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Cortical activation and functional connectivity during the verbal fluency task for adolescent-onset depression: A multi-channel NIRS study

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ABSTRACT

Objective: Depression disorder is accompanied by cognitive impairments. However, there is limited research focused on cognitive impairments and their neurological mechanism in adolescents with depression. The purpose of the current study is to illustrate the differences in brain activity patterns between depressed adolescents and healthy controls (HCs).

Method: A total of 72 adolescents with depression, as well as 74 HCs, were recruited. We utilized functional near-infrared spectroscopy (fNIRS) to monitor the concentrations of oxyhemoglobin (Oxy-Hb) in the brains of participants while they performed the verbal fluency task (VFT) to examine cognitive impairment in adolescents with depression.

Results: Our study demonstrated that adolescents with depression had significantly less cortical activation in the hemodynamic responses of Oxy-Hb at channels mainly located in the prefrontal cortex (PFC) than HCs during the 60-s task period (false discovery rate (FDR)-corrected $p < 0.05$). The mean channel-to-channel connectivity was 0.400 for HCs ($SD = 0.149$) and 0.303 ($SD = 0.138$) for adolescents with depression, and the HC group had a higher mean channel-to-channel connectivity strength than the depression group ($t = -15.586$, $p < 0.001$). For the patient group, we found significant negative correlations between HAMD scores and mean Oxy-Hb changes in Channel 38 ($r = -0.33$, $p < 0.01$), Channel 39 ($r = -0.34$, $p < 0.01$), Channel 41 ($r = -0.25$, $p < 0.05$), Channel 42 ($r = -0.28$, $p < 0.05$), and Channel 44 ($r = -0.27$, $p < 0.05$), and these channels were mainly located in areas with little difference between groups.

Conclusions: Our study provides neurological evidence about the executive function (EF) in depressed adolescents. Adolescents with depression exhibited an abnormal activation pattern and decreased task-related functional connectivity compared to HCs. The changed Oxy-Hb concentration of PFC during VFT was not sensitive to depression symptoms.

1. Introduction

Depression is a clinically common psychiatric disorder consisting of a persistent depressed mood and loss of interest in life (Rotenstein et al., 2016). In recent years, the incidence of depression in adolescents has been on the rise, bringing a huge burden of disease to society and families and seriously damaging the mental health of adolescents. Many adults with depression recall that the time of their first depressive episode can be traced back to their teenage years (Nikolakaros et al., 2020). Adolescent-onset depression is considered an ultra-risk indicator for chronic and recurrent dysfunction and impairment in adulthood (Avenevoli et al., 2008). Adolescent depression is accompanied by dysfunction of frontolimbic circuits (amygdala-dorsolateral PFC, amygdala-ventromedial FC (Connolly et al., 2017). Adolescent patients and healthy adolescents also appear to differ in regional cerebral blood flow in the executive, affective, and motor networks (T. C. Ho et al.,

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2013). More efforts are needed to advance our understanding of the neurodevelopmental underpinnings of depression in adolescents.

Psychopathological research commonly focuses on neuropsychological behaviors and the associated neuro-mechanisms(Diamond, 2013; Price and Duman, 2020). In the present study, we focused on the executive function (EF). EF refers to a series of neuropsychological abilities including reasoning, formulating goals and plans, maintaining attention, and flexibly changing goals and plans according to changing events (Ozga et al., 2018). Research on the brain activation patterns of adolescents found that the pivotal brain regions responsible for relevant cognitive ability gradually become specialized, and their activation increases, during adolescence(Shaw et al., 2006; Sowell et al., 2002). Cortical brain regions (e.g., the PFC) and EF performance undergo a protracted course of development, not reaching maturity until early adulthood (Sommerfeldt et al., 2016). Considerable evidence has illustrated that EF deficits are associated with depression in adults (McClintock et al., 2010; Taylor Tavares, Drevets and Sahakian, 2003). In considering the peculiar features associated with the developmental course of depression, conclusions about adults may not be generalized to children and adolescents with depression; hence, more evaluations and explorations of EF in adolescents with depression are needed. Moreover, there is a paucity of EF studies in adolescents with depression, and studies on whether EF deficits are implicated in adolescent depression have yielded inconsistent results. For example, previous studies found that adult depression was associated with specific short-term memory deficits (Imboden et al., 2020; Lauer et al., 1994), but a review found no evidence of impaired attention and memory in adolescents(Baune et al., 2014).

