FUNCTIONAL NEAR-INFRARED DIFFUSE OPTICAL SPECTROSCOPY (fNIRS) TO EXPLORE MENTAL HEALTH

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FUNCTIONAL NEAR-INFRARED DIFFUSE OPTICAL SPECTROSCOPY (fNIRS) TO EXPLORE MENTAL HEALTH

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Editorial: Functional near-infrared diffuse optical spectroscopy (fNIRS) to explore mental health

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Editorial on the Research Topic
Functional near-infrared diffuse optical spectroscopy (fNIRS) to explore mental health

Mental health disorders have been a long-term concern for society in general and have thus been increasingly studied by the scientific community. On the other hand, clinical assessment of mental health has heavily relied on subjective questionnaires and score sheets, due to a lack of objective measuring modalities. Over years, the functional near-infrared diffuse optical spectroscopy (fNIRS) has been attracting the attention of scientists and clinicians in the psychiatric field as a low cost and highly sensitive approach to assess cerebral hemodynamics that are closely associated with human functional capacities as well as symptoms of mental disorders.

This topic collection contains the review and research articles reporting the fNIRS methods for evaluating the mental health and probing various psychiatric diseases.The utilized methodologies & protocol as well as the key discoveries are summarized and highlighted in the following paragraphs.

Reviews of fNIRS on mental disorders

In the article authored by Crum, the mental health and cognitive reconstruction of ecological neuroscience by fNIRS are extensively reviewed. The reviews reveal that the broad investigation of brain could be carried out by the fNIRS, which is helpful in design of the experimental tasks for mental health cultivation and cognitive interventions.

Suicide is the most severe tragedy due to long-term major depressive disorder (MDD). However, there are no established biomarker for predicting suicidality. In the article authored by Lee et al., a total of seven studies on use of fNIRS for assessment and prediction of suicidality are reviewed. In all the studies, the suicidal subjects demonstrated the reduced cerebral hemodynamic responses to the tasks, when compared with the healthy controls. Moreover, one of these studies also found a correlation between the fNIRS signals and severity of the suicidality. This review article implies the great value of fNIRS for predicting and preventing the tragedy of suicide.

The spontaneous brain activity at rest is a nature status in which the brain dysfunction might also be reflected, especially for the severe mental disorders such as schizophrenia. Yanagi et al. conducted a review on use of fNIRS to detect the cerebral malfunction in schizophrenia patients. The related studies emphasize the low frequency (0.01–0.08 Hz) of the cerebral hemodynamics, from which the parameter of the amplitude of low frequency fluctuations (ALFF), or fractional ALFF, were extracted. The review analysis shows that both parameters in the frontal cortex were decreased during the rest states in schizophrenia patients, indicating the consistent evidences of spontaneous brain activity for probing schizophrenia by fNIRS.

Studies of fNIRS on diagnostics of psychiatric diseases

A large portion of the research articles contained in this topic collection are regarding the task protocol and the analysis approaches. In a study conducted by Ishii et al., a single-event related Japanese Shiritori task (i.e., word production) was applied to both MDD patients and healthy controls, and the fNIRS technology was used to evaluate the cerebral responses. During the period of word production, the MDD patients were found to have significantly smaller hemodynamic activation in prefrontal cortex area, and the oxy-hemoglobin changes were negatively correlated with the HAMD score. The outcomes presented in the study support the promise of combing the word production task and fNIRS for assessment of the cerebral function in MDD patients.

Verbal fluency task (VFT) is one of the most popular protocols to induce brain cortex activation, which is fully reflected in this topic collection. In the article authored by Wen et al., the VFT was compared with non-task (i.e., spontaneous brain activity), and the cerebral oxygenation activation on MDD, anxiety and depression (A&D) and healthy control (HC) populations were assessed by fNIRS. The outcomes show that VFT greatly enhanced the magnitude in power spectral analyses, but its intensity needs to be elevated for better characterizing the psychiatric diseases such as MDD and A&D.

In addition to VFT, other physiological manipulation are also emerging as alternative protocol to activate the brain cortex in psychiatric field. In this topic collection, Xiang et al. applied the Tower of London (TOL, i.e., the counting of picture movement) to the MDD and schizophrenia patients and compared with the healthy controls. During the performance of both protocols, the fNIRS successfully probed the difference in cerebral hemodynamics among the three groups, indicating the potential of TOL for distinguishing the psychiatric diseases from the healthy population. In another study conducted by Lang et al., the VFT protocol was compared with the high-level cognition task (HCT, in which the logical categorization is involved), and the prefrontal cortex oxygenation were measured on A&D patients and healthy controls. The results exhibit that more oxygen increment were activated by HCT than VFT, hence verifying it as an competitive protocol for A&D detection. Additionally, Tung et al. investigated the brain network and power during VFT task, and the fNIRS was used to assess the brain activation. The outcomes reveal that the high-functioning and low-functioning participants are different in activating the brain region connectivity, and the method of network topology appears to perform better than the method of activation power in analyzing the fNIRS data. This study also indicates that the left frontotemporal is a key region that actively responds to the VFT task.

In the above studies, the single parameter (e.g., average value, integral value, reaction time) extracted from oxygenation data were usually adopted to evaluate the brain activation, which may not be sufficient to differentiate among various disordered mental and healthy one. In recent year, several advanced data analysis approaches have been developed to improve the diagnostic accuracy for psychiatric diseases. As one of the representative examples, Chou et al. made the first attempt to utilize the two machine learning approaches, i.e., support vector machine (SVM) and deep neural network (DNN), to classify the first-episode schizophrenia (FES) patients and healthy subjects who have received the fNIRS during VTF tasks. The integral value and centroid value were used as the feature parameters for the machine learning. Both approaches were found to perform well in classifying the FES from healthy controls, with the satisfactory accuracy, sensitivity, and specificity. This study supports the use of artificial intelligence methods for screening of the psychiatric diseases.

Studies of fNIRS on therapeutic evaluation of psychiatric diseases

Methylphenidate (MPH) is a widely-used medicine to treat the children with attention deficit hyperactivity disorder (ADHD) or minor brain dysfunction. Thus far, the standard behavior approach to evaluate the MPH's effects have not been well established. Jang et al. used virtual reality working memory task to stimulate the children with ADHD who also received the MPH treatment, and fNIRS was used to assess the cerebral

oxygenation changes throughout the protocol. The outcomes show that reaction time of oxygen data was shorten after MPH treatment, indicating the potential of fNIRS in assessment of the therapeutic effects.

Acupuncture is a physical modality to treat a variety of mental disorders. Nevertheless, there are no objective criteria to evaluate the treatment effects. In a study conducted by Zhang et al., the VFT task was applied to the MDD patients after they received the acupuncture treatment and measured by fNIRS. Based on the data of cerebral hemodynamics, a single session of acupuncture did not show to improve the brain activation with the patients with mild and moderate depression. By contrast, the significant improvement of brain activation was observed in severe depression patients, and the degree of activation is correlated with the HAMD score. This study demonstrates the possibility of using fNIRS for therapeutic evaluation of mental disorders. Similarly, in another study on treatment of depression patient with repetitive transcranial magnetic stimulation (rTMS) (Kawabata et al.), the cerebral hemodynamic enhancement were also observed, indicating the great promising of fNRS for timely evaluation of therapy effects.

We hope this topic collection will provide timely and sufficient information for the scientists and clinicians working in field of psychiatry, particularly for those with fNIRS applications. We believe the emerging fNIRS technologies, along with the advanced brain activation protocol and data analysis approaches, will be great beneficial for diagnosis and therapy of various psychiatric diseases.

Author contributions

YS wrote the draft of editorial article. CH and TL revised the content and involved in the content writing discussion. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Use of Virtual Reality Working Memory Task and Functional Near-Infrared Spectroscopy to Assess Brain Hemodynamic Responses to Methylphenidate in ADHD Children

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Virtual reality (VR) neuropsychological tests have emerged as a method to explore drug effects in real-life contexts in attention deficit hyperactivity disorder (ADHD) children. Functional near-infrared spectroscopy (fNIRS) is a useful tool to measure brain activity during VR tasks in ADHD children with motor restlessness. The present study aimed to explore the acute effects of methylphenidate (MPH) on behavioral performance and brain activity during a VR-based working memory task simulating real-life classroom settings in ADHD children. In total, 23 children with ADHD performed a VR n-back task before and 2 h after MPH administration concurrent with measurements of oxygenated hemoglobin signal changes with fNIRS. Altogether, 12 healthy control (HC) subjects participated in the same task but did not receive MPH treatment. Reaction time (RT) was shortened after MPH treatment in the 1-back condition, but changes in brain activation were not observed. In the 2-back condition, activation of the left dorsolateral prefrontal cortex (DLPFC) and bilateral medial prefrontal cortex (mPFC) was decreased alongside behavioral changes such as shorter RT, lower RT variability, and higher accuracy after MPH administration. Bilateral mPFC activation in the 2-back condition inversely correlated with task accuracy in the pre-MPH condition; this inverse correlation was not observed after MPH administration. In ADHD children, deactivation of the default mode network mediated by mPFC reduced during high working memory load, which was restored through MPH treatment. Our results suggest that the combination of VR classroom tasks and fNIRS examination makes it easy to assess drug effects on brain activity in ADHD children in settings simulating real-life.

Keywords: virtual reality, fNIRS, ADHD, working memory, n-back, Methylphenidate, mPFC

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children. ADHD is defined by age-inappropriate symptoms of inattention, impulsivity, and hyperactivity. Patients with ADHD exhibit complex multisystem impairments in fronto-cingulo-striato-thalamic and fronto-parieto-cerebellar networks that mediate attention, inhibition, working memory, and timing (1). In addition to higher-order cognitive functions, abnormalities in sensorimotor processing and the default mode network have been identified in ADHD (1). ADHD affects approximately 5% of school-aged children and often persists into adolescence and adulthood (2). Consequently, patients with ADHD often experience impaired academic and social function, which increases the risk of other comorbidities including antisocial behavior, oppositional defiant disorder, and substance abuse (3). Hence, early diagnosis of ADHD and appropriate intervention are critical.

To date, administration of psychostimulant drugs, especially methylphenidate (MPH), has been a treatment of choice for ADHD children (4). However, in up to 30% of patients, MPH is ineffective or can be difficult to administer due to side effects such as insomnia, appetite loss, headaches, and irritability (5). Therefore, studies have been conducted to identify objective functional biomarkers by exploring the neural correlates of MPH effects (1). In these studies, various neuropsychological tests have been used to measure cognitive functions of interest in ADHD subjects. However, the utility of such computer-based tests for evaluating real-world performance is limited, because performance in a laboratory research setting may lack real-world translation. Indeed, traditional computerized neuropsychological tests are criticized for their lack of ecological validity. Similarly, there has been limited progress in research on how psychostimulants operate in real-life environments.

To overcome these limitations, the utility of virtual reality (VR) has been recognized in terms of diagnosis and treatment of ADHD. VR facilitates the creation of dynamic, immersive environments with three-dimensional stimuli in which attention can be tested in an environment comparable to that experienced in the real world, improving ecological validity (6). In the field of assessment, numerous studies have confirmed that continuous performance tests embedded in VR (VR-CPT) are as sensitive and accurate as traditional CPT (7–9). In addition, the efficacy of MPH has been verified through VR-CPT (10) and the effectiveness of VR rehabilitation programs, such as VR neurofeedback or cognitive training, have been demonstrated (6, 11). In a VR environment, training motivation is fostered by providing real-life contexts that connect cognitive training to goals of everyday life.

However, few studies have evaluated brain activity during VR tasks in ADHD patients. One of the reasons for the paucity of research on brain activity during VR tasks is due to difficulties in examination. It is physically challenging to perform functional magnetic resonance imaging (fMRI) or single-photon emission computed tomography (SPECT) scanning while using VR devices, especially for young ADHD patients with motor restlessness. Moreover, research on drug effects requires repeated pre- and post-administration imaging, which necessitates employment of a simple and easy tool to measure brain function. In this context, research using functional near-infrared spectroscopy (fNIRS) has been growing. fNIRS is a non-invasive imaging technique that uses near-infrared light to measure functional brain activity through changes in concentration of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (Hb). The main advantage of fNIRS over other functional neuroimaging modalities such as fMRI, SPECT, or magnetoencephalography (MEG) is its portability (12). The fMRI, MEG, and SPECT involve the use of large-sized equipment and the patient need to be in the supine position (13). In contrast, fNIRS facilitates the investigation of brain activation in ecologically valid settings as well as repetitive measurements with low-cost, safe, transportable instrumentation in the natural position (14). Furthermore, it is less sensitive to movement artifacts and shows greater spatial resolution than EEG. However, fNIRS can provide information on only cortical activity (13). Its inability to provide information on subcortical levels and cortical-subcortical connectivity can limit its use in studies on psychiatric disorders.

Nevertheless, over the last few years, fNIRS has been used extensively to investigate cortical alterations in patients with various psychiatric disorders, such as schizophrenia; mood, anxiety, and eating disorders; and substance use disorder (13). For example, using fNIRS, Kawakubo et al. (2009) found bilateral prefrontal cortex (PFC) hypoactivation during the verbal fluency task in patients on the autism spectrum disorder (15). In addition, it has been used to measure the therapeutic effect and efficacy of treatment and to identify life-time brain function development in patients with neurodevelopmental disorders such as ADHD to neurodegenerative disorders (13). Considering these previous studies and the advantages mentioned above, fNIRS is seen as a particularly suitable tool for evaluating participants who experience unavoidable movements, such as ADHD patients in clinical settings (16).

Various studies using fNIRS have been conducted in ADHD patients. In most studies using tasks for evaluating attention or inhibition, ADHD patients exhibited lower prefrontal activity than that of healthy control (HC) subjects during the task (17–20) although the results of studies using working memory tasks have been equivocal (21, 22). Furthermore, many studies have investigated the hemodynamic responses of MPH treatments using fNIRS, demonstrating that reduced right inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) activation in ADHD patients compared to HCs was normalized after single-dose MPH administration (23, 24). These results indicate that the neural correlates of MPH effects can be verified with fNIRS.

However, there has been limited research investigating the effects of medication on brain activity using fNIRS in VR tasks which simulates real-life classroom settings. As cognitive skills are ultimately applied in the classroom setting, especially in school aged children, attention and executive function can be better encapsulated in the virtual classroom environment than using traditional computerized neuropsychological tests. Furthermore, previous studies used

the Go/No-go and oddball tasks mainly to explore inhibitory function. However, inhibition alone is insufficient to explain the pathophysiological mechanisms of ADHD. Working memory (WM) impairment is considered a core deficit of ADHD associated with prefrontal dysfunction.

WM is defined as the ability to maintain information in an easily accessible state for a short period of time. According to the state-based model, the working memory contents are determined by perceptual & long-term memory representations being in a particular state of accessibility, maintained by neural activities controlled by the attentional processes (**Supplementary Figure 1**) (25). Information maintenance, an important element of working memory, is regulated by well-operated attentional processes, established by persistent neural activities in the relevant working areas (26). WM plays an important role in rapid processing and attention, and in turn, a large attention span and fast processing speed promote WM (27, 28). Rather than being determined by single brain region, WM appears to depend on good synchronization with the PFC and other brain areas, for example, the parietal cortex (27). In this process, the PFC is responsible for covering task-relevant information and for organizing fronto-parietal activity for sustained attention (29). For efficient activation of the WM network during task execution, the default mode network (DMN), which is activated in baseline cognitive state, performs deactivation coupling (30–32). The DMN is a large-scale brain network that consists of the core region of the medial prefrontal cortex (mPFC) and the postural cingulate/precuneus, along with inferior parietal lobule, lateral temporal cortex, and hippocampus (33). The DMN is largely related to mind wandering, which has known to affect performance of classroom of ADHD patients (34, 35). WM also plays an important role in maintaining focused behavior and improving classroom performance (36).

The N-back task is a well-known working memory paradigm which has been used extensively in functional neuroimaging studies on ADHD (37). A few studies investigated cortical brain activation using fNIRS during the n-back task. Herff et al. (2014) have found that different n-back conditions can be distinguished throughout fNIRS with high accuracy by the changes in hemodynamic response depending on the mental workload (38). Other studies using fNIRS also identified lower prefrontal complexity in patients with ADHD compared to in healthy control during the n-back task (39). However, few studies have explored the effects of MPH in relation to working memory using fNIRS in children with ADHD.

Based on these findings, we aimed to investigate the acute effects of MPH on behavioral performance and brain activity of children with ADHD during a VR n-back task in a virtual classroom setting. To the best of our knowledge, this is the first study using a VR-based working memory task and fNIRS to explore the effects of MPH in ADHD children.

METHODS

Subjects

Altogether, 23 right-handed Korean children with ADHD (age range, 7–16 years; mean age, 9.96 ± 2.82) and 12 healthy control (HC) children (age range, 7–14 years; mean age, 11.33 ± 2.93) participated in this study. The number of participants required for adequate statistical power was based on previous studies that investigated drug effects in ADHD patients through fNIRS (23, 40–42) and a previous study that described the optimal design for functional brain imaging (43). The detailed demographic and clinical characteristics of subjects are listed in **Table 1**. ADHD patients were recruited by posting a notice on the outpatient clinic of Gangnam Severance Hospital, and the HC were recruited by posting announcements to the local internet community. All participants were interviewed by a psychiatrist to confirm the ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (44). The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID 6.0) was administered to all participants by certified psychologists (45). Exclusion criteria for participants with ADHD were clinically significant medical or neurological disorders, developmental disabilities including autism spectrum disorder, intellectual disabilities, speech impairments, severe learning disabilities, schizophrenia, bipolar disorder, substance and/or alcohol use disorders, IQ <70, or illiteracy to read consent. Participants in the HC group were excluded if they had current or past history of mental illness, clinically significant medical disease or neurological deficits, IQ <70, and/or illiteracy to read consent. IQ was measured with the Wechsler Intelligence Scale for children (WISC-IV).

Several measurements were conducted to assess the psychological state of participants. The ADHD Rating Scales (ADHD-RS), an 18-question parent rating scale, was used to identify the presence of ADHD in children. Behavioral problems were assessed with the Korean version of the Child Behavior Checklist (CBCL), an 118-item parent-rated scale which queries behavioral problems in the past 6 months (46); Children's Depression Inventory (CDI) (47), a 27-item self-report scale to assess depressive symptoms (48); and State-Trait Anxiety Inventory for Children (STAI-C), a 20-item self-report scale were used to measure anxiety symptoms (49, 50). Simulator Sickness Questionnaire (SSQ), a 16-item self-report questionnaire was used to assess participants' subjective discomfort (disorientation, oculomotor symptoms, and nausea) after exposure to VR programs to measure simulator sickness due to discrepancies between vision and motion after VR use (51).

The protocol used for this study was approved by the Institutional Review Board of Yonsei University College of Medicine Gangnam Severance Hospital. Written informed consent and assent were obtained from all participants and one of their parents.

Procedure

We investigated the effects of ADHD medication in a controlled pre- and post-MPH study design, whereby participants performed n-back tasks with the 1-back and 2-back conditions. The experimental protocol is summarized in **Figure 1A**. Participants underwent a medication washout period of 2 days before the examination. On the examination day, participants were first assessed for demographic, clinical characteristics, and IQ. Participants subsequently performed a practice session

TABLE 1 | Demographic and clinical characteristics by group, comprising attention deficit hyperactivity disorder (ADHD) vs. healthy control (HC) subjects.

	ADHD ($n = 23$)	HC ($n = 12$)		
	Mean (SD)	Mean (SD)	X2/t	*p*
Age (years)	9.96 (2.82)	11.33 (2.93)	1.353	0.185
% Female	30.43	50	1.293	0.255
FSIQ	105.6 (12.81)	107.92 (10.6)	0.527	0.602
ADHD-RS-IV total	20.96 (14.51)	6.08 (3.68)	−4.64	<0.001***
ADHD-RS-inattention	12.3 (7.59)	4.25 (2.53)	−4.62	<0.001***
ADHD-RS-hyperactivity-impulsive	8.65 (7.55)	1.83 (1.7)	−4.137	<0.001***
CBCL total	62.41 (9.92)	49.08 (6.71)	−4.15	<0.001***
CBCL attention problem scores	64.41 (12.14)	52.58 (3.78)	−4.21	<0.001***
CDI	8.52 (6.1)	10.25 (7.85)	0.72	0.476
STAI-C				
STAI-C trait	29.09 (6.87)	30 (6.59)	0.378	0.708
STAI-C state	28.09 (8.96)	30.83 (7.04)	0.921	0.364
SSQ	18.14(22.32)	39.1(36.77)	1.983	0.057
MPH dose (mg)	29.35 (16.23)			
Comorbidity				
Tic disorder	$n = 1$			

*ADHD, attention deficit hyperactivity disorder; HC, Healthy Control; SD, standard deviation; FSIQ, full scale intelligence quotient; ADHD-RS, ADHD rating scale; CBCL, child behavior checklist; CDI, children's depression inventory; STAI-C, state-trait anxiety inventory for children; SSQ, simulator sickness questionnaire; MPH, methylphenidate. ***$p < 0.001$.*

to familiarize themselves with the VR environment and tasks. Participants then underwent two test sessions, one before dosing and the other 2 h after dosing. After the first session, MPH (Concerta, Metadate or Medikinet) was administered orally. Experimental doses were the same as the participants' regular dose. Each test session was conducted in the order of the introduction session followed by an n-back task. The HC performed only one test session after the practice session.

Virtual Reality Environment

The background of this VR task was a virtual classroom. The participants began by finding themselves in a typical classroom in a Korean school with desks facing ahead and blackboards in front of them. The participants' point of view was of the first person, facing the teacher, with other avatar classmates seated nearby (**Figure 1B**). The message "Please feel free to look around before class" offered the participants 15 s to adjust to the VR environment. A teacher avatar entered and informed participants of the rules of the N-back task, introduced as a game called "ABC Dungeon." The participants first carried out a practice task, called "game tutorial" comprising 10 stimuli for each condition. The practice session was repeated if the participants made more errors than the set standard. Before the actual task, the teacher avatar briefly explained the fNIRS device, and participants were encouraged to remain as still as possible. After receiving instructions, participants were guided to wear fNIRS gear, followed by the main task.

The n-back task consisted of three block sets. Each block set contained alternating 1-back (low WM load) and 2-back (high WM), and in-between 0-back (control) conditions (block length, 40 s; 20 trials with random display of capitalized letters from "A" to "G"). Each stimulus was presented for 500 ms with an interstimulus interval of 1.5 s. Overall block-set time was 160 s, and total session time was 8 min. The total number of trials in experimental conditions was 120. Subjects were instructed to press the button with their right index finger as quickly as possible, when the current stimulus was the same as the previously shown letter (1-back), or with the letter shown two screens back (2-back). Since it is extremely difficult for young ADHD patients to remain still when not performing a task, our baseline (control) task required participants to respond to each stimulus with a button press to rule out motion artifacts and equalize the motion load with the experimental task. To diminish habituation or practice effects in the post-MPH session, two task versions with different stimuli were employed. These two versions were randomly assigned to each subject.

The software was written in Visual Studio 2017(C#) and designed on Unity 2018.2. The avatars and structures comprising the virtual environment were built using a 3Ds Max 2014. We used the 3D development platform (Vizard 5.1; WorldViz, Santa Barbara, CA, USA) to develop the virtual classroom environment. Our VR classroom was implemented in the VR theater which provides a semi-immersive environment with a 2.18-m radius curved screen, providing 150° field-of-view (PACOM Display System Inc, Suwon, Kyungki-do, Republic of Korea; **Figure 1C**). Two projectors with HDTV resolution (1,960 × 1,080 pixels) were used to project the programs onto the screen. The system was driven by a desktop computer with Microsoft Windows 10 operating system, including a high-end graphics card (NVIDIA GeForce GTX 970) and 16 GB RAM of graphics memory.

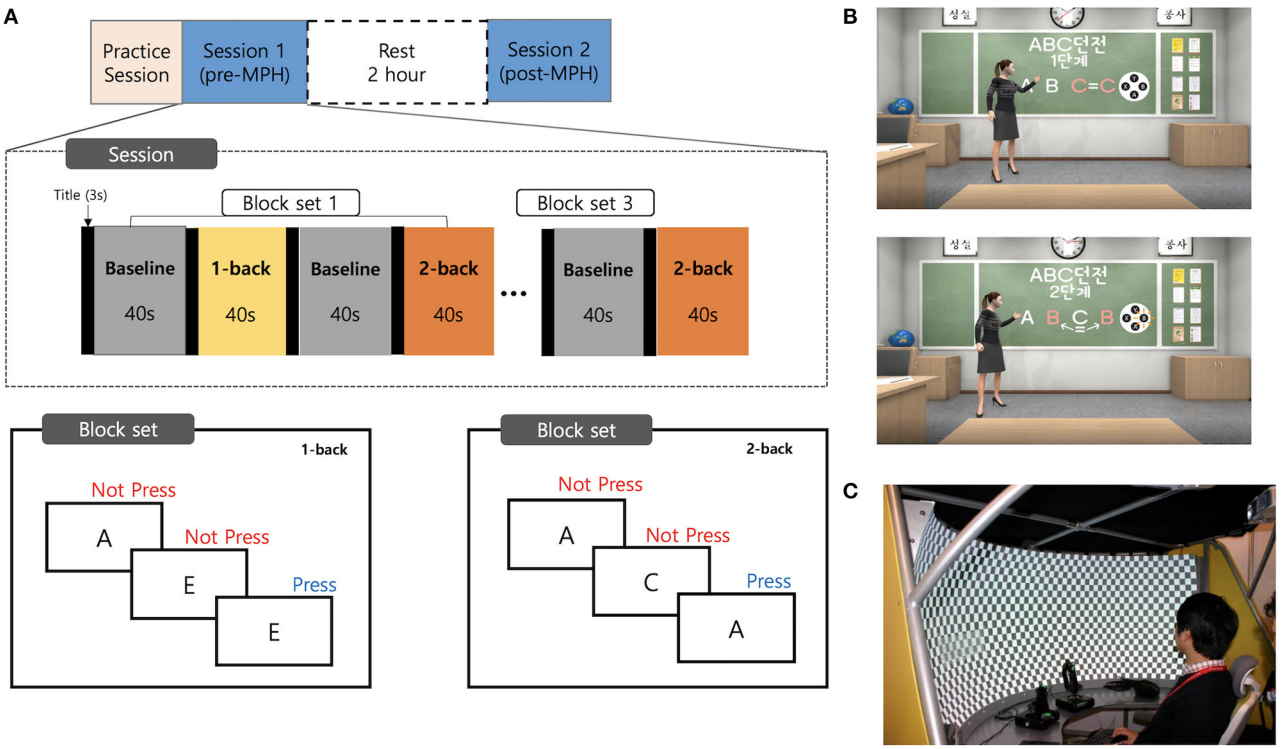

FIGURE 1 | Experimental design and virtual reality environment. **(A)** A schematic representation of the flow of pre- and post-MPH n-back task sessions. **(B)** Screenshots of the virtual classroom during introduction of the n-back task. **(C)** The virtual reality theater with the curved screen. MPH, methylphenidate.

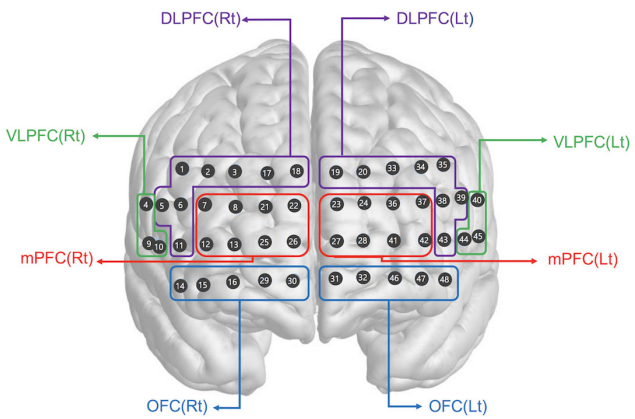

FIGURE 2 | Spatial profiles of fNIRS channels. The fNIRS probes were attached to the prefrontal area. The included channels are represented according to brain region location. DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; Rt, right; Lt, left.

fNIRS Measurements

We used a multichannel high density fNIRS device (NIRSIT; OBELAB, Seoul, Korea), which consisted of 24 laser diodes emitting two wavelengths (780/850 nm) and 32 photodetectors separated by a 1.5 cm unit distance. The laser and detector pairs were separated at a 3 cm distance. Sampling rate was 8.138 Hz. The alignment of 48 channels is shown in **Figure 2**. The fNIRS device was placed on the head according to the relevant standard positions of the International 10–20 system for EEG electrode locations. The center of the bottom line of the measuring channel was located on the FPZ. The threshold of signal-to-noise ratio was 30 dB such that slow drift of physiological noise and environmental noise was removed after filtering through a band-pass filter (0.005–0.1 Hz) of detected light signals. The modified Beer Lambert Law (MBLL) was used to convert raw light intensities into concentration changes in oxygenated hemoglobin (ΔHbO_2). The averaged oxy-Hb concentration changes ($avg\Delta HbO_2$) during the task period baselined from 5 s before task initiation was calculated in each channel after block averaging of multiple trials. Finally, the regional representative value of $avg\Delta HbO_2$ was extracted by averaging categorized channels based on the specified region of interest (ROI). The selection of the brain ROI was completed before data analysis. The 48 channels were categorized as right and left dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), medial prefrontal cortex (mPFC), and orbitofrontal cortex (OFC), which constituted eight ROIs. The channels corresponding to each region are shown in **Figure 2**. The MNI coordinates for each channel were defined based on the equipment coordinates. Using this information, the ROIs were designated in accordance with the Brodmann area template for each channel. Brain activation maps (**Figure 3A**)

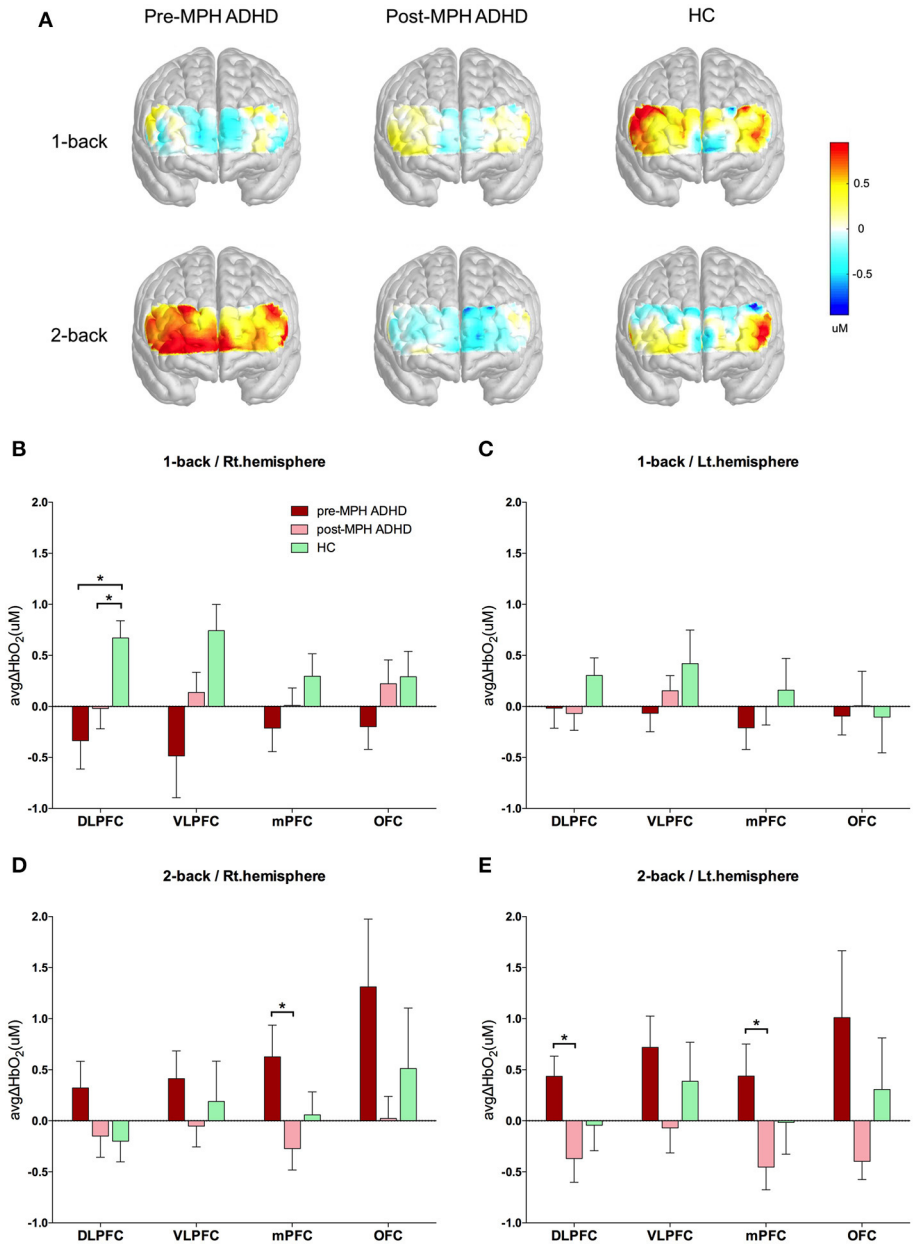

FIGURE 3 | Hemodynamic changes during performance of the n-back task. **(A)** The overall brain activation patterns are shown as signal maps with avgΔHbO_2 values presented in accordance with the color bar. The upper and lower lines show results for 1-back and 2-back condition, respectively, of each group. The mean avgΔHbO_2 values for 1-back condition in **(B)** right and **(C)** left hemispheres and 2-back condition in **(D)** right and **(E)** left hemispheres are represented as bar graphs. ADHD, attention deficit hyperactivity disorder; HC, healthy control; MPH, methylphenidate; Hb, hemoglobin; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; Rt, right; Lt, left. *$p < 0.05$.

were visualized using the avgΔHbO_2 per channel of each group according to 1-back and 2-back tasks.

Behavioral Data Analysis

For n-back task results, the total reaction time (RT), RT variability, and accuracy were used as dependent variables for analysis. RT variability was calculated by dividing the standard deviation of the individual RT by the mean value, as reported previously (52). We computed accuracy in each condition by dividing the correct answer (correct response and appropriate rejection) by total number of stimuli.

Statistical Analysis

Group differences in clinical characteristics between ADHD and HC groups were compared using an independent sample *t*-test for numerical variables or Chi square (χ^2) test for categorical

variables. The means and standard deviations of avgΔHbO_2 were calculated for each ROI and in each group to compare group differences and verify the effects of pre- and post-MPH effects on fNIRS results. For comparison of behavioral performance and fNIRS data between pre- and post-treatment conditions in ADHD participants, we used a two-tailed paired *t*-test. An independent two-sample two-tailed *t*-test was used for comparing variables between ADHD and HC groups. The normality of the data was evaluated by visual inspection of quantile-quantile plots and the Shapiro-Wilk test. To examine the association between behavioral performance and fNIRS data, we conducted correlation analysis using the Pearson's method. The statistical threshold was set at $p < 0.05$. All statistical analyses were completed with IBM SPSS version 25 (IBM Corporation, Armonk, NY, USA).

RESULTS

Demographic and Clinical Characteristics

Baseline characteristics of the study participants are presented in **Table 1**. ADHD and HC groups did not differ significantly in mean age, sex ratio, full scale IQ(FSIQ), CDI, STAI-C, or SSQ scores (**Table 1**). With regard to comorbidities, only one patient with ADHD had a tic disorder. Both ADHD patients and HC showed lower CDI and STAI-C scores than the cut-off (ADHD, CDI = 8.52, STAI-C trait = 29.09, STAI-C state = 28.07; HC, CDI = 10.25, STAI-C trait = 30, STAI-C state = 30.83; cut-off, CDI = 13, STAI-C trait = 36, STAI-C state = 36), indicating the absence of clinical depression and anxiety. As expected, significant differences were observed in the ADHD-RS ($t = -4.64$, $p < 0.001$), ADHD-RS-inattention and hyperactive-impulsive subscales scores (inattention, $t = -4.62$, $p < 0.001$; hyperactive-impulsive, $t = -4.137$, $p < 0.001$), CBCL total and attention problem subscale scores (total, $t = -4.15$, $p < 0.001$; attention problem, $t = -4.21$, $p < 0.001$). The mean ADHD_RS score of the ADHD patients was 20.96, which indicates relatively mild level of ADHD severity. The SSQ score was low in both groups (ADHD, 18.14; HC, 39.31) with few symptoms. The typical mean MPH dose of ADHD subjects was 29.35 mg (SD, 16.23 mg; range, 10–64 mg).

Behavioral Performance

The average accuracy rates and RTs in each n-back task for HC and ADHD participants are summarized in **Table 2**. Within-ADHD-subject analysis revealed shorter RTs in the 1-back condition and shorter RT, lower RT variability, and higher accuracy in the 2-back condition after MPH administration compared to that of pre-MPH. No significant differences in behavioral performance between conditions were observed for ADHD and HC groups.

fNIRS Results

Changes in avgΔHbO_2 measured using fNIRS are presented in **Figure 3** according to brain area and group. For the (low WM load) 1-back condition, no significant avgΔHbO_2 changes were observed in any area when comparing pre- and post-MPH conditions (**Figures 3B,C**; **Supplementary Table 1**). Compared to the HC group, both pre-MPH and post-MPH ADHD subjects showed significantly fewer avgΔHbO_2 signals in the right DLPFC (pre-MPH vs HC, $t = -2.443$, $p < 0.05$; post-MPH vs. HC, $t = -2.233$, $p < 0.05$; **Figure 3B**; **Supplementary Table 1**). For the (high WM load) 2-back condition, avgΔHbO_2 in pre-MPH ADHD subjects was significantly higher than that in post-MPH ADHD subjects in the left DLPFC and bilateral mPFC (left DLPFC, $t = 2.838$, $p < 0.05$, uncorrected; left mPFC, $t = 2.334$, $p < 0.05$, uncorrected; right mPFC, $t = 2.496$, $p < 0.05$, uncorrected; **Figures 3D,E**; **Supplementary Table 1**). No significant differences were observed when comparing the HC group with both pre- and post-MPH ADHD subjects. In the 2-back task, decreased activation was noted in several brain areas after MPH administration in ADHD subjects.

Association Between Behavioral Performance and fNIRS Results

We investigated the relationship between 2-back task accuracy (% correct) and mPFC activation. There was a negative correlation between accuracy and avgΔHbO_2 in the right and left mPFC in pre-MPH ADHD subjects (right mPFC, $r = -0.518$, $p < 0.05$; left mPFC, $r = -0.591$, $p < 0.05$; **Figures 4A,B**). After MPH administration, this correlation was not observed.

DISCUSSION

The present study aimed to investigate the feasibility of using fNIRS to investigate the neural substrates of single-dose MPH effects in children with ADHD during a VR working memory task. The combination of VR and fNIRS in this study revealed that this model was able to easily measure the effects of various drugs and interventions on children with ADHD in an environment simulating a real-world setting. Furthermore, it enables a setting that explores changes in brain activity during a neuro-rehabilitation program using VR environments. To our knowledge, this is the first study using a VR environment to measure the impact of MPH on working memory with fNIRS in ADHD subjects.

