

Neural correlates of negative emotion processing in subthreshold depression

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Abstract

Subthreshold depression (SD) is regarded as a major risk factor for major depression. However, little is known about the neural mechanism of negative emotion processing in SD. The study aimed to examine the different neural correlates for negative emotion processing in SD and health controls (HCs) and to investigate changes in functional connectivity in SD compared with HC. Blood oxygenation level-dependent (BOLD) responses of SD and HC were captured while performing a passive viewing task, which comprised a negative condition and a masked condition. A total of 42 SD and 32 HC adolescents participated in the study. Between-group comparisons revealed significant reduced activations in the superior frontal gyrus (SFG), middle frontal gyrus and middle cingulate gyrus. Region of interest (ROI) analyses did not find correlations between contrast values of the ROIs and depressive symptoms. In addition, we found a significant increased functional connectivity between the SFG and caudate, pallidum and insula, which was significantly correlated with depressive symptoms in the SD group ($P < 0.05$). Altered functional connectivity between the SFG and caudate, pallidum and insula may underlie the pathology of SD. This is the first study to investigate neural mechanisms of negative emotion processing in SD using task-based functional magnetic resonance imaging.

Key words: subthreshold depression; adolescence; fMRI; negative emotion

Introduction

Subthreshold depression (SD) refers to clinically relevant depressive symptoms that do not meet the criteria for major depressive disorder (Rodríguez *et al.*, 2012). According to two review studies by Kroenke and Rodríguez, SD is a mild form of major depression, which requires the presence of two to four criterion symptoms of depression for 2 weeks or longer (Kroenke, 2006). In contrast, major depression requires the presence of at least five of nine criterion symptoms of depression for 2 weeks or longer. Both SD and major depression require the presence of at least one of the core symptoms (depressed mood or anhedonia). Even though individuals with SD have fewer depressive symptoms than major depression, individuals with SD frequently report functional impairment and deteriorated quality of life (Da Silva Lima and de Almeida Fleck, 2007; MacQueen *et al.*, 2017). People with SD constitute a high-risk group because they have been associated with an increased risk of developing major depression and other adverse outcomes (Cuijpers and Smit, 2004; Tuithof *et al.*, 2018). Driven by variable changes and increasing stress associated with puberty, adolescence may represent a unique ‘window of vulnerability’ (Eiland and Romeo, 2013). As a common emotional condition, SD

has a high lifetime prevalence ranging between 20% and 30% in adolescence (Klein *et al.*, 2009; Rohde *et al.*, 2009). Previous studies reported that SD affected 32% and 23%–39% of university students in China and Europe, respectively (Mikolajczyk *et al.*, 2008; Jiang *et al.*, 2019). Despite a high incidence of SD in adolescents, the neural mechanism underlying SD remains largely unknown.

In recent five years, there has been an increased number of neuroimaging studies on SD. For instance, two studies found a significant decrease in functional connectivity in the cognitive control network (CCN) in SD compared with health control (HC; Hwang *et al.*, 2015; Schultz *et al.*, 2019). The CCN is composed of multiple frontal and parietal regions, namely the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and posterior parietal cortex (Kroenke, 2006). The CCN controls and coordinates multiple domains of cognitive control function, which includes attention, working-memory and executive function (Niendam *et al.*, 2012). Another two studies found increased functional connectivity between the default mode network (DMN) and habenula in SD individuals compared with HCs (Ely *et al.*, 2016; Zhu *et al.*, 2019). The DMN is composed of bilateral cortical regions in the medial and lateral parietal, medial prefrontal, and