Patients' performance on neuropsychological tasks can help us understand the nature of EF in adolescents with depression. Various approaches, such as the Stroop task, the Go/No-Go Task, and the Spatial Working Memory task, are used for the assessment of EF. Neuropsychological measurements combined with brain imaging techniques are capable of providing a perspective to observe the real-time brain function state during the EF process. Functional near-infrared spectroscopy (fNIRS) is a safe and non-invasive neuroimaging technique. It involves near-infrared light (650–1000 nm) penetrating tissues, and it can measure the concentrations of Oxy-Hb and deoxygenated hemoglobin (Deoxy-Hb) to estimate the underlying cognitive processes of probe-covered cerebral cortices under different cognitive tasks (Aslin et al., 2015; M. K. Yeung and Chan, 2021). fNIRS has better spatial resolution than electroencephalogram (EEG) and better temporal resolution than functional magnetic resonance imaging (fMRI); it has better tolerance to motion artifacts and is relatively inexpensive, portable, and easy to operate compared with other brain imaging technologies (Pinti et al., 2020). Therefore, fNIRS has been widely used to assess brain function in psychiatric disorders. Many studies have combined fNIRS and the verbal fluency task (VFT) to evaluate EF(Noda et al., 2017; Ohi et al., 2017; Michael K. Yeung, Lee and Chan, 2019). The VFT is one of the commonly used EF tasks that involves neuropsychological abilities like verbal recall, retrieval, working memory, and attention(Whiteside et al., 2016). The fNIRS-VFT paradigm is often used in studies to elicit different abnormalities relevant to each diagnostic group of major psychiatric disorders (Jolanta et al., 2010). Suto et al. used fNIRS-VFT to elucidate the differential frontotemporal cortical activation between depression and schizophrenia (Suto et al., 2004). A multicenter study with the largest sample size to date found that frontal cortical activation through fNIRS-VFT accurately distinguished between patients with depression and those with bipolar disorder or schizophrenia (Takizawa et al., 2014). However, the clinical applicability of fNIRS-VFT to the differential cortical activation and hemodynamic responses between depressed and healthy adolescents remains uncertain. A systematic review on fNIRS in depression included 49 studies (C. S. H. Ho et al., 2020), but only 1 of 49 articles reported on adolescents with depression, and its conclusions were limited by the sample size ($n = 10$)(Usami et al., 2014). Therefore, in this study, multi-channel NIRS covering the prefrontal and temporal lobes was used to illustrate the differential frontotemporal cortical activation and hemodynamic response between depressed and healthy adolescents through VFT.

2. Materials and methods

2.1. Subjects

The inclusion criteria for patient participants were age between 12 and 17 years, a DSM-5 diagnosis of depression, a current single or recurrent episode, and a 17-item Hamilton Depression Scale (HAMD-17) score of at least 18, which indicates moderate depression. Symptom stability was also required. The exclusion criteria were as follows: a lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder; posttraumatic stress disorder or eating disorders; a treatment history of electroconvulsive therapy. Healthy volunteers were recruited via WeChat advertisement. Through a brief face-to-face interview, psychiatrists confirmed that there was no significant depression or anxiety state in healthy volunteers.

The HAMD-17 and the Hamilton Anxiety Scale (HAMA) were administered by trained doctoral-level interviewers to evaluate depression and anxiety symptoms. Whether the patients had engaged in self-injurious behavior or suicidal attempts was assessed through the interview and recorded in the online medical system. A total of 72 adolescent patients with depression, as well as 74 matched healthy adolescents, were recruited for the present study between April 2020 and March 2021. We recruited 63 adolescent inpatients and 9 outpatients at Ningbo Kangning Hospital. This study was approved by the ethics committee of Ningbo Kangning Hospital, and participants and their parents or legal guardians signed informed consent forms.

2.2. Verbal fluency task

The VFT was executed during daytime. The VFT consisted of a 30-s pre-task baseline, a 60-s task period, and a 60-s post-task baseline. During the pre- and post-task baseline periods, the participants were asked to repeat counting from 1 to 5. During the task period, the participants were required to construct as many phrases as possible using three commonly used characters, such as "蓝" (blue), "大" (big), and "天" (sky). The three given characters changed every 20 s during the task period to reduce the time during which the subjects were silent.

2.3. NIRS measurement

The participants were seated comfortably in a quiet room, and hemoglobin concentrations were measured using a multi-channel near-infrared optical imaging system (NirScan, Danyang Huichuang Medical Equipment Co., Ltd., China). The sampling frequency was 11 Hz, and the wavelengths were 730, 808, and 850 nm–730 nm and 850 nm were the major wavelengths, and 808 nm was used as the isotopic wavelength for correction. We used the FPz channel (10/20 international system) as the center of the middle probe; a total of 31 SD probes (consisting of 15 sources and 16 detectors) with a fixed 3-cm inter-probe distance were placed to cover each subject's bilateral PFC and temporal cortices, and the lowest probes were positioned along the Fp1–Fp2 line (Fig. 1A). A total of 48 NIRS channels were established. The channels and the corresponding brain regions are presented in Supplementary Table 1. Most inpatients participated in the fNIRS evaluation within two days after hospitalization.