In the current study, task performance improved after MPH treatment; this was verified by shorter RT in the 1-back condition and shorter RT, lower RT variability, and higher accuracy in the 2-back condition compared to that in pre-medicated ADHD subjects. This result is generally consistent with previous studies reporting performance enhancing effects of MPH in ADHD patients (53–55). Conversely, there was no performance differences between pre- and post-medicated ADHD subjects and the HC group in the VR n-back task. This result was also reported in our previous study that examined VR-CPT performance in ADHD and HC subjects. In this study, scores were lower in the ADHD group than in the HC group in traditional CPT, but VR-CPT performance was not significantly different. Similarly, it is possible that VR increased the motivation of ADHD patients by presenting them with a more immersive environment in the current study, thereby improving their task performance, as reported in our previous VR study (56). Although the enjoyment or motivation of patients was not measured in this study,

TABLE 2 | N-back task performance for ADHD and control subjects.

	ADHD										HC	
	Pre-MPH vs. post-MPH		Pre-MPH		Pre-MPH vs. HC		Post-MPH		Post-MPH vs. HC			
	t	*p*	Mean	SD	*t*	*p*	Mean	SD	*t*	*p*	Mean	SD
1-back												
RT (ms)	3.15	0.005**	677.63	146.68	−1.159	0.255	602.83	119.84	0.118	0.907	609.18	189.61
RT variability (SD/mean)	1.26	0.221	0.31	0.14	−0.525	0.603	0.26	0.13	0.419	0.597	0.28	0.11
Accuracy (correct %)	−1.691	0.106	92.35	13.22	−0.05	0.961	95.07	9.32	−0.827	0.415	92.13	10.68
2-back												
RT (ms)	2.58	0.018*	792.14	160.09	−1.512	0.141	695.66	149.26	0.281	0.78	710.16	128.98
RT variability (SD/mean)	3.005	0.007**	0.46	0.16	−1.271	0.213	0.34	0.11	1.375	0.179	0.39	0.1
Accuracy (correct %)	−3.158	0.005**	82.33	12.2	0.869	0.391	87.59	12.18	−0.362	0.72	86.05	11.09

*RT and accuracy are presented for each condition. For ADHD subjects, data for pre-, post-MPH, and pre-MPH minus post-MPH are presented. T-values, p-values, and statistical significance in pre- and post-MPH columns are the results of Student's t-test between HC and each ADHD condition. Those in the pre- vs. post-MPH column are the results of a paired t-test. ADHD, attention deficit hyperactivity disorder; HC, healthy control; MPH, methylphenidate; SD, standard deviation; RT, reaction time. *$p < 0.05$, **$p < 0.01$.*

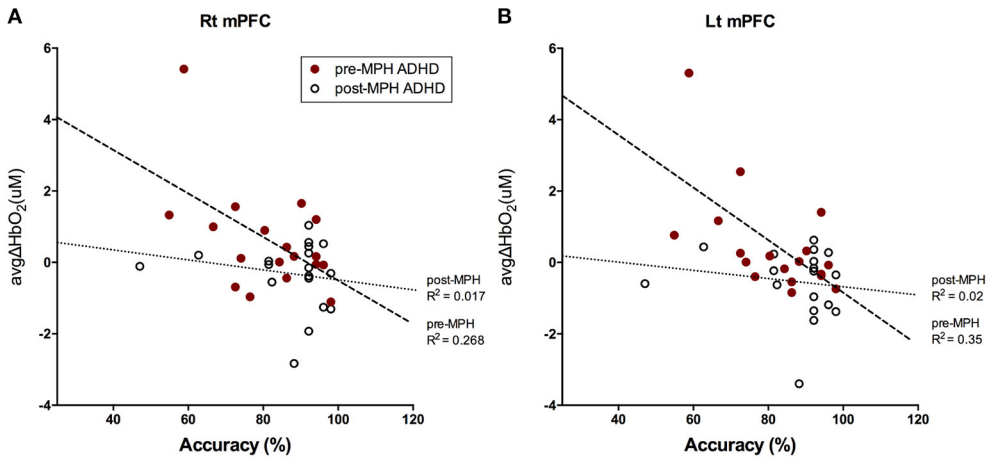

FIGURE 4 | Correlation between 2-back task accuracy and avgΔHbO_2 signals in bilateral mPFC. Correlations between accuracy (%) for 2-back task and avgΔHbO_2 values in **(A)** right mPFC and **(B)** left mPFC in pre-(red dot) and post-MPH (white dot) ADHD subjects were analyzed with Pearson's correlation test. Line and R2 value indicate the regression of the dataset (dashed, pre-MPH ADHD; dotted, post-MPH ADHD).

previous studies have shown that VR neuropsychological tests were perceived as more enjoyable to patients and increased motivation (9, 57). For precise interpretation, further research is needed on motivation and performance differences in ADHD patients when using VR.

We observed increased activation in the left DLPFC and bilateral mPFC in pre-medicated ADHD subjects during the VR 2-back task, which decreased after MPH administration. However, there were no significant differences between HC and ADHD children. In most NIRS studies comparing children with ADHD to HCs in different executive functioning tasks, altered prefrontal activity was reported: some studies reported reduced activity in ADHD (17–19), whereas others reported increased activity in ADHD (58, 59). The cause of these conflicting results is not clear, but a possible reason is the use of different cognitive tasks with different stimulus characteristics. Therefore, the brain areas associated with task performance in each study were not concordant, rendering the neural correlates of WM in ADHD subjects unclear. Previous meta-analyses revealed significant hypoactivation in the left inferior frontal gyrus/anterior insula and right middle frontal gyrus (60), bilateral superior frontal gyrus, and left medial frontal gyrus (61) in adult ADHD patients during the N-back task compared to that in HCs. Nevertheless, meta-analyses on the neural substrates related to WM in children with ADHD are limited. One meta-analysis on healthy children found no concordance in prefrontal regions related to the n-back task (62). In addition, the only study exploring the effects of MPH on brain function during a WM task reported that no specific brain area was activated by stimulants (54). These discrepancies may be due to varying brain maturity and subjective n-back difficulty according to age (62). Further, medication status may differentially affect brain activation. A previous study reported that medication-naïve ADHD patients showed a tendency toward lower activation than that of HCs, whereas non-naïve and HCs

did not differ significantly but showed similar activation (42). Given these conflicting results, it is difficult to conclude whether our findings agree with the literature.

Increased activation in bilateral mPFC was negatively correlated with accuracy of the 2-back task in pre-medicated ADHD subjects, whereas this association disappeared after MPH treatment. This result implies that mPFC was abnormally hyper-activated in ADHD subjects during the 2-back task, which was accompanied by low performance. The mPFC is a brain region that constitutes the default mode network (DMN) along with the medial and lateral parietal and temporal cortices (63). The DMN is associated with intrinsic brain activity and commonly deactivates during attention-demanding or goal-directed activity. Abnormal hyperactivity in DMN areas, indicating unsuccessful task-induced deactivation, is characteristic of ADHD patients (55, 64, 65). Impairment of sustained attention in ADHD may result from abnormal persistence or intrusion of DMN activity (64). In addition, several studies reported that psychostimulants normalized abnormal hyperactivity in the DMN, including the mPFC, in ADHD subjects, and even in children (55, 65, 66). Our study also demonstrated that MPH administration reduced mPFC activation while improving task performance, which indicated normalization of attenuated DMN deactivation in ADHD children. However, a double-blind placebo-controlled study involving other areas comprising the DMN should be performed to understand the relevance of these findings.

By contrast, in the 1-back condition, we found no difference in brain activation between pre- and post-MPH conditions. Given that only RT was shorter after MPH treatment for behavioral performance, and there was no significant difference in accuracy or RT variability, it can be assumed that the difference before and after drug was minimal due to the low level of 1-back difficulty, reflected by a ceiling effect from the pre-test. The only study that explored the effect of MPH during the n-back task in ADHD children reported no differences in brain function in the 1-back condition between pre- and post-drug administration, which is concordant with our study (67). In addition to exploring MPH effects in a VR environment, brain activity was also measured with fNIRS in this study in a VR-based WM task. Compared to the HC group, ADHD children showed lower activation of the right DLPFC, consistent with previous studies on ADHD and HC participants in which the right DLPFC was a ROI identified via fNIRS (37).

In the present study, the VR classroom environment provided a more ecologically valid and motivating task than that of traditional computerized cognitive tasks, suggested by the improved task performance of ADHD children. We propose several advantages of using a VR task over traditional computerized WM tasks. Previous studies have indicated that ADHD children find digital technology environments more enjoyable and are more immersed in the task (9, 68). None of the participants complained of side effects in SSQ, suggesting that the virtual classroom is a user-friendly tool. This may be regarded as an alternative for estimating how brain activity changes with WM in ADHD children after drug administration in a setting that simulates real-world classrooms.

Limitations

Our study has several limitations which we hope to address in future studies. First, the study design was not optimized for neuropharmacological analysis. A double-blind placebo-controlled or a cross-over design with drug-naive ADHD children should be conducted. Since we did not include a placebo group, the superior task performance in post-MPH ADHD subjects could be due to a repeat effect. In addition, unlike the ADHD patients, the HC did not repeat the tests, making it difficult to compare the HC group with the post-MPH group or to eliminate the time effect. Therefore, it is not entirely clear whether the changes in brain activation in the ADHD group were truly induced by the treatment or were simply a function of time. However, considering the NIRS imaging results, the improved behavioral performance was accompanied by changes in brain activity such as reduced hyperactivity of bilateral mPFC in post-MPH ADHD subjects, making it difficult to fully explain solely based on repeat effects. Further, WM tasks are generally considered to have strong test-retest reliability and to be relatively unaffected by practice effects (69). In addition, previous studies suggested that the effects of MPH on brain activity differ between drug-naive and non-naive ADHD subjects (42, 70, 71). Although our subjects may have exhibited weakened pure drug effects because they were a drug-non-naive group, it is relevant for feasibility because it is necessary to measure drug effects in non-naive subjects in real clinical practice. Further studies including both drug-naïve and non-naïve children could lead to accurate interpretations. Second, due to the limitations in our experimental design, such as the relatively small sample size and lack of a cross-over design, a liberal statistical threshold was adopted for this study. Third, the relatively wide age range of the subjects (7–16 years) and the lack of sex stratification could be problematic. A meta-analysis of fMRI studies related to the n-back task revealed widespread variability of prefrontal activation patterns across ages due to a protracted, step-wise maturation pattern of the prefrontal cortex (62). Although most ADHD research is conducted with similar age ranges to ours, it will help to narrow down the age range to elicit more accurate results on prefrontal function in child participants. In addition, although previous studies have shown sex differences, such as hypofrontality only in males, we did not conduct a subgroup analysis by sex due to the small sample size of this study (72, 73). Future studies with large sample sizes to analyze group effects by age and sex are needed. Fourth, the brain regions evaluated in this study were not wide enough to cover WM-related areas or DMN. The fNIRS probe covered only the prefrontal cortex and was unable to detect activity in deeper cortical structures unreachable by near-infrared light. Further studies covering wider areas or exploring connectivity between brain areas are needed to clearly interpret the results of this study. Fifth, we cannot determine if the VR n-back task is actually more effective or motivation-enhancing because we lack a comparison of a VR paradigm to a 2D version of the n-back task. Finally, we used a semi-immersive VR display, instead

of a more immersive HMD version of virtual reality, since simultaneously wearing HMD and fNIRS devices is difficult due to space overlap.

CONCLUSIONS

To our knowledge, this is the first study to explore the effects of MPH on brain activity during a VR-based WM task reproducing real-classroom settings in ADHD children. We observed that activation of bilateral mPFC decreased after MPH treatment in a high-load WM task. Further, bilateral mPFC activation was negatively correlated with task accuracy in pre-MPH condition; this correlation disappeared after MPH administration. These findings suggest that mPFC-mediated inappropriately excessive mind-wandering during a high-load WM task in ADHD children may have disappeared after MPH administration. Taken together, these results suggest that the combination of VR tasks and fNIRS examination is a technique that enables examination of the effects of interventions within a real-life setting in ADHD children and adolescents.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Yonsei University College of Medicine Gangnam Severance Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

EK and NL devised the project, the main conceptual ideas, and proof of the outline. EK, NL, and JY designed the detailed study design. JY, NH, JK, and JH examined participants, performed the experiments, and acquired and organized the data. SJ and JC conducted analyses of the experimental data, drafted the manuscript, and designed the figures with supervision from EK. JO and J-jK contributed to interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript. EK supervised the project. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.564618/full#supplementary-material

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Deep Neural Network to Differentiate Brain Activity Between Patients With First-Episode Schizophrenia and Healthy Individuals: A Multi-Channel Near Infrared Spectroscopy Study

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Backgrounds: Reduced brain cortical activity over the frontotemporal regions measured by near infrared spectroscopy (NIRS) has been reported in patients with first-episode schizophrenia (FES). This study aimed to differentiate between patients with FES and healthy controls (HCs) on basis of the frontotemporal activity measured by NIRS with a support vector machine (SVM) and deep neural network (DNN) classifier. In addition, we compared the accuracy of performance of SVM and DNN.

Methods: In total, 33 FES patients and 34 HCs were recruited. Their brain cortical activities were measured using NIRS while performing letter and category versions of verbal fluency tests (VFTs). The integral and centroid values of brain cortical activity in the bilateral frontotemporal regions during the VFTs were selected as features in SVM and DNN classifier.

Results: Compared to HCs, FES patients displayed reduced brain cortical activity over the bilateral frontotemporal regions during both types of VFTs. Regarding the classifier performance, SVM reached an accuracy of 68.6%, sensitivity of 70.1%, and specificity of 64.6%, while DNN reached an accuracy of 79.7%, sensitivity of 88.8%, and specificity of 74.9% in the classification of FES patients and HCs.

Conclusions: Compared to findings of previous structural neuroimaging studies, we found that using DNN to measure the NIRS signals during the VFTs to differentiate between FES patients and HCs could achieve a higher accuracy, indicating that NIRS can be used as a potential marker to classify FES patients from HCs. Future additional independent datasets are needed to confirm the validity of our model.

Keywords: deep neural network, near infrared spectroscopy, schizophrenia, machine learning, fNIRS, deep learning

INTRODUCTION

Schizophrenia (SZ) is a chronic psychiatric disorder characterized by psychotic symptoms, negative symptoms, and cognitive deficits and poses considerable burdens to society (1). Therefore, accurate diagnosis and early intervention are critical (2, 3). In clinical practice, schizophrenia is diagnosed by clinicians using diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), based on patient reports of symptoms, observation of behavior and functional changes; however, traditional clinical practice might be confounded because patients with SZ may deny their symptoms, and even experienced psychiatrists may have difficulty differentiating SZ from other mental illnesses (i.e., psychotic bipolar disorder) owing to similar symptomologies at acute stage (4).

To overcome these limitations of clinical interviews-based diagnosis of psychiatric disorders, many studies have attempted to develop objective biomarkers that can improve the accuracy of diagnosis and the ability to predict a patient's response to treatment and prognosis. Among a variety of neuroimaging modalities, functional near infrared spectroscopy (fNIRS) is a functional neuroimaging tool that measures the spatio-temporal neural activity of the brain non-invasively. Compared to existing imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance image (MRI), fNIRS is easier to administer, low-cost, and provides fair temporal and spatial resolutions (5). Many previous fNIRS studies reported reduced brain activity over the bilateral frontotemporal regions during various cognitive tasks in patients with SZ compared to controls [reviewed by Koike et al. (6) and Chou et al. (7)].

Recently, many studies have attempted to accurately classify patients with heterogeneous mental disorders. For instance, several studies used machine learning (ML) methods to accurately differentiate patients with SZ and healthy individuals with structural or functional neuroimaging tools and showed promising results (8). ML methods are capable of representing latent features of structural or functional changes in the brain, and this allows for better representation of SZ-related processes. Among ML methods, support vector machines (SVMs) are mostly adopted. SVM is an ML method which estimates a hyperplane with an optimal margin that could provide the best separation between two classes, which is determined by the maximum distance from any data point. Once defined, this hyperplane is used to classify the data (8, 9).

Recently, deep learning (DL) methodology such as deep neural network (DNN) has significantly improved the representation learning and classification in various areas such as speech recognition, natural image classification, and text mining (9). Two main features have made DNN unique compared to SVM. First, DNN is capable of data-driven automatic feature learning, which enables to remove the subjectivity in selecting the relevant features when there are too many features or no prior knowledge in selecting features. Second, by applying a hierarchy of non-linear layers, DNN can analyze complicated data patterns (8). Recently, DL methods have been applied in medical image analyses with promising results, including characterizing patterns of brain imaging data in patients with neurocognitive disorders (10–13) and schizophrenia (9, 14). However, most previous studies analyzed MRI data.

In the present work, we aimed to discriminate between patients with first-episode schizophrenia (FES) and healthy controls (HCs) on the basis of brain cortical activity during a verbal fluency test (VFT) measured using NIRS. We focused on the bilateral frontotemporal regions. We compared classification accuracies for two different machine learning methods: SVM and DNN. To the best of our knowledge, this is the first study using deep learning to automatically differentiate FES from HC based on brain cortical activity features.

MATERIALS AND METHODS

Study Subjects

A total of 33 patients with FES (18 men and 15 women; mean age [SD] =29.1 [6.4] years) were recruited at the Department of Psychiatry in Taichung Veterans General Hospital. Patients who fulfilled the criteria for SZ listed in the DSM-5 were recruited and the diagnoses were validated using the Mini International Neuropsychiatric Interview (MINI) (15) by board-certified psychiatrists (P.H.C). All patients were experiencing their first episode of psychosis and had received no more than 12 weeks of previous antipsychotic medication (16, 17). Thirty-four HCs (17 men and 17 women; mean age [SD] = 28.2 [9.9] years) were recruited and screened using the MINI. All study participants were right-handed, which was assessed by the Edinburgh Inventory (18). Other characteristics such as education level, VFT performance of study subjects, as well as the age of onset and duration of illness of FES patients were also recorded. Subjects were excluded if they had a history of substance abuse or dependence, intellectual disability, neurological disorders, or a medical condition that may affect

brain function. This study complied with the Declaration of Helsinki, and all participants received a complete explanation of the study and provided written informed consent. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (approval No. CF13044).

Clinical Assessments

We used the Positive and Negative Syndrome Scale (PANSS) (19) to evaluate psychiatric symptoms of the FES patients on the same day as the NIRS measurements. Patient antipsychotic doses are presented as chlorpromazine-equivalent doses (20, 21).

Verbal Fluency Test

Patients received 160-s block-design VFTs (both letter and category version) which has been adopted in many previous fNIRS studies (17, 22–26). There were three different time periods for the VFT: a 30-s pre-task period, a 60-s task period, and a 70-s post-task period. In the pre- and post-task periods, patients were asked to repeatedly count from one to five to control for and remove task-related motion artifacts. For the 60-s task period, study participants were instructed to say words that started with a phonological syllable presented by NIRS machine. In the letter fluency test (LFT), there three continuous 20-s sub-periods, which were initiated by a single Chinese syllable selected from nine options (first, /ㄅ(b)/, /ㄆ(p)/, or /ㄉ(d)/; second, /ㄊ(t)/, /ㄌ(l)/, or /ㄋ(n)/; third, /ㄇ(m)/, /ㄈ(f)/,or /ㄎ(dz)/). We chose these syllables based on their frequencies at the beginning of Chinese words. For the category fluency test (CFT), subjects were asked to produce as many words based on a given semantic cue for 20 s each (first: "fish," "birds," or "insects"; second: "sweets," "vegetables," or "fruits"; third: "vehicles," "home appliances," or "stationery items,"). Before beginning each task session, subjects were instructed on how to generate correct answers for VFTs. Each subject practiced three times to ensure that they understood the tests.

NIRS Instrument

A 52-channel NIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan) was used to measure changes in concentrations of oxygenated hemoglobin [oxy-Hb] of the brain in the present study. The NIRS probe attachments are thermoplastic 3 × 11 shells set, comprising 52 channels (**Figure 1**). The lowest probe line was set along the Fp1–Fp2 line, as defined by the international 10–20 system used in electroencephalography. The NIRS instrument measures changes in both [oxy-Hb] and [deoxy-Hb] (in mM) using two wavelengths (695 and 830 nm) of near-infrared light. The calculations were based on the Beer–Lambert law (27). We recorded the changes of [oxy-Hb] from baseline to the activation period and relative changes in [oxy-Hb] assessed with units of mM·mm. The data sampling rate for NIRS instrument was 0.1 s. A moving average methodology using a 5-s window width was applied and any motion artifacts were automatically detected and rejected by the machine (28).

The spatial information for each channel was estimated by using data from the Functional Brain Science Laboratory at Chuo University in Japan (29) based on the LONI Probabilistic Brain Atlas (LPBA40) (30). Because previous study indicated that [oxy-Hb] had stronger correlations with fMRI blood-oxygenation level-dependent signals (31), we used it as an indicator of brain cortical activity.

NIRS Signals and Feature Selection

Similar to Takizawa et al.'s study (32), two regions of interest (ROIs) were selected (**Figure 1**): the frontal region (R1, 11 channels) and the bilateral temporal region (R2, 20 channels). The changes in [oxy-Hb] and [deoxy-Hb] in the channels of these two respective regions of interest were averaged and transformed into representative "Region 1 (R1)" and "Region 2 (R2)" NIRS signals for each individual. According to the LBPA40 (30), the "Region 1 (R1)" NIRS signal consisted of signals from channels located approximately in the fronto-polar and dorsolateral prefrontal cortical regions, while the "Region 2 (R2)" NIRS signal consisted of signals from channels located approximately in the bilateral ventro-lateral prefrontal cortex and the superior and middle temporal cortical regions.

Two visual indices, integral and centroid value, of the bilateral frontotemporal regions during LFT and CFT (**Figure 2**) were generated automatically from the NIRS machine by evaluating the hemodynamic changes in [oxy-Hb] of the 10-s pre-task, 60-s task, and 55-s post-task period from the original 160-s VFTs. Details regarding the definition of integral and centroid value can be found elsewhere (32). In brief, integral value was calculated using the hemodynamic response of [oxy-Hb] during the 60-s activation task period by averaging the signal from channels within each region; the centroid value is an index of time-course changes throughout the VFT, with periods representing the timing of the hemodynamic response. The centroid value is indicated by the time shown with a perpendicular line from the centroid of the [oxy-Hb] signal change area during the entire task periods [from 0 (s) to 125 (s) [= 10 (s) + 60 (s) + 55 (s)]]; the integral value describes the size of the hemodynamic response during the 60-s test period (32). Therefore, a total of eight datasets were collected (integral and centroid values of R1 and R2, during an LFT and CFT, respectively).

Deep Neural Network

A DNN was utilized as a classifier to discriminate the patients with schizophrenia from healthy control (HC). The network had eight features as inputs (which included the integral and centroid values of the frontal and temporal regions during the two types of VFTs. in the NIRS signal) (**Figure 3**). The topology of this classifier is a fully connected, four-layer, feedforward network, which comprises two hidden layers with 512 neurons for each layer. The activation function of all neurons in the network is the rectified linear unit (ReLU) function. The network outputs 2 indices in the last layer that the index with larger value indicates positive (FES) or negative (HC).

Training of DNN

This DNN was trained with supervised learning since labeled data (FES or HC) were given. During training, stochastic gradient

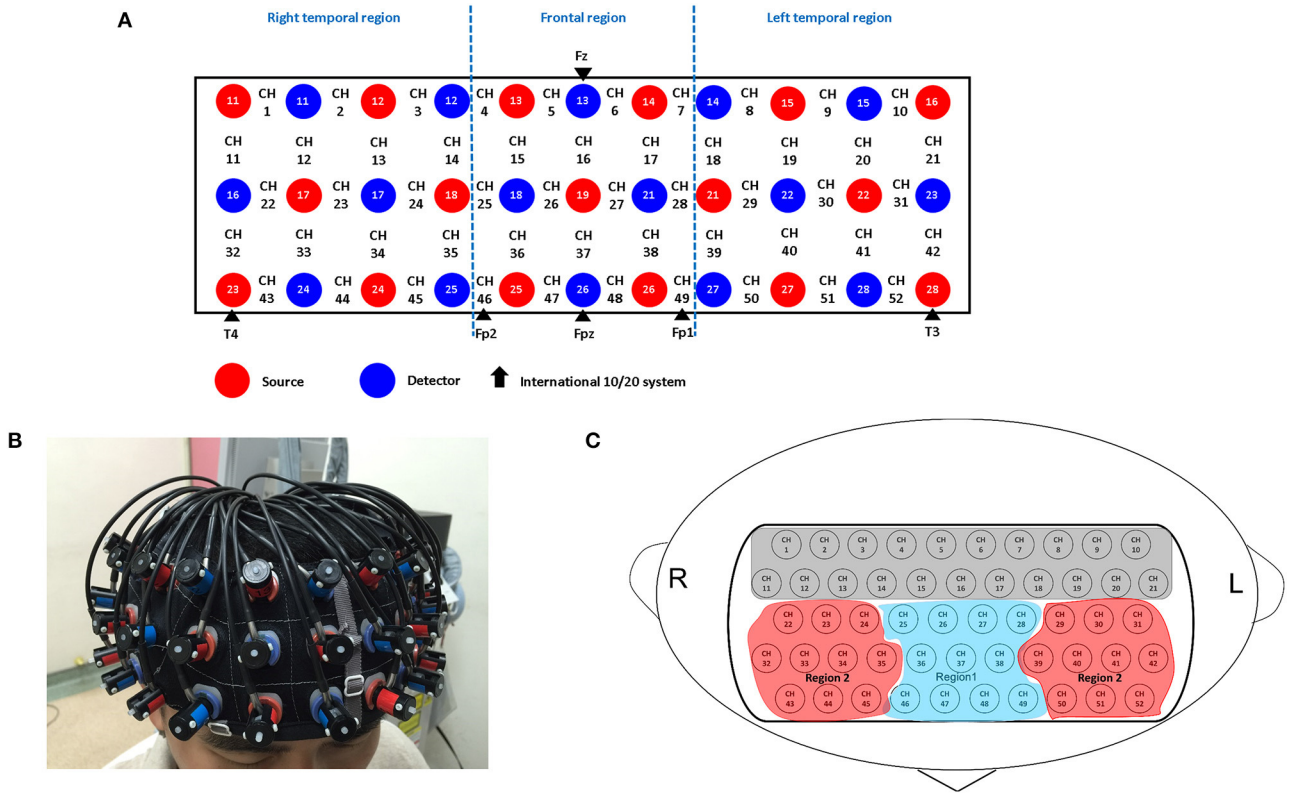

FIGURE 1 | Probe setting and measurement points for 52-channel NIRS. **(A)** The localizations of channels are set based on the international 10–20 electroencephalography system. Red and blue circles, respectively indicate the emitter and detector of the near-infrared light. **(B)** Probes with thermoplastic 3 × 11 shells are placed over the bilateral frontotemporal area. **(C)** Two regions of interest (Regions 1 and 2) in the present study. Region 1 consists of 11 channels (ch 25–28, ch 36–38 and ch 46–49); Region 2 consists of 20 channels; Right: (ch 22–24, ch 32–35 and ch 43–45); Left: (ch 29–31, ch 39–42 and ch 50–52).

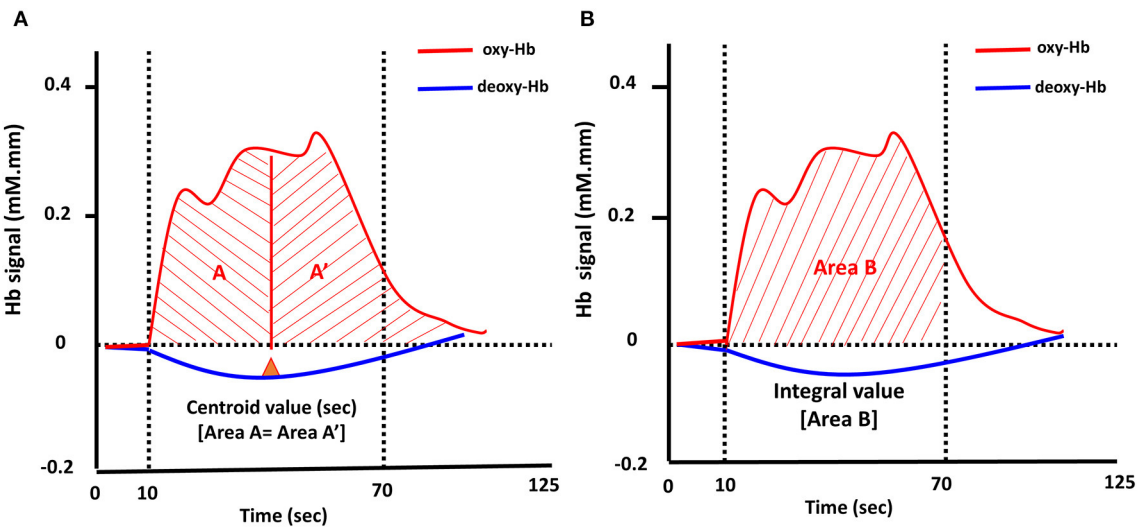

FIGURE 2 | Typical time-course pattern of NIRS signals during the VFT. The "centroid value" is defined by a perpendicular line from the centroid of the brain activation area during the task period **(A)**. The "integral value (Area B)" indicated the brain activity during the test **(B)**; Oxy-Hb, oxygenated hemoglobin; deoxy-Hb, deoxygenated hemoglobin.

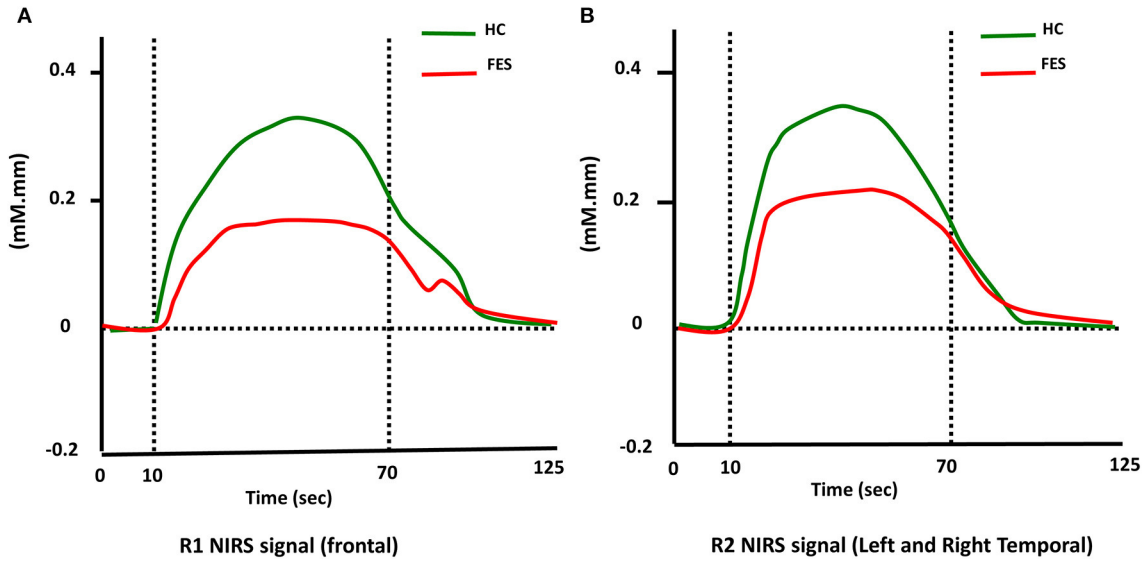

FIGURE 3 | Time courses of the hemodynamic responses of [oxy-Hb] in Region 1 (R1) and Region 2 (R2) in FES and HC groups. **(A)** and **(B)** show the time courses of the hemodynamic responses in R1 (frontal region) and R2 (temporal region), respectively.

descent (SGD) was employed for optimizing the parameters; error gradients were propagated backwards through layers, which was backpropagation. Each parameter in the network was randomly initialized and adjusted according to its corresponding gradient to loss to minimize the error between the predicted results and the labeled data. In addition, the dropout technique was incorporated to avoid overfitting, and the dropout rate was 0.18. Here a criterion was set that the learning stage was stopped when the value of cost function changes little through epochs, and according to experiences, the learning duration was expected to be 100 to 300 epochs.

In the training procedure, cross-validation was required since the performance of the DNN was evaluated here by validation accuracy, practically, which was shuffling the 67-example dataset (33 FES patients and 34 HCs) at first and then dividing it into seven groups. In each turn of cross-validation, one of the groups was used as the validation set and the other six groups were training sets, and the validation set contained 10 samples, and the training set the other 57 samples.

Support Vector Machines

In the present study, Support Vector Machine (SVM) was used to compare the performances with which by deep learning. In machine learning, SVM is a supervised-learning method that learns model from labeled training data, and has been used for classification of patients with different psychiatric diseases (33). The SVM methodology has been detailed elsewhere (34). Given a training dataset for classification, the SVM algorithm optimizes for the support vectors that is a subset of training data and represents a hyperplane dividing the training data into their labeled categories with gaps as wide as possible. The prediction is then made by evaluating the decision function with test data as input and support vectors as parameters. A model of SVM with hyper parameter c = 1.0 and with radial basis function (RBF) kernel ($\gamma = 1/\mathrm{Nt}$, Nt: the number of training examples) is built to run the SVM algorithm. The formation of the input data and processing of cross-validation are exactly the same to ensure consistency and fair comparisons.

Statistical Analysis

Firstly, Kolmogorov–Smirnov or Shapiro-Wilk tests were used to examine the distribution of the data. Basic characteristics in each group were compared using Student's t-tests for continuous variables and X^2 test for categorical variables. When the data was not normally distributed, a non-parametrical analysis, that is, Spearman's rho was used to examine correlations and the Mann–Whitney U-test was used to compare means. Otherwise, the t-test was used to compare means and Pearson's correlation coefficient was used to examine correlations. P-value < 0.05 was defined statistically significant. All statistical analyses were performed using STATA version 15.1. DNN and SVM were performed using Python with open source library packages including Keras, scikit-learn, and TensorFlow.

RESULTS

Demographic Characteristics

The study participants' demographic characteristics are presented in **Table 1**. There were no significant differences between the HC and FES groups in terms of age, sex, or education. However, the HC group had significantly better performance on the LFT (HC group, mean= 14.0, SD = 0.8; FES group, mean = 9.7, SD=0.8, $P < 0.001$) and CFT (HC group,

TABLE 1 | Characteristics of study participants.

	FES ($N = 33$)	HC ($N = 34$)	Statistics/ analyses	*P*-value
Age	29.1 (6.4)	28.2 (9.9)	$T = 0.42$	0.68
Education (graduate/undergraduate/high school degrees)	7/18/8	3/27/4	X^2 test	0.09
Right handed	33	33	X^2 test	1
Gender(M/F)	(18/15)	(17/17)	X^2 test	0.71
LFT performance	9.7 (0.8)	14.0 (0.8)	$t = -3.80$	$P < 0.001$
CFT performance	12.1 (0.7)	17.5 (0.8)	$t = -5.03$	$P < 0.001$
Onset age	27.2 (6.1)			
DOI (week)	102.8 (126.5)			
PANSS				
Positive	16.8 (5.3)			
Negative	17.5 (5.5)			
General psychopathology	33.9 (7.6)			
Total	68.1 (14.7)			
antipsychotics	426.9 (236.1)			

FES, first-episode schizophrenia; HC, healthy control; LFT, letter version of verbal fluency test; CFT, category version of verbal fluency test; DOI, duration of illness; PANSS, positive and negative symptom scale.

mean = 17.5, SD = 0.8; FES group, mean = 12.1, SD = 0.7, $P <$ 0.001) compared to the FES group.

Comparison of Hemodynamic Response of ROIs Across Clinical Groups

As shown in **Table 2**, during the LFT, significantly smaller integral values of [oxy-Hb] in the SZ than the HC group (R1: $P < 0.001$, $t = 3.859$; R2: $P = 0.003$, $t = 3.047$) were noted. On the other hand, there were no significant differences between two groups with regard to centroid values in both regions (R1: $P = 0.667$, $t = -0.433$; R2: $P = 0.138$, $t = -1.515$). During the CFT, smaller integral values of [oxy-Hb] in the SZ than the HC group were noted in both regions (R1: $P = 0.015$, $t = 2.507$; R2: $P = 0.006$, $t = 2.845$), and no significantly different centroid values between the two groups (R1: $P = 0.528$, $t = -0.635$; R2: $P = 0.796$, $t = -0.259$).

Classification Performance of DNN and SVM

In DNN, the topology of the network is determined by the experiments on network with different number of hidden layers and different number of neurons per layer, as shown in **Table 3**. A larger or deeper network generally performs better but harder to train. According to the results from the experiments, a 4-hidden-layer and 512-neurons-per-layer neural network was selected in the present study.

To reduce the effect of randomness, the cross-validation accuracy in each training set group is the average of the accuracies obtained by training and testing the network with different initializations five times. Therefore, the classification accuracy of DNN was 79.7%, sensitivity of 88.8%, and specificity of 74.9%. On the other hand, the result of classification accuracy using the eight features analyzed by SVM was 68.6%, sensitivity of 70.1.8%, and specificity of 64.6%.

Correlational Analyses

During the LFT, there was a significant negative correlation between R1 integral values and PANSS general psychopathology score (rho $= -0.371$, $P = 0.034$). In addition, there were significant negative associations between R2 integral values and PANSS negative (rho $= -0.551$, $P = 0.001$) and general psychopathology scores (rho $= -0.433$, $P = 0.012$). With regard to CFT, there was a significant positive correlation between R1 integral values and antipsychotic dosage (rho $= 0.403$, $P = 0.020$). In addition, there was significantly negative associations between R2 integral values and PANSS general psychopathology scores (rho $= -0.501$, $P = 0.003$).

DISCUSSION

To our knowledge, this study is the first to evaluate the classification performance of artificial intelligence to distinguish patients with FES and HCs using NIRS signals. In the present study, we employed SVM and DNN methods to automatically differentiate FES patients from HCs. The main findings can be summarized as follows. (1) We reached a fair discrimination accuracy using SVM on integral and centroid values of R1 and R2 during both types of VFTs (68.6%). (2) DNN achieved modestly higher predictive performance than the SVM approach (79.7%). (3) Compared to HCs, there was decreased cortical activity in FES patients during the LFT but not the CFT, indicating that deficits in cortical activity during phonemic processing may occur early in the course of SZ.

Comparison of Classification Performance Between DNN and SVM

In the present study, we found classification accuracy of DNN is better than SVM, which is consistent with many previous MRI studies demonstrating superiority of DNN over SVM (9, 14, 35). SVM, a shallow-structured architecture, are effective in solving many simple or well-constrained problems. However, several recent studies have demonstrated the benefits of using deep structures. DNN may be more robust in the wide variety of functions that can be parameterized by composing weakly non-linear transformations. DNN allows a system input to be compositing from raw data, thus allowing automatic discovery of the representations required for machine learning tasks (36). Finally, the appeal of hierarchical representations and the potential for combining unsupervised and supervised methods also contribute to the use of deep neural networks (9). However, in this study, we did not explore all possible deep learning advantages, such as the use of input data without feature extraction. Instead, we selected the features generated by NIRS machine. Nevertheless, our results showed that when using NIRS signals, the DNN-based model can achieve better classification performance than SVM model.

TABLE 2 | Comparison of frontal or temporal integral and centroid value of NIRS signals between FES and HC groups[a].

