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Stress and the brain: Perceived stress mediates the impact of the superior frontal gyrus spontaneous activity on depressive symptoms in late adolescence

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Abstract

Identifying factors for the prediction of depression is a long-standing research topic in psychiatry and psychology. Perceived stress, which reflects the tendency to appraise one's life situations as stressful and overwhelming, has emerged as a stable predictor for depressive symptoms. However, the neurobiological bases of perceived stress and how perceived stress influences depressive symptoms in the healthy brain remain largely unknown. Here, we investigated these issues in 217 healthy adolescents by estimating the fractional amplitude of low-frequency fluctuations (fALFFs) via resting-state functional magnetic resonance imaging. A whole-brain correlation analysis showed that higher levels of perceived stress were associated with greater fALFF in the left superior frontal gyrus (SFG), which is a core brain region for cognitive control and emotion regulation-related processes. Mediation analysis further indicated that perceived stress mediated the link between the fALFF in the left SFG and depressive symptoms. Importantly, our results remained significant even when excluding the influences of head motion, anxiety, SFG gray matter structure, and school environment. Altogether, our findings suggested that the fALFF in the left SFG is a neurofunctional marker of perceived stress in adolescents and revealed a potential indirect effect of perceived stress on the association between the SFG spontaneous activity and depressive symptoms.

KEYWORDS
anxiety, depression, psychoradiology, resting-state fMRI, stress, superior frontal gyrus

1 | INTRODUCTION

In the fields of psychiatry and psychology, there is a long-standing interest in identifying predictors for depression (Cole & Dendukuri, 2003; Field, Diego, & Sanders, 2001; Lehtinen & Joukamaa, 1994; Mazure, 1998), which is a common negative state characterized by low mood and aversion to daily activities (Beck, 1967). It is well established that the onset, duration, and severity of depression are influenced by a combination of genetic, environmental, psychological, and biological factors (Gotlib & Hammen, 1992; Lesch, 2004; Levinson, 2006; Saveanu & Nemeroff, 2012; Thase & Howland, 1995). As one of the crucial psychological factors, perceived stress refers to the degree to which events in a person's life are assessed as stressful, unpredictable and uncontrollable (Cohen, Kamarck, & Mermelstein, 1983; Phillips, 2012). A wealth of previous studies have suggested that perceived stress plays an essential role in the onset and development of depressive symptoms among different populations (Bay & Donders, 2008; Bergdahl & Bergdahl, 2002; Chao, 2014; Chen, Peng, Ma, & Dong, 2017; Eisenbarth, 2012; Farabaugh et al., 2004; Gao, Chan, & Mao, 2009; Ghorbani, Krauss, Watson, & LeBreton, 2008; Hewitt, Flett, & Mosher, 1992; Kuiper, Olinger, & Lyons, 1986; Lee, Joo, & Choi, 2013; Li, Yang, Zhang, Yao, & Liu, 2015; Lorenzo-Blanco & Unger, 2015; Martin, Kazarian, & Breiter, 1995; Rosal et al., 1997; Tsai & Chang, 2016; Williams, Turner-Henson, Davis, & Soistmann, 2017). For example, a number of cross-sectional studies have revealed a positive association of perceived stress with depressive symptoms among healthy individuals (Bergdahl & Bergdahl, 2002; Chen et al., 2017; Eisenbarth, 2012; Gao et al., 2009; Ghorbani et al., 2008; Kuiper et al., 1986; Lee et al., 2013; Williams et al., 2017) and clinical patients (Bay & Donders, 2008; Farabaugh et al., 2004; Hewitt et al., 1992; Li et al., 2015; Martin et al., 1995). Furthermore, several longitudinal studies have shown that perceived stress can predict subsequent depressive symptoms in different populations (Chao, 2014; Lorenzo-Blanco & Unger, 2015; Rosal et al., 1997; Tsai & Chang, 2016). Additionally, evidence from twin investigations has uncovered a large genetic correlation between perceived stress and depressive symptoms (Bogdan & Pizzagalli, 2009; Michalski et al., 2017; Rietschel et al., 2014), suggesting that there is a common genetic basis underlying these two constructs. In summary, perceived stress might be a potential predictor of depressive symptoms. Here, using resting-state functional magnetic resonance imaging (RS-fMRI), we investigated the neurofunctional basis of perceived stress and then explored how perceived stress influences depressive symptoms in the healthy brain. We adopted a multidimensional approach (i.e., a brain-stress-symptom approach) to explore the relationships between spontaneous brain activity, perceived stress and depressive symptoms in a large group of adolescents (N = 217).