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medial and lateral temporal cortices (Niendam *et al.*, 2012). The DMN is associated with a relaxed mental state and spontaneous cognition (Niendam *et al.*, 2012). More recently, Peng and colleagues found impaired functional connectivity of left amygdala in SD, which was correlated with the severity of depressive symptoms (Peng *et al.*, 2020). The amygdala is a hub region that is responsible for a wide range of functions, including emotion perception and regulation, memory, reward processing and decision-making (Pourtois *et al.*, 2013; Bickart *et al.*, 2014). In addition, Li and colleagues reported altered local activity and functional connectivity of the ACC in elderly individuals with SD (Li *et al.*, 2014). Only a few task-based neuroimaging studies investigated SD. Compared with healthy subjects, SD adolescents showed reduced activation in the ventral striatum when they performed a monetary incentive task, and the low ventral striatum activation predicted transition to subthreshold or clinical depression in previously healthy adolescents at 2 years of follow-up (Stringaris *et al.*, 2015). In summary, the neural mechanism underlying SD involves CCN, DMN and amygdala.

Changes in above-mentioned functional networks have been indicated in the pathophysiological mechanisms of major depression. These changes are thought to cause the core cognitive and emotional dysfunction in patients with major depression, leading to self-referential thinking, autobiographical memory retrieval, emotional interpretation bias and abnormal cognitive control (Hamilton *et al.*, 2012; Kaiser *et al.*, 2015). For instance, accumulated evidence has suggested that processing bias of negative information is one of the core characteristics of major depression (Gollan *et al.*, 2008; Roiser *et al.*, 2012). Impaired cognitive control and inhibition of negative emotion were observed in depression patients, which was reflected in reduced activation of DLPFC and dorsal anterior cingulate gyrus (Galynker *et al.*, 1998; Fales *et al.*, 2008; Respingo *et al.*, 2020). In contrast, depressed patients also demonstrated bias to negative stimuli, which was reflected in the activation of the limbic system, such as the ventral prefrontal cortex, amygdala, insula and hippocampus (Disner *et al.*, 2011; Palmer *et al.*, 2014). The interaction between the two above-mentioned aspects eventually forms the negative processing bias of depression. Based on the meta-analysis of 24 functional neuroimaging studies, Hamilton and colleagues proposed a two-step model of enhanced processing of negative information in depression, that is, high baseline activity in pulvinar and low striatal dopamine levels (Hamilton *et al.*, 2012).

The aim of this study was to examine the neural mechanism of negative emotion processing in adolescents with SD using functional magnetic resonance imaging (fMRI) data. We constructed an experimental paradigm of passive viewing task, with negative emotion stimuli selected from the International Affective Picture System (IAPS) (Lang Bradley and Cuthbert, 2008). The IAPS was considered as the gold standard of emotionally charged visual complex images that can be characterized by the approach-avoidance dimension as well as the discrete-category dimension (Mauss and Robinson, 2009). Specifically, we investigate the differences in neural correlates of negative emotion processing between SD participants and HCs. It was hypothesized that there were reduced activations at the DLPFC, cingulate gyrus and limbic regions in the SD group compared with the HC group. We further investigate changes in functional connectivity by using a generalized psychophysiological interaction (PPI) approach. We expected increased functional connectivity in the CCN and emotional network in the SD group compared with the HC group.

Materials and methods

Participants

Participants aged between 18 and 26 years were recruited by advertisements at Jinan University, Guangzhou, China. Participants were screened through three stages. First, all participants completed two online surveys of the Centre for Epidemiologic Studies Depression Scale (CES-D) and the Beck Depression Inventory-II (BDI-II) (Beck *et al.*, 1996; Jiang *et al.*, 2019). Second, the online survey of CES-D and BDI-II were performed again after 2 weeks. The participants scoring 16 or more points on the CES-D and 14 or more points on the BDI-II at two time points were considered as having SD. In contrast, the participants scoring <16 points on the CES-D and <14 points on the BDI-II at both assessments were considered as HC. Finally, the potential participant was invited to participate an individual face-to-face interview using the 24-item Hamilton Depression Rating Scale (HAMD-24) to confirm their eligibility ($8 \leq \text{HAMD-24} \leq 20$ for SD group and $\text{HAMD-24} < 8$ for HC group). The combination of three scales to determine the inclusion criteria of SD has been used in our previous study and other studies (Jiang *et al.*, 2020, 2021). All participants were right-handed and had normal or corrected-to-normal vision. Participants were excluded from the study if they (i) had severe suicidal tendencies; (ii) had a diagnosis of major depression, schizophrenia, bipolar disorder or other mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5); (iii) had heart, liver, kidney, respiratory, internal analysis, nervous and blood system and other serious diseases and (iv) received any form of interventions for depression within the past year. The study was approved by the ethics committee of the First Affiliated Hospital of Jinan University (reference 2019/028). Written informed consents were obtained from all participants and they were paid for their involvement in the study.