	Frontal region (R1)				Temporal region (R2)			
	Integral	***P*-value**	**Centroid**	***P*-value**	**Integral**	***P*-value**	**Centroid**	***P*-value**
LFT								
HC group	131.9 (12.0)	**0.0003**	56.5 (1.4)	0.6633	204.7 (17.4)	**0.0033**	56.8 (0.7)	0.1299
FES group	47.6 (18.4)		57.8 (2.8)		114.9 (23.9)		60.7 (2.4)	
CFT								
HC group	82.5 (12.8)	**0.0147**	57.2 (1.8)	0.5279	178.7 (17.8)	**0.0059**	60.7 (1.0)	0.7950
FES group	36.3 (13.3)		59.3 (2.8)		100.2 (21.2)		61.2 (1.6)	

[a] *The unit for NIRS signal is (mM.mm). Statistical significance was marked with bold character.*
FES, first-episode schizophrenia; HC, healthy control; LFT, Letter version of Verbal Fluency Test; CFT, Category version of Verbal fluency Test.

TABLE 3 | Nnetwork topology demonstrating comparison accuracy (%) of DNN.

hidden layers \ neurons per layer	64	128	256	512	1,024
1	55.7	58.2	63.6	62.0	69.4
2	61.4	65.1	74.2	79.1	78.8
3	60.2	65.1	76.0	78.0	79.1
4	61.7	66.5	77.1	**79.7**	79.4
5	51.7	63.4	72.9	79.1	78.6

DNN, deep neural network. Bold value indicated the best accuracy of performance.

Comparison With Previous fNIRS/MRI Studies Using Deep Learning or Machine Learning

Until now, there have been few NIRS studies using ML or DL method to classify patients with SZ and healthy individuals (37, 38). Li et al. (37) recruited a large sample of 120 SZ patients and 120 HCs and measured the hemoglobin response in the prefrontal cortex during the VFT using a multichannel NIRS instrument. They used PCA-based feature selection for data extracted from three types of NIRS data in each channel, and they achieved a maximum accuracy of 85.83% and an overall mean accuracy of 83.37% using SVM classifier. Yang et al. (38) measured the functional connectivity strength (FCS) as features derived from an individual channel during the VFT in 100 patients with schizophrenia and 100 healthy controls, and applied principal component analysis. They found that FCS from three channels on the medial prefrontal and left ventrolateral prefrontal cortices rendered accuracy as high as 84.67%, sensitivity at 92.00%, and specificity at 70%. However, due to the differences in study population recruited, usage of fNIRS features, and machine learning algorithms, it was difficult for us to directly compare these two studies.

On the other hand, there have been many structural or functional MRI studies using machine learning (e.g., SVM) technique reporting heterogeneous classification performances (with accuracies ranging from 60 to over 95%) in the classification of patients with chronic or first episode SZ against healthy individuals [reviewed by (8)]. However, there have been few MRI studies using deep learning to discriminate patients with schizophrenia and healthy controls. In the structural MRI study conducted by Pinaya et al. (9), the authors compared classification performance of deep belief network (DBN) and SVM between patients with schizophrenia and healthy individuals. They found DBN was slightly more accurate as a classifier (accuracy = 73.6%) than the SVM (accuracy = 68.1%) between patients with SZ and healthy individuals. However, the error rate of the DBN in classifying patients with first-episode psychosis (FEP) was 56.3%. In another study conducted by Vieira et al. (39), they used DNN to analyze a total of 956 participants (514 FEP and 444 HCs) and found that the best accuracies (70%) were achieved when DNN was applied compared to that when SVM was used (61.3%). In the present study, we demonstrated the classification accuracy of DNN (79.7%) was superior to that of SVM (68.6%), a finding similar to that reported by Vieira et al. However, Vieira et al. found it was difficult for the DNN models generalized to other sites, indicating that detection of individuals in the early stages of psychosis is more challenging. In the present study, we did not test our DNN model in another independent dataset, and future study using fNIRS dataset from other sites to test our DNN model is warranted.

Comparison of the Results of Correlational Analyses With Previous NIRS Studies

Similar to previous NIRS studies, we found that cortical activities over bilateral frontotemporal regions were negatively correlated with PANSS negative (17, 40) or general psychopathology scores (17, 28) during the both versions of VFTs. However, it is interesting to note that there was a significant positive correlation between frontal activity (R1 integral value) and antipsychotic dosage during the CFT, which has never been reported before. Antipsychotic treatment has been shown to improved cognitive function in first-episode and recent-onset schizophrenia (41). This finding probably indicated an improved cortical function after antipsychotic treatment and future studies are warranted to confirm our findings.

Limitations

There are several limitations in the present study. First, our study used small samples, which have been shown to yield unstable results (42, 43). Second, selection bias must be considered; this study used data from a tertiary hospital, and therefore the results

may not be generalized. Third, the effects of medication on brain function should be considered. Although FES patients in the present study were minimally treated with antipsychotic medication, previous study demonstrated that even short-term treatment with antipsychotics was associated with structural brain changes (44). Fourth, there were only training and validation groups in our analysis, failure to test performance on additional independent samples (i.e., testing group) may limit the interpretation of our results. Future studies recruiting larger numbers of subjects from multi-sites are warranted. Fifth, NIRS data used in training the DL algorithm applied binary labels (FES or HCs). This dichotomous classification is widely used in researches of ML or DL, but it can be a barrier to applying this methodology in clinical practice. Most psychiatric diseases have a continuous spectrum and psychiatric comorbidities are common in a patient. The effects of psychiatric comorbidities on the brain function were not considered in the present study. In conclusion, in the present study, we distinguished FES from HCs by applying DNN to analyze frontotemporal activities during VFT measured by fNIRS and demonstrated fair sensitivity and specificity. However, additional independent datasets are needed to confirm the validity of our model.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Taichung Veterans General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

P-HC designed the study, managed the literature searches, performed the NIRS measurements, assessments of study subjects, statistical analyses and wrote the first draft of the manuscript. Y-HY, R-XZ, and Y-LL revised the section Deep neural network, Support vector machines, and Statistical analysis of the manuscript, and performed SVM and DNN analyses supervised by T-TL. All authors interpreted the results, revised the manuscript and approved the final version submitted for publication.

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Understanding Mental Health and Cognitive Restructuring With Ecological Neuroscience

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Neuroimaging and neuropsychological methods have contributed much toward an understanding of the information processing systems of the human brain in the last few decades, but to what extent do cognitive neuroscientific findings represent and generalize to the inter- and intra-brain dynamics engaged in adapting to naturalistic situations? If it is not marked, and experimental designs lack ecological validity, then this stands to potentially impact the practical applications of a paradigm. In no other domain is this more important to acknowledge than in human clinical neuroimaging research, wherein reduced ecological validity could mean a loss in clinical utility. One way to improve the generalizability and representativeness of findings is to adopt a more "real-world" approach to the development and selection of experimental designs and neuroimaging techniques to investigate the clinically-relevant phenomena of interest. For example, some relatively recent developments to neuroimaging techniques such as functional near-infrared spectroscopy (fNIRS) make it possible to create experimental designs using naturalistic tasks that would otherwise not be possible within the confines of a conventional laboratory. Mental health, cognitive interventions, and the present challenges to investigating the brain during treatment are discussed, as well as how the ecological use of fNIRS might be helpful in bridging the explanatory gaps to understanding the cultivation of mental health.

Keywords: neuroimaging, functional near infrared spectroscopy, ecological validity, mental health, hyperscanning methods, psychotherapy, cognitive-behavioral therapy

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MENTAL HEALTH AND THE BRAIN

Mental health has long been a central topic of investigation in clinical psychology and psychiatry [see (1), for review], but it also has steadily been a growing subject of interest of government, education, and business institutions, as well as of other academic fields such as those comprising cognitive neuroscience and, importantly, of society on the whole. This sometimes leads to differences in how mental health is conceptualized, but it is most broadly understood as a latent construct for which people have normative reasons to want to try to cultivate (2) and, critically, it is probably not simply the absence of having a diagnosed psychiatric disorder. An analog to this is the concept of physical fitness: Physical fitness means different things to different people, but most would agree that it is important to overall well-being to try do things to develop it; although these "things" vary widely in variety and efficacy, they are at least clearly antithetical to physical stagnation. Physical fitness, then, is also not simply the absence of having a physical disease. More broadly, both physical well-being and mental health contribute and, indeed, largely

comprise one's overall well-being. However, it is worth noting that, from the perspective of cognitive neuroscience, these dimensions of physiological and psychological well-being are not categorically disparate: A particular sense of reductionism is widely adopted in which a material substrate—the brain—is a necessary condition by which mental phenomena can emerge, including mental illness. So, because the dualism of the Mind-Body Problem (3) is generally rejected, psychological well-being is equivalent to the same sense of physical well-being as is considered when discussing, for example, damage to the body from a broken bone, but with a more specific focus on the integrity of the organ whose neural systems make possible all the conscious experiences people typically consider—at a more common-sense level of explanation—as involving mental health (e.g., complex beliefs, desires, and emotions about the self, others, and world).

A SHIFT IN PERSPECTIVE AND DIAGNOSTICS

Fortunately, the many initiatives and movements away from mental health stigma have been exceedingly impactful, in that more people are beginning to discern that although psychopathological symptoms such as experiencing emotion dysregulation and engaging in maladaptive behavior might suggest a disordered mind, the presence of symptoms is not indicative of there being something fundamentally wrong with them—something inherently weak in their personhood—and, consequently, more people are reaching out for help [e.g., (4)]. At the same time, access to non-pharmacological forms of treatment to those seeking it have opened markedly: for instance, internet-based cognitive-behavioral therapy (CBT). Several reviews and meta-analyses have shown that internet-based CBT is effective for reducing mild to moderate psychopathological symptoms (5–12). This mounting shift of the general public in seeing mental health as something similar to physical well-being—as something toward which everyone can work to better their lives—is accompanied by a theoretical one in the clinical sciences regarding diagnostic classification. Namely, there has been a push for incorporating more dimensional features into the formal nosology in recent years, and for even adopting a predominately dimensional approach [see (13), for review]. In addition to the collection of psychometric data, computational and multifactorial approaches to psychopathology in cognitive neuroscientific research are becoming increasingly popular [see (14), for review] and powerful in their aim to improve the reliability and validity of diagnostic classification by providing important idiographic information about individuals that might better account for within-category heterogeneity and inform intervention methods (15). For example, neurocognitive "endophenotyping" is a more comprehensive approach to capturing disordered thinking, feeling, and behaving and not only improves knowledge on the nature of psychopathology but also stands to better inform clinicians' assessments [see, (16), for review]. So, having diminished mental health is not always the same thing as having a psychiatric disorder and, conversely, having a clinical diagnosis is not a requirement to engage in things that cultivate mental health; therefore, it is important that interventions such as CBT that teach strategies for everyday life are encouraged and available to everyone.

THE PRINCIPLE OF COGNITIVE MEDIATION

In general, interventions (e.g., psychiatric treatment, physical activity, diet, etc.,) are the instruments by which well-being is chiefly cultivated. Diseases (acquired or innate) and environmental events, as well as certain aspects of thinking, feeling, and behaving, can detract from people's well-being either directly or instrumentally. On some views, thinking (i.e., cognition) is central to understanding mental health, because it mediates the relationship between stressful environmental events and decreases in aspects of mental health, such as experiencing unhealthy, negative emotional distress [e.g., (17)]. Indeed, the role of cognition in emotion is one of the oldest subjects of discussion in psychology, tracing as far back as ancient Greek philosophers such as Epictetus in 108_{AD}, and was a topic around which there was considerable debate in the 20th century [see (18), for review]. An early example during this epoch of a simple model propounding the mediating role of cognition is the *stimulus-organism-response* model of William James' protégé, Robert Woodworth (19), but it was not until around the advent of what many consider the so-called "Cognitive Revolution" during the mid-20th century that more explicit cognitive-mediation models describing affective responding were formally developed. For example, clinical psychology has long appreciated the principle of cognitive mediation [see (20), for a review of this history], with Albert Ellis' (21, 22) *activating event-belief-consequence* (ABC) model of emotion. According this framework, emotional responses are largely the consequence of beliefs (e.g., appraisals) [see (23), for review], a particular class of propositional attitude (24), interacting with representations of goal-relevant events.

In cognitive psychology, theories of emotion generally accord to what has been termed the basic *modal model* of emotion, according to which emotional responses are part of a cyclic sequence: the *situation-attention-appraisal-response* sequence (25). For example, an individual attends to a goal-(in)congruent event and valuates (i.e., appraises) the descriptive representations of this fact in terms of its relevance to one's personal well-being (26), resulting in a valanced emotional response. This emotion-generative procedure is cyclical because responses are often the inputs to subsequent sequences; it is recursive and involves reciprocal causality (27–29). In clinical psychology, this is the framework on which all contemporary CBT-based forms of psychotherapy are predicated; that is, these theories postulate cognitive-vulnerability models [e.g., (30–35)]. More specifically, such interactions between the environment and cognition typically promote adaptive thoughts, feelings, and behaviors within the common range of human functioning, but they can also yield psychopathological symptoms. However, when the content of conceptual valuations (i.e., appraisals) lack empirical, logical, and practical grounding, they tend to engender

maladaptive behavior and emotional distress whose intensity, frequency, and duration not only harm mental health and conflict with personal goals but also tend to self-reinforce and, therefore, develop in individuals a disposition toward similar patterns of thinking and responding in the future, leading to further goal obstruction (35). It is for these reasons, and sense of perniciousness, that such appraisals are referred to as irrational or dysfunctional in the literature.

COGNITIVE RESTRUCTURING IN PSYCHOTHERAPY

So, cognition is contemporarily understood as a necessary mediator of the emotion-generative process, including those emotions which people would rather not experience and which detract from their mental health. Changing the dysfunctional aspects of cognition is typically taken on by the brains of other conspecifics in society, particularly clinicians, rather than on the part of the individual—at first. CBT-based schools of psychotherapy differ relative to one another on the nature of the dysfunctional cognitive operations underpinning particular types of mental illness and emotional distress and, therefore, also differ on the appropriate objects of cognitive change, but there are a number of rudimentary principles on which they agree (36). Namely, they differ from older schools of psychotherapy [e.g., psychoanalysis (37), person-centered therapy (38), etc.] in their de-emphasis of the past and adoption of an active-directive method of restructuring patients' thoughts [see (39), for a history of psychotherapy; see also (17, 40)]. More specifically, they accord to not only the principle of cognitive mediation but also that of cognitive penetrability (24): The idea that, in the case of human dysfunction, those cognitive operations mediating goal-incongruent events and unhealthy (negative or positive) emotions are modifiable. At a common-sense level of psychological explanation, this cognitive change is brought about via verbal intervention of a dialectical nature and, at a lower neurobiological level, by the same principles underpinning neurobiological change: activity-dependent, plasticity mechanisms [i.e., long-term potentiation; (41)]. Thus, cognitive restructuring refers to the aim and process of an intervention to supplant dysfunctional cognitions with more adaptive ones, and the predominate means by which to facilitate this cognitive change are verbal intervention strategies [see (42)]. However, as discussed below, bridging the explanatory gap between this understanding of cognitive change and one at the level of the brain and the information processing systems that work together to actuate it poses certain methodological challenges.

ECOLOGICAL CHALLENGES TO A NEUROSCIENCE OF COGNITIVE CHANGE

Cognitive neuroscientific research has discovered much in the clinical areas investigating relationships between the pathogenesis of psychopathological symptoms and abnormalities in the brain, such as hyper- and hypo-activation in regions supporting aspects of affective, semantic, and executive processing, as well as underconnectivity in the functional connections between such regions [see (43), for review]. Other research has focused on more structural, developmental, and genetic relations with functional aspects of the brain and psychopathological symptomology; a persisting problem in this enterprise that is worth noting is whether such brain abnormalities facilitate clinically significant symptoms or follow from them (44). As regards interventions and treatments for psychopathological symptoms, outcome measures of emotion, cognition, behavior, and physiology are best understood. These measures indicate the effects of an intervention. More successful treatments are those which lead to decreases in psychopathological symptoms and increases in positive emotion, rational beliefs, and adaptive behavior, as well as physiological changes in the brain (e.g., a less reactive amygdala in the case of anxiety disorders). However, little is understood at the levels of information processing and the brain about the cognitive and functional changes that take place throughout clinical interventions *in situ*—that underpin improvements to these features of mental health.

This is largely because experimental designs examining the effects of interventions on mental health only collect data periodically (e.g., before, halfway, and after treatment) rather than continuously within clinical settings at multiple periods [see (45)]. Methodologically, this has hitherto been infeasible, because neuroimaging techniques such as functional magnetic resonance imaging (fMRI) require clients to go to facilities to have their brains scanned. Such paradigms not only leave an explanatory gap regarding the neurocognitive mechanisms driving intervention effects but also raise a serious issue of ecological validity (**Figure 1**). The extent to which tasks represent functions at the level of the person and generalize in their predictability of responding in everyday-life situations is the degree to which they are valid, ecologically (46, 47). But when the neural correlates of cognitive change are investigated, studies typically use tasks relating to affective-reactivity, emotion regulation (e.g., reappraisal), or no task (e.g., resting-state) [e.g., (48–54)]. The blocked, event-related, or mixed experimental designs in these paradigms do not reflect the tasks of clients in clinical situations, nor does the testing environment reflect the interpersonal interactions (i.e., verbal intervention) that are integral to them. For example, although emotion regulation strategies for facilitating cognitive change have been found to correlate negatively with psychopathological symptoms [see (55), for review], these tasks fail to capture the recogitation that seems to be critical to disputing dysfunctional appraisal operations, do not target specific dysfunctional appraisal operations (i.e., instead, the contents and objects of reappraisal relate to the presented stimuli), and the stimuli seldom represent personally relevant, goal-incongruent situations; stimuli are also restricted to visual images rather than to the linguistic propositions clients might hear in real clinical situations. Thus, such paradigms are sufficient for investigating the neural bases of emotion regulation, but are ecologically limited in the ways they generalize to the clinical domain and, consequently, hinders our ability to

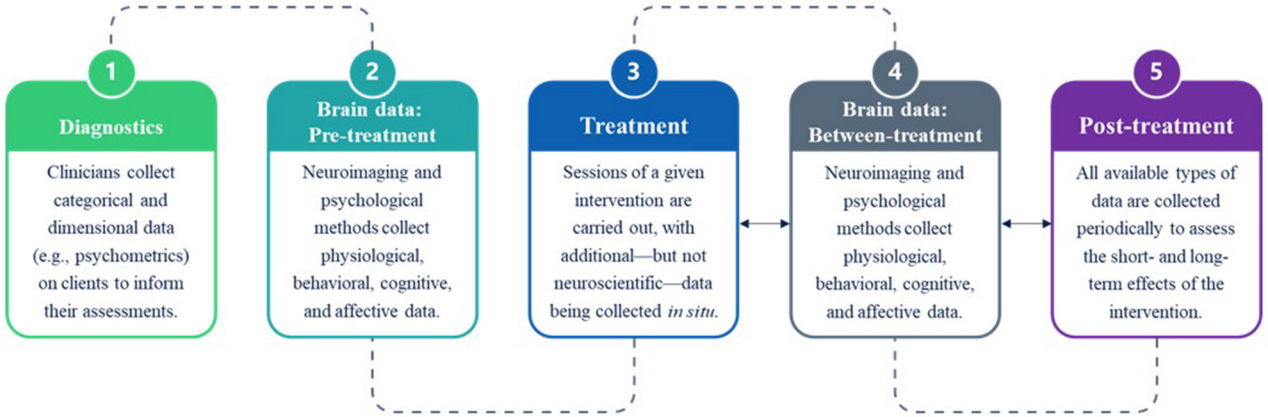

FIGURE 1 | Data collection in the clinical neuroscience of mental health interventions. After an initial evaluation period (1), paradigms investigating the periodic effects of treatment (3) on the brain typically collect data from clinical populations before treatment commences (2), between particular stages of treatment (4), such as at 6 weeks, and at short- and long-term stages subsequent to treatment (5), such as after 14 weeks. Note that no neuroscientific data are collected during the interpersonal interactions driving the treatment sessions, leaving an explanatory gap regarding the nature of the information-processing systems in the brains of both clinicians and clients that contribute to the observed effects of interventions (e.g., cognitive change, emotion regulation, functional connectivity, etc.).

bolster a neuroscientific understanding of the role of cognitive restructuring in cultivating mental health.

FUTURE DIRECTIONS AND CONCLUDING PERSPECTIVE

An important step toward addressing these ecological shortcomings and explanatory gaps in clinical cognitive neuroscience will be to take advantage of the ability of neuroimaging methods collect brain data in settings that better represent clinical situations. For example, functional near-infrared spectroscopy (fNIRS) is a relatively new, non-invasive neuroimaging technique (56, 57) that is similar to fMRI in its measurement of changes in concentrations of hemoglobin to infer changes in neural activation in the brain (i.e., neurovascular coupling), but differs in the sense that it is an optical rather than magnetic method: fNIRS calculates the attenuation of electromagnetic radiation, namely near-infrared light (650–1,000 nm), to index signal changes in oxygenated (HbO_2) and deoxygenated (HbR) hemoglobin [see (58)]. For more in-depth discussions of the methodology of fNIRS and the quality control and publishing standards that are emerging in this field, see Orihuela-Espina et al. (59), Quaresima and Ferrari (60), and Yücel et al. (61). Recent technological advancements to the portability and wearability (62), as well as multi-person use (63), of fNIRS systems have broadened the types of experiments that can be carried out [see (64, 65), for reviews]. One of the most important applications of these advances has been to use fNIRS to investigate cognition in different environments outside of conventional laboratory settings [e.g., (66); see (67), for review]. For example, one study recently used a wireless system to examine the neural correlates supporting the balancing task of slacklining (68). It has been suggested that this improved ecological validity might also provide greater sensitivity and explanatory power to clinically-relevant subjects of interest (45). For example, investigating links between etiopathogenic mechanisms, cortical abnormalities (functional and structural), and psychopathological symptoms is crucial to better understanding mental *illness*, and fNIRS is playing an active part in this research enterprise [see (69–71), for reviews], as well as in similar ones in the clinical domain [see (72), for review]. While these areas of research are in line with what other neuroimaging methods are investigating, fNIRS is also uniquely well-suited to investigate how mental *health* is cultivated within clinical interventions.

For example, multi-person fNIRS, namely fNIRS-based hyperscanning, is a technique by which hemodynamic changes and interpersonal brain dynamics (i.e., cross-brain synchronization) between two or more individuals can be observed whilst they engage in tasks in naturalistic or laboratory settings (73). This method would allow for the development of experimental designs that fractionate the interpersonal interactions occurring in real-world clinical settings and, importantly, to investigate the neurocognitive subsystems mediating cognitive restructuring, including those unique to clinicians. Hirsch et al. (74) represents a recent study that used fNIRS-based hyperscanning to examine the neural correlates of dialectical discourse. The design and multi-modal techniques employed in this study suggest a potentially promising direction for adapting future studies to use tasks involving verbal interactions that reflect the intervention strategies used in non-pharmacological treatments such as CBT-based interventions. For example, trials might be comprised of epochs for specific facets of verbal exchanges that typically occur between clinicians and clients (**Figure 2**). More specifically, one person (i.e., the client) utters some dysfunctional proposition and the other person (i.e., the clinician) listens to this, considers it, and then replies in a way that disputes it while the client listens. A design involving such epochs might require training prior to testing

FIGURE 2 | Example paradigm of a semi-clinical environment. Pairs of individuals are seated across a table with a full field of vision of each other in a normal room. A computer screen is positioned to the side of each participant's face to not obstruct natural facial information during verbal communication. Clinical interactions are then fractionated during fNIRS acquisition: A "client" utters a dysfunctional proposition while the "clinician" listens to this, then critically thinks about what makes the belief irrational, and finally verbally disputes the appraisal while the client carefully listens. These epochs would constitute one trial in a block; other blocks mnight involve reversing roles or changing the nature of the intervention strategy.

and some computer mediation (e.g., displaying propositions), at first, but would begin to bring a laboratory setting closer to a clinical one and, importantly, yield activation changes in the brain regions that are unique to each task and individual. Potentially, it could be those changes unique to the periods during which clinicians are required to think and speak in ways that dispute dysfunctional appraisals that become most critical to understanding how clients maintain their mental health subsequent to treatment, since such a paradigm raises the questions of how activation patterns between clinicians and clients on the same tasks might deviate and how these deviations might be experimentally rectified on the part of clients. In more naturalistic clinical situations, it might be difficult to separate these interpersonal interactions into clean epochs and blocks. Fortunately, data collected in ecological designs for which there is no *a priori* stimulus design and no computer mediation can now be analyzed. Namely, there are "brain-first" approaches to analyzing data to recover onsets and durations *a posteriori* [e.g., (75)]. Clearly, these possibilities suggest further research. Although there are other experimental methods capable of collecting data in intervention environments which might be useful in investigating these real-time interactions, such as electroencephalography, eye-gaze, ultrasound, heart rate, breathing rate, and forms of tomography, multi-modal approaches using a combination of these with fNIRS represent the best compromise of spatial and temporal resolution (76). In sum, assessing the intra- and inter-brain dynamics supporting the recogitation of thought in clinical situations might help to more clearly reveal the neurocognitive mechanisms underlying changes in mental health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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fNIRS Evaluation of Frontal and Temporal Cortex Activation by Verbal Fluency Task and High-Level Cognition Task for Detecting Anxiety and Depression

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Anxiety and depression are widespread psychosis which are believed to affect cerebral metabolism, especially in frontal and temporal cortex. The comorbidity patients of anxiety and depression (A&D) have more serious clinical symptoms. Functional near-infrared spectroscopy (fNIRS) is a noninvasive modality used to monitor human brain oxygenation, and it could be considered as a potential tool to detect psychosis which may lead to abnormal cerebral oxygen status when the brain is activated. However, how sensitive the cerebral oxygenation response to the cortex activation and whether these responses are consistent at different stages of A&D or different regions still remains unclear. In this study, a conventional physiological paradigm for cortex activation, i.e., verbal fluency task (VFT), and a relatively new paradigm, i.e., high-level cognition task (HCT), were compared to detect A&D through a longitudinal measurement of cerebral oxygen status by fNIRS. The A&D patients at the acute, consolidation and maintenance stages as well as the healthy subjects participated in the VFT and HCT paradigms, respectively. For the VTF paradigm, the subject was instructed to answer questions of phrase constructions within 60 s. For the HCT paradigm, the subject was instructed to categorize items, logical reasoning, and comprehensive judgment and write down the answers within 60 s. For most of the subjects, the oxy-Hb is found to increase remarkably, accompanied with a relatively small reduction in deoxy-Hb when subject to both paradigms. The statistical analyses show a relatively large variability within any group, leading to the significant difference that was only found between A&D at the acute stage and healthy subjects in the temporal lobe region ($p < 0.001$). Nevertheless, HCT would activate more oxygen increment when compared with the VFT, with a large integral value in oxy-Hb. On average, the oxy-Hb integral value of the A&D patients differs substantially at different stages when subject to HCT paradigm. Moreover, the prefrontal lobe and temporal lobe responses were more consistent to the HCT paradigm rather than the VFT paradigm. Under the VFT paradigm, however, no remarkable difference in integral value was found among the three stages, either at the prefrontal lobe or at the temporal

lobe. This study indicated that HCT, which is intensively involved in brain function, would activate more oxygenation changes in the cerebral cortex. Additionally, with good performance at distinguishing different stages according to the oxy-Hb criterion, the HCT has the potential to evaluate the therapeutic effects for A&D patients.

Keywords: functional near-infrared spectroscopy, high-level cognition task, verbal fluency task, anxiety, depression

BACKGROUND

It is well-known that the human brain controls emotions and cognitive activities. The prefrontal lobe of the brain is associated with the formation and expression of language. If the prefrontal lobe is damaged, these abilities will be significantly impaired. The temporal lobe of the brain is associated with autonomous consciousness; therefore, it is critical in language comprehension, hearing, visual processing, and facial recognition. Cognition is a major determinant of social function in patients with psychosis (1, 2).

Anxiety disorders and depression disorders are widespread psychiatric diseases. According to the WHO World Mental Health Survey, the comorbidity rate between anxiety and depression was 45.7% (3). The comorbidity patients (anxiety and depression, A&D) have a worse overall prognosis and more severe functional impairment (4, 5). Follow-up studies have found that, compared with major depressive disorder (MDD), A&D has a unique symptomatology that differs in cognitive control and emotion responses. A&D has a declined cognitive control regulation but enhanced emotion responses; MDD has declined cognitive control regulation and delayed emotion responses (6). Related studies support the possibility that A&D could be an independent psychosis.

It is difficult to diagnose psychosis through anatomical abnormalities by using regular brain imaging techniques such as MRI or CT. The symptoms of psychosis are often associated with brain function rather than anatomy or morphology. The functional near-infrared spectroscopy (fNIRS) technique is a non-invasive technique developed in recent years to assess brain function. fNIRS is capable of real-time acquisition of cerebral oxygen signals as well as dynamic monitoring of physiological and pathological processes in the cerebral cortex. Therefore, fNIRS has been widely used to assess brain function in psychosis (7, 8). In addition, the cerebral oxygen metabolism would elevate when performing brain-loaded cognitive tasks. The fNIRS technique measures the characteristics of cortex oxyhemoglobin and deoxyhemoglobin changes, which indirectly reflect the function of the brain.

The fNIRS has been utilized by numerous laboratories to design task models, including oral fluency and working memory tasks (9–11), which have been found to be associated with prefrontal and temporal activation. Neural activities within the dorsolateral prefrontal cortex (DLPFC) reflect the emotion responses, especially to negative stimulation. Post-treatment activation of the DLPFC would also enhance emotion controls. The activity of DLPFC in patients with depression decreased not only in cognitive tasks, such as the Stroop task, the emotional oddity task, the go/no-go task, and the self-judgment task (12–15), but also in emotion recognition tasks (16–19). The DLPFC has executive functions which are parts of cognitive abilities and contribute to predictions of future behavior consequences.

The activation of the frontal and temporal lobes has been repeatedly proven through tasks (20). At present, the most widely used cognitive task is the verbal fluency task (VFT). With less often adoption, the high-level cognition task (HCT) reflects the advanced thinking activity of the brain. High-level cognition refers to the formation of thought, such as conception, abstraction, judgment, reasoning, and execution, also known as rational cognition (21). Conceptual classification means categorizing things according to their different properties, such as agricultural products, animals, fruits, and so on. Critical thinking belongs to judgment and reasoning, such as the evaluation of processes, results, and methods (22). Execution ability is to solve problems or plan for the future through cognitive resources (23). High-level cognition is the most complex (24). Both VFT and HCT are advanced cognitive tasks. The verbal fluency task reflects the ability to pick up words. The high-level cognition task reflects the abilities of judgment, conception, and reasoning. VFT is to extract related concepts, while HCT is not only to extract related concepts but also to integrate and process the concepts, which has a high degree of complexity. In this study, the subjects were asked to define a concept, such as tree, student, dolphin, apple, chef, eggplant, and dog, and then categorize the concept and classify it, such as plant, occupation, animal, and fruit. Next, the subjects were asked to rate the difficulty of the question. Studies have shown that cognitive impairment of psychosis persists from the onset to remission stage (25), including declines in attention, memory, and executive function (26, 27). The HCT might be more appropriate for differentiating psychiatric disorders when compared with the conventional VFT. Thus far, the comprehensive comparison between VFT and HCT has not been conducted, which is the main goal of this study (28, 29).

In this study, we conducted the first attempt to extensively evaluate the VFT and HCT in the A&D population by using fNIRS. Based on the subject's knowledge background, a comprehensive assessment of cognitive abilities, including attention, memory, and discrimination, calculation, categorization, logical thinking, and other rational thinking abilities, was conducted. The subjects were required to apply multiple types of abilities in the HCT. The fNIRS was used to assess the differences between VFT and HCT, and data from the prefrontal and temporal lobes of the brain were collected and analyzed for comparison. The derived outcomes were used to

explore the task that can assess cerebral cortex function in A&D and provide aid in clinical diagnosis and intervention.

MATERIALS AND METHODS

Participants

According to the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) standard, the patients were diagnosed with depressive disorder and suffering from anxiety (30). The diagnosis was determined by three experienced physicians. From the outpatient or inpatient divisions of the Department of Psychiatric Health, First Hospital of Shanxi Medical University, we recruited 30 patients with A&D at the acute stage, consolidation stage, and maintenance stage, with 10 subjects in each group. In addition, 10 age-matched healthy controls (HCs), none of whom had a family history of psychosis, were also recruited. Those who have a history of neurological or other psychosis, substance abuse, severe medical illness, or cognitive dysfunction were excluded. All of the subjects were between 15 and 55 years of age. The four groups of subjects (i.e., HCs and the A&D at the acute, consolidation, and maintenance stages) participated in the VFT and HCT paradigm, respectively, resulting in a total of eight sets of hemodynamic data, with 10 data in each set. This study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University, and informed consent was obtained from each participant. All the subjects were native Chinese speakers with speaking and reading ability, had an educational background of high school or above, and were able to cooperate effectively with this study.

Clinical Assessments

For A&D, clinical assessment included age, duration of illness, intake of psychiatric medicine, and duration of medication. For A&D and HCs, the clinical symptoms were assessed using the Hamilton Depression Scale (HAMD-24) and the Hamilton Anxiety Scale (HAMA-14).

VFT Task and HCT Task

The task instructors were psychiatric clinicians with well-training. Guided by the instructor, it took ∼160 s for A&D and HC subjects to complete the VFT. During the 30-s baseline period, the subjects sat still in a chair and were required to repeat counting from one to five until the task began. During the 60-s task period, the subjects were asked to construct as many phrases as possible using simple words such as sky, earth, and big. At the end of the phrase constructions, the subjects were asked to repeat counting from one to five until the end of the task, which took 70 s. The subjects then rested for 5 min, and then the HCT was started. The detailed procedures for the HCT paradigm are depicted elsewhere (25–27). The subjects sat still in a chair and wrote down the answers on a paper for a few questions during the 60-s period. In this study, the subjects were asked to define a concept and classify it, such as tree, student, dolphin, apple, chef, eggplant, and dog, and then categorize the concept, such as plant, occupation, animal, and fruit. Next, the subjects were asked to rate the difficulty of the question. Prior to the tasks, the subjects were asked to repeat counting from one to five for a baseline period of 30 s until the task began. The task period took 60 s, and the subjects would repeat counting until the end of the task, which took 70 s. The subjects were asked to write down as many answers as possible. After the task was completed, the correct rate of answers was recorded.

fNIRS Detection

The principle of fNIRS is based on the absorption and scattering of near-infrared light in cerebral tissue. Photons are absorbed or scattered by hemoglobin in the tissue, causing attenuation of the light; thus, the hemoglobin content is estimated according to the modified Beer–Lambert law. The 3 × 11 probe holder was placed on the scalp surface, and the lowest channel was positioned at Fp1–Fp2 according to the international 10–20 system. The detection sites mainly covered the prefrontal and bilateral temporal lobe regions (31, 32), and the distance between two adjacent source-detector fibers was set at 3.0 cm, with the covering region between the source-detectors defined as "channel." The prefrontal lobe covered 18 channels, and the left and right temporal lobes covered 34 channels. The sampling rate of the fNIRS is 10 Hz.

A 52-channel fNIRS system (ETG-4100, Hitachi Medical Systems, Japan) was utilized to longitudinally monitor the oxygenation changes throughout the VFT or HCT paradigm. The fNIRS measurements include a 30-s baseline, a 60-s task (VFT or HCT), and a 70-s post-task recovery. The cerebral oxygenation variables measured from the fNIRS system, including the changes in oxy- and deoxy-hemoglobin (i.e., oxy-Hb and deoxy-Hb), were obtained. Moreover, a derived parameter, namely, integral value, was calculated from these oxygenation variables. Specifically, the integral value is defined as the sum of hemodynamic concentration (oxy-Hb or deoxy-Hb) from task beginning to task ending (i.e., 60-s task period).

Data Analysis

One-way ANOVA was used to test the significant difference of hemodynamic data among the four groups (i.e., HCs and A&D patients at the acute, consolidation, and maintenance stages). Regression analysis was performed to investigate the influence of age on hemodynamic data. $p < 0.05$ was considered significant for all statistical results.

RESULTS

Age-Related Changes in VFT and HCT

Table 1 shows that age has no influence on the oxy-Hb and deoxy-Hb data ($r < 0.1$, $p > 0.05$) for both VFT and HCT paradigms.

TABLE 1 | Standard deviation of age.

Stage	Mean	Standard deviation	Probability
Acute	60.4	18.2	
Consolidation	57.5	10.3	
Maintenance	61.6	17.9	
Healthy controls	32.1	10.6	>0.05

The Activation of HCT and VFT Tasks in the Prefrontal Lobe

Figures 1, **2** show the prefrontal oxygen response of A&D at different stages and a HC during the VFT and HCT. It can be seen that the concentration of oxy-hemoglobin responded more significantly to the task, increasing as the task is being performed and reaching a peak value at the end of the task. Thereafter, oxy-Hb gradually returned to baseline values. By contrast, the deoxy-hemoglobin concentration changed much less and with more fluctuations.

Additionally, we found that the oxy-Hb recovered more rapidly toward the baseline under the HCT paradigm than that under the VFT paradigm, which is anticipated. As mentioned earlier, the HCT generates more intensive stimulus to the brain cortex, activating more oxy-Hb response. Hence, it is reasonable to see the fast and sharp decrease when the HCT test stopped, leading to a fast recovery to the baseline.

For both VFT and HCT, the oxy-Hb response was generally lower in A&D than in HCs when performing the same task. Besides this, as shown in **Figures 1**, **2**, for the same A&D patient, the HCT produced larger oxy-Hb integral values, indicating a higher activation of the prefrontal lobes in this task. Under the HCT, the difference between normal and acute patients is more obvious compared with the VFT.

Figures 3, **4** show the average cerebral oxygen responses over A&D at different stages and HCs under the VFT and HCT, respectively. From the comparison, it is clear that the average responses of the HCs and A&D are similar to those of the representative subjects, i.e., the activation by HCT is greater than that by VFT. In addition, for either task, the hemodynamic response was much greater in HCs than in A&D. Nevertheless, the difference between the acute phase A&D patients and healthy controls in hemodynamic response (oxy-Hb and deoxy-Hb) was not significant under VFT ($p > 0.05$).

Activation Response to the Tasks in Patients at Different Stages

As shown in **Figure 5**, the acute, consolidation, and maintenance stages of A&D have, on average, a lower activation than that of healthy controls by the VFT, but the difference between these groups was not significant ($p > 0.05$). In addition, the prefrontal and temporal lobe responses were not always consistent at different stages, especially when the hemodynamic response was low.