Although the predictive role of perceived stress in depressive symptoms has been well established, less work has directly examined the neural mechanisms underlying perceived stress. Evidence from the existing literature has indicated that perceived stress is mainly associated with the functional and structural changes in the prefrontal cortex (PFC) (McEwen & Morrison, 2013; Michalski et al., 2017; Moreno, Bruss, & Denburg, 2017; Rubin et al., 2016; Treadway, Buckholtz, & Zald, 2013; Wang et al., 2005). For example, a perfusion fMRI study found that during a mental arithmetic stress task, perceived stress was correlated with cerebral blood flow changes in the ventral PFC (Wang et al., 2005). Another task-based fMRI (TB-fMRI) study using a monetary incentive delay paradigm revealed that perceived stress was linked with the activity in the medial PFC (Treadway et al., 2013). Moreover, higher levels of perceived stress have been associated with structural alterations in the PFC regions, including the superior frontal gyrus (SFG), middle frontal gyrus (MFG), and inferior frontal gyrus (IFG) (Michalski et al., 2017; Moreno et al., 2017; Rubin et al., 2016). In addition to the PFC, some regions (e.g., amygdala and hippocampus) in the limbic system have been found to be crucial for perceived stress (Holzel et al., 2010; Li et al., 2014; Piccolo, Noble, & Gene, 2018; Tottenham & Sheridan, 2010; Zannas et al., 2013; Zimmerman et al., 2016). In summary, the neurobiological substrates of perceived stress may reside in the prefrontal–limbic brain regions.

Given that perceived stress is commonly considered a personality style rather than a response to environmental stressors (Cohen et al., 1983; Cohen, Tyrrell, & Smith, 1993; Phillips, 2012), there may be stable individual differences in perceived stress because an individual may tend to reliably rate the same types of events as more stressful than other events. Thus, the brain bases of perceived stress may be manifested in the overall functional and structural brain differences, which could be detected more directly by using task-free designs (e.g., RS-fMRI and structural MRI [S-MRI]) but not TB-fMRI design (Biswal et al., 2010; Lerch et al., 2017; Mar, Spreng, & DeYoung, 2013), given that the TB-fMRI is limited to the activity in areas related to a certain task (Kong, Ma, You, & Xiang, 2018; Kong, Wang, Hu, & Liu, 2015). Whereas many studies have used S-MRI to examine the neurostructural basis of perceived stress (Holzel et al., 2010; Li et al., 2014; Michalski et al., 2017; Moreno et al., 2017; Piccolo et al., 2018; Rubin et al., 2016; Zannas et al., 2013; Zimmerman et al., 2016), few have used RS-fMRI to explore the neurofunctional substrates underlying perceived stress. RS-fMRI is a widely used neuroimaging method that can measure intrinsic brain activity and examine the neurofunctional bases underlying human behaviors (Biswal, 2012; Biswal et al., 2010; Raichle, 2010). There are many RS-fMRI data analysis methods, such as fractional amplitude of low-frequency fluctuations (fALFFs) and resting-state functional connectivity (RSFC). Unlike the RSFC method, which reflects the associations between different brain regions (Fox, Snyder, Vincent, & Raichle, 2007), the fALFF method measures the properties of spontaneous local brain activity (Zou et al., 2008), which can help target brain regions linked with a specific behavioral construct (Jung et al., 2017). To our knowledge, only two studies have used RS-fMRI to directly investigate the neural basis of perceived stress. First, perceived stress has been found to be associated with the RSFC between the amygdala and dorsolateral PFC immediately after an acute stress test (Quaedflieg et al., 2015). Second, a recent study based on a sample of 67 participants belonging to three age groups revealed that perceived stress was positively related to the RSFC between the amygdala and ventromedial PFC in adolescents, while a negative association was found in young adults, and no association was found in adults (Wu et al., 2018). Given that no studies have explored the association between perceived stress and resting-state local brain activity, here, we first used fALFF to identify the brain regions involved in perceived stress. Then, we investigated whether the brain regions related to perceived stress could be linked to individuals' depressive symptoms and how perceived stress affects depressive symptoms in the brain.

To conduct our investigation, RS-fMRI scans and standard measures of perceived stress and depressive symptoms were administered to participants. First, a whole-brain correlation analysis was conducted to uncover the brain areas related to perceived stress. In light of prior findings of the neural bases of perceived stress (Holzel et al., 2010; Li et al., 2014; Michalski et al., 2017; Moreno et al., 2017; Piccolo et al., 2018; Rubin et al., 2016; Treadway et al., 2013; Wang et al., 2005; Zannas et al., 2013; Zimmerman et al., 2016), the fALFF in the PFC regions (e.g., SFG, MFG, and IFG) and limbic regions (e.g., amygdala and hippocampus) might be linked with perceived stress. Second, correlation analyses and mediation analyses were conducted to probe the associations between perceived stress, depressive symptoms, and resting-state brain activity. Considering that the prefrontal–limbic system has also been considered to be of great importance in an individual's depressive symptoms (Disner, Beevers, Haigh, & Beck, 2011; Gong & He, 2015; Maletic et al., 2007; Palazidou, 2012) and perceived stress has been found to be a stable predictor for depressive symptoms (Chao, 2014; Lorenzo-Blanco & Unger, 2015; Rosal et al., 1997; Tsai & Chang, 2016), perceived stress might mediate the impact of the fALFF in the prefrontal–limbic regions on depressive symptoms. Finally, to assess the specificity of the findings, we carried out supplemental analyses in which several possible confounding factors (e.g., head motion, anxiety, structural brain differences, and school differences) were excluded.