2.4. Data processing and analysis

We used the NirSpark software package (HuiChuang, China) to analyze NIRS data. Data were preprocessed via the following steps. Motion artifacts were corrected by a moving SD and a cubic spline interpolation method. A bandpass filter with cut-off frequencies of

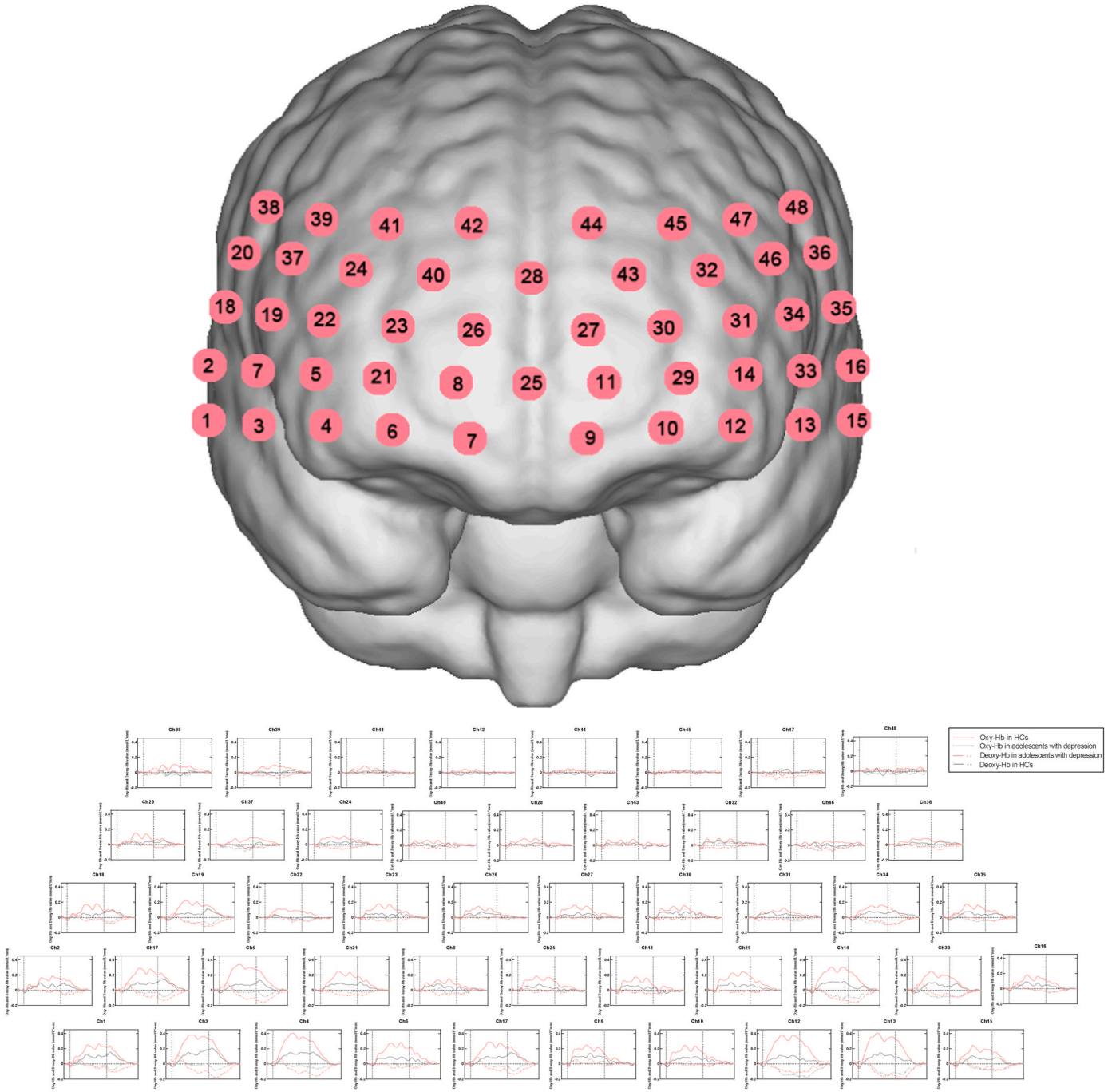

Fig. 1. (A) The position of channels. (B) Time courses of mean Oxy-Hb changes. Averaged individual waveforms of changes in Oxy-Hb and Deoxy-Hb concentrations in each channel during the VFT in HCs and adolescents with depression. Ch means Channel.