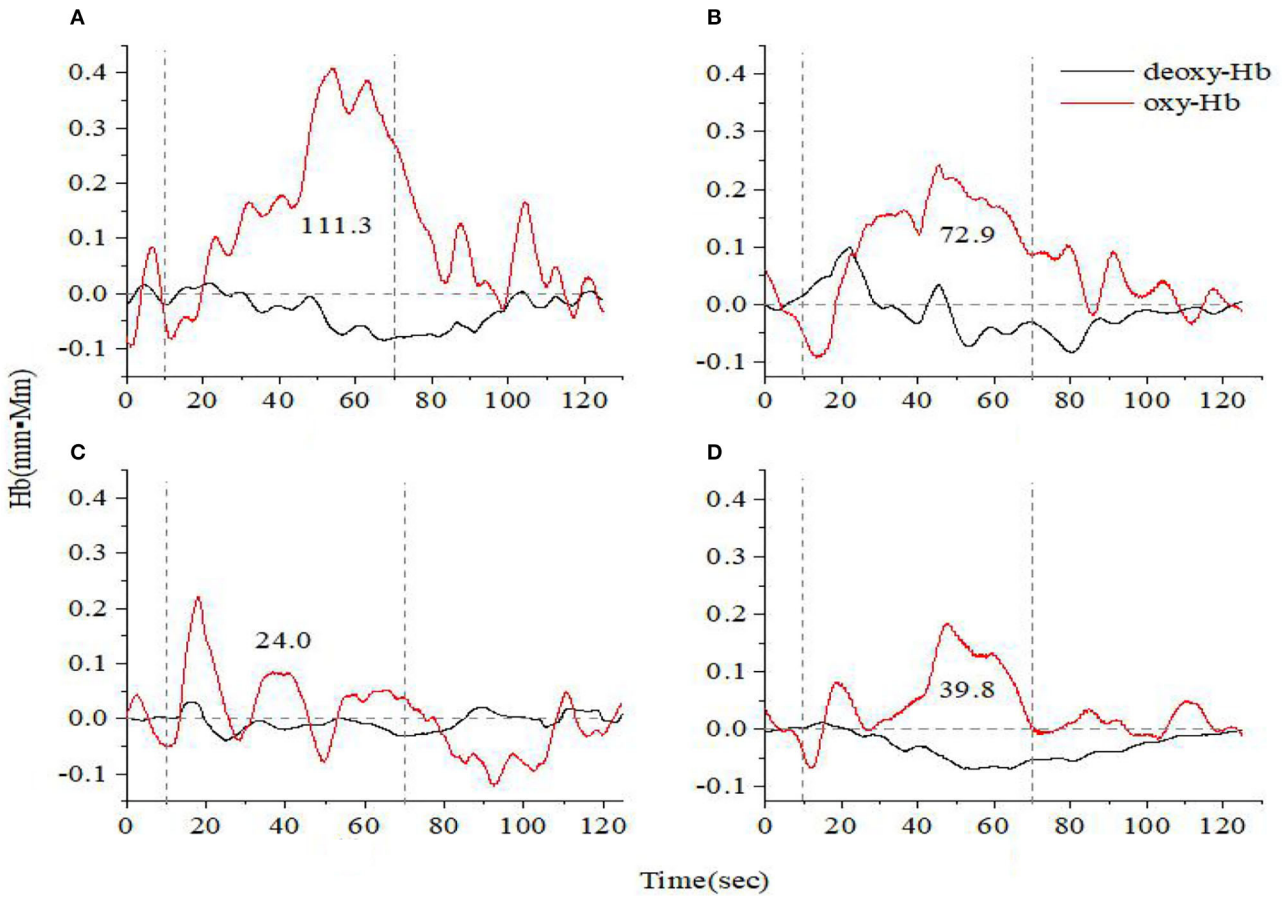

FIGURE 1 | Time course of hemoglobin concentration changes in a representative healthy control **(A)** and a representative anxiety and depression patient at the acute **(B)**, consolidation **(C)**, and maintenance stages **(D)**. All of them completed the verbal fluency task. The red line indicates the amount of change in oxyhemoglobin concentration (oxy-Hb), and the black line indicates the amount of change in deoxyhemoglobin concentration (deoxy-Hb). The numbers indicate integral values.

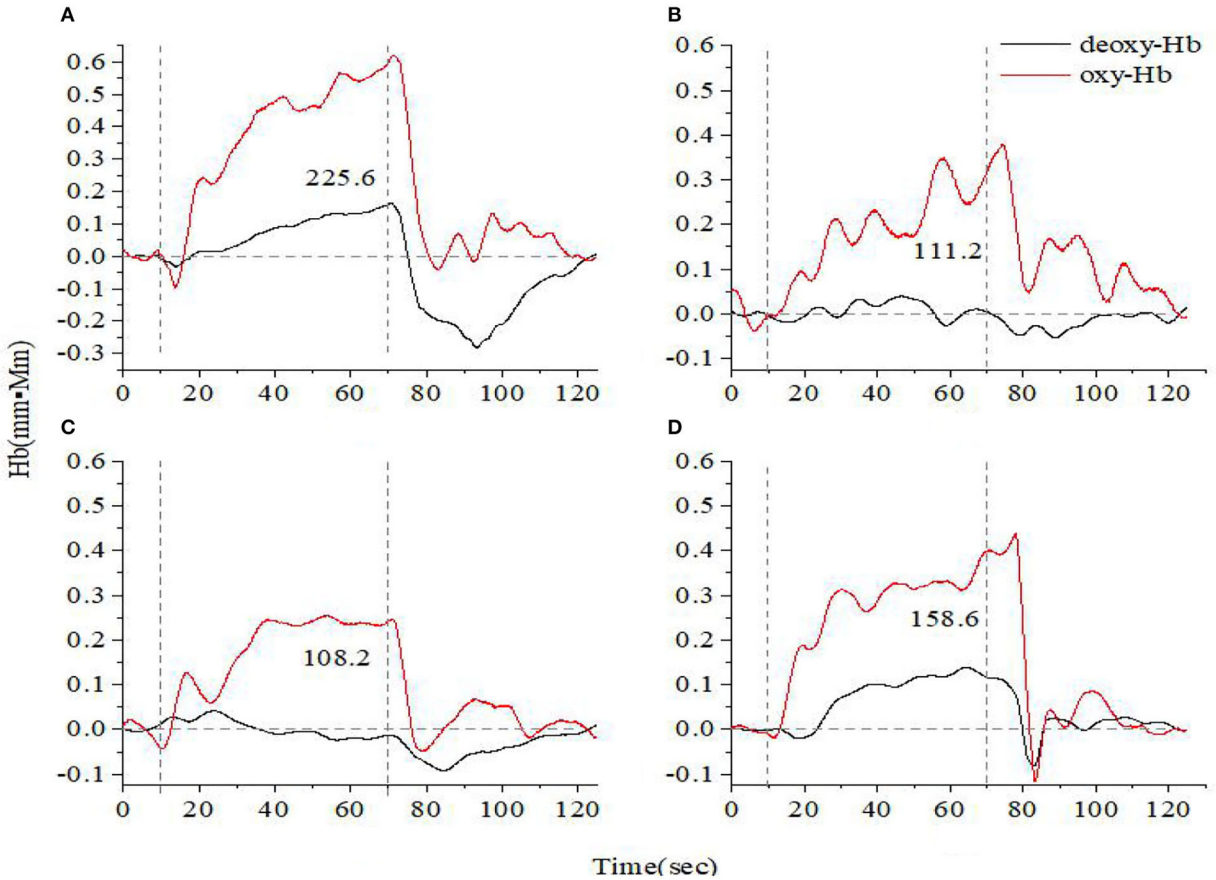

FIGURE 2 | Time course of hemoglobin concentration changes in a representative healthy control **(A)** and a representative anxiety and depression patient at the acute **(B)**, consolidation **(C)**, and maintenance stages **(D)**. All of them completed the high-level cognition task. The red line indicates the amount of change in oxyhemoglobin concentration (oxy-Hb), and the black line indicates the amount of change in deoxyhemoglobin concentration (deoxy-Hb). The numbers indicate integral values.

When HCT was used as the activation task, we found that the hemodynamic responses differed significantly across the different stages of A&D in the prefrontal lobe. The stages with oxy-Hb integral value from the largest to the smallest are consistent, i.e., in order—maintenance stage, consolidation stage, and acute stage. The integral values are consistent with the clinical symptoms. For example, the patients had the lowest mean hemodynamic response at the acute stage, an enhanced response at the consolidation stage, and the largest mean response at the maintenance stage, which was slightly larger than that of the healthy population on average. The cerebral oxygen activation in the temporal lobe at the different stages of A&D was consistent with the results in the prefrontal lobe.

However, we also found that the integral values within each group had a large variation, resulting in statistically insignificant differences (i.e., $p > 0.05$) between groups. Nevertheless, we found significant differences in temporal lobe integral values between A&D at acute stage and HCs when utilizing the HCT ($p < 0.001$). Besides this, the other significant tests among the four groups are marginal (i.e., the p-value is slightly larger than 0.05). Overall, the group differences under HCT were much better than that under the VFT.

The oxy-Hb of the VFT test is higher in the acute and the normal groups in the prefrontal than the temporal lobe. The HCT shows that all of them has higher oxy-Hb in the prefrontal lobe. The frontal lobe is mainly responsible for higher-level thinking, and the temporal lobe is responsible for memory and processing of information. The frontal lobe has a stronger cognitive function than the temporal lobe, so the oxy-Hb of the frontal lobe is higher than that of the temporal lobe. At the same time, HCT intensity was higher than that of VFT, so oxy-Hb was higher under HCT.

As mentioned earlier, the oxy-Hb integral values of the A&D patients at the maintenance period is slightly higher than those of healthy controls. Nevertheless, no significant difference was found between the two groups, which coincides with previous reports (33) and might be due to the small sample size or large individual variability.

DISCUSSION

We consider the HCT as a comprehensive capability of the human's advanced thinking and performance, such as integrating and processing concepts, making judgment, reasoning as well

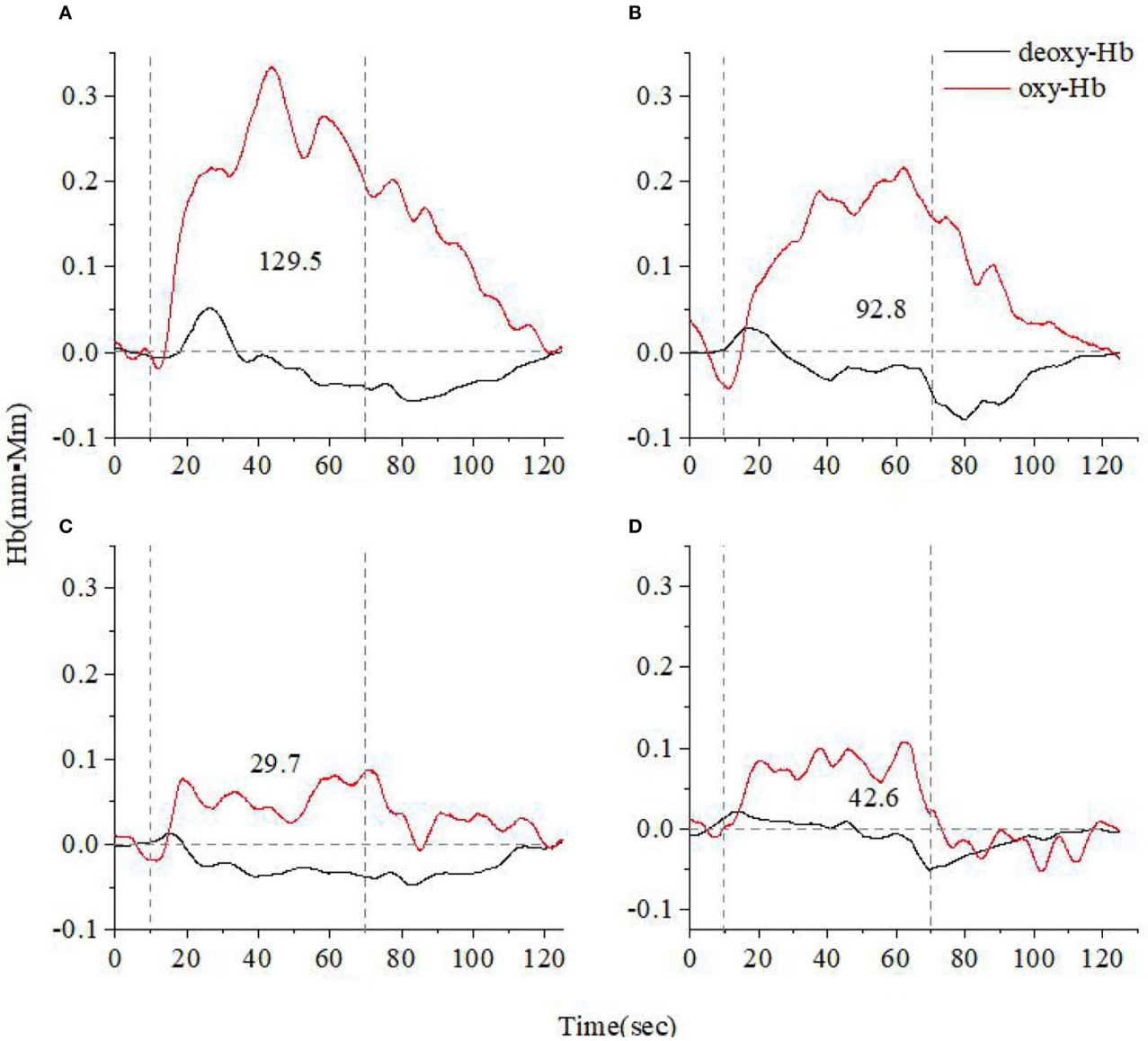

FIGURE 3 | Time course of the average hemoglobin concentration of 10 people under verbal fluency task (VFT) **(A)**. Time course of the average hemoglobin concentration of 10 anxiety and depression patients at the acute **(B)**, consolidation **(C)**, and maintenance stages **(D)**. All of them completed the VFT. The red line indicates the amount of change in oxyhemoglobin concentration (oxy-Hb), and the black line indicates the amount of change in deoxyhemoglobin concentration (deoxy-Hb). The numbers indicate integral values.

as executing to solve complicated problems. These advanced thinking and performance would generate more brain cortex activation when compared with the VFT that only involves simple thought and immediate response. Thus, the details of HCT vary a lot among different studies, and there are no standard procedures. Some studies used Stroop tasks and the Tower of London tasks (34–36). The patients' language memory, working memory, reaction speed, attention, processing speed, and executive function were measured. The emotion recognition tasks are used to evaluate executive function and reflect the subjects' various types of abilities, such as complex visual and spatial planning, working memory, and selective attention (37–39), which reflect the patient's executive functions, attention, discrimination, memory, and cognitive control. All of these tasks involve advanced thinking and performance. Hence, we defined these activities as "high-level cognition task" in this study and investigated the impact of HCT on oxygenation activation of the brain cortex.

This study confirms that HCT generates more intensive stimulus to the brain cortex, activating more oxy-Hb response. However, VFT only covers limited executive functions, such as word extraction ability, which are not enough to distinguish

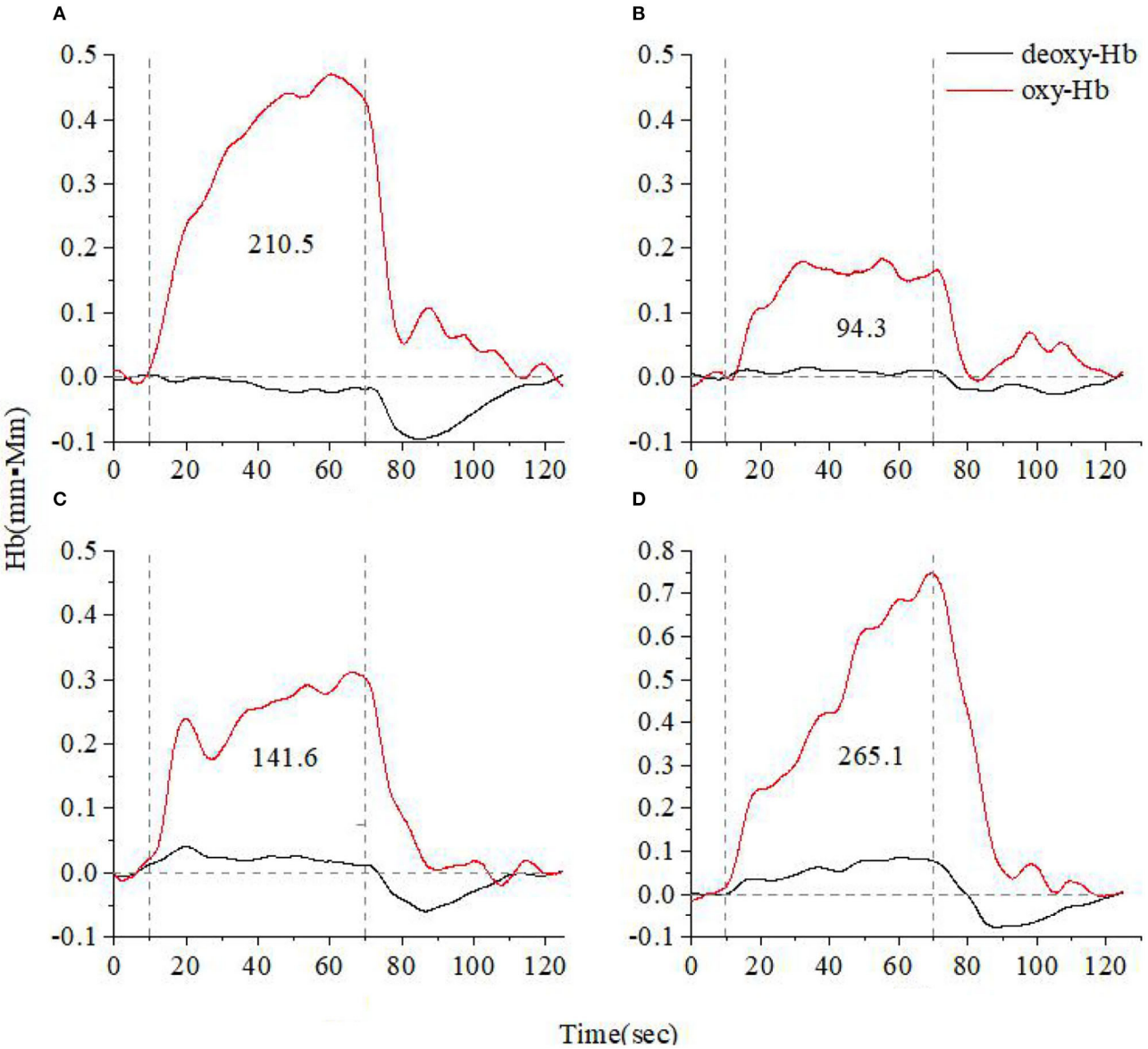

FIGURE 4 | Time course of the average hemoglobin concentration of 10 people under verbal fluency task **(A)**. Time course of the average hemoglobin concentration of 10 anxiety and depression patients at the acute **(B)**, consolidation **(C)**, and maintenance stages **(D)**. All of them completed the high-level cognition task. The red line indicates the amount of change in oxyhemoglobin concentration (oxy-Hb), and the black line indicates the amount of change in deoxyhemoglobin concentration (deoxy-Hb). The numbers indicate integral values.

different psychosis (40). According to the theory of brain function (22, 41, 42), the frontal lobe is mainly responsible for higher level thinking, and the temporal lobe is responsible for cognition and information processing. The frontal lobe has a stronger cognitive function than the temporal lobe.

The main objective of this study was to evaluate the task intensity for the frontal and temporal cortex activation paradigm in A&D by using the fNIRS technique. The VFT and HCT were adopted to perform cortex excitation. Among these, VFT is an established task and more commonly employed for fNIRS brain function assessment. For example, Herrmann et al. (43, 44) applied the VFT to psychiatric patients, and the fNIRS outcomes found remarkable hemoglobin changes in patients with depression during the task, indicating the cerebral function alternations in this population. The observation of these changes may provide insight into clinical diagnosis and guide interventions (45).

We recruited A&D at different stages (acute, consolidation, and maintenance) for task evaluation and compared them with age-matched HCs. The integral value of oxy-Hb during the task was used to represent the total amount of cortex activation. Individual and group-averaged cerebra oxygen responses showed

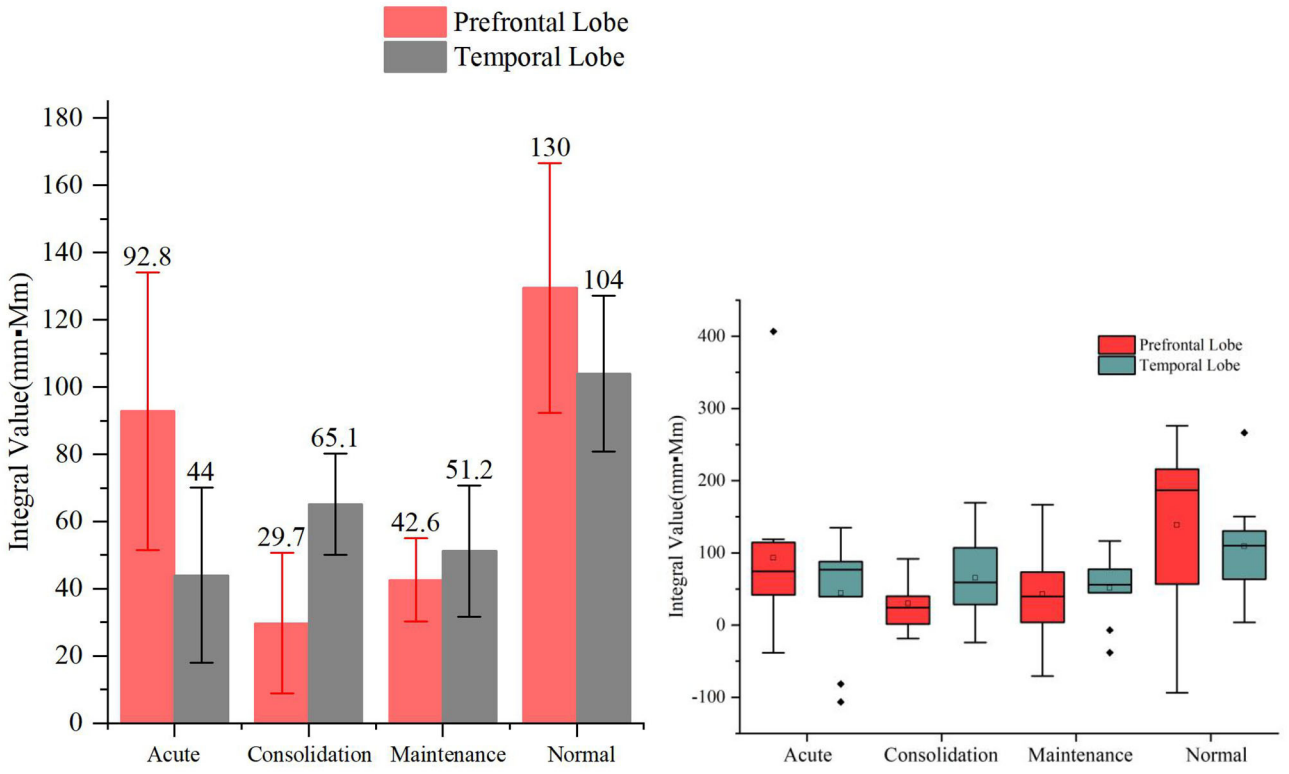

FIGURE 5 | Integral values (mean ± SD) of prefrontal and temporal oxy-Hb from the anxiety and depression patients at the acute, consolidation, and maintenance stages as well as the healthy controls during the verbal fluency task. No significant differences were found in the oxy-Hb integral values among the four groups.

that A&D generally had less cortex activation during the task compared to HCs (**Figures 1**–**4**). In both HCs and A&D, the HCT had a larger integral value of oxygen response than the VFT, indicating that the HCT is more intensive in activating the prefrontal and temporal lobes than the VFT. Thus, HCT can better reflect the function of the cerebral cortex. The possible reason is that the HCT is more challenging and would trigger a comprehensive response of human cognitive capacity. The reports from other research groups also support this explanation (46, 47).

Despite the relatively weak activation by the VFT, we found that the cerebral oxygen responses in A&D were generally lower than in HCs under this paradigm (**Figures 5**, **6**). However, the difference in blood oxygenation among the different stages of A&D was not significant, indicating that the VFT is not suitable as a stage marker. This may be due to the fact that the VFT does not sufficiently challenge the subjects' information processing abilities. By contrast, the HCT efficiently stimulates the advanced cognitive abilities in the human cerebral cortex. Although individual variability was found among subjects in the same group, A&D showed different responses at different stages. The response was lowest especially at the acute stage, then it was enhanced during the consolidation stage and ultimately became strongest during the maintenance stage, which is close to that of healthy individuals.

We performed the first evaluation of the HCT using the fNIRS technique, and the fNIRS measurement could detect a cognitive impairment of advanced function that is associated with A&D in a timely manner. Furthermore, the HCT would be helpful to predict the disease progression of A&D and identify the stage when integrated with clinical symptoms as assessed by HAMD-24 and HAMA-14. When the symptoms are relieved, the patients' advanced cognitive function can be partially restored to a pre-disease normal level, which provides an objective basis for the assessment of treatment effects.

Although we found an oxygen response difference between A&D and HCs, either individually or by group, statistical analyses reveal that the oxygen responses varied substantially within any group. Therefore, the significant differences in integral values were found only between A&D at the acute stage and HCs in the temporal lobe region ($p < 0.001$) when using the HCT. By contrast, no significant differences were found between any groups when using the VFT. The statistical outcomes might be affected by both the intensity and the duration of the task activating the cerebral cortex. Under the weak activation paradigm, cerebral oxygen changes associated with cognition are easily buried by baseline perturbations, leading to the outcome of non-significant differences. The frontal and temporal cortex task protocol needed to be further enhanced to better differentiate between healthy and psychosis.

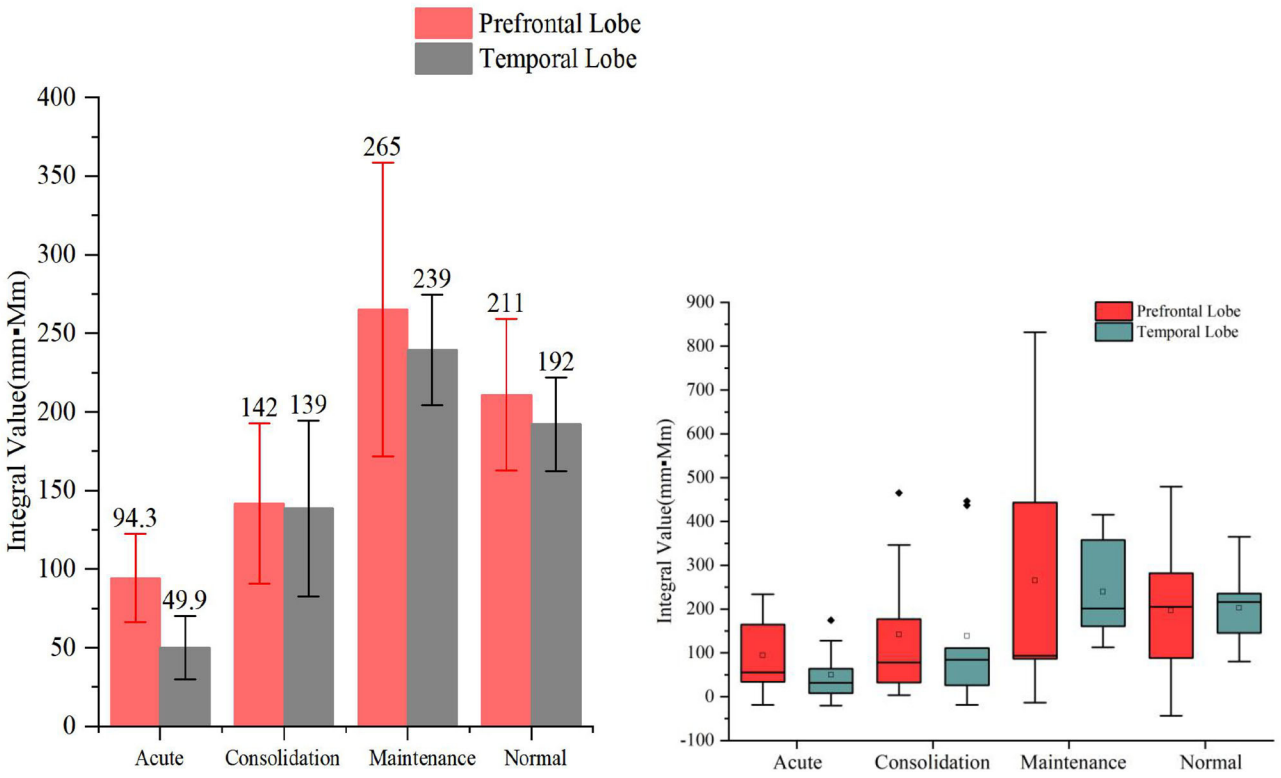

FIGURE 6 | The integral values (mean ± SD) of prefrontal and temporal lobe oxy-Hb from the anxiety and depression patients at the acute, consolidation, and maintenance stages as well as the healthy controls (HCs) under the high-level cognition task. The oxy-Hb integral values of both temporal lobes of the patients at the acute stages were significantly smaller than those of the HCs' ($p < 0.001$).

CONCLUSIONS

To conclude, the VFT generates a weaker cortex activation when compared with the HCT. Our study showed that HCT was associated with A&D and more efficient in differentiating the patients from healthy controls than the VFT. Moreover, the cerebral oxygen responses are related to progresses of A&D; thus, it could be used as a diagnostic tool to identify A&D and distinguish disease stages. In future studies, we will recruit more patients with different types of psychosis (e.g., depression, anxiety, and schizophrenia), with the aim to evaluate the comprehensive cognitive impairments by using the HCT paradigm.

LIMITATION

The relatively small size (i.e., 10 samples in each group) is the main study limitation. In future studies, first of all, we will enlarge the sample size to draw more solid conclusions. Second, we will focus on the longitudinal experimental design, collecting the cognitive status of two time points (baseline and follow-up), and carrying out cognitive training, such as abstract thinking training. Lastly, we should take into account pre-disease IQ (48), cognitive reserve, and the prevalence of cognitive impairment (49–51). We aim to compare how sensitive the oxygen response is to the HCT and VFT, which has not been reported in previous studies. Optimization of the HCT paradigm for diagnosis of psychiatric diseases will be our future work.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Hospital of Shanxi Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YX conceived of and led on the study design. DW and XL managed the literature searches. DW undertook the statistical analysis, under the supervision of YX. DW and XL wrote the first draft and the subsequent revisions of the manuscript. QL, QY, and MW contributed to collecting data. All the authors contributed to and have approved the final manuscript.

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MINI REVIEW
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Application of Near-Infrared Spectroscopy for Understanding Spontaneous Brain Activity During Resting State in Schizophrenia: A Mini Review

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Spontaneous brain activity occurs at rest, as represented by the default mode network. A resting paradigm is suitable for investigating brain function of patients with psychiatric diseases who may have difficulties adhering to goal-oriented tasks. Evidence accumulated in neuroimaging studies using functional magnetic resonance imaging has shown that the resting cerebral blood flow is impaired in psychiatric diseases. Near-infrared spectroscopy (NIRS), a simple neuroimaging modality, is an optimal tool for the resting paradigm, because it can offer a comfortable environment for measurement. Recent NIRS studies have demonstrated some promising data of altered resting activity in the prefrontal cortex of patients with schizophrenia, which may be exploited to develop further applications of NIRS in clinical psychiatry. Based on these findings, we emphasize the benefits of NIRS for assessing the prefrontal pathophysiology during the resting state and some methodological issues to be noted while analyzing cerebral blood flow using NIRS; moreover, we focus on interpreting these changes based on the complex nature of the spontaneous brain activity during resting state.

Keywords: NIRS, resting-state, spontaneous brain activity, medial prefrontal cortex, ALFF, fALFF, schizophrenia

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INTRODUCTION

While numerous lines of biological evidence have accumulated to support the pathophysiology of psychiatric diseases, a limited amount of the evidence is available to guide clinical management of these diseases. In order to effectively integrate the evidence from research into clinical practice, the translational aspects of biological evaluations in psychiatry need to be considered. In a trial undertaken in Japan, a simple neuroimaging modality, near-infrared spectroscopy (NIRS), was employed with the purpose of assisting the differential diagnoses of patients who manifested depressive symptoms. In this trial using NIRS, the prefrontal blood flow of the patients during a verbal fluency task was employed to distinguish major depression, bipolar disorder, and schizophrenia (1). This simple assessment approach was successfully trialed in psychiatric clinics in Japan. However, the reported sensitivity of this assessment approach of around 60% remains a limitation (2). This critical issue was partially addressed in a previous study, which reported a difficulty to biologically delineate the boundary between schizophrenia and bipolar disorder when categorized based on current clinical diagnostic criteria (3). A review on this assessment approach

raises some technical issues also, such as a variability in the performance of verbal fluency task among patients, which could be a confounding factor in analyzing prefrontal blood flow changes (4). To overcome these technical issues, a resting paradigm may be beneficial. A resting paradigm is readily accessible even for patients who have some difficulties in performing goal-oriented tasks. In addition, NIRS is suitable for a resting paradigm, because it can offer a quiet approach to neurophysiological measurements. NIRS is suitable for clinical settings on the basis of its simplicity. In this article, we outline the potential of NIRS to evaluate prefrontal pathophysiology with a resting paradigm, using cases of schizophrenia as an example.

SPONTANEOUS BRAIN ACTIVITY DURING RESTING STATE

Spontaneous brain activities occur during resting state. A specific feature of these activities is the activation of several brain regions during resting state, which is termed the default mode activity (5). The major brain regions where a default mode activity has been observed are the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC)/precuneus, inferior parietal lobule, and lateral temporal cortex (6, 7). This cluster of brain regions is called the default mode network (6, 7). Within the default mode network, the medial prefrontal cortex (mPFC) and PCC/precuneus are the core regions of this network that are constantly activated by any activities of the default mode network (5, 7, 8).

The other specific feature of the brain activity during resting state is the spontaneous low-frequency (<0.1 Hz) fluctuations of the cerebral blood flow (9). These fluctuations are synchronized among brain regions within the default mode network. By characterizing the simultaneous low-frequency (<0.1 Hz) fluctuations of the cerebral blood flow among brain regions in the resting paradigm, functional magnetic resonance imaging (fMRI) studies have identified various intrinsic brain functional networks other than the default mode network, such as the salience network and the executive network (9, 10). Furthermore, recent studies using brain functional network analysis have reported disease subtype-specific network impairments that may address future therapeutic interventions for psychiatric diseases (11–13). As such, resting-state neuroimaging is a promising tool that could be applied for the biological evaluation of psychiatric disorders.

DEFAULT MODE ACTIVITY IN SCHIZOPHRENIA

Accumulating evidence in fMRI studies has shown that the default mode network is impaired in schizophrenia (14–16). The initial research for the default mode network has elucidated the task-induced deactivation failure of the default mode network in patients with schizophrenia using a subtraction method that quantifies the difference of the activity between the resting state and the condition while performing cognitive tasks (17–19). Further studies of the default mode network have focused on analyzing the activity during extended task-free rest periods using the resting paradigm. The task-free paradigm has merit for the examination of psychiatric diseases, because it is easily applied to patients who may have difficulties adhering to goal-oriented tasks. In this paradigm, brain functional network research uses time domain analysis for low-frequency fluctuations of cerebral blood flow through examining the brain regional correlations during the extended rest periods. In addition, the intensity of the brain activity during resting state has been evaluated by analyzing the frequency domain of low-frequency fluctuations of regional cerebral blood flow.

One of the methods to quantify the intensity of brain activity in the resting paradigm is known as the amplitude of low-frequency fluctuations (ALFF). ALFF is calculated as the sum of the power across low-frequency ranges, such as 0.01–0.08 Hz, of cerebral blood flow fluctuations (20). In addition to the ALFF, fractional ALFF (fALFF), the ratio of the ALFF to the total power, is also used as an indicator that may receive less noise from physiological sources compared to the ALFF (21). Both ALFF and fALFF capture hemodynamic signals from the gray matter of brain, prominently in the core region of default mode network, namely, mPFC and PCC/precuneus (20, 21). Several studies examining ALFF or fALFF using the resting paradigm have shown that they are reduced in mPFC and PCC/precuneus in patients with schizophrenia (22–29). These findings suggest that the core region of the default mode network has diminished activity during the resting state in schizophrenia.

APPLICATION OF NIRS FOR MEASURING THE BRAIN ACTIVITY IN THE REST PERIOD

NIRS is a simple neuroimaging modality that is easy to use and offers non-invasive measurement. Details of the NIRS system have been described in previous reviews (30, 31). This system allows the measurement of cerebral blood flow without any acoustic scanner noises, which are inevitable when performing fMRI measurements. Additionally, the measurements with NIRS require fewer physical constraints, and hence, it is tolerant to small movements. Because of these benefits, it offers a relatively comfortable environment to the examinee, and thus, NIRS is an optimal modality to apply to the resting paradigm. In addition, test and retest studies have verified the stability of NIRS measurements for detecting brain networks during resting state (32–34). Given that the resting paradigm is easily adopted by patients with psychiatric diseases, NIRS is suitable for assessing the brain activity of these patients during resting state. Here, we will describe some technical issues relating to NIRS in interpreting hemodynamic signals. Following this, we will introduce NIRS studies of schizophrenia that examined brain activity using a resting paradigm and discuss the complex nature of spontaneous brain activity during resting state that is present in healthy subjects.

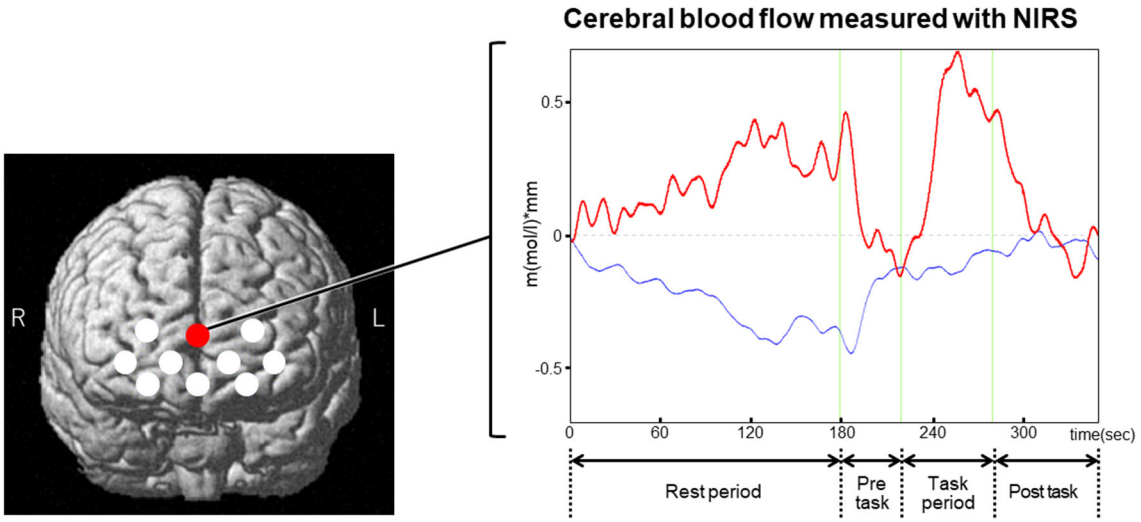

FIGURE 1 | An example of NIRS measurement using a resting paradigm that was followed by a verbal fluency task. The left figure displays NIRS channel locations that are indicated by the white and red circles. The red circle points to the channel that displays an example (right figure) for the time course of NIRS signals in a healthy subject. In this case, the NIRS signals were potently activated during the rest period. The activation of the signals was reversed during the subsequent pre-task, where the subject simply repeated a sequence of syllables (a, i, u, e, o). The NIRS signals were activated again during the task period for the verbal fluency task, which asks the subject to generate as many words as possible starting with presented syllables such as "a." The activation of the signals induced by the verbal fluency task was reversed during the post-task, which consisted of the same task as the pre-task. The magnitudes of the activated signals during the rest period were nearly comparable with those induced by the verbal fluency task. This potent activation of the NIRS signals may indicate some spontaneous cognitive activity that occurred during the rest period. Red bold line, oxy-hemoglobin signal; blue line, deoxy-hemoglobin signal.