Notably, in the present study, we focused on a large group of healthy students in late adolescence, which is a transition period characterized by cognitive and affective changes related to the reorganization of brain function and structure (Foulkes & Blakemore, 2018; Konrad, Firk, & Uhlhaas, 2013). Many previous studies have suggested that depressive disorders occur frequently during adolescence and adolescent-onset depressive disorders are related to greater physical health problems, psychosocial impairments and psychiatric comorbidity than adult-onset depressive disorders (Wilson, Hicks, Foster, McGue, & Iacono, 2015). Thus, studying the neural substrates of perceived stress and their relations to depressive symptoms in this period is extremely important, as the findings may help to identify distinct biomarkers related to perceived stress, which can be used by clinical and educational experts to develop corresponding intervening programs (e.g., neurofeedback training, Zotev et al., 2018) to decrease the occurrence of depression in adolescents.

2 | METHODS

2.1 | Participants

In total, 234 healthy 12th-grade students (122 females; mean age = 18.60 ± 0.78 years) from five local public high schools participated in this study, which is a part of our ongoing project to investigate the neurobiological substrates of adolescents' personality traits, well-being and academic achievement in Chengdu, China (Li et al., 2018; Wang, Kong, et al., 2017; Wang, Xu, et al., 2017; Wang, Dai, et al., 2018; Wang, Zhao, et al., 2018). Seventeen participants were excluded because of incidental MRI findings (i.e., unusual cysts, three participants) or a lack of behavioral data (14 participants); thus, 217 participants (110 females; mean age = 18.50 ± 0.55 years) were included in our data analyses. As a general sample of Chinese public high school students, all participants were right-handed as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). According to the participants' self-reports on a questionnaire and the records in the student archives from the schools, all participants had no history of neurological or psychological illnesses. The questionnaire included two items: Have you ever had any neurological illnesses? Have you ever had any psychological illnesses? The local research ethics committee of West China Hospital of Sichuan University approved the study protocol, and written informed consent was obtained from each participant prior to the experiments.

2.2 | Behavioral measures

The participants' perceived stress levels were measured using the Chinese version of 10-item Perceived Stress Scale (PSS) (Lu et al., 2017; Ng, 2013; Wang et al., 2011). As a popular measure of perceived stress that is sensitive to chronic stressors, the PSS might be used to assess an individual's chronic stress levels (e.g., monthly administering the scale and averaging the scores) (Cohen et al., 1983). The PSS is a 5-point Likert-type self-reported questionnaire with response options ranging from 1 (never) to 5 (very often). For each item (e.g., "How often have you been angered because of things that were outside of your control?"), individuals are asked to indicate the frequency with which it occurred in the past month. The scores for the PSS range between 10 and 50, with higher scores suggesting higher levels of perceived stress. This scale has been repeatedly used in different Chinese populations and has been shown to have adequate internal consistency (Cronbach's α = .70–.86), test–retest reliability (r = .68–.70) and external validity associated with work burnout, work engagement, depressive symptoms, and anxiety (Lu et al., 2017; Ng, 2013; Wang et al., 2011). In this research, the internal reliability for the PSS was adequate (α = .81).

The participants' depressive symptoms were evaluated using the Beck Depression Inventory (BDI), which is a well-known tool for assessing an individual's depressive symptoms during the past week (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Beck, Steer, & Carbin, 1988). It includes 21 items, and participants rate each item on a scale ranging from 0 (never) to 3 (very heavy). The scores for BDI range between 0 and 63, with higher scores suggesting higher levels of depressive symptoms. The Chinese version of BDI has demonstrated acceptable psychometric properties (Shek, 1990; Yeung et al., 2002). In this research, the internal reliability for the BDI was satisfactory (α = .84).

Considering that anxiety has been found to be related to perceived stress (Bergdahl & Bergdahl, 2002; Lee, 2012), depressive symptoms (Eysenck & Fajkowska, 2018), and resting-state brain activity (Tian et al., 2016; Xue, Lee, & Guo, 2018), we used the State Anxiety Inventory (SAI) (Spielberger, Gorsuch, & Lushene, 1988) to exclude the potential impacts of anxiety on the relationships among perceived stress, regional fALFF, and depressive symptoms. The SAI includes 20 items (e.g., "I feel frightened" and "I feel confused") that are rated on a 4-point Likert-type scale from 1 (not at all) to 4 (very much so). The scores for SAI range between 20 and 80, with higher scores suggesting higher levels of anxiety. The reliability and validity of the Chinese version of SAI have been well established in previous studies (Li & Lopez, 2004; Shek, 1988). In this research, the internal reliability for SAI was excellent (α = .88).

2.3 | Image acquisition and preprocessing

We used a 3.0 T Siemens-Trio Erlangen MRI scanner to obtain the brain images, and the scanner was located at West China Hospital of Sichuan University. First, each participant took part in an 8-min RS-fMRI scan including 240 echo-planar imaging volumes (repetition time/echo time = 2,000/30 ms; flip angle = 90°; slices = 30; matrix = 64×64; thickness = 5 mm; field of view = 24×24 cm^2; voxel size = $3.75 \times 3.75 \times 5$ mm^3). During the image acquisition, we asked each participant to lie comfortably, close his/her eyes, and remain awake without thinking about anything purposely. Additionally, we collected the T1-weighted anatomical images of all participants, and the scanning parameters were as follows: repetition time/inversion time/echo time = 1,900/900/2.26 ms; slices = 176; matrix = 256×256; flip angle = 9°; voxel size = $1 \times 1 \times 1$ mm^3.