0.01–0.20 Hz was used to remove physiological noise (e.g., respiration, cardiac activity, and low-frequency signal drift). The modified Beer-Lambert law was used to convert optical densities into changes in Oxy-Hb and Deoxy-Hb concentrations. We used Oxy-Hb as our primary indicator in the following analysis because the Oxy-Hb signal generally has a better signal-to-noise ratio than Deoxy-Hb (Strangman et al., 2002). VFT block waveforms were calculated with a block range set of 0–125 s, a pre-baseline range set of 0–10 s, and a post-baseline range set of 70–125 s. We used a 60-s task period of constructing phrases as the time window to analyze mean Oxy-Hb changes. Linear fitting was applied to the data between these two baselines. According to the waveforms of individuals in all 48 channels, each channel's averaged waveforms of Oxy-Hb and Deoxy-Hb changes of all subjects in the two groups were obtained.

Statistical analysis was conducted using SPSS 16.0 (IBM Corp., NY, USA). The NirSpark software package, GraphPad Prism 8, and Adobe Illustrator software were used to generate figures and graphs. Data normality was tested via the Shapiro–Wilk test. Demographic data were analyzed by unpaired *t*-tests or chi-square tests. Unpaired *t*-tests were also used to compare Oxy-Hb changes between patients and HCs to determine any differences in brain activation between the two groups. Functional connectivity was analyzed by performing Spearman's correlation between the time series of each channel-to-channel pair. A *p*-value less than 0.05 was considered statistically significant, and all *p*-values were two-tailed. The statistical results were corrected for multiple comparisons across channels by the false discovery rate (FDR).

Additionally, we calculated the Spearman's correlation coefficient between changes in brain region activation and clinical outcomes in the depression group.

3. Results

3.1. Demographic and clinical characteristics

The demographic characteristics of subjects in each group are presented in Table 1. The depression group included 14 males and 58 females (mean age = 14.29 years; $SD = 1.34$). The healthy control group included 20 males and 54 females (mean age = 15.54 years; $SD = 1.46$). Adolescents with depression and HCs showed no difference in age ($t = -1.064$, $p > 0.05$), gender (chi-square = 2.289, $p > 0.05$), or education ($t = 0.477$, $p > 0.05$). In contrast, the adolescents with depression exhibited more self-injurious behaviors ($t = 39.823$, $p < 0.001$) and suicidal attempts ($t = 33.681$, $p < 0.001$). The mean HAMD and HAMA scores of patients were 19.43 ($SD = 4.16$) and 19.64 ($SD = 7.80$), respectively. Furthermore, we found that the HAMD scores were significantly correlated with the HAMA scores in patients ($r = 0.486$, $p < 0.001$).

3.2. Mean Oxy-Hb changes during the VFT

The grand average waveforms of Oxy-Hb and Deoxy-Hb changes in both groups are shown in Fig. 1B. The Oxy-Hb waveform of many channels in the HCs quickly rose to its peak value with a large slope during the task, and the waveform gradually returned to the baseline level after the task. During the task period, the patient group showed less cortical activation in the hemodynamic responses of Oxy-Hb than HCs at Channels 4, 21, 27, 29, and 37 (mainly located in the dorsolateral PFC), Channels 6, 7, 10, and 25 (mainly located in the frontopolar area), Channels 1, 13, and 15 (mainly located in the middle temporal gyrus), Channels 5, 12, 14, and 22 (mainly located in the pars triangularis of Broca's area), Channels 17 and 18 (located in the subcentral area), Channels 16 and 33 (mainly located in the superior temporal gyrus), Channel 19 (mainly located in the pre-motor and supplementary motor cortex), and Channel 3 (mainly located at temporopolar area) (FDR-corrected $p < 0.05$; see Fig. 2A and B and Supplementary Table 1). Deoxy-Hb with a lower signal-to-noise ratio than Oxy-Hb was not our primary indicator; therefore, its results are presented in Supplementary Table 1.

Table 1
Demographic and clinical data (mean ± *SD*).