Methodological Issues in Interpreting NIRS Signals

While the NIRS system has advantages in terms of its simplicity and economical efficiency, it has some technical limitations that need to be noted when analyzing the cerebral blood flow. A major limitation is that NIRS signals lack precise information to detect cortical activity. NIRS measures hemodynamic signals up to only a cortical surface at a depth of 2–3 cm from the skin (35–37) by using an infrared source and detector probes that are chiefly set on the forehead (30, 38). Because the NIRS signals are scattered near-infrared light signals that are emitted from the source probe and caught by a detector probe, the spatial resolution of the NIRS channel defined by these probes is not enough to annotate the hemodynamic signals of the precise cortical regions. In addition, NIRS signals include contamination of peripheral hemodynamic factors such as skin perfusion, even in the limited frequency range of blood flow fluctuations for ALFF (0.01–0.08 Hz) (39). However, a previous study analyzing the cerebral blood flow during resting state with simultaneous measurements of NIRS and fMRI demonstrated that the NIRS signals detected in most of the channels were highly correlated with the signals of brain tissue in the fMRI measurement (40). Taken together, this suggests that NIRS detects the hemodynamic signals that reflect the cortical activity in roughly segmented cortical area, although the influence of signals from the peripheral tissues cannot be fully excluded.

Complex Nature of the Brain Activity During Resting State

The discovery of default mode activity was prompted by the observation that our brain is not resting when we are resting (7). Although the default mode network was termed for the activated brain regions at rest, this network is more active in the tasks demanding self-referential mental activities (6–8). Furthermore, it is known that the spontaneous cognition toward internal mentation such as self-referential mental activity often occurs during resting state (6, 7). These lines of evidence suggest that a high variability of brain activation could be generated during resting state depending on one's own spontaneous cognitive status. **Figure 1** displays a NIRS measurement in a channel located on the superficial part of mPFC in a healthy subject. The NIRS signals demonstrate a potent activation during resting state, which are nearly comparable with those induced by the following verbal fluency task. This potentiation of the brain activity may reflect some ongoing spontaneous cognitive activity that occurred in the rest period. As suggested in this case, spontaneous cognitive activities could occur in the resting paradigm. These spontaneous activities may hamper the attainment of a stable baseline of brain activity during resting state for each subject. Such a complex nature of brain activity during resting state needs to be noted in interpreting changes of cerebral blood flow during the extended rest period.

Examining Brain Activity With NIRS During Resting State in Schizophrenia

Recent studies have demonstrated some promising findings with NIRS to capture the alteration of frontal activity during resting state in schizophrenia. An initial study using two-channel NIRS reported a reduction of the frontal blood flow in the rest period in patients with chronic schizophrenia (41). Recent studies using NIRS whose channels cover the entire forehead demonstrated that the magnitude of brain activation as well as ALFF and fALFF were decreased during resting state in the channels located around the mPFC region in patients with chronic schizophrenia (42, 43). Given that mPFC is a core brain region of the default mode network where spontaneous brain activities occur during resting state in healthy subjects depending on their spontaneous cognitive state, these results suggest that the spontaneous activities were deficient in the patients with chronic schizophrenia. That is to say, the decreased activity during resting state that was observed in the vicinity of mPFC in chronic schizophrenia may represent the impaired ability of patients to produce and maintain the function of the default mode network such as the self-referential mental activity. Based on these findings, we emphasize the benefits of NIRS for assessing the prefrontal pathophysiology of schizophrenia using a resting paradigm. Moreover, the benefits of NIRS for the resting paradigm could be exploited to develop further applications of this modality not only for schizophrenia but also for other psychiatric diseases. Although resting-state NIRS findings are only in the early stages of application in psychiatry, the resting-state NIRS may develop valid biomarkers adjunctively with other neuromodalities to offer some elucidation on the prefrontal pathophysiology of the psychiatric diseases.

FUTURE DIRECTION

This review focused on changes in regional spontaneous brain activity within limited reports of the resting-state NIRS for patients with schizophrenia. Considering that this technique also enables the assessment of functional brain connectivity, further investigations with NIRS using the resting paradigm should be explored in patients with schizophrenia. Previous NIRS studies using the resting paradigm have reported impairments in functional brain connectivity in patients with major depression (44–46). These features of NIRS with the resting paradigm encourage further applications of the technique to differentiate among major psychiatric disorders, including schizophrenia, based on pathophysiology. Cross-diagnostic studies using NIRS with the resting paradigm may contribute to the identification of disease-specific or disease subtype-specific changes among these disorders. The changes observed in resting-state NIRS studies could be further developed by applying this simple assessment system in daily psychiatric clinical practice. These challenges are inherent in the search for a biomarker-driven classification of psychiatric disorders, which may address the heterogeneity of these disorders and provide a baseline for future biomarker-driven therapeutics in psychiatry.

CONCLUSION

In summary, NIRS is a valid tool to assess the spontaneous brain activity during resting state. Previous studies have provided some promising evidence that NIRS could detect the disease-associated alteration of prefrontal activity in a resting paradigm in schizophrenia. Although some methodological limitations of NIRS and the complex nature of resting brain activity need to be noted while interpreting NIRS signals, the simplicity of NIRS in relation to a resting paradigm is advantageous for routine applications in clinical psychiatric settings. Further clinical applications of NIRS should be explored with a resting paradigm to develop a biomarker that may address future therapeutic interventions for psychiatric diseases.

AUTHOR CONTRIBUTIONS

MY wrote the manuscript and OS edited it. Both authors have read and approved the final manuscript.

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SYSTEMATIC REVIEW
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Clinical Utility of Functional Near-Infrared Spectroscopy for Assessment and Prediction of Suicidality: A Systematic Review

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Introduction: Suicide is a pressing psychiatric concern worldwide with no established biomarker. While there is some evidence of the clinical utility of functional near-infrared spectroscopy (fNIRS) in assessing and predicting suicidality, no systematic review of such evidence has been conducted to date. Therefore, this review aimed to systematically review and gather evidence from existing studies that used fNIRS signals to assess suicidality and its associated changes in the brain, and those that examined how such signals correlated with suicide symptomatology.

Methods: PubMed, EMBASE, and Cochrane Library databases were used in a systematic literature search for English-language articles published between 2000 and December 19, 2020 that focused on the utility of fNIRS for (i) assessing suicidality and its associated changes in the brain, and (ii) correlating with suicide symptomatology. Studies were included if they utilised fNIRS to evaluate variations in fNIRS-measured cerebral hemodynamic responses in patients with different mental disorders (e.g., major depressive disorder, schizophrenia), as well as in healthy controls, of any age group. Quality of evidence was assessed using the Newcastle-Ottawa quality assessment scale.

Results: A total of 7 cross-sectional studies were included in this review, all of which had acceptable quality. Across all studies, fNIRS demonstrated reduced cerebral hemodynamic changes in suicidal individuals when compared to non-suicidal individuals. One study also demonstrated the potential of fNIRS signals in correlating with the severity of suicidality.

Conclusions: This review provides a comprehensive, updated review of evidence supporting the clinical utility of fNIRS in the assessment and prediction of suicidality. Further studies involving larger sample sizes, standardised methodology, and longitudinal follow-ups are needed.

Keywords: assessment, prediction, functional near-infrared spectroscopy, suicid*, major depressive disorder, schizophrenia, bipolar disorder, systematic review

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INTRODUCTION

Suicide, which occurs across the lifespan, is a major public health concern, given that it remains an important contributor to mortality in all regions of the world (1). According to the World Health Organisation, suicide accounted for 1.4% of all deaths worldwide in 2016, and ∼800,000 deaths every year are due to suicide. Suicidal ideation can be defined as thinking about or planning suicide, while a suicide attempt is a non-fatal, self-directed, potentially injurious behaviour with the intention to end one's life (2). For every adult death by suicide, it is estimated that there are more than 20 others who attempt suicide, with about 2.5% of the world's population attempting suicide at least once in their lifetime (3, 4). All things considered, there is evidently a pressing need for interventions, therapeutic or otherwise, aimed at reducing the risk of suicide and, consequently, preventing suicide more effectively (5, 6).

Despite the increasing global prevalence of suicide over the years, suicidality in individuals can still be said to be under detected, given its complex, multifaceted nature (7–9). Furthermore, reliable biological predictors for the risk of suicidality do not yet exist, given the almost exclusive reliance on self-reported suicide intent and the limited predictive value of identified non-biological risk factors and at present (10–12). As such, there exists a need for objective methods (i.e., those not biassed by opinion or interpretation) to ascertain suicidality in individuals swiftly so that appropriate intervention can be administered to ensure patient safety, especially since suicidal thoughts and behaviours have not declined appreciably in the past decades (10, 12). This can be done by assessing for, as well as making modifiable risk factors of suicide like trauma, pain, and social isolation, targets of clinical interventions (13–15). Traumatic experiences have shown to be an important risk factor for suicide, as they may be associated with significant psychosocial impairment (16). Additionally, a study by Serafini et al. (17) also found that an individual's unique sensory processing patterns, in addition to their traumatic experiences, are often involved in the pathophysiology of major affective disorders and other negative outcomes (e.g., suicidality). As such, they should also be considered when assessing for suicidality in the clinical setting.

In recent years, there has been a marked increase in the number of studies focusing on suicide-specific diagnosis and biomarkers, the latter of which are measurable biological parameters that increase risk of a disease, which includes brain imaging, genomic and biochemical markers (18–20). In particular, the use of brain-imaging modalities such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG) has been employed to help in the diagnosis of psychiatric disorders and suicidality. fMRI, in particular, has also been used in the investigation of suicidal thoughts and behaviours (21). fMRI studies have provided evidence of increased suicide risk in association with differences in activation of areas of the brain, such as the prefrontal cortex (22). There are, however, limitations to the aforementioned imaging methods, including but not limited to high costs, various contraindications associated with the use of the imaging devices, and equipment inaccessibility.

In contrast, functional near-infrared spectroscopy (fNIRS) provides various advantages that makes it an ideal choice for interrogating brain function, one of which is that it is non-invasive (23). It also provides temporal resolution comparable to that of fMRI, involves neither ionising radiation nor loud noise, and is portable and relatively inexpensive, hence allowing for it to be repeated on patients as and when needed in their natural environment (24–27). Furthermore, it is readily amenable to integration with other technologies including electroencephalography (EEG) (28). fNIRS is a type of spectroscopy that utilises light sources between a spectral window of 650–1,000 nanometres, which can penetrate organic tissues and are preferentially absorbed by haemoglobin (29). Variations in oxygenated haemoglobin (oxy-Hb), used as an indicator of cortical activation, are then computed using the variance in absorbance using a modified version of the Beer-Lambert law (30). fNIRS research has been rapidly expanding across a wide range of areas in recent years (31). In psychiatry, fNIRS has been used in studies involving patients with major depressive disorder (MDD), schizophrenia and bipolar disorder (BD), in which such patients demonstrate considerably decreased prefrontal cortical activation in comparison to healthy controls when participating in cognitive tasks like the verbal fluency task (VFT) (32–34). The correlation between prefrontal cortical activation and suicidality has been less frequently examined and is, therefore, less established.

To the best of our knowledge, no systematic review has been conducted to date to evaluate the use of fNIRS in assessing and predicting suicidality. As such, the aim of this study was to systematically review and gather clinical evidence from the latest available literature, focusing on the utility of fNIRS for (i) assessing suicidality and its associated changes in the brain, and (ii) correlating with suicide symptomatology. Overall, we hope to provide a comprehensive, up-to-date review of the literature exploring the clinical utility of fNIRS as a biomarker for suicidality.

METHODS

Data Sources and Search Strategy

We conducted this study using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (35). A systematic review was completed based on English-language literature published between 2000 to 19 December 2020, focusing on the utility of fNIRS for (i) assessing suicidality and its associated changes in the brain, and (ii) correlating with suicide symptomatology. The three electronic databases utilised in the search were PubMed, EMBASE and Cochrane Library. The following search terms were used: "spectroscopy", "near-infrared", "near-infrared spectroscopy", "fNIRS", and "optical topography" (separated by OR), in combination with the term "suicid*". These terms were searched as both text words and subject headings. Original research articles, human studies and conference proceedings in the English language were included,

TABLE 1 | Risks of bias within studies selected.

	Selection				Comparability	Exposure		
Study sources	**Is the case definition adequate?**	**Representative of cases**	**Selection of controls**	**Definitions of controls**		**Determination of exposure**	**Same method for determining cases and controls**	**Non-response rates**
Baik et al.	⋆		⋆	⋆	⋆	⋆		
Hirose et al.	⋆		⋆	⋆	⋆	⋆	⋆	
Tsujii et al.	⋆		⋆	⋆	⋆⋆	⋆	⋆	
Pu et al.	⋆		⋆	⋆	⋆	⋆	⋆	
Ota et al.	⋆		⋆	⋆	⋆	⋆	⋆	
Zahid et al.	⋆		⋆			⋆	⋆	
Matsuoka et al.	⋆		⋆	⋆	⋆	⋆	⋆	

Each star represents one points (each study can obtain a maximum of 9 points), whereby the more stars given, the less prone to bias the study is.

whilst abstracts, case reports and reviews were excluded. No funding was obtained for this systematic review.

Eligibility Criteria and Data Collection

The primary outcome of interest for this systematic review was the variations in fNIRS-measured cerebral hemodynamic responses and their correlations with suicide symptomatology across patients with different mental disorders, as well as amongst healthy controls.

All studies retrieved from the databases were independently reviewed by two reviewers (YQL and CH) based on title and abstract. Where appropriate, full-text papers were extracted for a further inspection. Full-text reviews were subsequently conducted on selected studies that fulfilled the inclusion criteria, whereby the study characteristics and findings were extracted. Information included in data review consist of the authors, country, year published, conditions investigated, sample size and gender, mean age, diagnostic criteria, suicidality measure(s), medication use (if any), type of NIRS device utilised, paradigm utilised, brain areas studied, and main findings of the study.

Quality Assessment of the Included Studies

As recommended by the Cochrane Collaboration (36), the Newcastle-Ottawa quality assessment scale (NOS) (37) was used to assess the risk of bias of the studies included in this review. The NOS assigns a maximum of 9 stars to each study with scores of 0–3, 4–6, and 7–9 indicating low, medium and high quality, respectively. These studies were independently rated by two reviewers (YQL and CH), and the results of this quality assessment are presented in **Table 1**. Any discrepancies in assessment were discussed before finalisation. All studies were deemed to be of acceptable quality, having been awarded a minimum of 4 stars.

RESULTS

Study Selection

A total of 8,687 citations were identified from our database search, with 704 from PubMed, 1,338 from EMBASE, and 6,645 from Cochrane Library. After reviewing the titles, abstracts, and removing duplicated publications, 10 articles were selected. Of these, 7 studies met the inclusion criteria and were included in this analysis (**Table 2**). The selection process is displayed in **Figure 1**, constructed according to the PRISMA statement. Five of the studies were from Japan, one study from the USA and one study from Korea. All seven studies were cross-sectional in nature.

Correlation of fNIRS Signals With Suicidality

All 7 papers reported on fNIRS studies, in which changes in cerebral hemodynamic responses were correlated with suicidality in a total of 954 participants. These studies were inclusive of patients with MDD, schizophrenia, bipolar disorder and autism spectrum disorder (ASD), as well as healthy individuals. The majority of the studies adopted the VFT, except for one study that used anagram tasks, as their paradigm. The fNIRS instruments utilised included the 52-channel ETG-4000 (Hitachi), 24-channel ETG-4000 (Hitachi), NIRSIT (OBELAB), and Model 200A (fNIR Devices LLC).

According to our assessment of the author's conclusions, studies on MDD showed oxy-Hb concentration values have significant negative correlation with suicidality in the sample population based on measures such as the Hamilton Depression (HAM-D) scores as well as patient's previous history of suicide attempts. Tsujii et al. (40) also demonstrated that significant negative correlation was still present after correcting for confounding factors such as age, gender and estimated IQ, and the suicide attempt (SA) group was noted to have smaller hemodynamic response than the non-attempt (NA) and healthy control (HC) group in the left precentral gyrus during VFT. VFT also induced widespread frontotemporal cortical activation in HCs and NAs, whereas SAs showed significant activation only in the left superior frontal gyrus, left middle frontal gyrus, bilateral inferior frontal gyrus, and right precentral gyrus. SAs also showed significant correlation between the severity of suicide ideation and hemodynamic responses in the right dorsolateral prefrontal region, in contrast to NAs who did not show such correlation. Hemodynamic responses in the right middle frontal gyrus were

TABLE 2 | Summary of peer-reviewed studies investigating functional near infrared spectroscopy (fNIRS)-measured cerebral hemodynamic responses and their correlation with suicidality.

References	Country	Year	Condition	Sample size (male/female)	Age (mean ± standard deviation)	Diagnostic criteria (instrument)	Suicidality measure(s)	Medication	NIRS device	Paradigm	Brain areas	Main findings
Baik et al. (38)	Korea	2019	MDD	MDD: 51 (17/34) HC: 63 (24/41)	MDD: 37.62 ± 14.36 HC: 33.42 ± 12.57	DSM-5	HAM-D	NIL	NIRSIT (OBELAB): 24 dual-wavelength laser diodes (780/850 nm) and 32 photo detectors separated by a 1.5 cm unit distance	VFT, Stroop task, two-back task	PF	- Relatively reduced left PF oxy-Hb changes for MDD patients - Positive correlation between VFT asymmetry index and HAM-D suicide item for MDD patients - Stronger effect of MDD severity on suicidal ideation with relatively greater association with left PF asymmetry for MDD patients
Hirose et al. (39)	Japan	2018	BD	BD, SA: 20 (6/14) BD, NA (control): 28 (14/14)	SA: 33.5 ± 11.4 NA: 38.7 ± 12.0	DSM-IV	History of suicide attempt; MINI	NIL	52-channel ETG-4000 (Hitachi)	VFT	F	- Smaller hemodynamic responses in various regions; delayed activation timing of NIRS signal in PF region for SA group - Significant, positive association between current suicide risk significantly and delayed activation timing in PF region for all BD patients
Tsujii et al. (40)	Japan	2017	MDD	MDD: 68 (24/44) - SA: 30 (8/22) - NA: 38 (16/22) HC: 40 (15/25)	MDD - SA: 37.6 ± 10.0 - NA: 38.8 ± 9.7 HC: 38.2 ± 10.5	DSM-4, HAM-D	History of suicide attempt	Daily doses converted to equivalent doses of Imipramine, chlorpromazine and diazepam	52-channel ETG-4000 (Hitachi)	VFT	PF, T	- Smaller hemodynamic response in left precentral gyrus for SA group - Significant correlation between severity of suicidal ideation and hemodynamic responses in right DLPFC for SA group
Pu et al. (41)	Japan	2015	MDD	MDD: 67 (29/38) HC: 67 (29/38)	MDD: 58.1 ± 16.0 HC: 58.1 ± 17.8	DSM-4	HAM-D	Daily doses of all antidepressants were converted to an equivalent dose of imipramine	52-channel ETG-4000 (Hitachi)	VFT	F	- Significantly smaller regional hemodynamic changes for MDD patients with suicidal ideation - Negative correlation between severity of suicidal ideation (as measured by HAM-D) and hemodynamic changes in DLPFC, OFC and FPC regions for MDD group

(Continued)

TABLE 2 | Continued

References	Country	Year	Condition	Sample size (male/female)	Age (mean ± standard deviation)	Diagnostic criteria (instrument)	Suicidality measure(s)	Medication	NIRS device	Paradigm	Brain areas	Main findings
Ota et al. (42)	Japan	2020	ASD	ASD: 20 (16/4) HC: 29 (16/4)	ASD: 29.05 ± 6.39 HC: 27.20 ± 4.16	DSM-5	MINI	NIL	24-channel ETG-4000 (Hitachi)	VFT	PF	- Significant positive correlation between current suicide risk score and centroid value in PF region for ASD patients
Zahid et al. (43)	USA	2020	NIL	296 (67/229)	18.8 ± 1.2	NIL	BDI;	NIL	Model 200A (fNIR Devices LLC)	Anagram tasks	DLPFC	- DLPFC activity associated with suicidal ideation in sex-specific ways
Matsuoka et al. (44)	Japan	2020	SZ (ROSZ)	SZ: 86 (46/40) - SA: 24 (12/12) - NA: 62 (34/28) HC: 119 (68/51)	SA: 25.4 ± 6.6 NA: 25.9 ± 7.3 HC: 26.5 ± 5.1	DSM-4	History of suicide attempt	Daily doses of all AP, BZD and APK drugs were converted to chlorpromazine, diazepam and biperiden equivalent doses	52-channel ETG-4000 (Hitachi)	LFT	F	- Right DLPFC brain activity of SA subgroup significantly lower than NA group

MDD, Major depressive disorder; HC, Healthy control; DSM, Diagnostic and Statistical Manual; HAM-D, Hamilton Rating Scale for Depression; VFT, Verbal fluency test; PF, Prefrontal; BD, Bipolar disorder; SA, Suicide attempter; NA, Non-suicide attempter; MINI, Mini International Neuropsychiatric Interview; F, Frontal; T, Temporal; DLPFC, Dorsolateral prefrontal cortex; OFC, Orbitofrontal cortex; FPC, Frontopolar cortex; ASD, Autism spectrum disorder; BD, Beck's Depression Inventory; SZ, Schizophrenia; ROSZ, Recent-onset schizophrenia; AP, Antipsychotic; BZD, Benzodiazepine; APK, Antiparkinsonian; LFT, Letter fluency task.

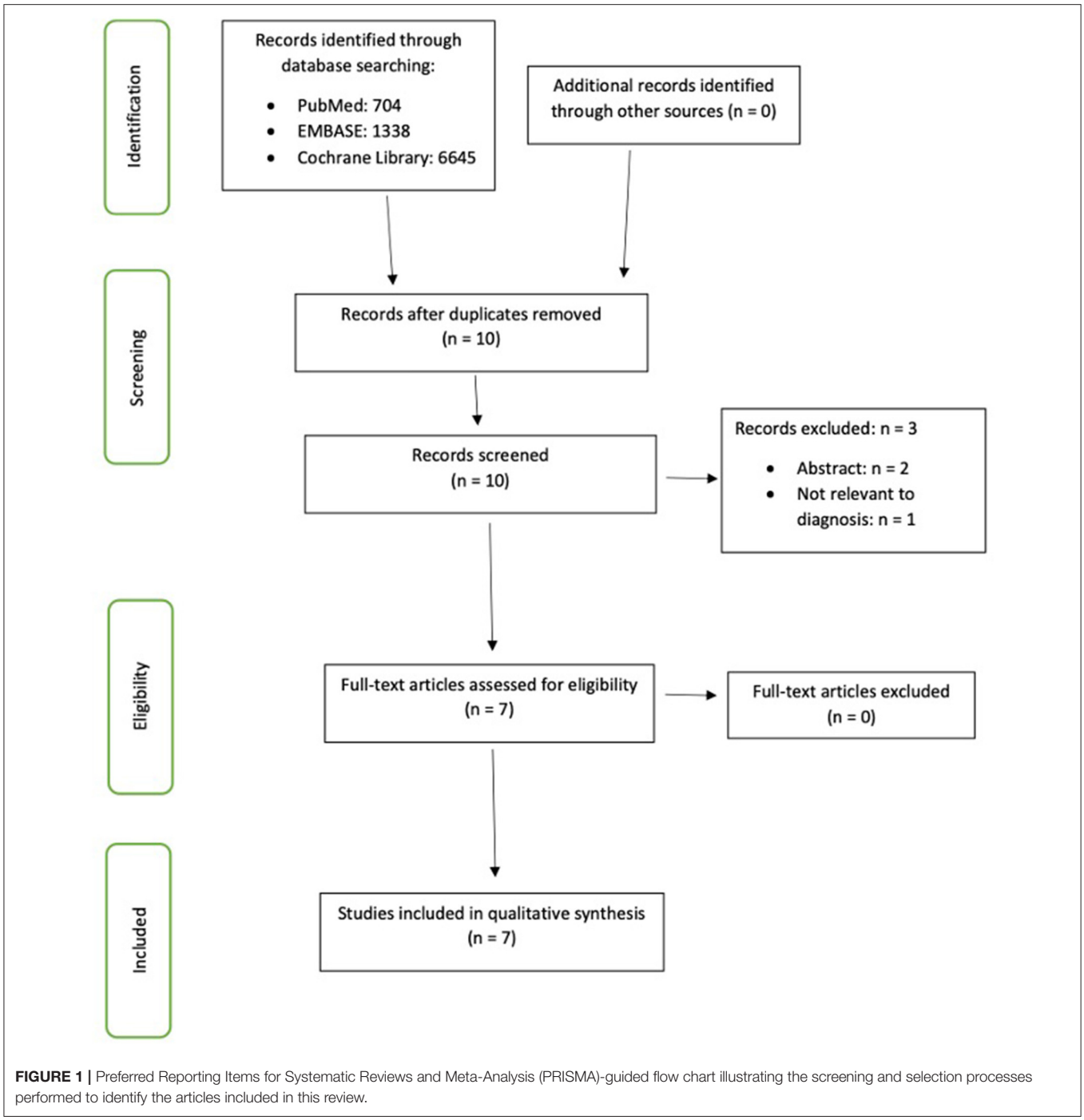

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)-guided flow chart illustrating the screening and selection processes performed to identify the articles included in this review.

also negatively correlated with aggression and hopelessness in the SAs but not in the HCs and NAs.

Such negative correlation was corroborated by Baik et al. (38), who also showed that MDD patients have relatively reduced left prefrontal oxy-Hb changes during VFT than HCs, and amongst the MDD patients, there was significant positive correlation between asymmetry index for VFT and the suicide item of HAM-D. With relatively greater left prefrontal asymmetry, the effect of depression severity on suicide ideation was also noted to be stronger. Additionally, Pu et al. (41) also noted that regional hemodynamic changes in the right dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and right frontopolar cortex (FPC) regions in patients with MDD with suicidal ideation were significantly smaller than those without suicidal ideation, and similar differences were also noted between patients with MDDs and HCs. In patients with MDD, hemodynamic changes during VFT correlated negatively with the severity of suicidal ideation (as measured

by the HAM-D questionnaire), in the DLPFC, OFC, and FPC regions.

In patients with BD, similar findings were discovered. Hirose et al. (39) showed that depressed BD patients with history of SA had smaller hemodynamic responses by VFT in the bilateral precentral and superior temporal gyri, and left supramarginal, inferior frontal, post-central and middle temporal gyri, as compared to BD patients without history of suicide attempts. SA patients also exhibited delayed activation timing of the NIRS signal in the PF region, and delayed activation timing of NIRS signal was significantly and positively associated with current suicide risk

Assessing prefrontal hemodynamic response and suicide risk in ASD, Ota et al. (42) showed that there was significant positive correlation between the current suicide risk score, and their centroid value in the prefrontal region, while there was no significant differences between the ASD and control groups in terms of the mean oxy-Hb changes induced by VFT for each channel.

Matsuoka et al. (44) assessed prefrontal dysfunction and history of suicide attempts among patients with recent onset schizophrenia, and results showed that SA group had significantly lower brain activity in the right DLPFC during the letter fluency task as compared to the NA group.

Finally, Zahid et al. (43) assessed 296 undergraduates for suicidal ideation and monitored them using a fNIRS device whilst they engaged in anagram tasks. This study found that DLPFC activity was associated with suicidal ideation in gender-specific ways. During the homogenous 3-letter anagram trials, males who reported suicidal ideation displayed significantly reduced levels of blood oxygenation across the DLPFC compared to males who did not suicidal ideation, which indicated reduced neural activation during the task. In contrast, females who did not report suicidal ideation displayed reduced levels of blood oxygenation compared to females who reported suicidal ideation. As for the 5-letter anagrams task during the event-related trials, male who reported suicidal ideation displayed elevated levels of blood oxygenation and neural activation at several locations compared to males who did not report suicidal ideation, while females who reported suicidal ideation tended to exhibit lower levels of neural activation than those who did not report suicidal ideation. The findings from this study suggested that there are distinct patterns of neural activity across the DLPFC that differentiate individuals who report suicidal ideation from those who do not, and the patterns are dependent on both the gender and nature of the cognitive task allocated.

DISCUSSION

Considering the findings of the reviewed papers, our systematic review demonstrates the clinical potential of fNIRS signals as a biomarker that differentiates suicidal individuals from non-suicidal individuals. A few studies also found that smaller prefrontal (PF) and DLPFC hemodynamic responses during cognitive tasks correlated with the severity of suicidal ideation. As a reliable, established biomarker for suicidality does not yet exist, such information would be fundamental in determining the extent to which fNIRS can be used to assess and predict suicidality in a clinical setting.

To date, this is the first systematic review on fNIRS findings in relation to suicidality with the goal to provide a comprehensive, up-to-date overview of information surrounding the utility of fNIRS for (i) assessing suicidality and its associated changes in the brain, and (ii) correlating with suicide symptomatology in different study populations (i.e., patients with different psychiatric disorders, as well as healthy controls). Based on the collective findings of the reviewed papers, most of the studies were conducted in Japan, while the most common paradigm used is the VFT, a common, validated neuropsychological test used to ascertain executive function and language content (45, 46). Participants of the VFT are typically instructed to generate as many unique words as possible that begin with a particular letter during the task for a restricted duration of time varying between 30 and 60 s (47). The VFT has shown to be able to elicit distinct differences between depressed patients and healthy control in both performance and neuroimaging responses (46, 48).

Conversely, all seven studies focused on hemodynamic changes in discrete brain regions. It would also be worthwhile to explore how functional connectivity, which is the temporal dependency of neuronal activation patterns of anatomically separated brain regions (49), differs between SAs, NAs, and HCs. Also, none of them demonstrated data on the sensitivity and specificity comparing suicidal and non-suicidal individuals, which would be important in determining the clinical validity of fNIRS as a biomarker for suicidality. This points to the need for future studies with standardised methods of analyses, which would then allow for more accurate comparisons to be made (50). In a similar vein, despite the use of the VFT as the paradigm in most of the studies reviewed, there were variations in other factors such as the devices used to measure NIRS signals or how suicidality was measured, which reduces the validity of the comparisons made. Future research focusing on the clinical utility of fNIRS in assessing and predicting suicidality could also include longitudinal studies with longer follow-up durations spanning 6–12 months. All the reviewed studies are cross-sectional in nature, meaning that they are unable to provide any information on the prognostic potential of fNIRS for suicidality. Longitudinal studies would be beneficial in providing a better understanding of the fNIRS-measured cerebral hemodynamic responses as a marker for suicidality and investigate whether it is a state or trait-dependent marker of suicidality.

Despite the several advantages of fNIRS over other imaging modalities such as fMRI, its limitations cannot be discounted. First, near-infrared light has limited spatial resolution (around 1 cm) and depth of penetration, thus rendering it unsuitable in the measuring of cortical hemodynamic responses to cognitive stimuli when deep brain regions with crucial roles in psychiatric disorders are involved (25, 51). Studies involving the use of fMRI, on the other hand, found disrupted neural responses in both the insula cortex and subgenual anterior cingulate cortex in depressed SAs, but not in depressed NAs and HCs, which led to greater aversion to uncertainty (52, 53). Jung et al. (54) also found

that depressed NAs had decreased functional neural network connectivity (FNC), and that the degree of FNC was associated with suicidal ideation. Second, layered and/or dark-coloured hair attenuate near-infrared light, resulting in poor optical contact and affecting signal quality (51, 55). Third, fNIRS signals are susceptible to corruption by signals arising from respiratory rate, heart rate and blood pressure fluctuations, thus affecting signal interpretation (33, 56). Taken together, however, the effects of these limitations on fNIRS data could be alleviated by statistical data processing and enhanced data-collecting protocols (24, 28, 30, 56). The use of other neuroimaging modalities like fMRI could also be employed to supplement the findings of fNIRS scans, thus allowing for a more comprehensive assessment of neurophysiological changes.

Our review also comes with certain limitations. First, at the time of our study, there was limited existing literature on the topic of fNIRS and its correlation with suicidality. As such, the data available formed a small sample size, leading to a higher risk of confounding and selective biases, along with reduced power. Furthermore, out of the seven studies reviewed, five were conducted in Japan, hence limiting the ecological validity of our findings. However, this review was able to synthesise the information available to provide an up-to-date overview of studies exploring fNIRS and its clinical utility in assessing and predicting suicidality, hence facilitating future research and developments in this topic. Second, most of the studies used the VFT as the paradigm. Although the VFT is simple and can be conventionally administered, it would be worthwhile to ascertain the effects of other paradigms such as the Emotional Stroop task and investigate other brain regions besides the prefrontal cortex. Third, we only included papers published in English and searched in three databases, and there may have been publication bias as there may have been other papers published in other languages and/or on other platforms. Nevertheless, our review's strength lies in it being the first systematic review to evaluate the use of fNIRS in assessing and predicting suicidality. It also provides a comprehensive overview of studies that have been conducted in this area of the fNIRS research landscape.

In conclusion, current literature has provided sufficient evidence regarding fNIRS as a complementary tool for the assessment and prediction of suicidality in the clinical setting, as there have been consistent attenuated hemodynamic signals in different cortical brain regions, along with correlations between hemodynamic changes and degree of suicidality, when comparisons are made across depressed patients with a history of suicide attempts, those with no history of suicide attempts, and healthy controls. As such, the result of an individual's fNIRS scan could potentially be taken as an objective measure of suicidality; it could also be indicative of one's predisposition to suicidality. While our systematic review has shed light on the promising potential of fNIRS to be used as an objective method of assessing and predicting suicidality, further methodological improvements, such as those aimed at enhancing signal quality, are of crucial importance in ensuring replicability in future studies. Future studies with larger sample sizes, standardised methodology, as well as longitudinal follow-up with participants, are also recommended to further our knowledge of fNIRS and its clinical utility in psychiatric clinical practise and research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YL and CH: conceptualization, data extraction, and review. YL and GT: writing. CH: review and manuscript amendment. All authors contributed to the article and approved the submitted version.

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Prefrontal Cortex Activation During Verbal Fluency Task and Tower of London Task in Schizophrenia and Major Depressive Disorder

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Background: Cognitive dysfunction is a common clinical feature of mental disorders. A number of functional near-infrared spectroscopy (fNIRS) studies have shown reduced prefrontal activation during the verbal fluency task (VFT) in schizophrenia (SZ) and major depressive disorder (MDD). However, no studies have examined and compared the brain activation patterns during the Tower of London (TOL), which is another classic, high-sensitivity executive function testing tool, in these two serious mental disorders. This study aimed to assess the characteristics of brain activation during the two different cognitive tasks in SZ and MDD patients.

Methods: This study recruited 30 patients with SZ, 30 patients with MDD, and 30 demographically matched healthy controls (HCs). The hemodynamic changes of the prefrontal cortex (PFC) were measured using 32-channel fNIRS during performance of the TOL task and VFT task.

Results: SZ patients showed poorer VFT performance than MDD patients and HCs, and the two patient groups showed poorer TOL performance than HCs. Compared to HCs, both of the patient groups exhibited a significant decreased activation in the extensive PFC. Particularly in certain channels in the dorsolateral PFC (DLPFC), SZ patients exhibited significantly decreased hemodynamic changes than the MDD patients.

Conclusions: Patients with SZ and MDD have different levels of impairment in different cognitive domains and different patterns of brain activation during the two cognitive tasks. Further research is needed to determine the use of fNIRS for clinical evaluation and diagnosis.

Keywords: SCH, MDD, functional NIRS, VFT, TOL

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INTRODUCTION

Cognitive dysfunction is gaining attention as a common clinical feature of mental disorders, which has a large impact on quality of life and long-term prognosis. Cognitive dysfunction is considered to be a core feature of schizophrenia (SZ) in addition to other positive and negative symptoms (1). Cognitive function starts to decline many years before the first psychotic symptoms manifest

themselves in the context of SZ (2). Major depressive disorder (MDD) is characterized by impaired affect, cognitive dysfunction, and significant psychosocial impairment that may persist from weeks to years. It suggested that the cognitive dysfunction in MDD persists following symptomatic remission, which may contribute to social dysfunction and suicide ideation (3).

Many neuroimaging studies have demonstrated that cognitive deficits in patients with SZ and MDD are associated with prefrontal cortex (PFC) dysfunction (4, 5). A fMRI study provided evidence that salience network abnormality may play a critical role in the pathogenesis of these two mental disorders (6). Multichannel functional near-infrared spectroscopy (fNIRS) is a relatively new method for investigating the hemodynamic activity of the cerebral cortex. Compared with other neuroimaging methodologies (such as fMRI or SPECT), fNIRS has superior time resolution and can be used flexibly. Unlike EEG and MEG, its data are not much susceptible to electrical noise, since it is an optical imaging modality (7).Because of its wide applicability, more and more researchers are using fNIRS to study brain function in psychiatric disorders (8).

The verbal fluency task (VFT) is a representative cognitive task in the fNIRS studies to assess executive function, which is regarded as associated with the function of PFC. The classic VFT takes two forms, phonemic or semantic word fluency, requiring participants to generate as many words as possible beginning with a certain letter or belonging to a certain category of words (9). Many studies have found hypofunction of PFC in SZ or MDD during VFT (10, 11). However, VFT only covers a restricted aspect of executive function. Different areas of tasks are needed to explore the cognitive function in patients with mental disorders.

The Tower of London (TOL) task is another classic, high-sensitivity executive function testing tool that mainly reflects planning and problem-solving abilities (12). The TOL task requires participants to apply many types of ability, such as complex visual and spatial planning, working memory, and selective attention (13). A previous fNIRS study found reduced prefrontal activation during TOL in first-episode SZ (14). A study compared cognitive and executive function in SZ and MDD patients, which showed that patients' performance was lower than HCs, and SZ performed worse than MDD (15). However, no study has compared the brain activation patterns between SZ and MDD patients during the TOL task and VFT task using fNIRS. Taken together, this study aimed to assess the different characteristics of brain activation in SZ and MDD patients during the VFT and TOL task. Furthermore, we are interested in finding whether fNIRS can distinguish between these two mental disorders.

Abbreviations: fNIRS, Functional near-infrared spectroscopy; VFT, Verbal fluency task; SZ, Schizophrenia; MDD, Major depressive disorder; TOL, Tower of London; PFC, Prefrontal cortex; DLPFC, Dorsolateral prefrontal cortex; VLPFC, Ventrolateral prefrontal cortex; FPPFC, Frontopolar prefrontal cortex; ch, Channel; HCs, Healthy controls; PANSS, Positive and Negative Syndrome Scale; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Rating Scale for Anxiety; Oxy-Hb, Oxygenated hemoglobin; deoxy-Hb, Deoxyhemoglobin; ANOVA, One-way analysis of variance; FDR, False discovery rate.

METHODS

Participants

This study recruited 30 patients with SZ and 30 patients with MDD from the Psychiatry Department of Renmin Hospital of Wuhan University in China, from December 2015 to August 2016. Thirty demographically matched healthy volunteers were taken to serve as healthy controls (HCs). The patients were diagnosed by two experienced psychiatrists according to the DSM-V criteria. All participants were aged from 18 to 50 years. They had normal IQ and received education in junior high school and above. Exclusion criteria included neurological or severe somatic disease, alcohol/substance abuse, and uncooperative patient. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate psychiatric symptoms in patients with SZ (16). The depressive and anxious symptoms were evaluated by the Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Anxiety (HAMA) in MDD patients (17, 18). All of the patients enrolled were taking medications, and the medication information is shown in **Table 1**. Daily doses of all antipsychotics were converted to an equivalent dose of chlorpromazine; antidepressants, to that of imipramine; and anxiolytics, to that of diazepam (19). The ethics committees of Renmin Hospital of Wuhan University approved the study. Written informed consent was obtained from all subjects.