The DPARSF toolbox (Yan, Wang, Zuo, & Zang, 2016), which utilizes Statistical Parametric Mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK), was employed to preprocess the RS-fMRI data. As described in our previous studies (Wang, Xu, et al., 2017; Wang, Zhao, et al., 2018), the data preprocessing was conducted with the following steps: discarding the first 10 images to ensure signal stabilization, correcting for slice timing and head motion, realigning, normalizing with $3 \times 3 \times 3$ mm^3 resolution, smoothing using an 8-mm full-width at half-maximum Gaussian kernel, and removing linear trends. No participants were excluded during preprocessing because the rotational or translational parameters were less than ±1.5 mm or ± 1.5°. Additionally, a set of nuisance covariates (i.e., global mean signal, white matter signal, cerebrospinal fluid signal, and six head motion parameters) were excluded using a regression analysis. Finally, the framewise displacement (FD; Van Dijk, Sabuncu, & Buckner, 2012) was calculated as a measure of head motion and was treated as a covariate in the subsequent data analyses.

2.4 | fALFF-behavior correlation analysis

Through implementing the procedure developed by Zou et al. (2008), we used the DPARSF toolbox to compute the fALFF for each participant (Yan et al., 2016). To do so, we first converted the time courses in each voxel to the frequency domain. Next, the mean square root at a low-frequency range (0.01–0.08 Hz) was obtained after computing the square root of each frequency in the power spectrum. A fractional score, referring to the amplitudes at a low-frequency range (0.01–0.08 Hz) divided by the amplitudes over the entire frequency range (0.01–0.25 Hz), was then calculated as the measure of the fALFF. Finally, the normalized score of the fALFF (i.e., Z-fALFF) was computed to rule out the global effects of variability between participants.

To detect the brain regions for which the fALFF is linked with perceived stress, a whole-brain correlation analysis was conducted using PSS scores as the variable of interest and sex, age, and FD as the variables of no interest. Moreover, to investigate sex differences in the relationship between perceived stress and the regional fALFF, a condition-by-covariate interaction analysis (e.g., Kong et al., 2014; Wang, Dai, et al., 2018; Yamasue et al., 2008) was conducted using sex as a condition, PSS scores as the variable of interest and age and FD as the variables of no interest. The Gaussian random field approach was employed to determine the regions of significance (Qiu et al., 2018; Wang, Zhao, et al., 2018; Worsley, Evans, Marrett, & Neelin, 1992), with a threshold of $p < .005$ at voxel level and $p < .05$ at cluster level (minimum cluster size: 148 voxels; $61 \times 73 \times 61$ dimension; 70,831 voxels in the mask; the estimated size of spatial smoothness was [11.46, 12.13, and 11.38 mm]). The above analyses were conducted using the REST software (Song et al., 2011). For the subsequent analyses, we extracted the average fALFF values from the cluster that was specifically associated with perceived stress and detected from the whole-brain correlation analysis.

2.5 | Confirmatory cross-validation analysis

To validate the robustness of the link between perceived stress and resting-state brain activity, a balanced fourfold cross-validation procedure utilizing a machine learning approach was implemented (Kong, Wang, et al., 2015; Supekar et al., 2013; Wang, Dai, et al., 2018; Wang, Xu, et al., 2017; Yang et al., 2016). The purposes of this analysis were to investigate the stability of the association of perceived stress with resting-state brain activity and to test whether the relation between perceived stress and resting-state brain activity was influenced by factors such as data distribution and outliers. For the analysis, a linear regression algorithm was conducted using PSS scores as the dependent variable and the fALFF of the voxels specifically associated with perceived stress as the independent variable. To evaluate how well the dependent variable could be linked to the independent variable, $r_{(\text{predicted, observed})}$ was computed using a balanced fourfold cross-validation method (Kong, Wang, et al., 2015; Supekar et al., 2013; Wang, Dai, et al., 2018; Wang, Xu, et al., 2017; Yang et al., 2016). The data were first divided into four subsets to guarantee that there were no significant differences among the distributions of these variables across the subsets. Then, the data from three subsets were used to build a linear regression model, with one subset left out. This model was further employed to predict the unused data subset. The $r_{(\text{predicted, observed})}$, which represents the correlation between the actual observed data and the predicted data, was finally obtained after the data of all subsets had been predicted. The significance of $r_{(\text{predicted, observed})}$ was determined using a nonparametric testing method (Kong, Wang, et al., 2015; Supekar et al., 2013; Wang, Dai, et al., 2018; Wang, Xu, et al., 2017; Yang et al., 2016). By randomly shuffling the data of the independent variable, we used the original dependent variable and the shuffled independent variable to calculate the $r_{n(\text{predicted, observed})}$. The null distribution of $r_{(\text{predicted, observed})}$ was obtained by repeating this procedure 5,000 times. Through subtracting the percentile of the true $r_{(\text{predicted, observed})}$ in the null distribution from one, the significance of $r_{(\text{predicted, observed})}$ was obtained. Sex, age, and FD were controlled for in this analysis.