	HCs (n = 74)	Adolescents with depression (n = 72)	t/Chi-square value	p
Demographics				
Age (year)	15.54 ± 1.46	14.29 ± 1.34	−1.064	0.289
Gender (M/F)	20/54	14/58	2.289	0.162
Education (year)	8.67 ± 2.21	8.81 ± 1.27	0.477	0.634
Clinical characteristics				
Self-injurious behavior	Yes (n = 0)/no (n = 74)	Yes (n = 49)/no (n = 23)	39.823	<0.001
Suicidal attempt	Yes (0)/no (74)	Yes (n = 30)/no (n = 42)	33.681	<0.001
HAMD-17	NA	19.43 ± 4.16	NA	NA
HAMA	NA	19.64 ± 7.80	NA	NA
Medications	NA		NA	NA
One SSRI antidepressant				
Escitalopram	NA	7	NA	NA
Fluoxetine	NA	26	NA	NA
Sertraline	NA	23	NA	NA
Venlafaxine	NA	1	NA	NA
Fluvoxamine	NA	1	NA	NA
Two antidepressants	NA	9	NA	NA
Antidepressant-antipsychotic combo	NA	5	NA	NA
Benzodiazepine	NA	18	NA	NA

Note: HAMD-17: 17-item Hamilton Depression Scale; HAMA: Hamilton Anxiety Scale; NA: not applicable.

3.3. Connectivity

After functional connectivity calculation, two 48 × 48 correlation matrices were generated for adolescents with depression and HCs (Fig. 3A and B). The mean channel-to-channel connectivity strength was 0.400 ($SD = 0.149$) for HCs and 0.303 ($SD = 0.138$) for adolescents with depression. The HC group had a higher functional connectivity strength than the depression group ($t = -15.586$, $p < 0.001$; see Fig. 3C). The HC group had a significantly higher connectivity strength than the patients at 21-pair channel-to-channel connectivity (all p-values < 0.05; see Table 2 and Fig. 3D). For exploration, we checked the channel pairs that showed significant differences in connectivity strength between groups and found that channel 22 had the highest frequency of occurrence (seven times) among channel pairs.

3.4. Correlations with clinical characteristics

For the adolescents with depression, we found significant negative correlations between HAMD scores and mean Oxy-Hb changes in.

Channel 38 ($r = -0.33$, $p < 0.01$), Channel 39 ($r = -0.34$, $p < 0.01$), Channel 41 ($r = -0.25$, $p < 0.05$), Channel 42 ($r = -0.28$, $p < 0.05$), and Channel 44 ($r = -0.27$, $p < 0.05$), and these channels were located mainly in the frontal eye fields (see Fig. 4A–E). We defined the channels located in the dorsolateral PFC as Cluster 1 (Channels 4, 21, 23, 24, 26,27, 28, 29, 30, 32, 37, 39, 40, 43, and 47) and as a region of interest and aimed to explore the relationship between the severity of depression symptoms and the activation of Cluster 1 ($p > 0.05$). However, we did not find any correlation between them. Other characteristics, including age, grade, and HAMA score, were not correlated with the mean Oxy-Hb changes of any channel.

4. Discussion

To our knowledge, this is the largest sample using fNIRS to examine the hemodynamic responses in adolescents with depression and HCs during VFT. In general, compared to HCs, the patient group displayed abnormal activation patterns. More specifically, adolescents with depression had significantly less cortical activation in the hemodynamic responses of Oxy-Hb at channels mainly located in the PFC than HCs. Moreover, we observed that the mean channel-to-channel connectivity strength of adolescents with depression was weaker than that of HCs.

A previous meta-analysis documented that, relative to healthy participants, adolescents with depression showed abnormal whole-brain activation patterns associated with altered cognitive processing (Miller et al., 2015). In this study, we found that adolescents with depression showed less cortical activation in the hemodynamic responses of Oxy-Hb than healthy subjects at channels mainly located in the PFC cortex. The Oxy-Hb curve of healthy participants showed that, mainly in the inferior frontal gyrus, cortical activation increased rapidly at the beginning of the VFT, maintained a high level during VFT, and then decreased rapidly at the end of the task. However, the Oxy-Hb curve of the depression group during the VFT was indicative of executive dysfunction, with a low activity level at all channels, which was in keeping with previous NIR-related research on adult depression (Feng et al., 2019; M. K. Yeung and Lin, 2021). The VFT is thought to be one of the measures of EF, sensitive to frontal and temporal cortex damage (Abrahams et al., 2004; Fusar-Poli et al., 2011; He et al., 2018) and related to verbal processes.