Activation Task

This study used the VFT and the TOL as cognitive tasks. Participants were asked to complete both tasks on the same day. The VFT was designed in four blocks consisting of a 30-s task period and a 30-s rest period, which was similar to previous studies (12, 20). At the beginning of the task, there was a 30-s pre-scanning. The participants needed to list as many items as possible that belong to the specific category (four-legged, vegetables, household appliances, and fruits) during the task period, while repeat counting from 1 to 5 in the rest period. The task performance was the mean number of the correct items of the four blocks. The TOL had six blocks, which also consist of a 30-s task period and a 30-s rest period. During the task period, the participants were asked to observe two pictures (A and B) on the computer screen, image how many moves will have to be made to make the arrangement of balls in picture "A" look like the arrangement of balls in picture "B," and pressed the key that corresponds with the number of moves. Then, the computer switched to the next pictures automatically. The subjects would do nothing but sit during the rest period. The accuracy and average response time were recorded as the task performance.

fNIRS Measurements

This study used a 32-channel fNIRS machine (CW5, TechEn Inc., American) to measure the relative concentration changes of oxygenated hemoglobin ([oxy-Hb]) and deoxyhemoglobin ([deoxy-Hb]) using two wavelengths (695 and 830 nm) of infrared light, based on the modified Beer–Lambert law. In this system, 3*7 probe arrangement was adopted, consisting of 11 light sources and 10 light detectors. The distance between pairs of probes was set at 3.0 cm, and the temporal resolution was

TABLE 1 | Demographics, clinical information, and task performance.

	SZ ($n = 30$)	MDD ($n = 30$)	HC ($n = 30$)	*P*
Age (years)	27.23 ± 7.04	29.40 ± 8.87	27.27 ± 7.90	0.483
Gender (men/women)	14/16	12/18	12/18	0.835
Education (years)	13.90 ± 2.44	14.33 ± 2.45	15.20 ± 1.65	0.086
Duration of illness (months)	28.71 ± 31.14	26.71 ± 24.72	–	–
PANSS	72.1 ± 6.58	–	–	–
HAMD	–	25.2 ± 6.65	–	–
HAMA	–	17.5 ± 6.77	–	–
Medicine (mg/day)				
Antipsychotics	412.50 ± 181.20[A]	150.00 ± 32.07[A]	–	–
Antidepressants	41.90 ± 17.71[B]	86.67 ± 7.93[B]	–	–
Anxiolytics	5.30 ± 2.60[C]	6.18 ± 0.53[C]	–	–
VTF performance (*n*)	7.65 ± 2.33[a,b]	9.53 ± 2.45	9.76 ± 1.83	0.001*
TOL performance				
Total responses (*n*)	11.87 ± 5.34[b]	12.43 ± 5.08[c]	17.63 ± 3.75	0.000*
Correct responses (*n*)	7.80 ± 5.25[b]	9.40 ± 4.70[c]	14.03 ± 4.93	0.000*
Accuracy (%)	0.64 ± 0.22[a,b]	0.75 ± 0.24	0.79 ± 0.22	0.020*
Average responses time (s)	12.39 ± 7.43[b]	10.57 ± 2.94[c]	8.45 ± 2.18	0.008*

PANSS, Positive and Negative Syndrome Scale; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Rating Scale; SZ, Schizophrenia; MDD, Major depressive disorder; HC, Healthy control.

[a] *The difference between SZ and HC is significant.*

[b] *The difference between SZ and MDD is significant.*

[c] *The difference between MDD and HC is significant.*

[A] *The chlorpromazine equivalent dose.*

[B] *The imipramine equivalent dose.*

[C] *The diazepam equivalent dose.*

* *means that the difference is statistically significant.*

set to 0.02 s. The measurement area between a detector and source probe pair was defined as a channel (ch). The source–detector probes were placed on the prefrontal areas. According to the international 10–20 system, the 32 channels' positions were as follows: ch3, ch7, ch11–14, ch19–22, ch24, ch26–27, ch29–30, and ch32 in dorsolateral PFC (DLPFC); ch1–2, ch9–10, ch23, and ch31 in ventrolateral PFC (VLPFC); and ch4–6, ch8, ch15–18, ch25, and ch28 in frontopolar PFC (FPPFC) based on Brodmann's area (21) (see **Figure 3**).

fNIRS Pre-processing

This study used HOMER, a MATLAB-based graphical user interface program to analyze the functional brain data from NIRS (22). First, in order to remove instrument noise and physiological interference, the raw data were filtered using bandpass filtering techniques within the range of 0.01–0.2 Hz. Then, the optical density was translated to hemoglobin concentrations. We focused on [oxy-Hb] because the change of [oxy-Hb] is a more direct response to task-related brain activation (23). The last 5 s of the rest period was used as the baseline. We calculated the average [oxy-Hb] of the task period and baseline in each channel for each participant during the VFT and TOL task. Then, the mean [oxy-Hb] change was calculated by subtracting the baseline mean values from the task period mean values.

Statistical Analysis

All data were imported into SPSS (version 26.0) for statistical analyses. One-way analysis of variance (ANOVA) was used to compare differences in demographic characteristic and task performance among HC, SZ, and MDD; Kruskal-Wallis test was used when variance between groups was not homogeneous. Sex-based group difference was evaluated using the chi-square test. Paired *t*-test was performed to compare the average [oxy-Hb] of each channel during the task period and baseline to determine which channels were activated during tasks. Then, two-way ANOVA was performed to compare the mean [oxy-Hb] change of each channel during different cognitive tasks between groups. *Post-hoc* comparisons were made with the LSD method to reveal the source of ANOVA. The false discovery rate (FDR) was utilized to correct for multiple comparisons. Significance level was set at a $P < 0.05$.

RESULTS

Demographics, Clinical Information, and Task Performance

There were no significant differences in age, gender, and education between the two patient groups and HCs. The SZ patients showed poorer VFT performance than the MDD patients and HCs, and the mean number of the correct items there was significantly lower. The two patient groups showed poorer TOL performance than HCs. The accuracy of SZ patients was statistically lower than HCs, and the average response time of SZ patients was longer. MDD patients also had longer average responses time than HCs, but there was no difference

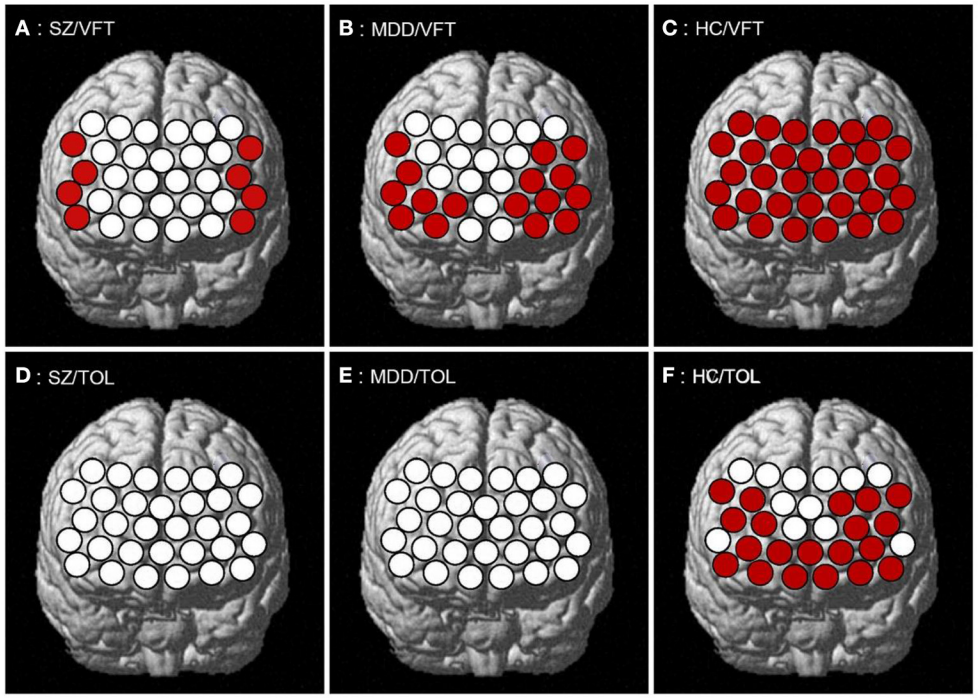

FIGURE 1 | PFC activation during the task. **(A–C)** respectively represents the PFC activation of SZ, MDD, HC in VFT; **(D–F)** respectively represents the PFC activation of SZ, MDD, HC in TOL.

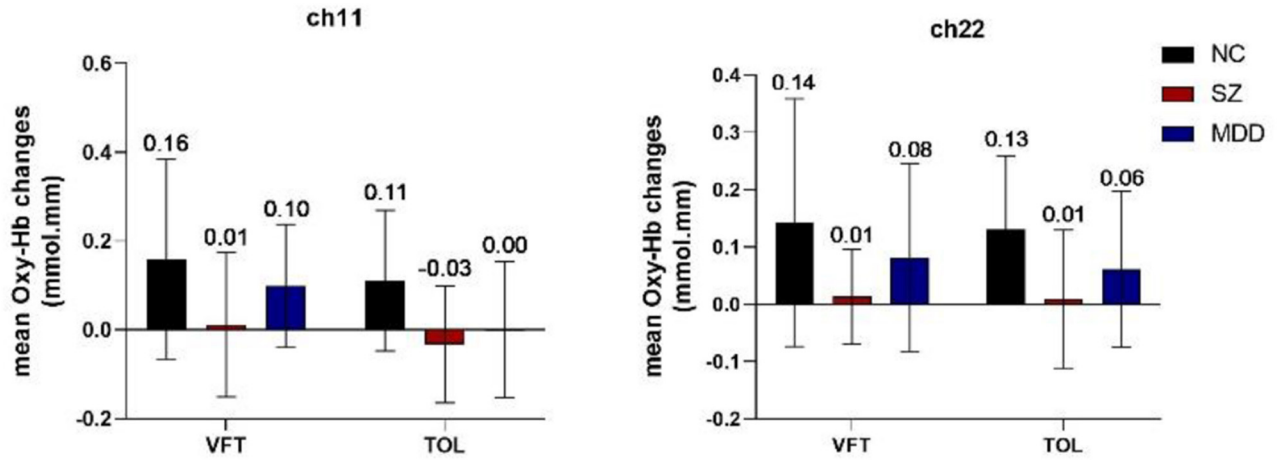

FIGURE 2 | Mean [oxy-Hb] changes in ch11 and ch22.

in the accuracy. However, the accuracy of MDD patients was statistically higher than SZ patients (see **Table 1**).

PFC Activation During the Task

SZ patients showed a significant increase in the eight channels of the PFC (ch1–2, ch9–10, ch12, ch21, ch23, and ch31 in the VLPFC and part of the DLPFC; t = 2.473–5.180, FDR p = 0.019–0.049) during the VTF task, while none of the 32 channels had significant activation in the TOL task. MDD patients showed a significant increase in 16 channels of the PFC (ch1–3, ch5, ch7–12, ch19–23, and ch31 in the VLPFC, DLPFC, and part of the FPPFC; t = 2.108–4.525, FDR p = 0.011–0.044) during the VFT task; also, there was no significant activation in all channels during the TOL task. HCs showed a significant increase in all channels (t = 2.183–9.112, FDR p = 0.013–0.047) of the PFC during the VFT task and in 20 channels (ch1, ch3–9, ch11–15, ch19–23, ch28, and ch31 in the VLPFC, DLPFC, and FPPFC; t = 2.064–4.901, FDR p = 0.021–0.048) during the TOL task (see **Figure 1**).

Group Comparison of the Degree of the PFC Activation

Two-way ANOVA indicated a main effect of group in all channels, and a main effect of task in most channels. There was no significant interaction between group and task. *Post-hoc* comparisons showed that compared to HCs, both of the patient groups exhibited significantly decreased mean [oxy-Hb] changes in all channels. Especially in ch11 ($F = 11.818$, FDR $p = 0.047$) and ch22 ($F = 10.830$, FDR $p = 0.027$) in the DLPFC, SZ patients exhibited significantly decreased mean [oxy-Hb] changes than the MDD patients. In most channels, the mean [oxy-Hb] changes were higher for the VFT task than for the TOL task (see **Figure 2**). The positions of ch11 and ch22 are shown in **Figure 3**. **Figures 4**, **5** show the time course of mean hemodynamic changes (*Z*-values) of all channels during the VFT and TOL tasks, respectively.

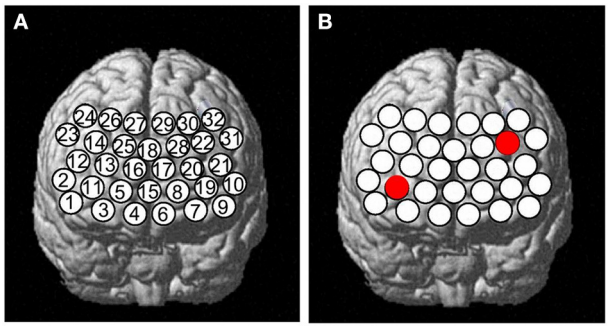

FIGURE 3 | A panel **(A)** Thirty-two channels' positions and **(B)** shows ch11 and ch22.

DISCUSSION

To the best of our knowledge, this is the first fNIRS study to compare the different characteristics of brain activation between SZ and MDD patients during the VFT and TOL task. We found that SZ patients showed poorer performance on VFT than MDD patients and HCs, and the two patient groups showed poorer performance on TOL than HCs. fNIRS results indicated that the activation of the extensive PFC in the two patient

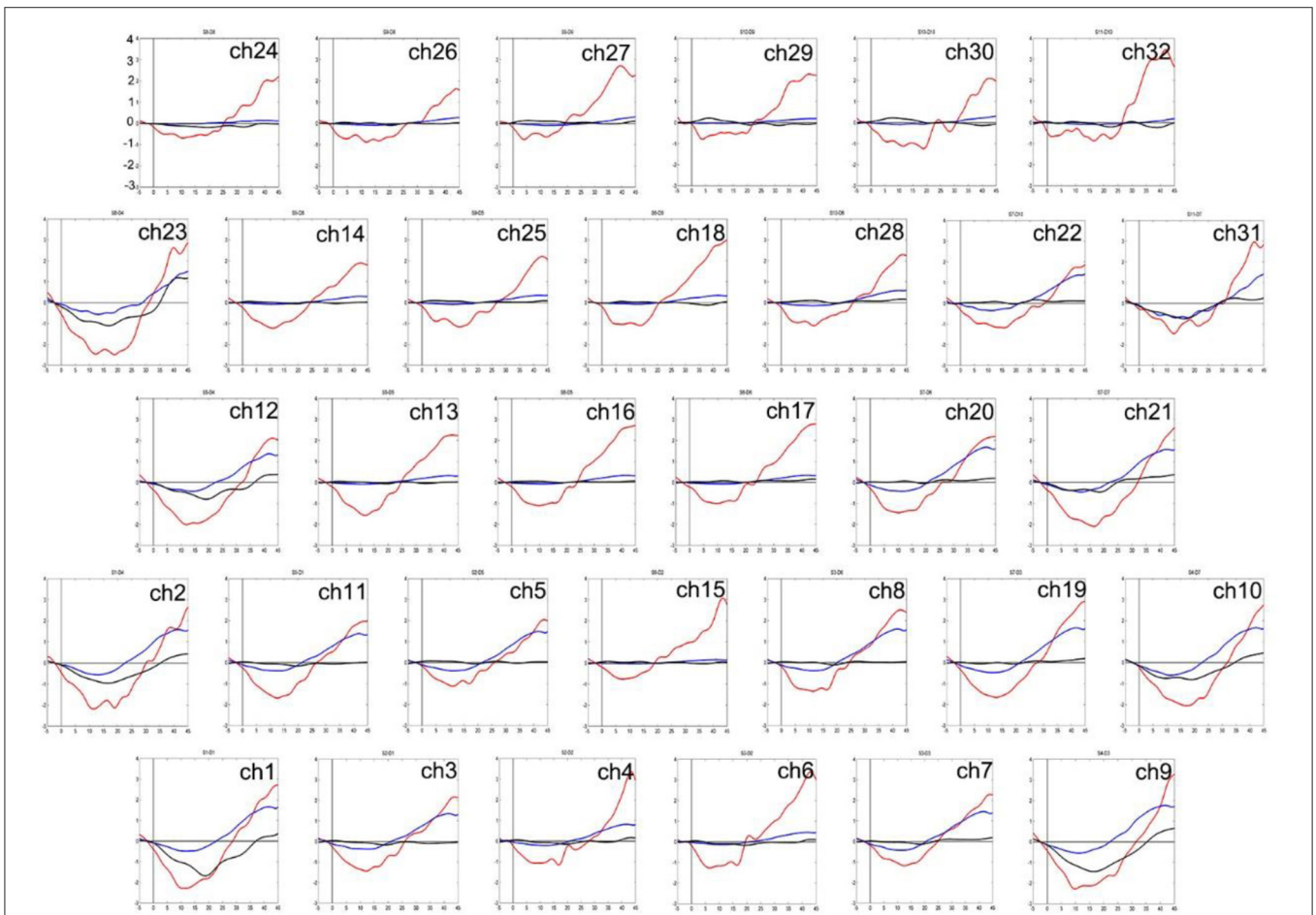

FIGURE 4 | The time course of mean hemodynamic changes (*Z*-values) of 32 channels during the VFT task. The ordinate is the mean hemodynamic changes (*Z*-value, $*10^{-1}$ mmol.mm), and the abscissa is the time course of the task. HCs (red); MDD patients (blue); SZ patients (black).

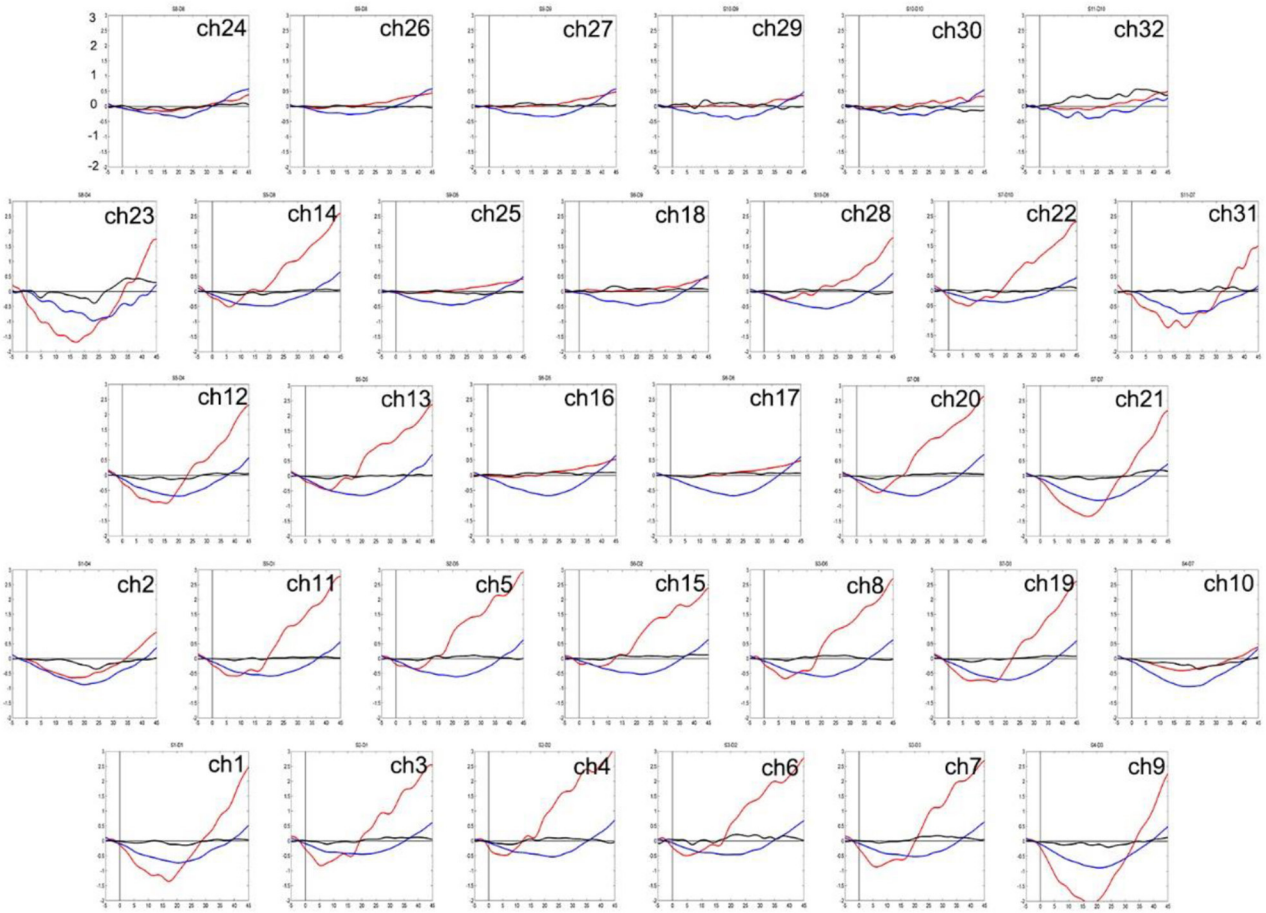

FIGURE 5 | The time course of mean hemodynamic changes (*Z*-values) of 32 channels during the TOL task. The ordinate is the mean hemodynamic changes (*Z*-value, $*10^{-1}$mmol.mm), and the abscissa is the time course of the task. HCs (red); MDD patients (blue); SZ patients (black).

groups was significantly lower than that in HCs during the two tasks. Particularly in certain channels in the DLPFC, SZ patients exhibited significantly decreased hemodynamic changes than MDD patients.

VFT Performance and TOL Performance

In the VFT, the mean number of the correct items generated was significantly lower in SZ patients than in MDD patients and HCs. These results were consistent with previous reports (20, 24). The VFT, which emphasizes information processing and memorizing ability, required participants to do some relevant memory retrieval with a limited range. The results indicated that SZ patients have cognitive impairment in memory retrieval and attention. One study was inconsistent with our results, which showed no significant difference in VFT performance among the three groups (25). The possible reason is that the study used a simpler letter fluency version that had a high successful execution rate for subjects, including psychiatric patients. In our study, we used semantic a word fluency task that could distinguish patients with more severe cognitive impairment.

In the TOL task, the accuracy and the average response time, respectively, reflect the accuracy and efficiency of planning and problem-solving ability. The results showed that SZ patients performed poorly, both accuracy and efficiency were lower, which were similar to a previous study (26). However, there have been no previous fNIRS study of TOLs in MDD patients. Our results showed that MDD patients planned and dealt with problems less effectively than HCs but had higher accuracy than SZ patients, which suggested that executive function impairment was more severe in SZ patients and were consistent with a previous study (15). Perhaps the TOL task could better distinguish between mental disorders and HCs due to both patient groups showing poorer TOL performance.

Considering the impact of IQ on the results, a previous study suggested that despite the controls' higher IQ scores, the groups showed comparable performance in most parameters of the three cognitive tasks (27). Our participants had normal IQs and no statistical difference in years of education, so the effect of IQ on the results was not taken into account. The duration of illness may also affect the results. A 1.5-year longitudinal study found that cognitive function, daily living skills, social function, and

social activity were nominally improved over a 1.5-year follow-up period in SZ patients (28). The patients involved in the present study had an average illness duration of more than 24 months, and they all had cognitive impairment. Further longitudinal research is needed to explore the relationship between cognitive dysfunction and duration of illness.

Reduced PFC Activation in the Patient Groups During Cognitive Tasks

The present result indicated that PFC activation was more extensive during the VFT than during the TOL task. The HCs showed activation in PFC during the TOL task, but there was no significant activation in patient groups. This is an interesting result, and not in line with our expectations. This could be due to the difficulty of the TOL task, or the fact that other deep brain regions were activated during the TOL task but fNIRS could not detect it. Our research focused on the PFC, and some MRI studies found that the TOL task also activated the frontostriatal and the parietal cortex (29, 30). Our results suggested that the patients failed to recruit enough PFC resources with the task and did not show the expected activation of task-related areas exhibited by the HCs, which was consistent with a previous study (14).

Most previous fNIRS studies of the VFT showed reduced PFC activation in SZ patients and MDD patients compared with HCs (11, 31). However, it is difficult to distinguish between MDD and SZ using only the mean [oxy-Hb] change in fNIRS signal. Simultaneously performing two cognitive tasks, SZ patients exhibited significantly decreased hemodynamic changes than the MDD patients in certain channels in the DLPFC (ch11: $p = 0.047$; ch22: $p = 0.027$). The result indicated that the DLPFC is crucial for executive function. This was consistent with several fMRI studies that show that the PFC is reliably activated during planning tasks (32, 33).

Combining our results with some previous studies has found that SZ patients have poorer task performance and cognitive function than MDD patients, such as in the VFT (20, 24), the TOL task (15), and the n-back task (34), which reflect executive function and working memory. Our results showed that SZ patients exhibited significantly decreased hemodynamic changes than the MDD patients in specific regions in the DLPFC during the two tasks, which indicated that the DLPFC is crucial for executive function. A previous MRI study using the TOL task in MDD showed that visuospatial planning *per se* was associated with increased frontostriatal activity and visuospatial planning load was associated with increased parietal activity (29). Another MRI study in SZ found that the TOL task activated several brain regions, including the DLPFC, the inferior frontal gyrus, and the parietal cortex (30). In addition to the PFC, the differences between the two diseases in other areas of the brain such as the parietal lobe should also be explored.

LIMITATIONS

This study has several limitations. First, the statistical significance notwithstanding, the sample size of the study was relatively small. Second, all of the patients enrolled were taking medications, and the effect of medications on the fNIRS data cannot be ruled out. Longitudinal follow-up research was also not performed. Third, fNIRS can only measure the distance between 3 and 5 cm below the scalp, and cannot detect deeper brain areas. Our study showed that combining the two cognitive tasks can distinguish between SZ and MDD patients in specific brain regions. It is possible that a combination of fNIRS and other techniques could better search for biomarkers to distinguish the two diseases.

CONCLUSIONS

Patients with SZ and MDD have different levels of impairment in different cognitive domains and PFC activation was more extensive during the VFT than during the TOL task. SZ patients exhibited significantly decreased hemodynamic changes than the MDD patients in specific regions in the DLPFC, which could be used as targets for subsequent physical therapy such as rTMS. Further research is needed to determine the use of fNIRS for clinical evaluation and diagnosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of Renmin Hospital of Wuhan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WG, WH, LZ, and SC designed the study. XY and LY performed the study. XY undertook the imaging data analysis and wrote the first draft of the manuscript. WG and WH revised the manuscript.

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The Changes in Concentration of Cerebral Oxygenated Hemoglobin During Single Event-Related Japanese Shiritori Task in Patients With Major Depression Disorder: Comparison With Healthy Subjects

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Patients with major depressive disorder (MDD) have been reported to show cognitive impairments in attention, cognition control, and motivation. The purpose of this study is to compare and examine the characteristics of frontal and temporal cortical activity in outpatients with MDD during the word production task (Shiritori) using a single event-related Near-Infrared Spectroscopy (NIRS) measurement method that was originally devised. The subjects were 29 MDD patients and 29 age matched healthy controls. In this task, one session consisted of two contrasting conditions (word production task, control condition), and all subjects alternated between these conditions. Each word was visually presented by a monitor for 0.3 s as an activation task and a fixed circle was presented for 12 s. In the activation task, subjects had to immediately generate a noun that starts with the last syllable of the presented word and they were required to say only creatures. From the data obtained at each measurement point during the 20 trials, and averaged waveform during activation task (20 trials) was calculated for each channel. During the word production task, the MDD patients showed significantly smaller activation than the controls in the prefrontal cortex area and inferior parietal area, especially in the left area. In addition, there was a significant negative correlation between Δoxy-Hb at the bilateral temporal lobe area and HAM-D total score in the MDD patients. These findings suggest that a single event-related NIRS measurement during Japanese shiritori tasks may be useful tool for evaluating psychophysiological indices in MDD patients, that relationship between activation and symptom may be of help in predicting functional outcome in patients.

Keywords: near-infrared spectroscopy, single event related design, major depressive disorder, Japanese word production task, cognitive impairment

INTRODUCTION

Patients with major depressive disorder (MDD) have been reported to show cognitive impairments in executive function, processing speed, attention, and memory (1). The prefrontal cortex plays an important role in the pathology of MDD. Although the definitive pathology of MDD remains unclear, advances in neuroimaging technology have gradually made it possible to identify affected brain regions and networks. Such techniques and methodologies have been proposed as biomarkers for a more reliable diagnosis of psychiatric disorders, including MDD. Under these circumstances, near-infrared spectroscopy (NIRS) has also been reported to be useful as a research tool for various psychiatric disorders including MDD (2, 3). Near-infrared spectroscopy is a method of irradiating the head with near-infrared light absorbed by hemoglobin in the blood, measuring changes in cerebral blood flow in the cerebral cortex by the absorption rate, and indirectly measuring brain activity.

Near-infrared spectroscopy is a relatively new neuroimaging method, was approved in Japan by the Ministry of Health, Labor and Welfare in 2009 as an advanced technique for assisting with the diagnosis of depression. Furthermore, in 2013, NIRS received medical insurance coverage as a supplementary diagnosis. Near-infrared spectroscopy examination has been used clinically as a psychophysiological useful objective indicator reflecting cognitive function.

Near-infrared spectroscopy uses non-invasive light, and has a high temporal resolution (0.1 s) and low spatial resolution (2–3 cm); however, it can be used relatively easily to measure dynamic changes of brain function. The technique makes it possible to visually grasp such changes (4, 5). Changes in the hemoglobin concentration measured by NIRS have been shown to closely correlate with the blood oxygenation level on fMRI (blood oxygenation level-dependent signal) and to be reproducible (6).

Many previous studies using NIRS in MDD patients have generally shown reduced changes in oxy-Hb levels in the frontal lobe region during verbal fluency tasks (VFT) (7). It has been repeatedly reported that depressed patients have less changes in cerebral blood flow in the left prefrontal cortex during VFT than healthy subjects (8, 9). In addition, it is considered that the decrease in left prefrontal cortex function in MDD reflects the loss of interest and especially the symptom of motor rest among the depressive symptoms (10). On the other hand, some NIRS studies on MDD suggest functional decline not only in the left but also in the right prefrontal cortex (11, 12). In a previous using NIRS, Noda et al. (3) investigated the relation between the severity of MDD and frontal lobe activation. It was shown that the right lateral lobe had a significant negative correlation with the total score of the 21-item Hamilton Rating Scale for Depression (HAM-D). This result suggests that the severity of depression affects cognitive function. In fact, Liotti and Mayberg (13) review evidence that strongly suggests the right dorsolateral prefrontal cortex is an important brain structure in emotional/cognitive interactions in negative mood states. Therefore, the severity of depression and depressed mood are closely associated with brain dysfunction and might be observed as an abnormal laterality in depression.

However, many studies using NIRS based on verbal tasks that have been reported to date evaluate brain activity using block design (continue the task for 20–30 s) that intermittently measures blood flow during tasks. However, block design method still have problems with the reproducibility of individual data (14–16). With this block design, it is considered that some patients have difficulty in maintaining attention and concentration on tasks for a long time, and data are likely to vary due to performance and control tasks depending on the stage and condition of the disease. Indeed, Wang et al. (17) reported in a meta-analysis that patients with MDD have impaired sustained attention and may have greater intra-individual variability. Therefore, in this study, we adopted an event-related design to reduce the sustained attention load and overcome performance factors. Therefore, event-related design was adopted in this study. It is a method of calculating event-related blood flow responses obtained by repeating a single task about 20 times or more in order to accurately measure neural activity. It is considered that the variation in performance depending on the patient's condition can be suppressed by repeating a single task, as compared with the task of continuing to perform for a certain period. We hypothesize that we are observing changes in cerebral blood flow based on neurovascular responses. However, it seems to be a change in cerebral blood flow that reflects neural activity with a certain latency.

Furthermore, the "Shiritori" task used in this study is a very popular word chain game generating a word that begins with the last syllable of the preceding word in Japan. In the English-speaking world, it is called "Grab on Behind" or "Last and First." Since this game is a familiar task that emphasizes the some cognitive functions, including working memory, it is considered to be a task that is easy to teach and easy for many Japanese to understand the rules. In a previous study using block design, Kondo et al. (18) reported that change in blood flow in patients with MDD in the frontotemporal cortices during a similar shiritori task was reduced compared to healthy individuals. In addition, they reported that task performance in the healthy group was higher than in depressed patients, and that there was a correlation between NIRS data and task performance.

Therefore, in this study, the change of oxygen-Hb concentration during the shiritori task was measured by single event-related NIRS measurement in healthy subjects and patients with MDD. The purpose of this study was to explore the usefulness of this measurement method and its potential as a psychophysiological index that reflects the cognitive function of depressed patients.

MATERIALS AND METHODS

Participants

Twenty-nine out-patients with MDD (34.1 ± 7.8 years) and 29 healthy controls (31.0 ± 6.2 years) participated in the study (**Table 1**). The patients were recruited from the outpatients at Kurume University Hospital, and were diagnosed using ICD-10 criteria by two trained psychiatrists. Almost all patients except for

TABLE 1 | Subject characteristics.

Characteristics	Patients ($n = 29$)	Controls ($n = 29$)	Group difference *P*-value
Age (years: mean± SD)	34.1 ± 7.8	31.0 ± 6.2	0.11
Gender (female/ male)	11/18	13/16	0.59
IQ (JART)	99.3 ± 7.3	103.1 ± 5.7	0.03
Duration of illness (years)	4.2 ± 3.8	NA	NA
Antidepressants (imipramine equivalents) (mg/day)	92.5 ± 79.2	NA	NA
HAM-D total score	15.6 ± 4.5	NA	NA

JART, Japanese Adult Reading Test; HAM-D, Hamilton Rating Scale for Depression; NA, no applicable.

two were medicated with antidepressants. The clinical status of all patients was evaluated by experienced psychiatrists using the HAM-D. All participants were native Japanese speakers and were judged from the Edinburgh Inventory to be right-handed (19). The Japanese version of the National Adult Reading Test assessed their mean intelligence quotient (IQ) values (20). No subjects had a head injury, neurologic disorder, alcohol/substance abuse, epilepsy, visual disabilities, aphasia, or dyslexia.

Permission for the study was obtained from the ethics committee of Kurume University. After completed description of study, written informed consent was obtained from all participants.

Procedure

NIRS Measurement

A 44-channel NIRS system (ETG4000; Hitachi, Tokyo, Japan) measured oxy-Hb changes during tasks covering from the frontal to temporoparietal regions as a recording unit at a sampling frequency of 10 Hz. Oxy-Hb changes were calculated from the difference in absorbance based on the modified Beer–Lambert law. The middle point of the injector–detector probe pairs was defined as a channel. The depth of each channel is supposed to measure changes at points 2–3 cm from the scalp that correspond to the cerebral cortical surface. According to the International 10–20 system used in electroencephalography, we placed probes along the Fp1–Fp2 line to the lowest anterior probes; left channel 19 and right channel 22 (**Figure 1**). To avoid movement artifacts, participants were instructed to minimize their movements and jaw fixation during examination. The pre-task baseline was determined as the mean during 1 s preceding the word presented, while the post-task baseline was determined as the mean during 1 s from 10 to 11 s after the word was presented. Linear fitting was applied to the data between these two baselines. Next, an averaged waveform for oxy-Hb concentration changes was created, and an area approximation value obtained by analyzing every 100 ms was used as an analysis target (Δoxy-Hb). For the relationship between each channel and anatomic region, NIRS data were converted to a normalized brain image template (three-dimensional composition indication unit; Hitachi).

Task Design

Brain activation was measured during word production. The advantage of NIRS is that it is relatively insensitive to body movements during measurement; therefore, this apparatus can obtain data in an overt task. For this examination, each subject sat on a comfortable chair and was required to perform word production. One session consisted of two contrasting conditions (word production task, control condition), and all subjects alternated between these conditions. Each word was visually presented by a monitor for 0.3 s as an activation task and a fixed circle was presented for 12 s. In the activation task, subjects had to immediately generate a noun that starts with the last kana character of the presented word and they were required to say only animal nouns. Thus, this task was the animal category version of the Japanese shiritori word game, as well as a word production task. For example, when the noun "SU-I-KA" (watermelon) was presented, the subject said the noun "KA-RA-SU" (crow). In the control condition, subjects were required to say the syllables "A-I-U-E-O" repeatedly. The word production task was repeated 20–25 times per session (**Figure 2**).

Statistical Analysis

In order to reduce the variability of each reaction, a single task was performed up to 25 times, and the data was analyzed for the 20 times averaged waveforms that could be performed correctly. In addition, the data used for the analysis was limited to the data of subjects with a correct answer rate of 80% or more. In other words, subject data that could not answer correctly at least 20 times by 25 times of stimulation were excluded (note that in this study, all subjects were able to answer correctly by 80% or more). Raw NIRS data were preprocessed by applying a low pass filter with cutoff frequencies of 0.5 Hz. Strangman et al. (21) reported that oxy-Hb changes correlate more strongly with blood-oxygen-level dependent (BOLD) functional MRI signal than do deoxygenated hemoglobin changes; therefore, we adopted the oxy-Hb changes as activation data. We used histograms at each channel to confirm a normal distribution. Profile comparisons between the healthy and patient groups were performed using the unpaired *t*-test except for data on the subject's gender (χ^2). In the comparison between groups of Δoxy-Hb, due to the nature of the data, the variability was large and the normality could not be confirmed by the Shapiro-wilk test, so the Mann-Whitney U-test, which is a non-parametric method, was performed. For the relationship between Δoxy-Hb and HAM-D total score, Spearman's rank correlation coefficient was calculated for each channel. For analyzing cortical activation, we adopted the false discovery rate correction method [Benjamini and Hockberg method (22)] and set the value specifying the maximum false discovery rate to 0.05. Stat View. 5.0 (SAS) was used as statistical software.

RESULTS

Oxy-Hb Changes During Shiritori Task

Major depressive disorder patients were associated with a significantly smaller increase in oxy-Hb than controls at 12 channels (left ch.4: $U = 231.00$, $p = 0.0032$; left ch.6: $U = 240.00$,

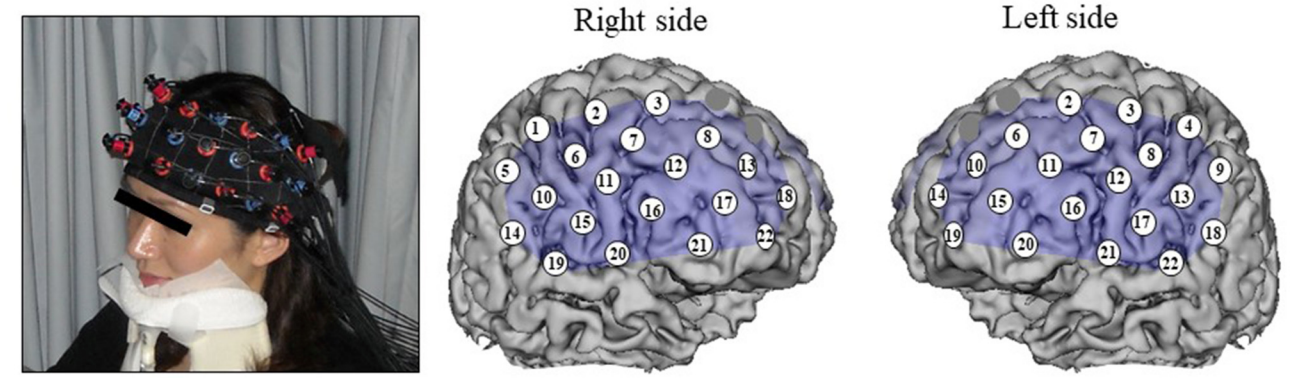

FIGURE 1 | Measurement point of 44 channels for NIRS. **(A)** Jaw fixation in order to eliminate influence of head movement. **(B)** Spatial position of the channels arranged of magnetic resonance imaging.