fMRI stimuli and task

The fMRI paradigm has been used in previous studies (Wong *et al.*, 2020). The visual stimuli, consisting of 24 colored images with negative affect, were selected from the IAPS (Lang Bradley and Cuthbert, 2008). The images were chosen based on the IAPS standardized scores with matched levels of valence and arousal (mean valence = 3.18 ± 0.73 , mean arousal = 6.42 ± 0.56). The content of the images included attacks, bloody wounds, snakes and dead bodies. Each image had a matched 'masked' variation generated by scrambling the pixels. The images were also being rated by the participants after they have completed the MRI scanning procedure. Arousal and valence ratings of the images using Self-Assessment Manikin 9-point scale (Bradley and Lang, 1994) were performed on E-Prime software. The rating results are as follows: valence = 3.18 ± 0.73 , arousal: 6.42 ± 0.56 . The rating results by our subjects are: valence = (3.19 ± 1.60) , arousal = (6.11 ± 1.83) , which are comparable to the parameters of the images.

The experiment was conducted in a block design using E-Prime software. The stimuli were presented in 12 blocks with each block lasting 20s, and there were four images in each block with each image lasting 5 s. The 12 blocks comprised of 6 blocks corresponding to the negative condition and 6 blocks corresponding to the masked stimuli condition. Block order was presented in an interleaved manner. To allow the participants to return to baseline affect condition, the blocks were separated by a black fixation cross screen lasting 10 s. The task only required the participants to attend to the presented images.

MRI data acquisition

Imaging data were collected at the First Affiliated Hospital of Jinan University using a GE Discovery MR750 3.0-Tesla System, with an eight-channel phased-array head coil. The participants were scanned in a supine, head-first position with symmetrically placed cushions on both sides of the head to decrease motion. Functional images were obtained with a gradient echo-planar sequence [repetition time (TR) = 4000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; voxel size = 2.25 × 2.25 × 3.00 mm³]. Structural T1-weighted images (TR = 8.212 ms; TE = 3.22 ms; voxel size = 0.47 × 0.47 × 1.00 mm³) were also acquired.

fMRI preprocessing and whole-brain analysis

Analyses were carried out using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK) implemented in MATLAB R2013b (Mathworks). Preprocessing included realignment of functional time series to correct for head motion, co-registration of functional and anatomical data, segmentation for extracting gray matter, spatial normalization to the Montreal Neurological Institute space, and spatial smoothing (Gaussian kernel, 6 mm full width at half maximum (FWHM)).

Whole-brain analyses were first conducted separately for the SD and HC groups. We used general linear model (GLM) to perform statistical analysis. The onset times for each block were modeled as separate regressors with a canonical hemodynamic response function. The parameters for the effects of the negative and neutral blocks were estimated. Individual contrasts were analyzed at the 1st level with six motion covariates using the fixed effect model. The 1st level results were then entered into the 2nd level for random effect analysis. The contrast (negative vs masked stimuli) was entered into two-sample t-tests to examine the group difference between the SD and HC groups. The thresholds for the t-images were $P < 0.005$ (uncorrected) at the voxel level and $P < 0.05$ (Family Wise Error (FWE) corrected) at the cluster level.