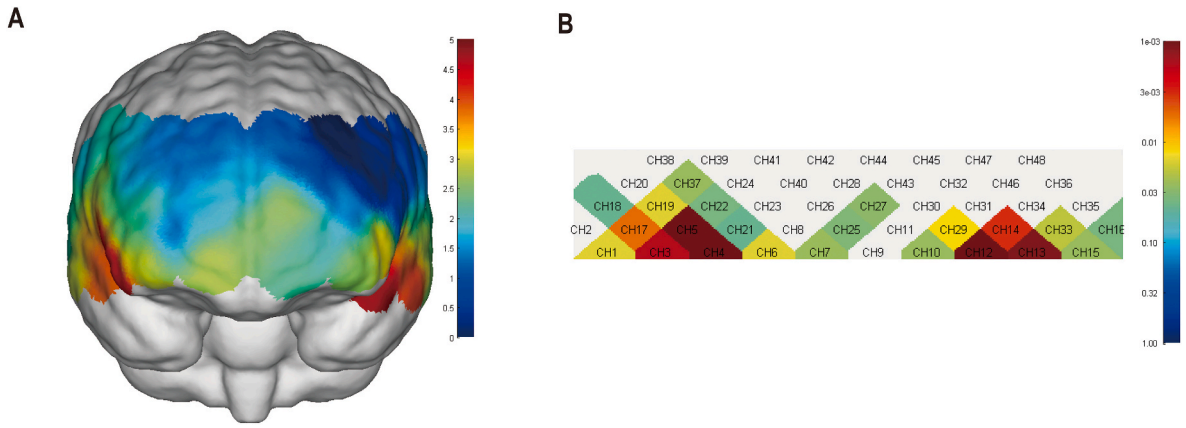

Fig. 2. (A, B) *p*-values of each channel activation for patients compared to HCs.

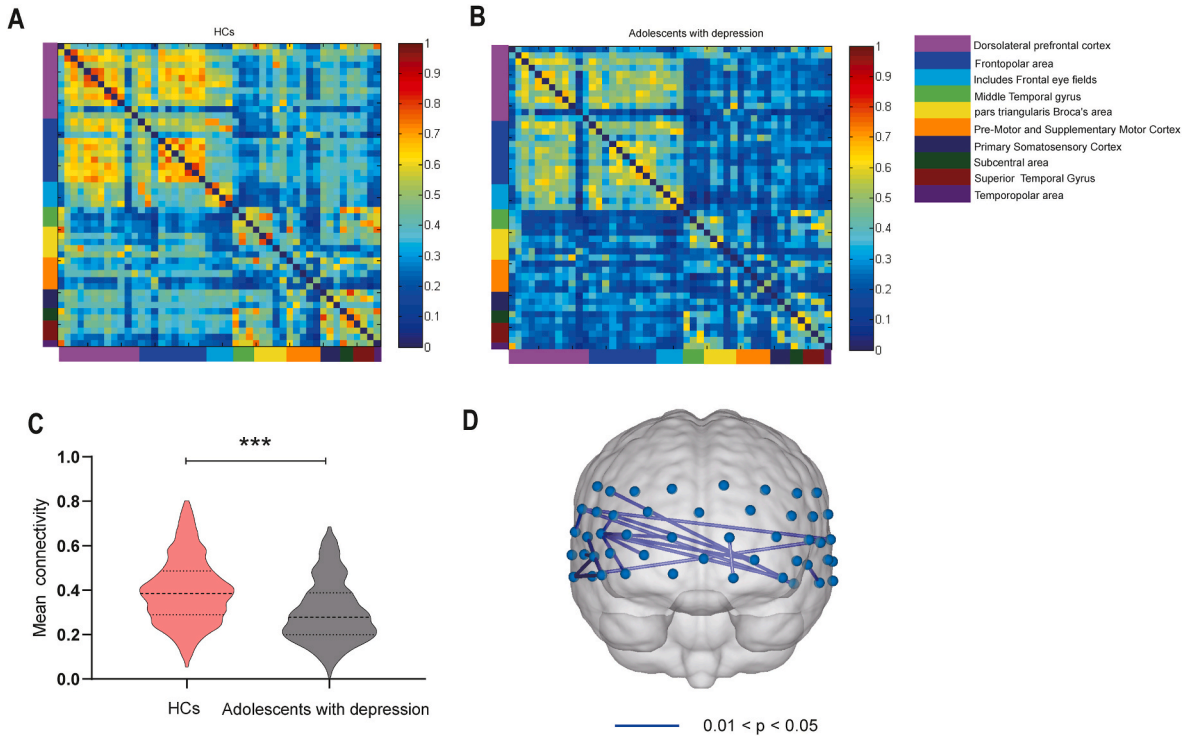

Fig. 3. (A, B) Connectivity between the hemodynamic response of 48 channels. (C) The HC group had a higher mean channel-to-channel connectivity strength than the depression group. (D) Twenty-one pairs had significantly higher channel-to-channel connectivity in the HC group than in the patient group (FDR-corrected $p < 0.05$). ***$p < 0.001$.