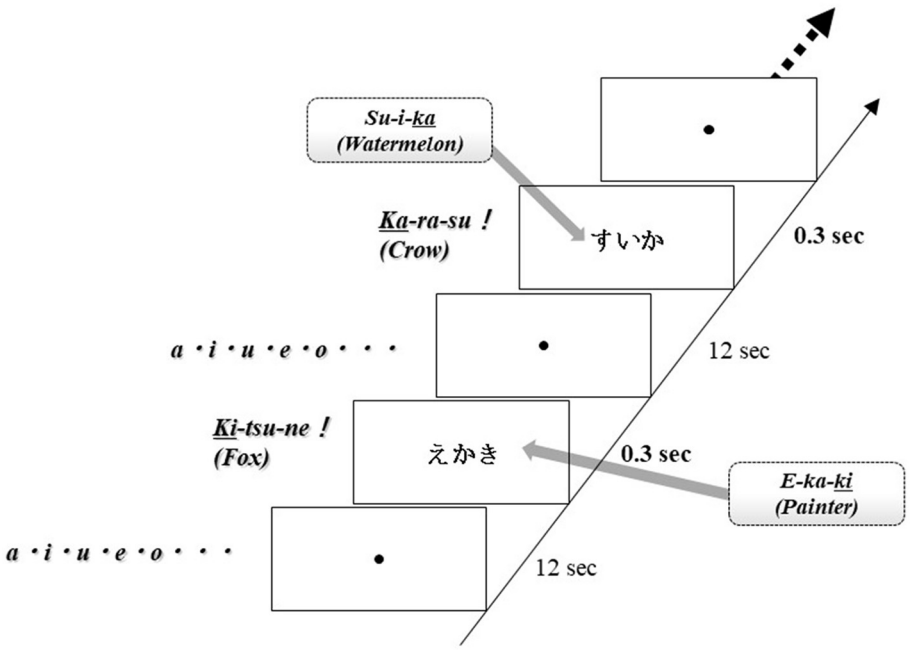

FIGURE 2 | Task design. One session comprised two contrasting conditions (word production tasks, control conditions), and all subjects alternated between these conditions. Each word was visually displayed on the screen for 0.3 s as an activation task and then a fixed circle was displayed for 12 s. In the activation task, subjects were instructed to say a noun immediately starting with the last kana character of the displayed word. The word production task was repeated 20–25 times per session.

$p = 0.0050$; left ch.7: 256.00, $p = 0.0105$; left ch.9: $U = 175.00$, $p = 0.0001$; left ch.10: $U = 227.00$, $p = 0.0026$; left ch.11: $U = 217.00$, $p = 0.0016$; left ch.12: $U = 216.00$, $p = 0.0024$; left ch.13: $U = 244.00$, $p = 0.0061$; left ch.18: $U = 264.00$, $p = 0.0149$; left ch.22: $U = 239.00$, $p = 0.0077$; right ch.8: $U = 209.00$, $p = 0.0010$; and right ch.11 $U = 208.00$, $p = 0.0016$). Waveforms are shown in **Figure 3**.

Correlation Between Oxy-Hb Changes and Clinical Variables

Δoxy-Hb revealed a significant negative correlation with HAM-D score at left ch.22 ($r = -0.55$, $p = 0.0033$) and right ch.19 ($r = -0.59$, $p = 0.0013$) for patients with MDD (**Figure 4**). However, Δoxy-Hb in neither channel was significantly correlated with imipramine equivalents and duration of illness.

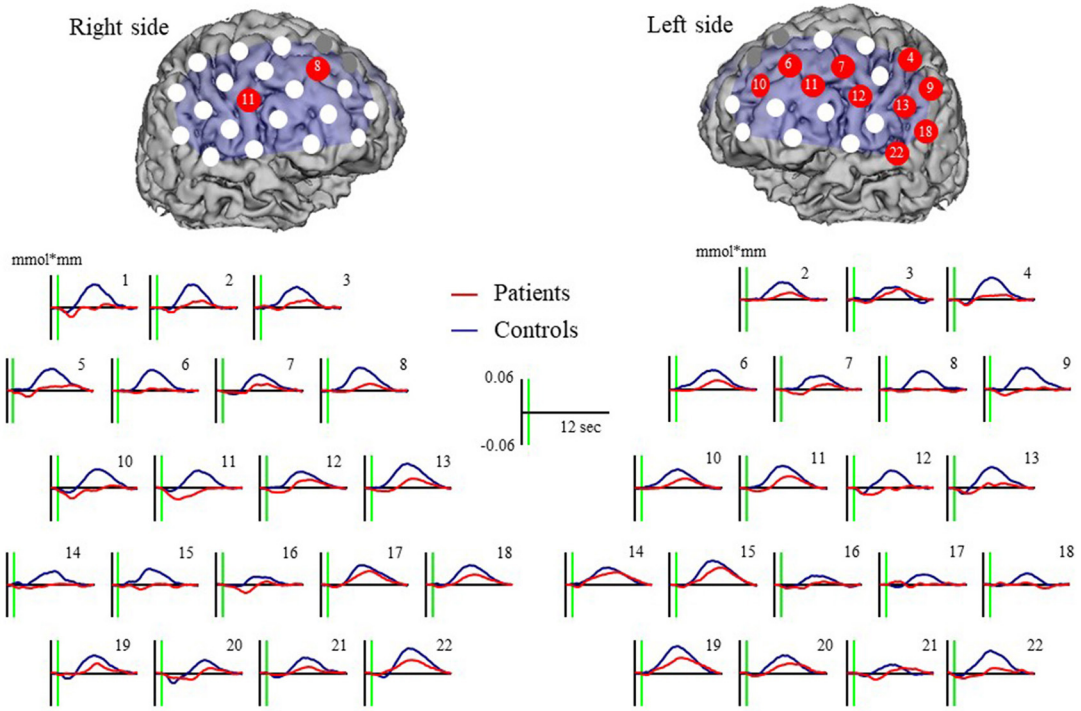

FIGURE 3 | Oxy-Hb grand mean waveforms and channels both with patient and control groups. Red dots indicate channels that significant difference between groups.

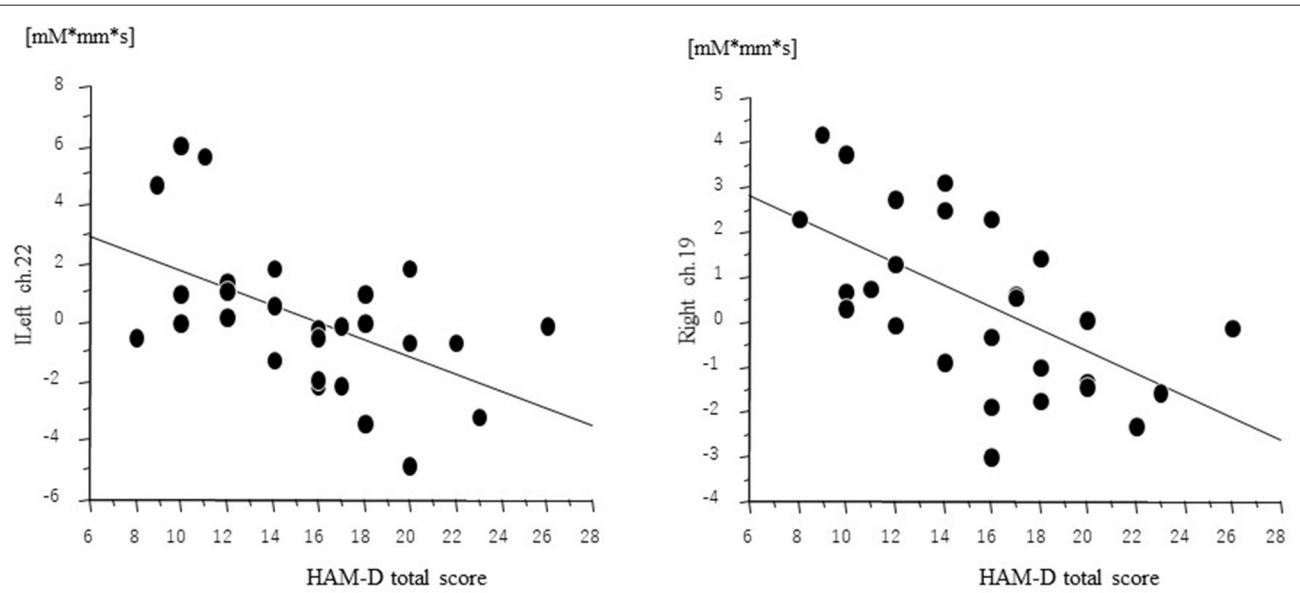

FIGURE 4 | Relation among oxygenated hemoglobin changes (Δoxy-Hb) and HAM-D total score.

DISCUSSION

In this study, we compared the hemodynamic changes of MDD patients and healthy subjects during the Shiritori task using the single event-related NIRS measurement method. Furthermore, we investigated the relationship between the patient's local cerebral blood flow and the HAM-D total score.

The previous study suggested that NIRS measurement using an event-related method enables researchers to obtain more

efficient averaging and to be free from artifacts (23). In the Shiritori task, attention must be paid to the task, the last syllable must be extracted from the word, temporarily held, and then the word with the beginning syllable that matches the last syllable must be searched from the memory, corrected, and answered. This task is associated with the characteristics of both letter and categorical verbal fluency. That is, it requires a wide range of cognitive abilities such as attention, retrival, and working memory. Inoue et al. (24) reported that the dorsolateral prefrontal cortex was activated in the shiritori task in a study using functional MRI. In addition, Yamamoto et al. (25) reported that the shiritori task is suitable for elucidating the brain network related to language in studies using magnetoencephalography. Thus, we thought that the shiritori task of performing overt word production would enable the evaluation of psychiatric patients.

In this study, Δoxy-Hb in the MDD group was significantly lower in the bilateral mid-frontal region, the parietal association region and the left temporal region than in the healthy group, indicating low activation of PFC in patients with MDD as in the previous study. In particular, a decrease in activity was observed in a wide range in the left region. Previous studies using VFT reported that depressed patients had less blood flow changes in the left prefrontal cortex than the controls (8, 9). Such left prefrontal cortex function has also been confirmed by other neuroimaging methods such as fMRI, this is thought to be because VFT is associated with left DLPFC dysfunction compared to other prefrontal cortex function tests (26). A number of previous studies demonstrated increased cortical activity in a depressed group using an n-back working memory task and some demonstrated a higher linear load response in patients with MDD than the normal controls, indicating that hyperfrontality in MDD was more evident in higher cognitive demanding condition. On the other hand, using Tower of London task, Elliott et al. (27) showed reduced neural response in cortical regions, particularly in VLPFC and DLPFC for patients with MDD compared with healthy controls, where patients' performance was impaired. From these previous studies, it is considered that the cerebral hemodynamic response is greatly affected by the difference in task load level and performance. The performance impact was minimized in this experimental design. However, the relationship between neural responses and cognitive demands may cause differences from previous findings using other cognitive tasks. In the future, it will be necessary to make a comparative study that takes into account the level of cognitive demand for issues.

Furthermore, in this study, the MDD group showed significantly lower values than the healthy group not only in the frontal region but also in the parietal association region. The parietal association region is also an area related to higher brain functions such as attention control linked to prefrontal cortex function (28). In working memory tasks such as VFT, previous studies have shown that the phonological loop is associated with the left parietal association region and the central execution system is associated with the prefrontal cortex region (29). Therefore, in the Shiritori task, it is possible that the PFC function is involved in the word generation task and the parietal association region is evoked by phonological working memory. The low activity of the parietal association region in the patient group of this finding may be due to not only dysfunction of the frontal region in MDD, but also a deficiency of the control network with the parietal association region that functionally binds to it.

Regarding the correlation analysis between clinical symptoms and activation values, a significant negative correlation was shown between the bilateral temporal regions and the HAM-D score. This is consistent with previous findings that left prefrontal cortex dysfunction reflects depressive symptoms. In the largest meta-analysis of neuroanatomical differences in MDD using previous cortical thickness measurements, it found that MDD was associated with cortical thinning in the insula, anterior and posterior cingulate, and temporal gyri (30): areas key in salience (31), internal mentation (32), and switching between internal thought and executive control (33). It is not clear whether these anatomical and functional defects are specific or state markers in MDD. However, previous longitudinal studies have found a negative correlation between changes in activation and changes in depressive symptoms in the temporal region (34). According to a study examining the effects of MDD on workplace productivity in eight different countries, the impact of MDD in the workplace is considerable across all countries, both in absolute monetary terms and in relation to proportion of country GDP (35). The MDD can influence the performance of workers who are "present" at work, i.e., presenteeism. Previous research suggests that presenteeism accounts for the majority of the costs (36, 37). This may be more severely impacted by cognitive impairments associated with MDD (38), there is a need to establish an objective index of rehabilitation including cognitive function in MDD patients, in the future, it will be necessary to carry out a longitudinal study that takes into consideration the dosage and duration of illness.

The present research involved several limitations. The first was the size of samples. In this study, we reported the correlation between oxy-Hb changes and HAM-D total score. However, since the size of samples was small, we could not assess the relevance to subordinate items, such as that conducted by previous report (39). Second, all of the patients were on medication. Previous studies reported no change in the oxy-Hb concentration in the PFC during VFT before and after the administration of drug in MDD (2, 40). In our study, the administration of drug in patients was lower, while the duration of illness was longer than in previous studies. This suggests that the decrease in cerebral blood flow variability at temporal region might be a trait marker in patients with MDD, even though the symptoms are stable. Third, there are methodological problems such as the relative value of NIRS data, low spatial resolution, and the possibility of being affected by other than cerebral blood flow such as skin blood flow. Compared to these methodological restrictions, the NIRS system is a methodology that has many advantages such as high time resolution and excellent portability. Also, regarding the handling of data after examination, the fact that the measured data can be immediately converted into a two-dimensional image and fed back to the subject will be a great advantage for clinical application.

In conclusion, NIRS measurement with Single event related design might be a useful psychophysiological method in patients with MDD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Kurume University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

KM: conception and design of the study. YI and YS: analysis and interception of data. YI, AK, and SN: collection and assembly of data. YI: drafting of the article. YS, MS, and HK: critical revision of the article for important intellectual content. YS and KM: final approval of the article. All authors contributed to the article and approved the submitted version.

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Task and Non-task Brain Activation Differences for Assessment of Depression and Anxiety by fNIRS

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Diagnosis and treatment of the patients with major depression (MD) or the combined anxiety and depression (A&D) depend on the questionnaire, sometimes accompanied by tasks such as verbal fluency task (VFT). Functional near infrared spectroscopy (fNIRS) is emerging as an auxiliary diagnostic tool to evaluate brain function, providing an objective criterion to judge psychoses. At present, the conclusions derived from VFT or rest (non-task) studies are controversial. The purpose of this study is to evaluate if task performs better than non-task in separating healthy people from psychiatric patients. In this study, healthy controls (HCs) as well as the patients with MD or A&D were recruited ($n = 10$ for each group) to participate in the non-task and VFT tasks, respectively, and the brain oxygenation was longitudinally evaluated by using fNIRS. An approach of spectral analysis is used to analyze cerebral hemoglobin parameters (i.e., Oxy and Deoxy), characterizing the physiological fluctuations in the non-task and task states with magnitude spectrum and average power. Moreover, the standard deviation of oxygenation responses during the non-task was compared with the peak amplitude during the task, with the aim to explore the sensitivity of the VFT task to brain activation. The results show that there is no significant difference ($p>0.05$) among the three groups in average power during non-task. The VFT task greatly enhanced the magnitude spectrum, leading to significant difference ($p<0.05$) in average power between any of two groups (HC, MD, and A&D). Moreover, 40% patients with A&D have an intermediate peak (around 0.05 Hz) in the magnitude spectrum when performing the VFT task, indicating its advantage in characterizing A&D. We defined a rate of the non-task standard variation to the task peak amplitude (namely, SD-to-peak rate) and found that this rate is larger than 20% in 90% of the MD subjects. By contrast, only 40% HC subjects have an SD-to-peak rate larger than 20%. These results indicate that the non-task may not be sufficient to separate MD or A&D from HC. The VFT task could enhance the characteristics of the magnitude spectrum, but its intensity needs to be elevated so as to properly explore brain functions related to psychoses.

Keywords: functional near-infrared spectroscopy, non-task, verbal fluency task, anxiety, depression

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BACKGROUND

Depression and anxiety are two psychoses that affect millions of people in the world, and their comorbidity rate is high (1). Clinical symptoms and functional impairment are more severe in patients with the combined anxiety and depression (A&D) (2), and the major consequences include emotional, cognitive, and somatic symptoms. It has been found that the brain functions of A&D are different from either depression or anxiety alone. Patients with depression have the suppressed functions of brain regions that regulate emotion and cognition, thus exhibiting the relevant clinical symptoms (3, 4). By contrast, the alterations in cerebral cortex function occur in specific regions for A&D patients, particularly in the prefrontal lobe and temporal lobe, affecting execution, language, memory, and attention, as evidenced by the declined cognitive control ability (5).

Rapid advances in neurological imaging technologies, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), permit observation of the changes in both brain structure and function. Although fMRI could obtain functional parameters such as oxy-hemoglobin index, the high cost precludes its routine use in psychiatric studies. In addition, fMRI measurement is strictly limited by body posture, making it difficult to perform verbal or cognitive tasks simultaneously. EEG provides rapid assessment of neural activity in the cerebral cortex and has been widely utilized in cognition and autonomic control. However, EEG does not directly reflect brain metabolism.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive, functional neuroimaging technique that could assess brain function by quantifying cerebral oxygenation at the microvasculature level (6–8). After more than 40 years of development, this technology has been used for evaluation of cerebral function (9–11) and extended to the clinical field of psychiatry, as one of the objective modalities for probing psychoses (12). fNIRS is sensitive to external stimulation or events; it allows for longitudinal monitoring of the changes in brain metabolism. Hence, fNIRS is frequently adopted for brain functional assessment when various tasks are performed (13).

The non-task (i.e., doing nothing) is a resting state that is easy to implement. The spontaneous brain activity during non-task period can be used as a baseline reference for brain activation (14). In EEG studies, the features in the resting state were found to be associated with a variety of neuropsychiatric disorders (15). fMRI can explore brain function by measuring the temporal variations of blood oxygenation level dependence (BOLD) as well as the fluctuations in resting spontaneous neural activity (16–18). Besides these, the spectral analysis of fNIRS permits the assessment of the autoregulation of brain function. The non-task does not generate motion artifacts and the obtained fNIRS signal is more reliable, with minimal signal noise. Recently, minor brain damage in the early stage of Alzheimer's was detected from the non-task EEG-fNIRS data (19). On the other hand, however, non-task does not challenge the brain function, which can only be realized by task paradigm (20).

The verbal fluency task (VFT) is a simple task that is widely used to assess language extraction and processing abilities (21, 22). fNIRS was also applied on the VFT task to distinguish different types of psychoses (23). In some studies, major depression (MD) patients were found to have the reduced responses in the orbitofrontal cortex (OFC) and frontal cortex (24), and the activation level is associated with the severity of MD symptoms (25). The schizophrenia patients were also found to have the reduced responses in the dorsolateral prefrontal cortex (DLPFC) (26), and bipolar disorder patients have the same performance in the left inferior frontal gyrus (IFG) (27). Under the VFT task, the prefrontal lobe is well activated (28), when compared with the non-task. In some fNIRS studies, it was found that the damaged cerebral cortex can be detected from both the non-task and the task. Hence, fNIRS technology is sensitive to both cognitive tasks and static state. However, task and non-task have not been extensively compared thus far.

Therefore, the comparison of cortex oxygen responses between VFT task and non-task will contribute to the detection of psychoses such as MD and A&D. In addition, an in-depth analysis of the response pattern of brain oxygenation variables in healthy and psychiatric populations would effectively evaluate and further optimize fNIRS for the detection of psychoses (29).

MATERIALS AND METHODS

Participants

In this study, 10 patients with MD and 10 patients with A&D diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) (30) criterion were recruited at the outpatient clinic of the Department of Mental Health, First Hospital of Shanxi Medical University. The diagnosis was conducted by three experienced physicians according to the consistent criteria. Ten healthy controls (HCs) were recruited from the local community. The subjects were in the age range between 15 and 55 years. The average age of the subjects for MD, A&D, and HC, represented by mean $\pm$ standard derivation, are 29.8 ± 11.8, 30.0 ± 11.4, and 31.8 ± 11.1, respectively. Every two of the three groups are aged-matched ($p > 0.05$). The time-course changes in cerebral cortex oxygenation during the VFT task and non-task were measured and analyzed among the three groups of subjects. All subjects have education level of high school level or above, and those who have neuropathy, severe physical diseases, substance abuse, or high suicide risk were excluded. The study was approved by the Ethics Committee of the First Hospital of Shanxi Medical University. After the study design was explained, all of the participants signed the consent form.

Methods

fNIRS Data Acquisition

The oxygenation data were collected by the Hitachi ETG-4100 fNIRS instrument (52CH) at the First Hospital of Shanxi Medical University. The subjects completed the non-task and VFT protocol individually. Prior to experiments, the subject wore a helmet embedded with numerous near-infrared light sensors, covering the prefrontal region and both temporal lobes. The near-infrared light sensors were placed over the scalp according

to the 10–20 international system. Each channel of the near-infrared signals is collected from a source–detector (S–D) pair, at the separation of 3.0 cm. A total of 11 S–D channels are located on the prefrontal lobe, and 20 S–D channels are located on the right and left temporal lobes. For each S–D channel, the near-infrared light is injected from the two laser sources (695 and 830 nm) alternately into the human scalp. The reflected signals from the brain cortex are collected by the optical detector and used to calculate the oxygenation responses. The laser power (8 mW) is sufficiently low so as to be approved for clinical usage. Both prefrontal lobe and temporal lobes are reported to be activated to the VFT task. For all the subjects, the oxygenation data obtained from each channel were averaged over the prefrontal lobe and temporal lobes, yielding the average responses to the VFT task and non-task respectively.

Firstly, the 160-s non-task data were collected from all subjects. The non-task requires the participant to sit in a chair, open their eyes and look forward, and repeatedly count 1 through 10, with the thumbs and index fingers of both hands performing counter-finger movements in rhythm until the end of the task (31). The subject was then asked to rest for 5 min. Subsequently, 160-s VFT task data were collected from all subjects. The fNIRS signals were collected for 30 s as the baseline prior to the task. During the VFT task, the subject was asked to construct the phrase with the simple words such as sky, earth, and human, lasting for 60 s (32, 33). The post-task fNIRS signals were collected for 70 s, repeatedly counting from 1 through 10. The cerebral oxygenation variables at each channel, including concentration of oxygenated hemoglobin (Oxy) and deoxygenated hemoglobin (Deoxy), were calculated from fNIRS signals according to the Beer–Lambert law. These variables at different channels were then averaged over the prefrontal region and both temporal lobes, yielding the cortex responses to the task or non-task.

Data Analysis

The spectral analysis was used to investigate the time-course oxygenation variables (Oxy and Deoxy) curves, yielding the relationship between frequency and the magnitude of spectrum (34–36). This spectrum relationship is to characterize the oxygenation oscillations of the three populations (MD, A&D, and HC). Specifically, the Oxy/Deoxy data were collected using the fNIRS instrument at the sample time of 0.1 s, leading to a total of 1,600 data points over the 160-s measurement period. These time-course curves were preprocessed by a Hanning window to reduce the effect of spectral leakage. Then, fast Fourier transform (FFT) was applied to transform the time-course curve into the frequency domain, from which the magnitude spectrum of the same length was obtained over the 0.01–16.0-Hz range, at the sample rate of 0.01 Hz. The average power, defined as the average of magnitude square over the whole spectrum (0.01–16.0 Hz), was calculated for each individual. In addition, the rate between the standard deviation of the Oxy/Deoxy curve during non-task and the peak amplitude during VFT task was calculated, in order to explore the sensitivity of the VFT task to brain activation. Furthermore, the Bland–Altman analysis is adopted to assess the dispersion of the intra-group data, and the threshold is set as 1.96 times of standard deviation (SD).

RESULTS

Comparison of the Rate of Brain Activation Between Non-task and VFT Task

Figure 1 shows the rate of the Oxy/Deoxy standard deviation during the non-task to the maximal change (i.e., peak amplitude) during the VFT task, namely, SD-to-peak rate, for the three groups. It can be seen that 90% of the MD patients had an SD-to-peak rate larger than 20% (**Figure 1A**), while 40% of the HCs have a rate larger than 20% (**Figure 1B**). As for the A&D patients, 60% of the group have a rate larger than 20% (**Figure 1C**). Additionally, it is also found that the intra-subject variability of this rate was large in each group of subjects, and no significant differences were found between groups. Regression analyses indicate that the age is not relevant ($p > 0.05$) to the NIRS outcomes (i.e., Oxy and Deoxy).

Distribution in the Degree of Brain Activation in the Non-task State

Figure 2 exhibits the Bland–Altman analysis of the Oxy integral values by the non-task. As seen clearly, 10% (1/10) of the data points are outside the limit of 1.96 times the standard deviation, regardless of the group (i.e., MD, HC, or A&D). The Bland–Altman analysis of the Deoxy exhibits a similar conclusion. These results indicate that the healthy and mental-disordered populations have similar intra-subject variability.

The Difference Between Non-task and VFT Task in the Oxy Magnitude Spectrum

The average magnitude spectra of Oxy time-course curves during non-task and VFT task in the three groups are shown in **Figures 3**, **4**, respectively. Under non-task, it can be seen that the magnitude decreased with the increase in frequency (**Figure 3**). The groups in magnitude order from largest to the smallest were HC, A&D, and MD. The average magnitude during the VFT task were substantially higher than that during the non-task (around twice), while the order remained the same (i.e., HC, A&D, and MD).

The Oxy average power (represented by mean ± standard derivation) during non-task is 4.8± 9.3, 1.7±1.3, and 3.2±5.1 $(10^{-2} \cdot \text{mm}\cdot\text{Mm})^{-2}$ for HC, MD, and A&D, respectively, and no significant difference ($p > 0.05$) was found among the groups. This average power was greatly enhanced during VTF task, reaching 14.0 ± 9.8, 2.9 ± 3.4, and 6.7 ± 4.5, respectively. Furthermore, a significant difference ($p<0.05$) was found between any of the two groups (i.e., HC, MD, and A&D).

Characteristics of the Typical Magnitude Spectrum in the Task State

We also found that the variability of the Oxy magnitude spectrum curve at the non-task state is small, regardless of the group. Hence, the average magnitude spectrum curve would well-represent the individual responses. By contrast, there is much

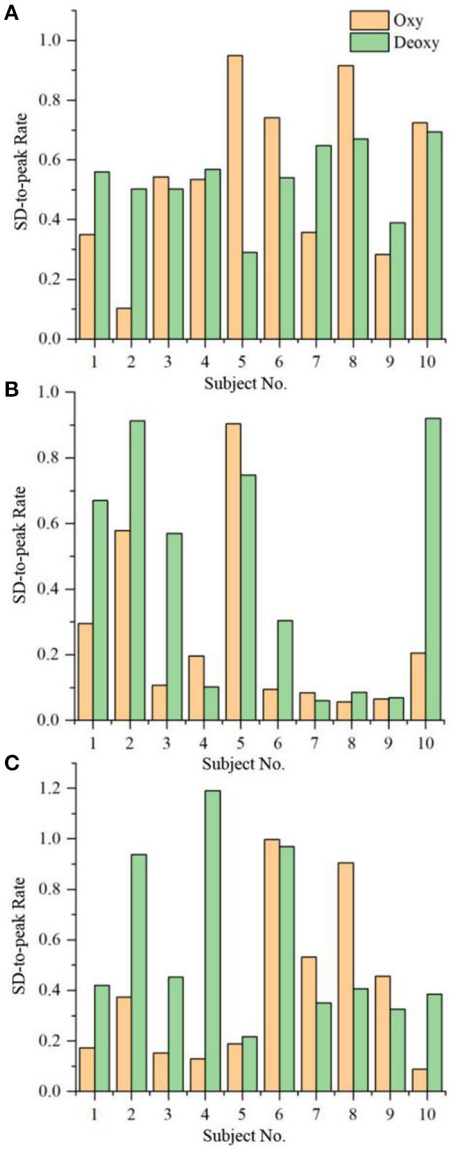

FIGURE 1 | The rate of the Oxy/Deoxy standard deviation during non-task to the maximal change (i.e., peak amplitude) during VFT task for the three groups, i.e. **(A)** MD, **(B)**, HC and **(C)** A&D.

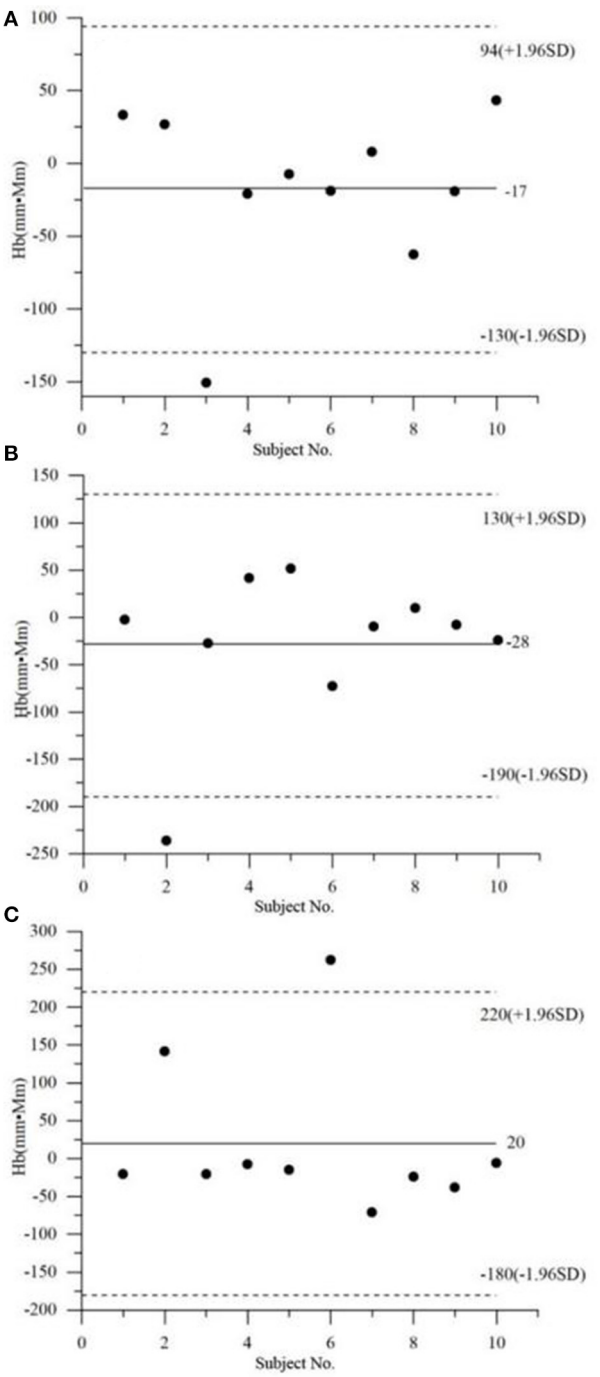

FIGURE 2 | Bland–Altman analysis of the Oxy integral values (i.e., area of the Oxy curve) by the non-task, in the three groups, i.e., **(A)** MD, **(B)** HC, and **(C)** A&D.

larger inter-subject variability in the Oxy magnitude spectrum when the VFT task was performed. **Figure 5** shows the typical Oxy magnitude spectrum curve from a representative individual in each group. The MD exhibits the magnitude spectrum curve similar to that of HC, with a small peak value around 0.05 Hz (**Figures 5A,B**). By contrast, four of the 10 A&D showed a strong intermediate peak around 0.05 Hz (**Figure 5C**). This is because not all of the A&D patients had such strong intermediate peak, whose frequency also varied in a range (i.e., not the same frequency). Therefore, the average spectrum curve of the A&D population did not clearly exhibit the strong intermediate peak. Nevertheless, none of the HC and MD groups were found to have such a special feature.

DISCUSSION

fNIRS is an easy-to-use and low-cost technology for assessing brain function that is associated with cerebral metabolism. This technology has also been used as the auxiliary tool for

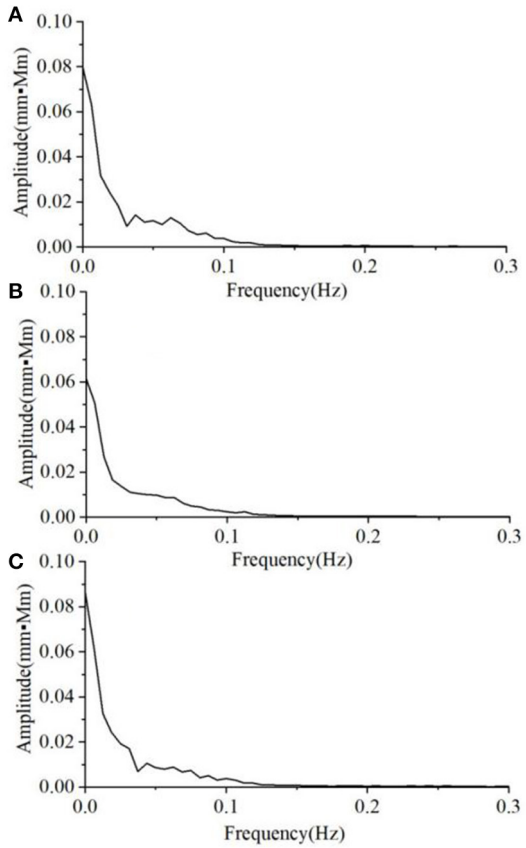

FIGURE 3 | The average magnitude spectrum of the Oxy time-course curves during non-task, in the three groups, i.e. **(A)** HC, **(B)** MD, and **(C)** A&D. Note that the magnitude is almost zero at the range of 0.3–16.0 Hz and not shown in the figure.

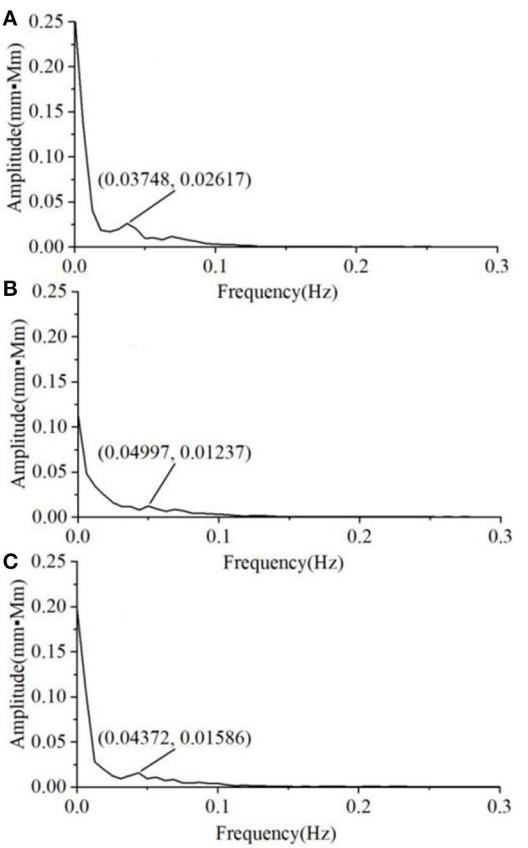

FIGURE 4 | The average magnitude spectrum of the Oxy time-course curves during the VFT task in the three groups, i.e. **(A)** HC, **(B)** MD, and **(C)** A&D. Note that the magnitude is almost zero at the range of 0.3–16.0 Hz and not shown in the figure.

diagnosis of psychoses (37). For example, the fNIRS was used to assess the autoregulation capacity of the brain cortex, which may be affected by psychoses. The protocols of non-task or task were adopted for this assessment (38, 39). The specificity and sensitivity of psychiatric diagnosis relies on several factors including the detection techniques, experiment protocols, and stimulus intensity. At present, the conclusions derived from VFT or rest (non-task) studies are controversial, and no oxygenation parameters were claimed to diagnose the psychiatric diseases. Several factors might account for this reason, such as the task intensity and duration for evoking the brain cortex, the intra-subject variability, and the oscillation characteristics related to the mental disorders. This study is designed to explore if the VFT task is strong enough to challenge the brain cortex, when compared with the rest state. We also investigated if the oscillation characteristics, which are generally evaluated by the rest state, could be affected by the VFT task.

A total of 30 subjects were recruited to participate in this study, with 10 for each group (HC, MD, and A&D). The sample size ($n = 10$) might not be large enough to observe the statistical difference. Nevertheless, the similar sample size ($n = 6$–12) is often reported in the NIRS studies exploring the brain cortex functions, along with statistical analysis results (40–44). The sample size is limited to the subject's availability and willingness to participate in the study. More subjects will be recruited and the advanced analysis algorithms will be explored, which is one objective of our future works.

A comparative study on brain oxygenation response by task and non-task was conducted on the 30 subjects. VFT was chosen as the task model because it is most widely used in psychiatric evaluation, and the changes in the brain oxygenation were found during the task period. Moreover, we assessed the task and non-task states in both amplitude change and spectrum. Previous studies have shown that MD patients have the reduced brain metabolism and task responses, indicating a cognitive impairment (45). Furthermore, the insufficient performance of MD patients was also observed when conducting the VFT task (46).

In order to evaluate the brain oxygenation activation by the VFT task, an index of SD-to-peak was calculated for each subject. We found that 90% of MD patients have a rate larger than 20%, indicating that MD is associated with the deficiency in brain

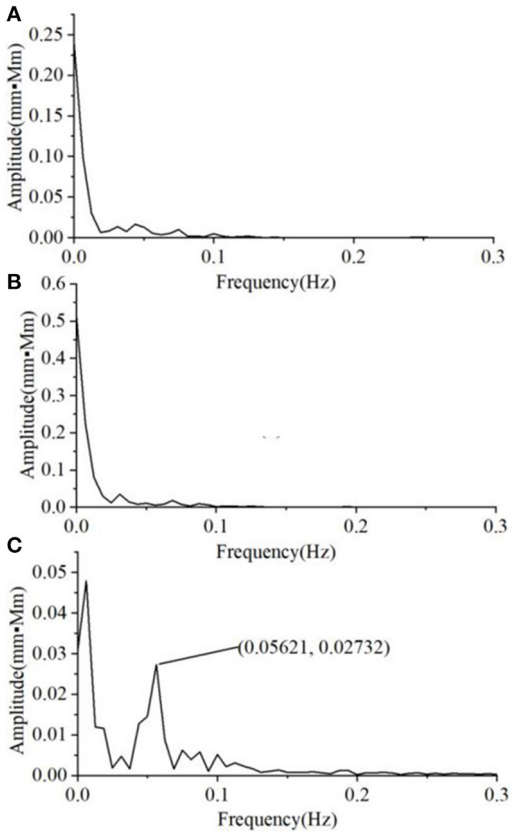

FIGURE 5 | The typical Oxy magnitude spectrum curve from a representative individual in each of three groups, i.e. **(A)** HCS, **(B)** MD, and **(C)** A&D. Note that the magnitude is almost zero at the range of 0.3–16.0 Hz and not shown in the figure.

oxygen activation by the VFT task, which would be a marker of depressive state. By contrast, this rate is larger than 20% in 40% HC and 60% A&D populations, respectively (**Figure 1**), indicating that majority of A&D responded positively to the VFT task. These observations exhibit that fNIRS has the potential to separate the depression through the brain oxygenation activation, if proper task is implemented.