2.6 | Mediation analysis

To examine the indirect effect of perceived stress on the association between resting-state brain activity and depressive symptoms, we conducted a mediation analysis using the SPSS macro PROCESS including the bootstrapping approach (Hayes, 2013). To this end, the fALFF of the voxels specifically associated with perceived stress was considered the independent variable (X), PSS scores were considered the mediator variable (M), BDI scores were considered the dependent variable (Y) and sex, age and FD were considered the controlling variables. According to standard conventions (Hayes, 2013), Path c is the relation of X and Y, Path c′ is the relation of X and Y after adjusting for M, Path a is the relation of X and M, and Path b is the relation of M and Y after adjusting for X. The indirect effect, referring to c − c′ or a × b, was estimated. The point estimates of the indirect effects were considered significant if the bootstrapped 95% confidence intervals (CIs) (5,000 iterations) did not include zero.

TABLE 1 Means, *SDs*, and correlations of measures (N = 217; 110 females, 107 males)

	Mean	*SD*	Age	PSS	BDI	SAI	FD
Age	18.50	0.55	–				
PSS	26.85	4.83	0.05	–			
BDI	6.88	6.21	0.04	0.53***	–		
SAI	39.51	7.04	0.06	0.58***	0.47***	–	
FD	0.17	0.06	−0.02	0.03	−0.03	0.03	–

Note. All participants self-reported their sex and age, which were consistent with the corresponding records in the student archives from the schools.
Abbreviations: BDI, Beck Depression Inventory; FD, framewise displacement; N, number; PSS, Perceived Stress Scale; SAI, State Anxiety Inventory; SD, standard deviation.
***p < .001.

3 | RESULTS

3.1 | Neurofunctional substrates of perceived stress

Table 1 shows the averages, *standard deviations*, and correlations of all measures included in the current study. To examine the validity of the PSS used in this study, we collected data from a questionnaire related to stressful life events (i.e., Adolescent Self-Rating Life Events Checklist; Liu, Liu, Yang, & Zhao, 1997) in a subsample of our participants (23 students, see Supplemental Methods). We found that perceived stress was positively associated with the number of stressful life events (r = .42, p = .060) and the impact of stressful life events (r = .45, p = .041) after controlling for sex and age. Perceived stress was not significantly correlated with age (r = .05, p = .474) or head motion (FD; r = .03, p = .623). Significant sex differences in perceived stress were observed [$t_{(215)}$ = 3.22, p = .002]. We then investigated the neurofunctional substrates of perceived stress.

To uncover the relationships between perceived stress and the regional fALFF, a whole-brain correlation analysis was performed with sex, age, and FD as covariates. After correcting for multiple comparisons with the Gaussian random field approach, perceived stress showed a positive association with the fALFF in the left SFG (Table 2 and Figure 1). No other significant associations were obtained in this analysis. Additionally, to explore whether there were sex differences in the association between perceived stress and the regional fALFF, a condition-by-covariate interaction analysis was performed with sex as a condition, perceived stress as a covariate of interest and age and FD as covariates of no-interest. We found no sex differences in the association between perceived stress and the regional fALFF after correcting for multiple comparisons.

We next implemented a confirmatory cross-validation analysis to check the robustness of the relation between perceived stress and the fALFF in the cluster (i.e., the left SFG) that was significantly associated with perceived stress and identified from the whole-brain correlation analysis. The results indicated that perceived stress could be stably linked to the fALFF in the left SFG ($r_{(\text{predicted, observed})}$ = .27, p < .001) after controlling for sex, age, and FD.

TABLE 2 Summary of brain regions associated with perceived stress

		Peak MNI coordinate				
Region	BA	*x*	*y*	*z*	Peak *Z* score	Cluster size (voxels)
Controlling for age, sex, and head motion						
Left SFG	10	−18	51	15	3.92	212

Note. The threshold for significant regions was set as follows: p < .005 at voxel level and p < .05 at cluster level, Gaussian random field approach.
Abbreviations: BA, Brodmann's area; MNI, Montreal Neurological Institute; SFG, superior frontal gyrus.