Previous studies found activation in the dorsal anterior cingulate cortex, left inferior frontal gyrus, left posterior temporal lobe, left inferior parietal lobe, and medial supplementary motor area (SMA) under the VFT (Allen and Fong, 2008; Wagner et al., 2014). The altered hemodynamic response of the prefrontal and temporal cortex is a possible underlying mechanism of EF dysfunction in adolescents with depression.

The brain is considered a dynamic and interconnected functional network. Most neurobiological studies on adolescents with depression have investigated the resting-state functional connectivity (RSFC). For example, researchers have observed that adolescents with depression demonstrated a weaker RSFC between the right amygdala and right superior frontal gyrus and a decreased connectivity between the right insula and right middle frontal gyrus (Lee et al., 2019). To our knowledge, very few studies on depressed adolescents have centered on the task-related functional connectivity. In fact, RSFC could illustrate the spontaneous fluctuations in brain activity (Dickerson, 2007; Fox and Raichle, 2007), but a better understanding of task-related functional connectivity could contribute to knowing more core features of the cognitive function of adolescents with depression. Our study found that, relative to HCs, adolescents with depression showed a characteristic weaker pattern of frontotemporal functional connectivity, inflicting an abnormal interrelationship among the neurophysiological activities of the frontotemporal lobe. The frontotemporal connectivity alterations may be an important aspect of the pathophysiology of depression. The VFT is associated with the process of retrieval. Considerable progress has been made in understanding the crucial roles of the temporal and frontal lobes for memory(Foster, 1996; Simons and Spiers, 2003). While performing the VFT, the prefrontal and temporal lobe might form a part of a memory functional network to execute the memory retrieval process (Simons and Spiers, 2003). The abnormal connectivity pattern of the frontotemporal lobe in the retrieval process is also an important manifestation of EF impairment in adolescents with depression. Furthermore,

Table 2
Channel pairs with significant differences in connectivity strength between groups (mean ± *SD*).

Channel to channel	Connectivity strength		*t*	FDR-corrected *p*
	Adolescents with depression	HCs		
1–4	0.33 ± 0.50	0.61 ± 0.34	−3.876	0.033
1–5	0.26 ± 0.50	0.57 ± 0.39	−4.260	0.025
1–35	0.33 ± 0.47	0.47 ± 0.42	−3.391	0.048
4–5	0.26 ± 0.49	0.78 ± 0.24	−3.790	0.033
4–19	0.22 ± 0.53	0.64 ± 0.32	−3.668	0.033
5–17	0.54 ± 0.47	0.70 ± 0.3	−3.675	0.033
5–19	0.37 ± 0.53	0.76 ± 0.22	−3.878	0.033
6–22	0.46 ± 0.51	0.5 ± 0.41	−3.732	0.033
8–22	0.5 ± 0.53	0.43 ± 0.43	−3.605	0.033
9–27	0.21 ± 0.47	0.76 ± 0.26	−3.669	0.033
10–22	0.14 ± 0.51	0.48 ± 0.34	−4.007	0.030
10–39	0.53 ± 0.47	0.51 ± 0.39	−3.419	0.047
11–22	0.19 ± 0.53	0.46 ± 0.36	−4.127	0.025
11–24	0.27 ± 0.48	0.6 ± 0.28	−3.582	0.035
12–20	0.15 ± 0.46	0.44 ± 0.39	−3.600	0.033
13–14	0.36 ± 0.49	0.75 ± 0.26	−3.540	0.037
18–20	0.19 ± 0.4	0.8 ± 0.24	−3.488	0.041
20–35	0.52 ± 0.47	0.52 ± 0.44	−3.630	0.033
22–23	0.61 ± 0.48	0.54 ± 0.38	−3.548	0.036
22–24	0.25 ± 0.48	0.73 ± 0.27	−4.204	0.025
22–26	0.28 ± 0.51	0.37 ± 0.44	−3.643	0.033

research has shown that abnormal modulation of effective fronto-temporal connectivity is also associated with the response to happy and sad face emotions in adult depression (Goulden et al., 2012), suggesting possible impairments in processing emotional face stimuli in adolescents with depression. In addition, Channel 22, located in the pars triangularis of Broca's area (BA 45), had the highest frequency of occurrence (seven times) in channel pairs, with significant differences in connectivity strength between groups. BA 45 involves the processing of phonemic and semantic fluency tasks(Wagner et al., 2014); thus, we considered whether there might be verbal processing impairments in adolescents with depression.

