruptive behaviors (yellow). (D) PCC-insular cortex connectivity associated with Rating Scale for Disruptive Behavior Disorder (DBDS) scores (blue). (E) Correlation between DBDS score and beta value extracted from the amygdala-orbitofrontal cortex. (F) Overlap between figures A+B+C and D.

MDD show higher RSFC from the prefrontal cortex to the inferior parietal lobe compared to HCs. Hyperactivity of the DMN is associated with rumination in patients with MDD.³⁸ Rumination and negative emotion affect and magnify each

other in impulsive people and lead to impulsive behaviors in patients with MDD.³⁹ Barrocas et al⁴⁰ reported that female sex with higher rumination and severity of depression might predict non-suicidal self-injury, based on a study of 617

Table 3 Default mode network resting-state connectivity

Regions	BA	k*	Talairach coordinates			T**	P _{uncorrected} ***
			x	y	z		
Default mode network – PCC seed connectivity (disrup- MDD < HC)							
Left insula	13	124	−35	9	15	5.58	<0.001
Left precentral gyrus	WM	95	−39	−9	24	4.33	<0.001
Left inferior parietal lobe	WM	121	−35	−33	27	5.01	<0.001
DBDS scores associated with PCC RSFC in disrup- MDD patients							
Left insula	13	91	−33	12	18	4.06	<0.001

Notes: *k, cluster size in voxels. **T, t-test statistical value. ***P_{uncorrected}, uncorrected voxel-wise probability value. P<0.001, statistically significant.

Abbreviations: WM, white matter; BA, Brodmann's area; disrup- MDD, patients with major depression and disruptive behavior; HC, healthy controls; DBDS, Rating Scale for Disruptive Behavior Disorder; PCC, posterior cingulate cortex; RSFC, resting-state functional connectivity.

Chinese students. Moreover, in the present study, the score of disruptive behaviors in ^{disrup-}MDD patients was positively correlated with RSFC from the PCC to the left insular cortex. The insula is thought to have a crucial role in filtering information to promote behavior choice with early evaluation of sensory and affective stimuli, as well as in perceiving the body's physiologic response.^{41,42} Meanwhile, PCC-insula connections are part of both the salience network (cingulate and orbital fronto-insular cortices) and the DMN.⁴³ We cautiously speculate that the DMN might be partially connected with the salience network in ^{disrup-}MDD patients. Salience network refers to the brain system that plays an important role in identification of relevant stimuli to promote flexible behaviors.⁴⁴ It has been suggested that the salience network controls the down-regulation of the DMN and the upregulation of attention networks.⁴⁵ To date, few studies have investigated the salience network in disruptive behaviors. However, it has been suggested that the key neurobiology of ADHD, which is frequently accompanied by disruptive behaviors, is dysfunction in the salience network that controls the balance between the DMN and attention networks.^{44,45}

Limitations

There were several limitations in the current study. First, the small number of participants might not be sufficient to generalize the results to a larger population and controlling multiple comparisons during analyzing brain data. In addition, we used ROIs of the bilateral amygdala and PCC, while prior work has used ipsilateral and amygdala subregions to show a dissociable functional network.²⁹ Finally, the clinical consistency of ^{disrup-}MDD patients was not fully confirmed because, in the literature, 12.5%–30% of patients diagnosed with MDD also report later progression to bipolar disorder.⁴⁶ Future studies should include a larger number of participants with a longer observation period and vary across amygdala regions.

Conclusion

Adolescents with MDD and disruptive behaviors showed lower RSFC from the amygdala to the OFC and the parahippocampal gyrus and higher PCC RSFC compared with HC participants in a cluster that included the left precentral gyrus, left insula, and left parietal lobe. Depressive mood might be correlated with the affective network, and disruptive behavior might be correlated with the DMN.

Acknowledgments

This study was funded by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare,

Republic of Korea (A120013); a grant from Student Mental Health Research Center Project through Korea Brain Research Institute supported by the Ministry of Science, ICT & Future Planning (2231-415, KBRI-20130007); and a grant from the Korea Creative Content Agency (R2014040055).

Disclosure

The authors report no conflicts of interest in this work.

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