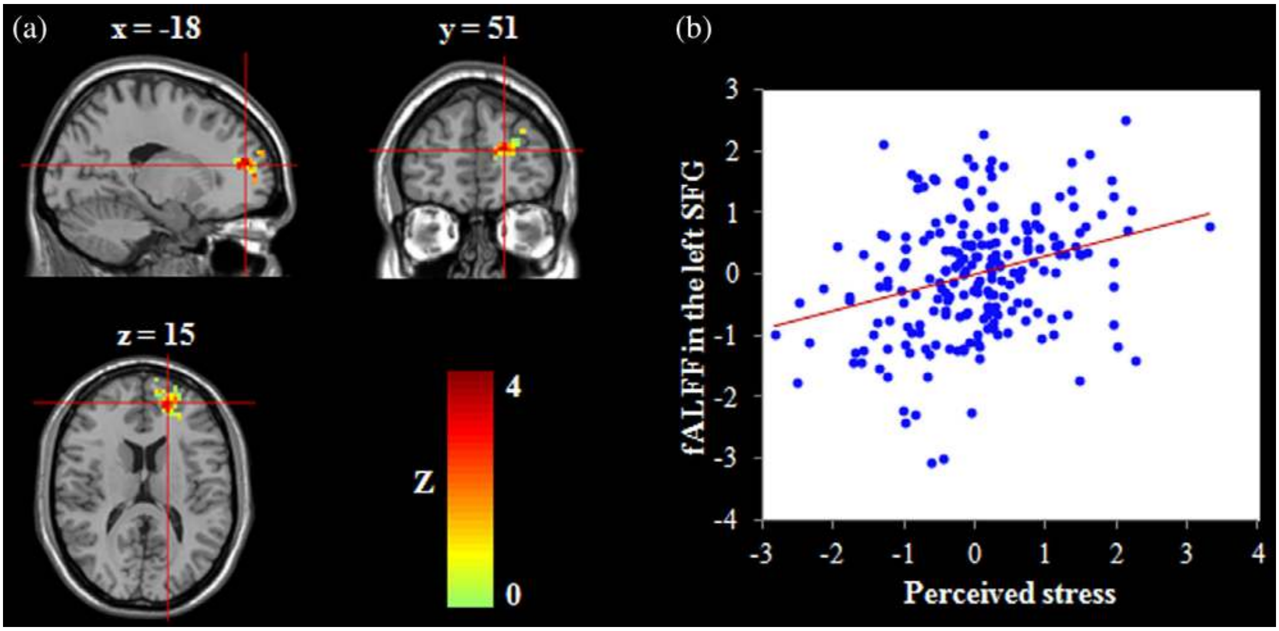

FIGURE 1 Brain regions that are linked with perceived stress. (a) Brain image showing that the fALFF in the left SFG was positively associated with perceived stress. (b) Scatter plots depicting the correlation between perceived stress and the fALFF in the left SFG. The scores on the *x*-axis represent the standardized residuals of the perceived stress scores after sex, age and head motion were regressed out. The scores on the *y*-axis represent the standardized residuals of the SFG's mean fALFF values after sex, age, and head motion were regressed out. fALFF, fractional amplitude of low-frequency fluctuation; SFG, superior frontal gyrus [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Brain regions linking perceived stress and depressive symptoms

After obtaining the functional brain basis of perceived stress, we further explored the associations between perceived stress, depressive symptoms, and resting-state brain activity by collecting the BDI scores. We first verified the positive correlation of perceived stress with depressive symptoms ($r = .53$, $p < .001$). Further regression analysis revealed that perceived stress accounted for additional variance in depressive symptoms ($\triangle R^2 = 26.5\%$, $\beta = .53$, $p < .001$) after adjusting for sex, age, and FD. Next, we tested whether individual differences in depressive symptoms could be linked to the fALFF in the identified brain region (i.e., the left SFG) that was significantly associated with perceived stress. We found a significant correlation of depressive symptoms with the fALFF in the left SFG ($r = .28$, $p < .001$). Further regression analysis revealed that the fALFF in the left SFG accounted for additional variance in depressive symptoms ($\triangle R^2 = 6.6\%$, $\beta = .27$, $p < .001$) after adjusting for sex, age, and FD.

The above results showed that there was a close relation among perceived stress, the regional fALFF, and depressive symptoms, but the nature of this relation remained unclear. To test whether perceived stress could mediate the link between the regional fALFF and depressive symptoms, a mediation analysis was conducted. Interestingly, perceived stress played a mediating role in the relation between the fALFF in the left SFG and depressive symptoms (indirect effect = 0.157, 95% CI = [0.090, 0.260], $p < .05$). After controlling for sex, age, and FD, perceived stress still mediated the impact of the fALFF in the left SFG on depressive symptoms (indirect effect = 0.146, 95% CI = [0.080, 0.248], $p < .05$; Figure 2). In summary, the association between spontaneous SFG activity and depressive symptoms may be explained by perceived stress.

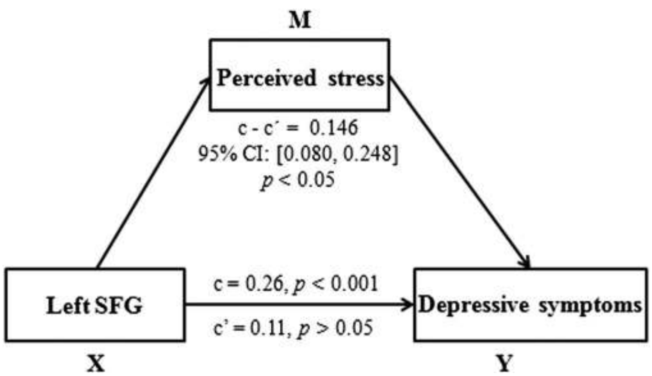

FIGURE 2 Perceived stress mediates the effect of the resting-state activity in the left SFG on depressive symptoms. Standardized regression coefficients were presented in the path diagrams. Sex, age, and head motion were treated as covariates in the model. SFG, superior frontal gyrus

3.3 | Supplemental analyses

To evaluate the specific nature of the above results, we conducted supplemental analyses by excluding several possible confounding factors (e.g., head motion, anxiety, structural differences in the SFG, and school differences). The results showed that our findings were not affected by head motion, anxiety, SFG gray matter volume (GMV), or school environment (see Supplemental Results).

4 | DISCUSSION

This investigation was performed to examine the functional brain substrates underlying adolescents' perceived stress and to explore the nature of the relationships between resting-state local brain activity, perceived stress, and depressive symptoms. Higher levels of perceived stress were linked to greater fALFF in the left SFG. Furthermore, perceived stress mediated the impact of spontaneous SFG activity on depressive symptoms. Importantly, these results persisted even when head motion, anxiety, SFG GMV, and school environment were adjusted for, showing the specificity of the findings. Overall, the current research reveals the fALFF in the left SFG as a neurofunctional marker for perceived stress in adolescents and provides a potential brain-stress-symptom pathway for predicting depressive symptoms in which perceived stress mediates the association between spontaneous SFG activity and depressive symptoms.