ROI and PPI analysis

To address how SD could modulate negative emotion processing, exploratory region of interest (ROI) analyses were performed on the current two-sample t-test results. The functional ROIs were created with a 6 mm radius spherical mask centered at the local peaks of the activation clusters. To assess correlation with behavioral performance in SD group, Pearson correlation analyses were performed on the mean contrast value of ROIs and severity of depressive symptoms. Finally, to further investigate the changes on functional connectivity, PPI analyses were performed (Friston et al., 1997). For each participant, BOLD signal time series were extracted from the seed regions Volume-of-Interest (VOIs) and entered into the PPI analyses. New GLMs were constructed with four regressors: (i) the psychological regressor representing negative emotion processing, (ii) the physical regressor representing the VOI eigenvariate, (iii) the interaction between the psychological and physiological regressors and (iv) the motion regressor. Individual PPIs were calculated for each participant, which were entered into the 2nd level for two-sample t-tests. The thresholds were $P < 0.005$ (uncorrected) at the voxel level and $P < 0.05$ (FWE corrected) at the cluster level.

Results

Social and demographic characteristics

In the current study, the SD group comprised 42 participants (mean age = 22.19 ± 1.97) and the HC group comprised 32 participants (mean age = 21.50 ± 3.13). The demographic characteristics of the participants are shown in Table 1. There was no

Table 1. Demographic characteristics of the participants

Characteristics	SD (n = 42)	HC (n = 32)	t/X ²	P
Age, mean (s.d.)	22.19 (1.97)	21.50 (3.13)	1.094	0.279
Male (%)	16 (38.10%)	7 (21.88%)	2.231	0.135
Female (%)	26 (61.90%)	25 (78.12%)		
Education (years)	15.62 (1.91)	15.00 (2.62)	1.125	0.266
BDI-II	24.10 (7.43)	1.94 (2.45)	18.09	<0.001
CES-D	28.29 (7.36)	6.34 (4.79)	14.66	<0.001
HAMD-24	15.67 (3.56)	1.88 (1.64)	22.21	<0.001

Table 2. Coordinates, cluster size and t-values of significant activations for the between-group contrast (HC > SD). The thresholds are $P < 0.05$ (FWE corrected) at the cluster level

Label	L/R	Cluster				t
		size	x (mm)	y (mm)	z (mm)	
Superior frontal gyrus	L	232	-18	45	30	3.73
Middle cingulate gyrus	R		6	27	30	3.17
Middle frontal gyrus	L		-27	24	36	3.08
Middle cingulate gyrus	R	186	6	-3	36	3.65
Middle cingulate gyrus	L		-9	-24	36	3.52

R, right; L, left.

Table 3. Coordinates, cluster size and t-values of significant changes in functional connectivity for the between-group contrast (SD > HC). The thresholds are $P < 0.05$ (FWE corrected) at the cluster level

Label	L/R	Cluster				t
		size	x (mm)	y (mm)	z (mm)	
Superior temporal gyrus	R	259	63	-21	3	4.52
Pallidum	R		30	-12	-6	3.30
Middle temporal gyrus	L	359	-51	-18	-12	4.40
Caudate	R	517	15	21	-3	3.83
Insula	L		-33	21	-3	3.34

R, right; L, left.

significant difference between the HC and SD groups in terms of age, gender and education years. In contrast, the BDI, CES-D and HAMD-24 scores in the SD group were significantly higher than those in the HC group ($P < 0.001$).

fMRI whole-brain results

Between-group comparisons revealed that the HC group had significantly greater BOLD responses than the SD group (HC group > SD group) in the left superior frontal gyrus (SFG), left middle frontal gyrus (MFG) and bilateral middle cingulate gyrus (Table 2, Figure 1). The results were the same when including the covariates of age and gender.