We found that, although there were significant negative correlations between HAMD scores and mean Oxy-Hb changes in Channels 38, 39, 41, 42, and 44 in the depression group, at those channels with large cortical activation differences between groups, especially located in the dorsolateral PFC, no association was observed between the HAMD score and PFC hemodynamic activation. This demonstrated that the changed Oxy-Hb PFC concentration during VFT was not sensitive to depression symptoms. This was not in line with previous research (Liu et al., 2014; Uemura et al., 2014). The influence of antidepressants on the NIRS signals should be attached importance (Takamiya et al., 2017; Tomioka et al., 2015). We thought the inconsistency could be due to the different medication/treatment status of patients—some patients had regularly taken medication before hospitalization, while some had started taking medication after hospitalization, and the effect of equivalent doses was not analyzed in hemodynamic responses. Furthermore, our study revealed that hemodynamic responses did not differ between suicidal attempters and non-attempters. However, previous studies found that depressed patients with suicidal attempts, compared with non-attempters, exhibited reduced hemodynamic responses in the left PFC (Pu et al., 2015; Tsujii et al., 2017).

5. Limitations

There were several limitations to the current study. First, because our study employed a cross-sectional design, we were unable to monitor treatment responses to explore potential predictions for longitudinal prognoses. Therefore, long-term follow-up and NIRS measurements should be conducted to investigate predictive biomarkers related to the onset of depression, clinical symptoms, and functional outcomes. Identification of intrinsic brain activity differences by fNIRS between adolescents with depression and HCs is helpful for clinical diagnosis, treatment, and prognosis. Second, we did not analyze the number of phrases to evaluate the behavior performance on the VFT. Finally, our

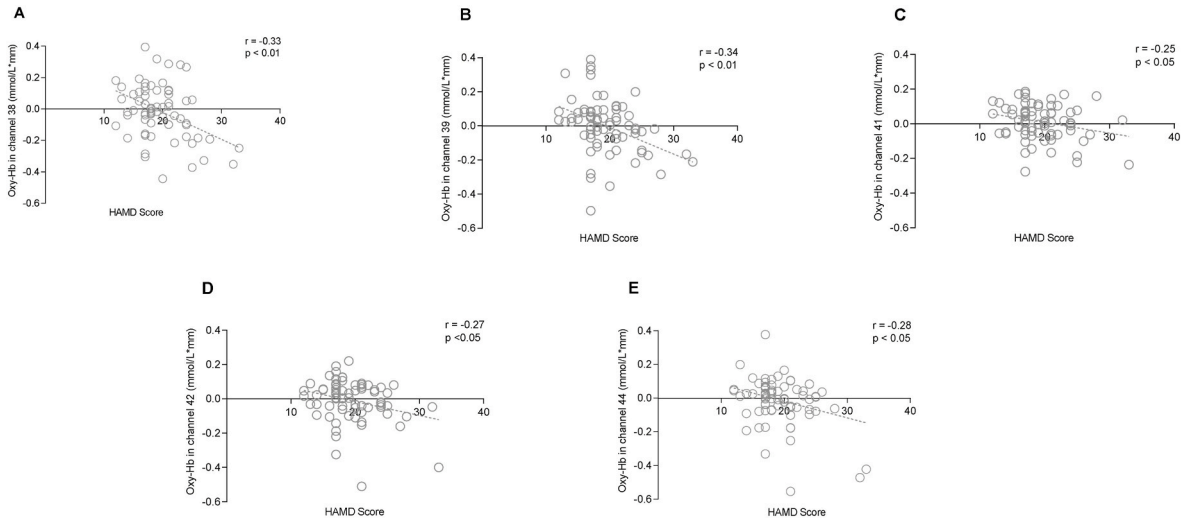

Fig. 4. Associations between channel Oxy-Hb changes and clinical characteristics in the depression group.

study did not control for medications taken by participants; hence, we cannot rule out the influence of drugs on our present findings.

6. Conclusion

In conclusion, our findings reveal that the fNIRS-VFT paradigm detects the alterations of cortical activation and functional connectivity during the VFT for adolescent-onset depression but is not sensitive to depression symptoms.

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Author statement

All authors have seen and approved the final version of the manuscript being submitted. We warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

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Author contributions

WW and DS designed the study; XL and FC performed the study, analyzed the results, and wrote the paper together; SH, BW, HZ, and ZZ contributed to sample collection and clinical evaluations; WZ, XM, and XL revised the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

No conflict of interest was reported by the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.01.040.

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