We first observed that the fALFF in the left SFG was positively linked with perceived stress, which is consistent with the finding of a TB-fMRI experiment showing an association between perceived stress and activity in the medial SFG during a monetary incentive delay task (Treadway et al., 2013). The functioning of the SFG has also been found to be associated with acute psychosocial stress (Pruessner et al., 2008) and chronic life stress experiences (Li et al., 2016). Evidence from two voxel-based morphometry studies has further shown that the SFG gray matter structure is related to individuals' early life stressful events (Tyborowska et al., 2018) and recent stressful events (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012). Thus, our result may considerably advance previous findings linking the SFG and stress-related processing. The SFG is generally considered a core brain region in the cognitive control system (Niendam et al., 2012) and for emotion regulation-related processes (Frank et al., 2014), which are hypothesized to be crucial for perceived stress that emphasizes the subjective cognitive and emotional adjustment for objective stressors (Cohen et al., 1983; Phillips, 2012). Additionally, the positive association of the fALFF in the left SFG with perceived stress may reflect a compensatory mechanism to counteract functional or structural brain abnormalities (Bing et al., 2013; Kong et al., 2018; Orr et al., 2013; Wang, Zhao, et al., 2018), which might be linked to the outcomes or difficulties induced by higher levels of perceived stress. For example, higher levels of SFG spontaneous activity have been observed in patients with stress-related psychopathologies, including posttraumatic stress disorder (Bing et al., 2013), substance abuse disorder (Orr et al., 2013), major depressive disorder (Liu et al., 2014), and social anxiety disorder (Qiu et al., 2015). Furthermore, evidence from investigations in healthy participants has indicated that increased spontaneous activity in the SFG is related to decreased psychosocial functions, such as regulation of emotion (Pan et al., 2014), life satisfaction (Kong, Hu, Wang, Song, & Liu, 2015) and dispositional optimism (Wu et al., 2015), which are variables negatively associated with perceived stress (Baldwin, Chambliss, & Towler, 2003; Extremera, Duran, & Rey, 2009; Pau & Croucher, 2003). In summary, greater fALFF values in the left SFG may be related to decreases or defects in stress-related functions (e.g., cognitive control and emotional regulation), which may further lead to higher levels of perceived stress.

Interestingly, we found that perceived stress served as a mediator in the link between SFG spontaneous activity and depressive symptoms. Behaviorally, the association of perceived stress with depressive symptoms has been well established in previous investigations (Bay & Donders, 2008; Bergdahl & Bergdahl, 2002; Chao, 2014; Chen et al., 2017; Eisenbarth, 2012; Farabaugh et al., 2004; Gao et al., 2009; Ghorbani et al., 2008; Hewitt et al., 1992; Kuiper et al., 1986; Lee et al., 2013; Li et al., 2015; Lorenzo-Blanco & Unger, 2015; Martin et al., 1995; Rosal et al., 1997; Tsai & Chang, 2016; Williams et al., 2017). This association was replicated in the current sample (r = .53, p < .001). Hierarchical regression analysis further revealed that even after excluding the influences of sex, age, school differences, head motion, total GMV, anxiety, the fALFF in the SFG and the GMV in the SFG, perceived stress still accounted for additional variance in depressive symptoms ($\triangle R^2$ = 7.3%, β = .35, p < .001). Therefore, our study presented further evidence for the predictive role of perceived stress in depressive symptoms. At the neural level, we observed that variance in depressive symptoms could be explained by the fALFF in the left SFG, which fits well with the findings of numerous RS-fMRI studies that have revealed associations between depressive symptoms and local spontaneous activity and connectivity in the SFG (Iwabuchi et al., 2015; Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Sundermann, Beverborg, & Pfleiderer, 2014). Evidence from a recent RS-fMRI research further demonstrated that electroconvulsive therapy changed the local spontaneous activity and connectivity in the SFG, which, in turn, reduced depressive symptoms in elderly major depressive disorder patients (Kong et al., 2017). Moreover, the structure of the SFG has been repeatedly reported to be associated with depressive symptoms among different populations (Peng, Chen, Yin, Jia, & Gong, 2016; Zhao et al., 2014). As mentioned above, the SFG is well known to be implicated in processing cognitive control and emotion regulation (Frank et al., 2014; Niendam et al., 2012), which are critical influential factors for depressive symptoms (Joormann & Gotlib, 2010; Siegle, Ghinassi, & Thase, 2007). Thus, our finding regarding the relation between depressive symptoms and the fALFF in the left SFG may substantiate the role of SFG function in depressive symptoms. Collectively, our study indicated that perceived stress may be a potential mechanism linking the fALFF in the left SFG with depressive symptoms.