ROI and PPI results

Four ROIs were identified from the two-sample t-tests: left SFG, left MFG and bilateral cingulate gyrus. First, we conducted the normality test on our data and found that both HAMD data did not satisfy the normal distribution condition in both SD ($u = 0.917$, $P = 0.005$) and HC ($u = 0.888$, $P = 0.003$) groups. We

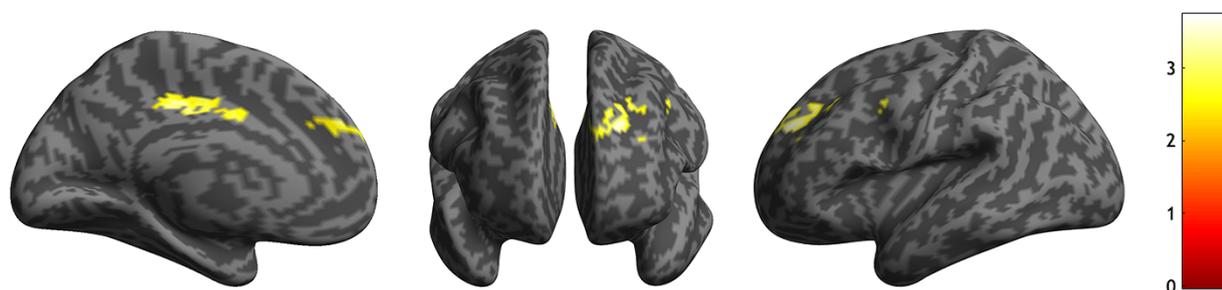


Fig. 1. Different activations in the SD and HC groups. Compared with the HC group, the SD group demonstrated reduced activations at the SFG, MFG and middle cingulated gyrus. The thresholds for the t-images were $P < 0.005$ (uncorrected) at the voxel level and $P < 0.05$ (FWE corrected) at the cluster level.

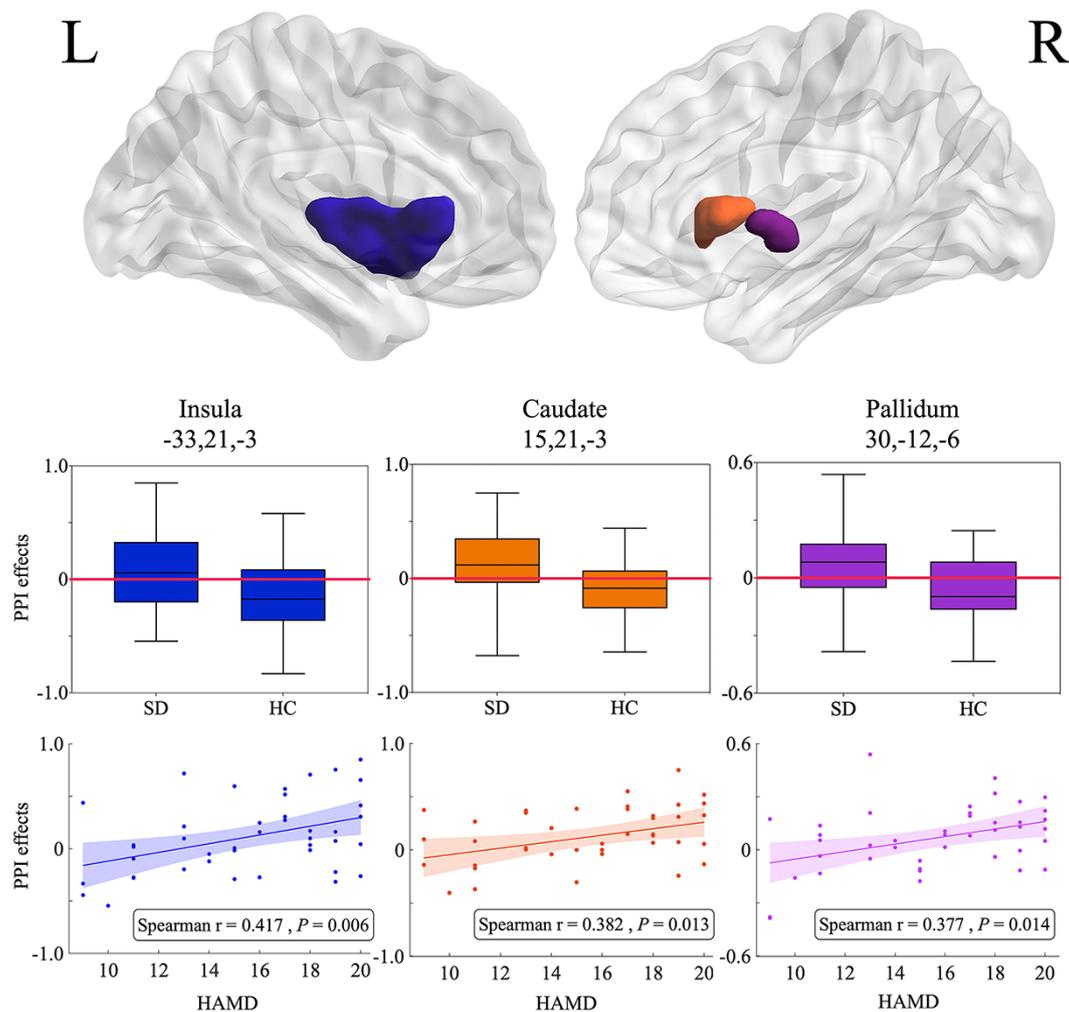


Fig. 2. SFG seed functional connectivity maps (SD group > HC group). The upper panels show a significant between-group difference of functional connectivity between the SFG and insula (blue), caudate (orange) and pallidum (purple). The maps from the two-sample t-tests were thresholded at $P < 0.05$ (FWE corrected). The middle panels show increased functional connectivity between the SFG and insula, caudate and pallidum in the SD group than the HC group. The lower panels show significant correlations between functional connectivity and depressive symptoms.

then conducted Spearman correlation analysis and we did not find significant correlations between the mean contrast values of ROIs and depressive symptoms in the SD group ($P > 0.05$). Compared with the HC group, the SD group demonstrated enhanced functional connectivity between the left SFG and right superior temporal gyrus (STG), right pallidum, left middle temporal gyrus (MTG), right caudate and left insula (Table 3). Furthermore, depressive symptoms were significantly correlated with

enhanced functional connectivity between the SFG and insula ($r = 0.417$, $P = 0.006$), pallidum ($r = 0.377$, $P = 0.014$) and caudate ($r = 0.382$, $P = 0.013$) (Figure 2). The ROI analyses were repeated in HC participants. There were no significant correlations between depressive symptoms and functional connectivity of SFG-insula ($r = -0.151$, $P = 0.408$), SFG-pallidum ($r = -0.302$, $P = 0.093$) and SFG-caudate ($r = -0.089$, $P = 0.629$). The results were the same when including the covariates of age and gender.

Discussion

Individuals with SD have been shown to be in an intermediate position between patients with major depression and healthy individuals, suggesting that SD may exist on a spectrum with major depression (Rodríguez et al., 2012; Zhang et al., 2020). The objective of this study was to characterize the neural mechanisms exhibited by SD adolescents to process negative emotion stimuli. Different activations were revealed at the left SFG, left MFG and bilateral cingulate gyrus in SD and HC groups. Importantly, there was increased functional connectivity between left SFG and insula, pallidum and caudate in the SD group, which was correlated with depressive symptoms.