Our research had several limitations that should be acknowledged. First, we used only several self-reported scales to assess perceived stress, depressive symptoms, and anxiety, although the validity and reliability of these scales have been well established. It is necessary for future studies to use multiple techniques (e.g., peer-rating or experiencing sampling) to decrease the response bias and enhance measurement accuracy. Second, we based our research on a group of adolescent students in the same grade, which may constrain the generalizability of the current findings to other populations (e.g., children and adults). Nevertheless, our findings observed in this age range may help us to understand the underlying mechanisms that may affect the onset and/or course of depression in late adolescence and adulthood, given that prior evidence has revealed that individuals with both an adolescent-onset and recurrent episode depression have most severe psychosocial impairments in adulthood (Wilson et al., 2015). Third, we revealed only that the fALFF in the left SFG was linked with perceived stress but failed to observe the relations between perceived stress and the fALFF in other prefrontal–limbic brain regions that have been found in prior investigations (Holzel et al., 2010; Li et al., 2014; Michalski et al., 2017; Moreno et al., 2017; Piccolo et al., 2018; Rubin et al., 2016; Wang et al., 2005; Zannas et al., 2013; Zimmerman et al., 2016). Because we employed fALFF as the only measure of brain function and GMV as the only measure of brain structure, other measures of brain function (e.g., RSFC) and structure (e.g., cortical surface area and cortical thickness) may be used to further explore the neurobiological bases of perceived stress and their relations to depressive symptoms. Fourth, the fALFF analysis used in the present study relied on only an 8-min scan, although there is evidence showing that a scan length less than 8 min may be able to ensure adequate reliability of fALFF analysis (Somandepalli et al., 2015; Zuo et al., 2010). Given that some evidence has indicated that the reliability of RSFC analyses can be improved by increasing the scan length to 12–16 min (Birn et al., 2013), future researchers may consider using a longer scan times to calculate fALFF and then explore its association with perceived stress and depressive symptoms. Additionally, we observed a mediation association between spontaneous SFG activity, perceived stress, and depressive symptoms and this association was independent of several variables (e.g., head motion, anxiety, structural brain differences, and school differences). However, the observed mediation association may be influenced by other confounding factors (e.g., shared genetic predisposition, brain development, and other stress-related individual characteristics), which might have effects on the three variables in the mediation model. Future researchers are encouraged to explore the effects of these factors on the association between spontaneous brain activity, perceived stress, and depressive symptoms.

Finally, the data used in the current study were not temporally discernable. Thus, it cannot come to a causal conclusion about the association between spontaneous SFG activity, perceived stress and depressive symptoms because these three variables may be temporally interchanged and temporality across these variables cannot be assessed. In particular, there may be three possible mediation models in the association between SFG, perceived stress and depressive symptoms (Model 1: X = SFG, M = perceived stress, Y = depressive symptoms; Model 2: X = perceived stress, M = SFG, Y = depressive symptoms; Model 3: X = perceived stress, M = depressive symptoms, Y = SFG), given that several previous longitudinal studies have suggested that perceived stress is a stable antecedent for depressive symptoms (Chao, 2014; Lorenzo-Blanco & Unger, 2015; Rosal et al., 1997; Tsai & Chang, 2016). In addition to Model 1, which was examined in the above analyses, we further revealed that there was a significant indirect effect for Model 3 (indirect effect = 0.078, 95% CI = [0.011, 0.148], $p < .05$) but not for Model 2 (indirect effect = 0.038, 95% CI = [−0.002, 0.080], $p > .05$). Considering these findings and the cross-sectional design used in this research, there may be other possible mediation associations between spontaneous SFG activity, perceived stress, and depressive symptoms. Given the potential ethical issues in the research of stress in human beings, it may be difficult to use more sophisticated methods (e.g., experimental designs; Maxwell & Cole, 2007; Maxwell, Cole, & Mitchell, 2011) to determine the causal direction of the relationship between spontaneous brain activity, perceived stress and depressive symptoms. Additionally, it is worth noting that Path a in our main mediation model (i.e., Model 1) may be inflated due to double dipping (i.e., Path a was calculated using the fALFF of the voxels that were specifically associated with perceived stress and detected from the whole-brain correlation analysis), which may bias results away from the other potential paths. Thus, the mediation association observed here may be just a possible mechanism linking spontaneous SFG activity, perceived stress, and depressive symptoms, given the lack of temporality or prior data establishing temporality across these three variables.

In conclusion, this research provides initial evidence for a neurofunctional marker underlying perceived stress by revealing that the fALFF in the left SFG is linked to perceived stress in a sample of students in late adolescence. Additionally, our study provides pioneering evidence suggesting that the relation between spontaneous SFG activity and depressive symptoms is mediated by perceived stress. These findings jointly suggest the important role of perceived stress and the fALFF in the left SFG in adolescent depressive symptoms and introduce new research directions for examining how individual psychological characteristics affect depressive symptoms in the brain. Finally, the current findings may add to the development of psychoradiology, a new field of radiology with the purpose of not only improving our understanding of the mechanisms underlying psychiatric disorders, but also having great potential to play the clinical role in guiding diagnostic and treatment planning decisions in psychiatric patients (Kressel, 2016; Lui, Zhou, Sweeney, & Gong, 2016; Port, 2018).

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CONFLICT OF INTEREST

The authors declare no competing conflict of interest.

DATA AVAILABILITY STATEMENT

The data and code that support the findings of this study are available from the corresponding author upon reasonable request. The data and code sharing adopted by the authors comply with the requirements of the funding institute and the institutional ethics approval.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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