Previous neuroimaging studies on SD focused on resting-state and only one task-based fMRI were identified. The study used a monetary reward fMRI task in adolescents and found that activity in the ventral striatum was reduced in SD relative to healthy subjects (Stringaris et al., 2015). Importantly, low ventral striatum activation predicted transition to SD in previously healthy subjects at 2 years of follow-up. The current results did not find significant results on the ventral striatum. However, we found enhanced functional connectivity between the SFG and caudate, which belongs to the dorsal striatum. Neural activity during negative emotion processing in major depression has been widely investigated, and the studies consistently found decreased activity at SFG and MFG during negative emotion processing in depression individuals relative to healthy controls (Fu et al., 2008; Wang et al., 2008). For instance, Fu and colleagues found decreased activity in SFG and MFG during negative facial emotion processing in major depression patients, which were then increased following cognitive behavioral treatment (Fu et al., 2008). The current results showing reduced activation at the SFG and MFG are consistent with the literature. The SFG and MFG are located within the DLPFC, which has been implicated in planning complex cognitive behavior, personality expression, decision-making, moderating social behavior as well as emotional processing (Zwanzger et al., 2014; Keuper et al., 2018; Notzon et al., 2018). Accordingly, prior research has shown that abnormalities in the DLPFC are implicated in the pathology of depression (Koenigs and Grafman, 2009). First, resting-state studies have reported lower levels of DLPFC activity in depression than in healthy individuals (Galynker et al., 1998; Avissar et al., 2017). Another line of evidence suggested that antidepressant medication-induced recovery from depression was associated with increased activation in DLPFC (Phan et al., 2005). Stimulation studies reported a significant reduction in depressive symptoms after stimulation to the DLPFC (Loo and Mitchell, 2005; Avery et al., 2006). Furthermore, neuroimaging studies have demonstrated activation of DLPFC during the regulation of negative emotion through reappraisal strategies (Phan et al., 2005). A meta-analysis in depression demonstrated decreased activation of SFG in response to negative emotion stimuli (Fitzgerald et al., 2008). Our results showing reduced activation at the SFG and MFG suggest that the change of neural function has already taken place even at the stage of SD. Importantly, the reduced activity of SFG and MFG suggests an important role of DLPFC for negative emotion processing in SD.

The DLPFC, comprised of SFG and MFG, is an important region within the prefrontal cortex. The DLPFC passes through the caudate and putamen, continues to the lateral globus pallidus and finally to the thalamus (Tekin and Cummings, 2002). Given the anatomical connectivity of DLPFC, neuroimaging studies have found co-activations of the DLPFC and caudate/putamen.

For instance, Gabbay and colleagues reported increased functional connectivity between the dorsomedial prefrontal cortex and striatal regions, such as caudate and putamen in adolescents with major depression (Gabbay et al., 2013). A recent stimulation study demonstrated that higher functional connectivity between the DLPFC and striatum predicted better treatment response of stimulation in depressed participants (Avissar et al., 2017). Aversive emotional reactions induced by negative stimuli could be attenuated by emotion regulation strategies, and this process was likely to be mediated by the DLPFC (Ochsner and Gross, 2005; Goldin et al., 2008).

Furthermore, the current results found that depressive symptoms were significantly correlated with enhanced functional connectivity between the SFG and insula. The insula, receiving and sending out information to limbic-related structures, plays an important role in emotional processing, particularly negative emotion processing (Shah et al., 2009; Zhang et al., 2020). Increasing evidence of neuroimaging studies has indicated that insula cortical activity and connectivity were altered in depression individuals (Sliz and Hayley, 2012). For instance, increased insula activation was reported in depression patients while viewing negative emotion stimuli (Malejko et al., 2021). Furthermore, several meta-analysis studies have highlighted the role of insula in depression (Gong et al., 2020). Taken together, it is observed that enhanced SFG–insula connectivity may underlie the pathology of SD.

Limitations

Although individuals of SD are at a higher risk to develop depression, direct comparison between SD and major depression is needed. The current study did not include the depression group; thus we could not conclude that the observed alterations in brain activation would also be found in clinical depression. In addition, a longitudinal design would enable direct comparison along the spectrum from SD to major depression.

Conclusions

In summary, we found a significant decreased activation at the SFG, MFG and middle cingulate gyrus in the SD group compared with the HC group. The PPI results found a significant increased functional connectivity between the SFG and caudate, pallidum, insula, STG and MTG. Importantly, the enhanced functional connectivity between the SFG and insula, caudate and pallidum was significantly correlated with depressive symptoms in the SD group.

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Conflict of interest

The authors have no competing interests to declare.

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