With the approach of Bland–Altman to analyze the distribution of the Oxy integral values in MD, HC, and A&D, we found that 10% (1/10) of the data points are outside of the 1.96 times the standard deviation (**Figure 2**), regardless of the group. This observation demonstrates that MD, HC, and A&D are similar in terms of individual data distribution.

As for the spectral analysis, we found that the magnitude is decreased with the increase in frequency. For each individual, the magnitude spectrum was mainly focused at 0.05–0.1 Hz, indicating low-frequency oscillations in the spontaneous state. Under the non-task protocol, no significant difference was found among the three groups (**Figure 3**), indicating that static status would not alter the characteristic of low-frequency oscillation.

When performing the VFT task, we found that the magnitude of spectrum was substantially enhanced for all the individuals, with HC being the highest, A&D the second, and MD the lowest. In the past, it is difficult to separate MD and A&D by using fNIRS or other neuroimaging modalities. In this study, 40% A&D patients were found to show a strong intermediate peak (around 0.05 Hz) in the magnitude spectrum when performing the VFT task, while this strong intermediate peak was not found in HC and MD populations. Although the underlying mechanism for this difference is unclear, this observation is beneficial for future diagnosis of the A&D disease.

Our spectral analyses of oxygenation data verified this hypothesis, i.e., the magnitude during the VFT task is much higher than that during the non-task status. We also observed that the Oxy average power has no significant difference among the three groups during non-task. By contrast, a significant difference was found between any of the two groups. These outcomes indicate that the parameter of average power, when enhanced by the VFT task, also characterizes well the diseased populations.

The aim of the repeated number counting and rhythm finger movement is to enforce the subjects to concentrate on this tedious task and minimize the intra-subject variability resulting from random thinking. According to the literature (47), the finger movement would primarily evoke the activities in the parietal lobe, rather than the prefrontal lobe and temporal lobes that were measured with fNIRS in this study. Hence, the fNIRS signals originating from finger movement can be considered as a small portion of the baseline data.

Nevertheless, the baseline data (including those from number counting and finger movements) may also affect the data analyses. The potential solution for minimizing the baseline effect would be increasing the task intensity (e.g., VFT duration) as well as utilizing the advanced algorithms (e.g., independent component analysis—ICA) to separate the baseline signals, which will be one objective of our future works.

As the summary, the outcomes derived from this study demonstrate that the standard VFT (60 s) might not be able to evoke sufficient oxygenation changes in the brain cortex, as evidenced by the >20% SD-to-peak rate in the majority of subjects, especially in MD patients. We also found that the VFT might enhance the oscillation characteristics of Oxy curves. The intra-subject variability is similar among the three groups. All of these discoveries have not been reported in the previous studies. We believe that the fusion of multiple parameters, rather than the single parameter, would better localize the target diseases (MD or A&D), along with the advanced algorithm (e.g., artificial intelligent algorithm). The conclusion derived from this study might be helpful in future exploring the advanced diagnostic approaches.

CONCLUSIONS

To conclude, fNIRS is an easy-to-use technology for longitudinally monitoring brain function (48), and its efficiency for psychosis diagnosis relies on the physiological protocol. In this study, we used fNIRS to compare between task and non-task states in brain oxygenation activation and to explore the

characteristic markers of MD and A&D. We found that the MD is associated with the deficient activation in brain oxygenation, evidenced by the relatively large SD-to-peak rate. In addition, A&D is characterized by the intermediate peak in spontaneous low-frequency oscillations. Nevertheless, the precise diagnosis of MD and A&D is negatively affected by the intra-subject variability. The optimal tasks, with small intra-subject variability and the enhanced oxygenation activation, need to be developed to further explore the brain functions associated with psychoses (13, 49).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Hospital of Shanxi Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DW and XL conceived of and led on the study design, managed the literature searches, and undertook the statistical analysis, under the supervision of YX, and wrote the first draft. HZ and YC made the subsequent revisions of the manuscript. QL and QY contributed to collecting data. All authors contributed to and have approved the final manuscript.

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Neural Activation *via* Acupuncture in Patients With Major Depressive Disorder: A Functional Near-Infrared Spectroscopy Study

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Background and Objective: Acupuncture is used as an alternative treatment for patients with major depressive disorder (MDD). The associated therapeutic effect of acupuncture is often attributed to its modulatory effect on the activity of the pre-frontal cortex (PFC), although the mechanism is not well-studied. We employed a repeated measures design to investigate the brain modulatory effect of acupuncture on the PFC in a group of patients with MDD and investigated whether the modulatory effect is influenced by the severity of the disease.

Methods: A total of 47 patients diagnosed with MDD were enrolled in this functional near-infrared spectroscopy experiment. The severity of depressive symptoms was measured at baseline using the Hamilton Depression Rating Scale-24 (HAMD). The cortical activation in the bilateral PFC areas during a verbal fluency task (VFT) was measured before and after a single session of acupuncture in the Baihui acupoint. We further explored the potential correlation between the severity of MDD and task-related activation before and after acupuncture.

Results: A single session of acupuncture significantly tended to enhance the activation level of the left frontopolar cortex in patients with severe depression during VFT, but a null effect was found in those with mild to moderate depression. Among patients with severe depression, a strong correlation was observed between HAMD scores and the change in VFT-related activation after acupuncture in the left dorsolateral PFC (DLPFC).

Conclusion: A single session of acupuncture did not significantly modulate the activation of the left PFC in patients with mild to moderate depression; however, it demonstrated a tendency to enhance the activation of the frontopolar area in patients with severe depression. Among patients with severe depression, there is a correlation between the activation by acupuncture of left DLPFC during executive functioning and the severity of depressive symptoms, suggesting that the brain activity induced by acupuncture is likely to be influenced by the baseline disease severity in patients with MDD.

Keywords: major depressive disorder, acupuncture, pre-frontal cortex, neuroplasticity, functional near-infrared spectroscopy (fNIRS)

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INTRODUCTION

Patients with major depressive disorder (MDD) present with impaired pre-frontal cortex (PFC) functioning, that is, decreased cerebral blood flow (1) and glucose hypometabolism (2) in the PFC during either resting or task conditions. The level of reduced neural activation is correlated with the severity of the disease (3). The PFC is implicated in cognitive processing and emotion regulation (4), which explains the cognitive and emotional deficits associated with MDD. Severe depression is associated with serious consequences, such as suicidal ideation and behaviors (5). Therefore, there is a need to develop novel treatment approaches for MDD and conduct mechanistic studies to scientifically underpin the efficacy of those treatments.

Acupuncture, a therapeutic modality of traditional Chinese medicine (TCM), has been applied as an alternative treatment for the regulation of cognition and emotion in patients with MDD. Acupuncture is characterized by the insertion of thin needles into acupoints on the human body. The needle is twirled several times until the patients feel a sensation of "de-qi," which literally means "the arrival of vital energy" (6). The dysregulation caused by MDD can be explained by the concept of "Yu," which refers to "mental constraint" (7). According to a recent meta-analysis, acupuncture is a useful treatment modality to reduce the severity of depressive symptoms, with a moderate effect size (8). The acupoint Baihui (GV20), which belongs to the Governor Vessel, is positioned at the highest point on the head where all the Yang meridians converge. Acupuncture in Baihui is widely used by TCM practitioners to treat neuropsychiatric disorders, because it is believed to be the key point that can regulate the "qi" of the Governor Vessel and release mental constraints. The activation of the PFC induced by Baihui electro-acupuncture has also been previously reported (9). Antidepressant treatments lead to a reduction in depressive symptoms and are often associated with increasing PFC activity during cognitive tasks (2, 10). Enhanced levels of PFC activity are also linked with the therapeutic effects of excitability-enhancing brain stimulation in patients with depression (11). Therefore, there is a possibility that the modulatory effect of Baihui acupuncture on the activation of the PFC can, at least partly, contribute to its therapeutic effects on MDD. However, the modulatory effect of Baihui acupuncture on the activation of the PFC has not yet been well-established. Functional near-infrared spectroscopy (fNIRS) has become a popular brain imaging technique. With fair temporal and spatial resolutions, fNIRS is a suitable neuroimaging modality for investigating regional neural dynamics associated with the whole process of acupuncture manipulation (i.e., needle insertion, twirls, and removal) (12). In this study, we first conducted an fNIRS experiment to reveal the modulatory effects of Baihui acupuncture on the PFC among a group of individuals diagnosed with MDD. Besides, according to previous literature, the activity of the PFC is likely to be correlated with the severity of MDD symptoms (13); therefore, we then explored the potential relationship between the severity of MDD and activation response to acupuncture. We hypothesized that (1) a single session of Baihui acupuncture could increase the activation of the PFC during executive functioning in patients with depression, and (2) the activation response to acupuncture could be influenced by the baseline severity of depressive symptoms.

METHODS

Participants

A total of 47 patients (mean age = 39.70 ± 12.24 years, 37 females) who met the criteria for MDD of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, were consecutively enrolled from the West China Hospital outpatient clinic. The patients were invited to participate in this experiment if they met all of the following inclusion criteria: (1) aged between 18 and 60 years; (2) right-handed, as assessed by the Edinburgh Handedness Inventory (EDI) [patients whose EDI laterality quotient, that is (right–left)/(right + left), was >0.4 were considered as right-hand dominant] (14); (3) severity of depressive symptoms score ≥8 according to the Hamilton Depression Rating Scale (HAMD); and (4) having >6 years of formal education. Patients were excluded if they met any of the following exclusion criteria: (1) any known mental disorder excluding MDD, such as schizophrenia, substance use disorder, or obsessive-compulsive disorder; (2) serious cardiovascular or neurological diseases; (3) intellectual disabilities or language or hearing impairments; or (4) pregnancy. Patients were requested to provide written informed consent before their enrollment. The demographic and clinical details of the patients who participated in the study are presented in **Table 1**. The study was approved by the Human Research Ethics Committee of West China Hospital (Ethics approval number: WCH201801201134).

Procedures

The entire experiment comprised three stages: a 160-s verbal fluency task (VFT) before the acupuncture session (pre-acu), a 220-s acupuncture manipulation, and a 160-s VFT after the acupuncture session (post-acu).

Verbal Fluency Task

A Chinese-language phonological VFT was utilized in this study. The task required patients to generate words beginning with a given Chinese character. VFTs are the most widely used and reliable paradigm to elicit activity in the PFC (15–17). Neural activity during VFTs has also been proposed as a surrogate biomarker to differentiate patients with MDD from healthy controls (18).

The 160-s block-designed VFT, which was used in this study, consisted of a 30-s pre-task period, three consecutive blocks of 20-s word-generating tasks, and a 70-s post-task period (**Figure 1**). In the pre- and post-task periods, patients were asked to repeatedly count from one to five aloud.

During each 20-s task period, one of three Chinese characters (i.e., "白," "河," and "中," which mean "white," "river," and "middle," respectively) was given as an auditory cue from the control computer place behind a patient. Patients were asked to generate as many words as possible that start with the given character. When the given character was "白," patients could generate words such as "白天" (daytime), "白领" (white-collar),

TABLE 1 | Demographic and clinical characteristics of included participants.

Participant characteristic	Participants ($n = 47$)	Mild to moderate depression ($n = 33$)	Severe depression ($n = 14$)	Between-group difference[#] p
Demographic				
Age (years, mean ± SD)	39.70 ± 12.24	42.21 ± 11.63	33.79 ± 11.99	0.029*
Male/female	10/37	9/24	1/13	0.242
Education (years, mean ± SD)	14.32 ± 3.07	14.12 ± 2.77	14.79 ± 3.75	0.560
Clinical				
Number of depressive episodes (mean ± SD)	1.94 ± 1.12	1.85 ± 0.97	2.20 ± 1.48	0.715
Age at disease onset (years, mean ± SD)	34.66 ± 13.60	37.00 ± 13.17	29.14 ± 13.40	0.071
Duration of disease (years, mean ± SD)	5.04 ± 6.58	5.21 ± 7.36	4.64 ± 4.43	0.620
Number of antidepressant medications in current episode, % (*n*)				
None	63.83% (30)	78.57% (19)	57.58% (11)	0.299
One	25.53% (12)	14.29% (10)	30.30% (2)	
Two	8.51% (5)	7.14% (4)	12.12% (1)	
HAMD-24 scores (mean ± SD)	29.87 ± 10.48	24.30 ± 6.47	43.00 ± 4.64	<0.001***

SD, standard deviation; HAMD-24, 24-item Hamilton Depression Scale.
Antidepressant medications included selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.
[#]Comparisons between patients with mild to moderate and severe depression.
**$p < 0.05$; ***$p < 0.001$.*

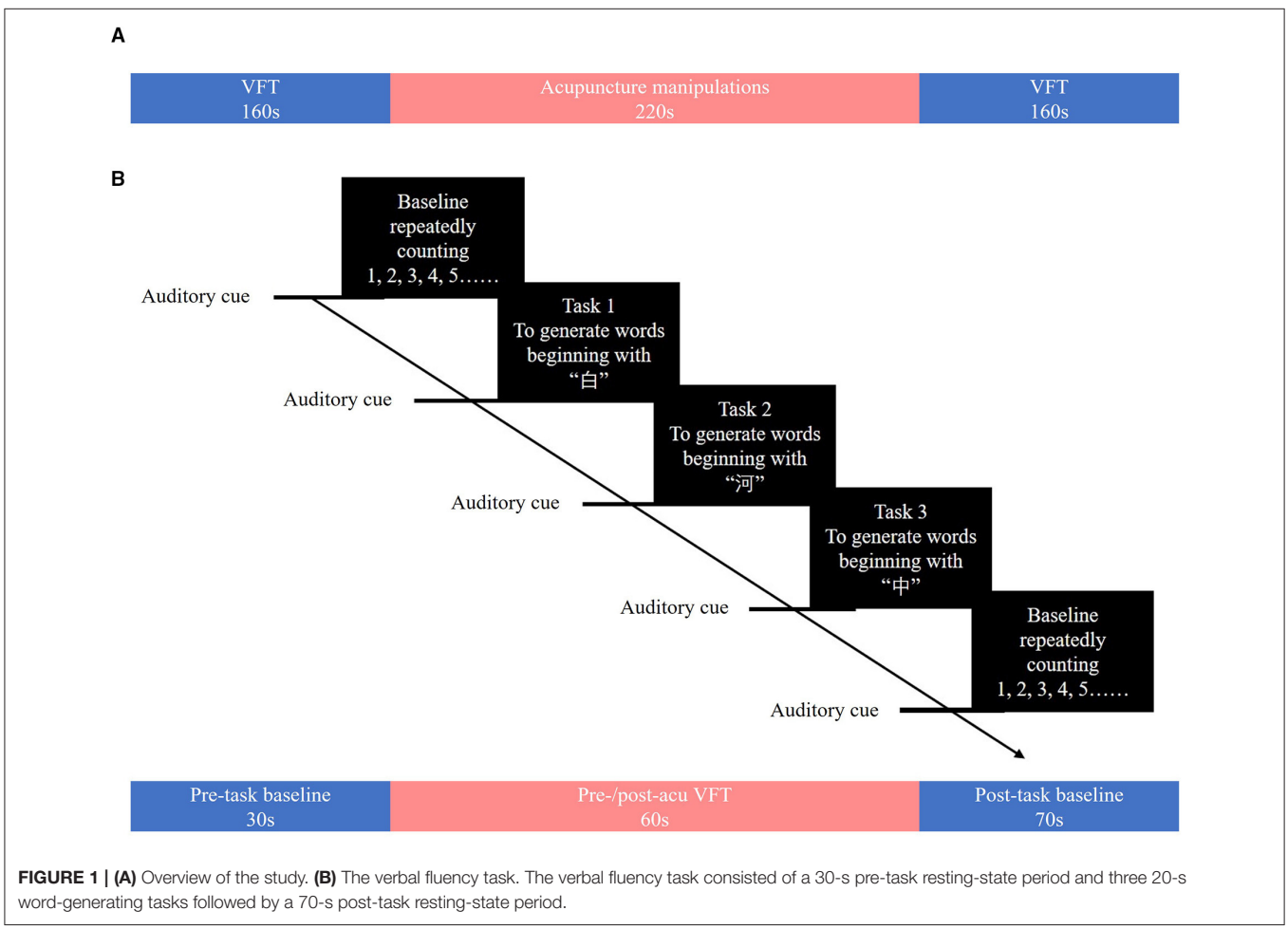

FIGURE 1 | (A) Overview of the study. **(B)** The verbal fluency task. The verbal fluency task consisted of a 30-s pre-task resting-state period and three 20-s word-generating tasks followed by a 70-s post-task resting-state period.

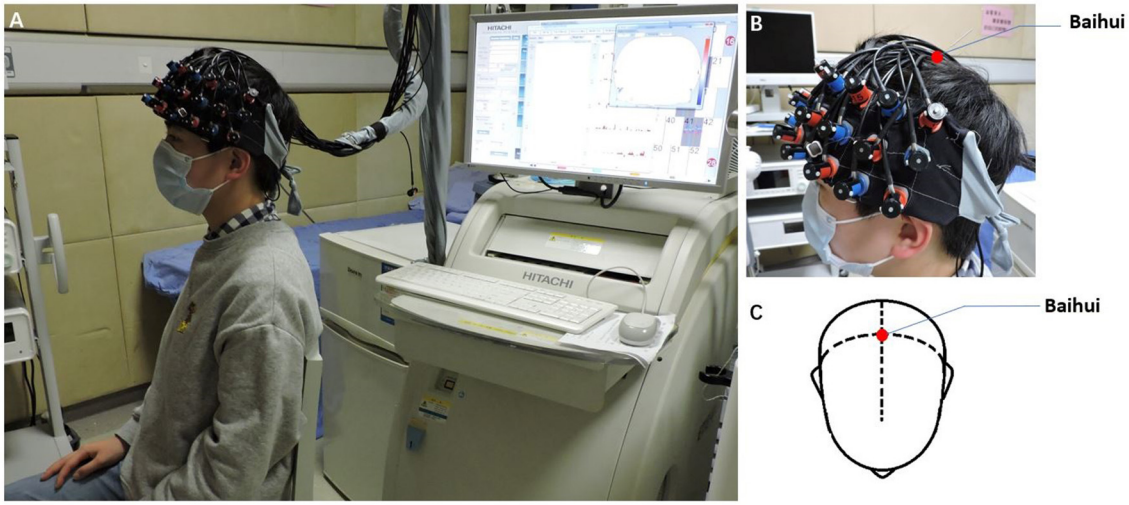

FIGURE 2 | Performing acupuncture. **(A)** Patients were asked to sit and relax on the seat in front of a near-infrared spectroscopy instrument. **(B,C)** The Baihui acupuncture point is shown.

or "白菜" (Chinese cabbage). The Chinese characters used in the pre-acu and post-acu VFT were different to avoid practice effects. During the task, patients were asked to sit down and relax in front of an fNIRS instrument (**Figure 2A**) and keep their heads and bodies as motionless as possible.

Acupuncture Manipulations

The acupuncture procedure used in the present study was the same as that described in the study by Fernandez Rojas et al. and consisted of three phases of acupuncture manipulations: 5-s needle insertion, three 10-s needle twirls, and 5-s needle removal, interleaved with 30-s resting-state periods (12). The acupoint Baihui, which was used in the study (**Figures 2B,C**), is located at the intersection point of the midline and the line connecting the ear lobes (19). A qualified TCM acupuncturist performed all these acupuncture manipulations. Patients were asked to sit and relax with their eyes closed and hands resting on their laps during the manipulations.

fNIRS Data Acquisition

We used a 52-channel continuous-wave NIRS instrument (ETG-4100 Optical Topography System; Hitachi Medical Co., Japan) with a temporal resolution of 10 Hz to collect imaging data during the two VFTs. The system is equipped with 17 emitters that emit laser lights at two wavelengths (695 and 830 nm) and 16 detectors that detect the corresponding lights after absorption and scattering. A "3 × 11" measurement patch set with the emitter and detector probes positioned alternatingly at 3-cm intervals (**Figure 3A**) was attached to a nylon cap with several elastic straps used to guarantee good contact to the heads of patients.

In this experiment, we defined the PFC area consisting of 11 channels (Channels 25/26 27/28/36/37/38/46/47/48/49, covering Brodmann 10/11/46/47, which is indicated by a red box in **Figure 3**) as a region of interest (ROI), in line with other previous fNIRS studies (18, 20). For consistency of measurement patch placement across patients, the international 10–20 system (21) was used to standardize the placement of the probes. Specifically, the detector number 13 was located at Fz, and simultaneously, channels 49 and 46 were placed in FP1 and FP2, respectively (**Figure 3A**).

Next, a three-dimensional probe position unit for the optical topography system, EZT-DM401 (Hitachi Medical Corporation, Japan), was used to sequentially measure the anatomical landmarks on the heads of patients (nasion, the pre-auricular points anterior to the left and right ears, inion, and Cz) and the probe positions of the optical topography system in the real-world (RW) stereotaxic coordinate system. Subsequently, the RW spatial location data were converted to obtain the cortical positions of 52 channels on the standard Montreal Neurological Institute (MNI) template using the toolbox of NFRI functions (22) available in NIRS-SPM v4.1. The 52-channel patch covered the PFC (**Figure 2B**) including the ROI defined in this study.

Statistical Analysis of fNIRS Data

The two toolboxes HOMER2 (23) and NIRS-SPM v4.1 (24) were used in the quantitative analysis of NIRS signals and to calculate the activation maps of oxy-hemoglobin (oxy-Hb) levels. We decided to use oxy-Hb rather than deoxy-hemoglobin (deoxy-Hb) levels because the former is thought to be the most sensitive indicator of regional cerebral blood flow (25) and has a close correlation with the blood oxygen level-dependent response (26, 27).

At first, noisy channels were identified and pruned from the measurement list using the HOMER2 function *hmrPruneChannels* (dRange = 10^3-10^7 and *SNRthresh* = 5) (28). Next, optical density (OD) was transferred from optical intensity using the HOMER2 function *hmrintensity2OD*. OD is defined as

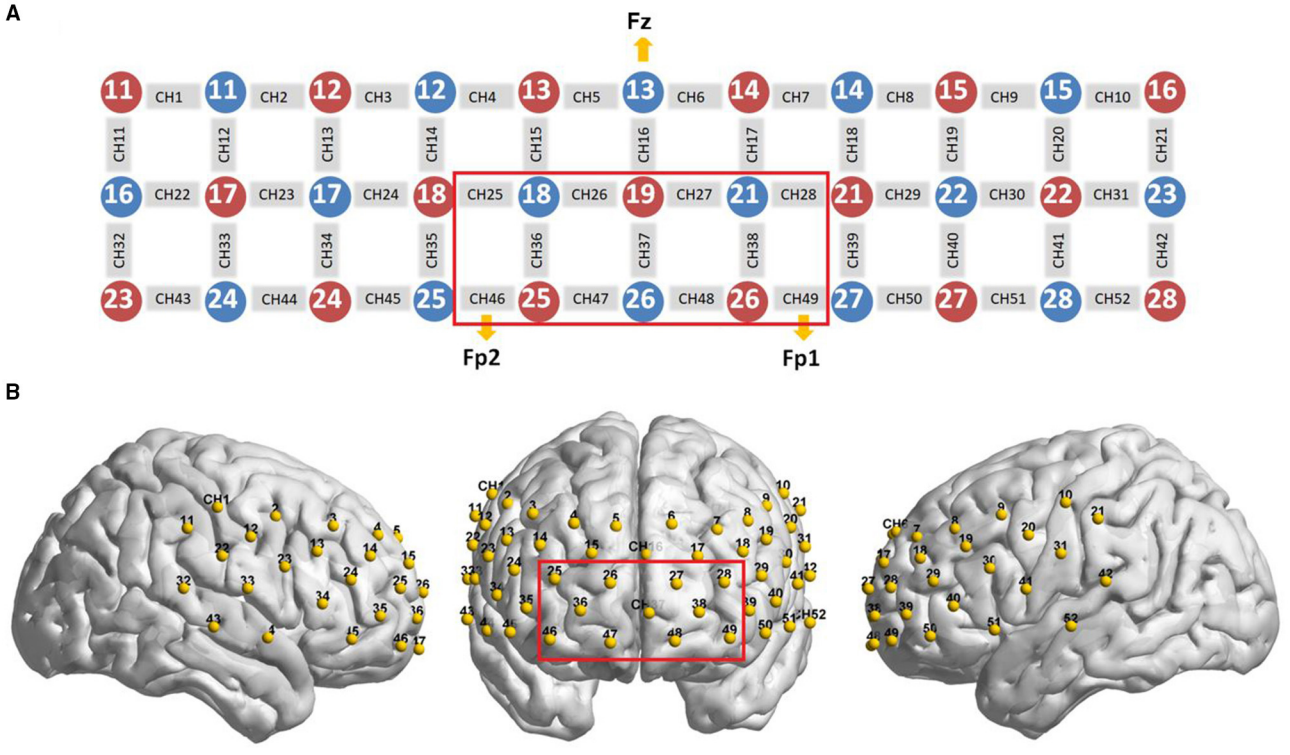

FIGURE 3 | Optode probe set. **(A)** A "3 × 11" measurement patch set with 17 emitter and 16 detector probes positioned alternatively is shown; when the detector number 13 was located at Fz, channels 49 and 46 were placed in FP1 and FP2, respectively. **(B)** The optode probe was placed on the pre-frontal and temporal cortex. The red frame denotes regions of interest.

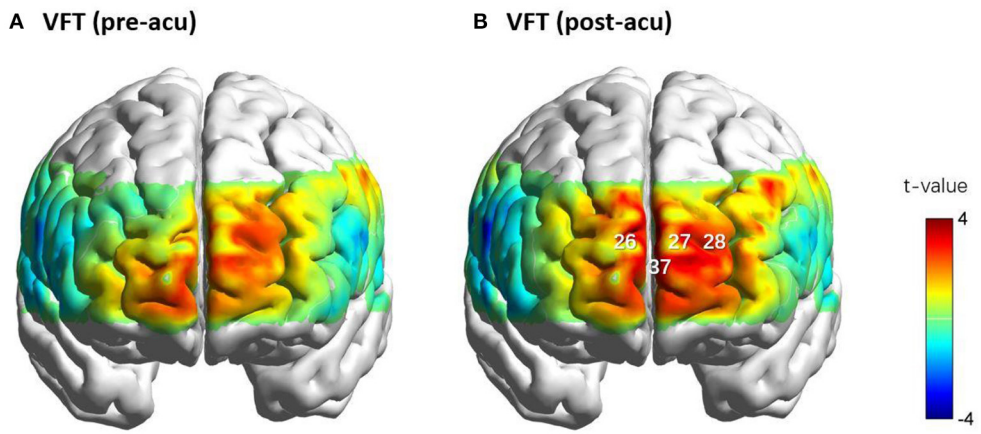

FIGURE 4 | Cortical activation maps of oxy-Hb level during the VFTs before **(A)** and after acupuncture **(B)**. Oxy-Hb level changes in CHs 26, 27, 28, and 37 during the VFTs before and after acupuncture. CHs 26, 28, and 37 were located in the frontopolar area, and CH 28 was located in the left dorsolateral pre-frontal cortex. CH, channel; oxy-Hb, oxy-hemoglobin; VFT, verbal fluency task.

the logarithmic intensity ratio of the light falling on the material to that of the light transmitted through the material (29).

The channel-wise motion artifacts were then detected by the HOMER2 function *hmrMotionArtifactByChannel*, which was applied to detect the time point where the optical signal was greater than AMPthresh (=5.00, amplitude threshold) or STDEVthresh (=10.00, standard deviation threshold) over the time interval tMotion (=3.0, a predefined time-window) and to mark over ± tMask 0.50 s around that time point as a motion artifact. Channels with too many motion artifacts were rejected.

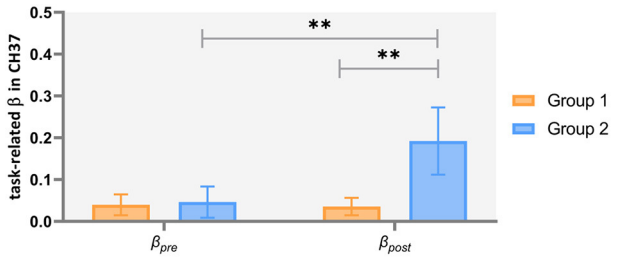

FIGURE 5 | Task-related brain activation in channel 37 in patients with mild to moderate depression (Group 1) and severe depression (Group 2). $^{**}p < 0.01$.

Subsequently, OD was converted into the concentration changes of oxy-Hb with the modified Beer–Lambert law (30) using NIRS-SPM v4.1. Next, we executed an effective method, wavelet minimum description length (Wavelet-MDL), which is a detrending algorithm to overcome the problem of the presence of an unknown global trend due to breathing, cardiac, vasomotion, or other experimental errors (31). A hemodynamic response function (HRF) filter was then adopted for temporal smoothing to swamp the intrinsic temporal correlations and attenuate high-frequency components (32).

A general linear model (GLM) approach, which has been described extensively in the fNIRS literature (33–35), was then applied to analyze the fNIRS time series in our study. The experimental design matrix for the GLM analysis included two predictors representing boxcar functions corresponding to onsets of word-generating blocks and post-task baseline convolved with an HRF. Word-generating β-values, one of the GLM's weights, representing the oxy-Hb level changes in word-generating stages, and post-task β-values, representing the oxy-Hb level changes in the post-task period, were computed at each channel. Then we defined task-related β-values as word-generating β-values minus post-task β-values.

Afterward, a one-sample t-test with the false discovery rate (FDR) method (36) (at a corrected p level <0.05) was conducted on task-related β-values at each channel. Images were created using the *nirs2img* function in the xjview toolbox (https://www.alivelearn.net/xjview/xjView%208%20Manual.pdf), in which the t-values of each channel with their corresponding MNI coordinates were converted to an image file. Next, the transformed image files with linear interpolated t-values were rendered over a standardized brain model using a BrainNet Viewer toolbox (http://www.nitrc.org/projects/bnv/) (37). A paired two-sample t-test was conducted to compare task-related β-values between the post-acu and pre-acu VFTs (β_{post} vs. β_{pre}) at the channels that were significant during the one-sample t-test.

Based on the knowledge regarding the differential neuroplastic responses in patients with mild to moderate depression compared to those with severe depression, we repeated the analyses in two separate groups: Group 1 (mild to moderate MDD, HAMD scores of $\leq$35) and Group 2 (severe MDD, HAMD scores of $>$35) (38). A two-way repeated measures analysis of variance (ANOVA), with time (pre- and post-acu) as the within-subject factor and group (mild to moderate and severe depression) as the between-subject factor, of task-related β-values was performed for all significant channels with $p < 0.05$. A significant main effect or interaction effect was followed with simple effect analyses. With the FDR correction, Pearson's correlation coefficients were calculated between the HAMD scores and VFT-related $\Delta\beta$ ($\beta_{post-}\beta_{pre}$) at the significantly activated channels.

In case any significant between-group (i.e., severity group) difference in baseline characteristics was found, a two-way repeated measures analysis of covariance (ANCOVA) would also be performed with the covariate on task-related β-values for all significant channels. Significant group main effect or interaction effect of group by time was followed up with simple effect analysis including the covariate.

RESULTS

Cortical Activation During the Pre-acu and Post-acu VFTs

The changes in the oxy-Hb level during the post-acu VFT significantly increased in the frontopolar area (channels 26, 27, and 37) and dorsolateral PFC (DLPFC, channel 28) compared to that in the post-task baseline (FDR-corrected $p = 0.017$, 0.008, 0.036, and 0.021, respectively). Nevertheless, a significant activation of oxy-Hb level changes was not found at any channel during the pre-acu VFT. However, paired t-tests showed that task-related β-values during the post-acu VFT (β_{post}) were higher than those during the pre-acu VFT (β_{pre}) at these channels but did not reach statistical significance ($p > 0.05$). The activation maps for oxy-Hb level changes during the pre-acu and post-acu VFTs are shown in **Figure 4**.

Two-way repeated ANCOVAs were performed separately on the task-related β-values in channels 26, 27, 28, and 37. In channel 37, we found non-significant covariate-by-group interaction [$F_{(1, 43)} = 0.976, p = 0.329, \eta^2_{partial} = 0.022$], indicating that the regression slopes for the covariate did not differ between both groups, as well as a significant main effect of group [$F_{(1, 44)} = 5.302$, $p = 0.026$, $\eta^2_{partial} = 0.108$] and a significant time by group interaction effect [$F_{(1, 44)} = 5.759$, $p = 0.021$, $\eta^2_{partial} = 0.116$]. Simple effect analysis showed that, in Group 2 (patients with severe symptoms), the post-acu task-related β-values were higher than the pre-acu values [$F_{(1, 44)} = 7.945$, $p = 0.007$], and during the post-acu VFT, the task-related β-values in Group 2 were higher than those in Group 1 (patients with mild to moderate symptoms) [$F_{(1, 44)} = 8.145$, $p = 0.007$] (**Figure 5**). There was no significant main effect or interaction effect in other channels ($p > 0.05$).

A two-way repeated measures ANOVA with time as the within-subject factor and group as the between-subject factor on task-related β-values was also conducted considering that the age differences between the groups might not be random (see SI text and **Supplementary Figure S1** for details in Supplementary Materials) and yielded the same results as the ANCOVA.

In view of channels 26, 27, and 37 forming a cluster, and all were located in the frontopolar area, we used the

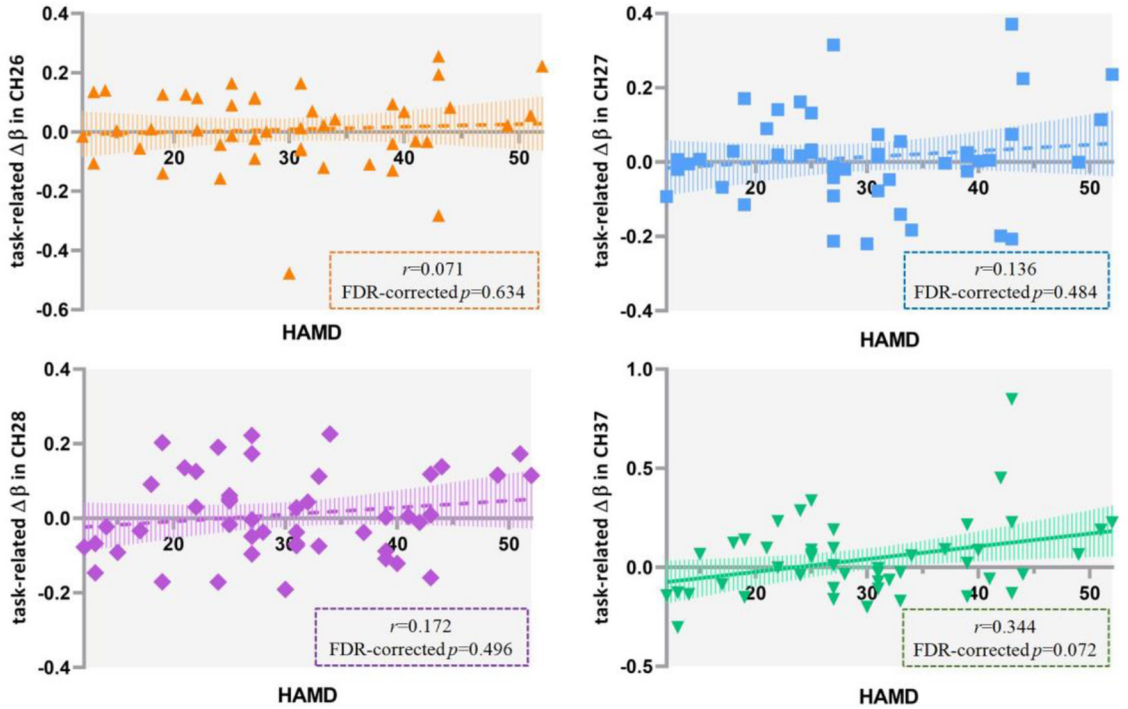

FIGURE 6 | Correlation between HAMD scores and the VFT-related Δβ ($\beta_{post-}\beta_{pre}$) in 47 patients with major depressive disorder. HAMD, Hamilton Depression Rating Scale-24; VFT, verbal fluency task.

averaged data from the three channels in the analysis of ROI 1 and conducted a two-way repeated measures ANOVA as well as ANCOVA on this area. Similar results were found (see SII text and **Supplementary Figure S2** for details in Supplementary Materials).

Correlations Between HAMD Scores and Cortical Activation

The results of Pearson's correlation analysis showed that HAMD scores were positively correlated with the VFT-related $\Delta\beta$ ($\beta_{\text{post}-}\beta_{\text{pre}}$) in channel 37 at a marginally significant level ($r = 0.344$, FDR-corrected $p = 0.072$) in all the included patients (**Figure 6**), as well as in ROI 1 ($r = 0.255$, $p = 0.087$), but not in single-channel 26, 27, or 28 (FDR-corrected $p > 0.05$). Among the patients with severe depression as seen in **Figure 7**, there was a positive correlation between HAMD mean-centered scores and $\Delta\beta$ in channel 28 ($r = 0.714$, FDR-corrected $p = 0.016$). However, the correlation was not found in patients with mild to moderate depression (FDR-corrected $p > 0.05$).

DISCUSSION

We investigated the PFC activation in response to a single session acupuncture therapy in the Baihui acupoint among a group of patients with MDD. A single session of acupuncture did not significantly increase the activation of the left PFC areas during executive functioning in patients with MDD with mild to moderate symptoms, but it tended to increase the activation of frontopolar areas in patients with severe symptoms. Additionally, a significant correlation between the severity of depressive symptoms and task-related left DLPFC activation by acupuncture was found in patients with MDD with severe symptoms.

The results of this experiment reveal that the activation of the PFC by acupuncture might be modulated by the severity of MDD. Antidepressant medication is the gold standard for the treatment of depression, and its mechanism of action has been extensively studied. According to previous literature, the treatment response to antidepressant medication could be predicted by the initial depression severity: that is, the benefits from antidepressant medications increase with the severity of depression symptoms (4). The antidepressant effect of medications is closely linked with neural activation, specifically in the PFC (39). Many researchers hypothesize that the therapeutic effect of acupuncture on depression may be, at least in part, attributed to the modulation of the PFC. Although the pathogenesis of MDD has not been fully elucidated, there is evidence indicating structural and functional changes in the PFC of patients with MDD (1). A previous fNIRS experiment showed that enhanced activation in the frontopolar areas was associated with the improvement of depressive symptoms in a group of adolescents with depression (40), indicating that the activation of the frontopolar areas is correlated with antidepressant treatment response. The left DLPFC is the most widely studied area in patients with MDD. The imbalance between the left and right DLPFCs (hypoactive left and hyperactive right in patients with MDD) has been linked to negative emotional bias,

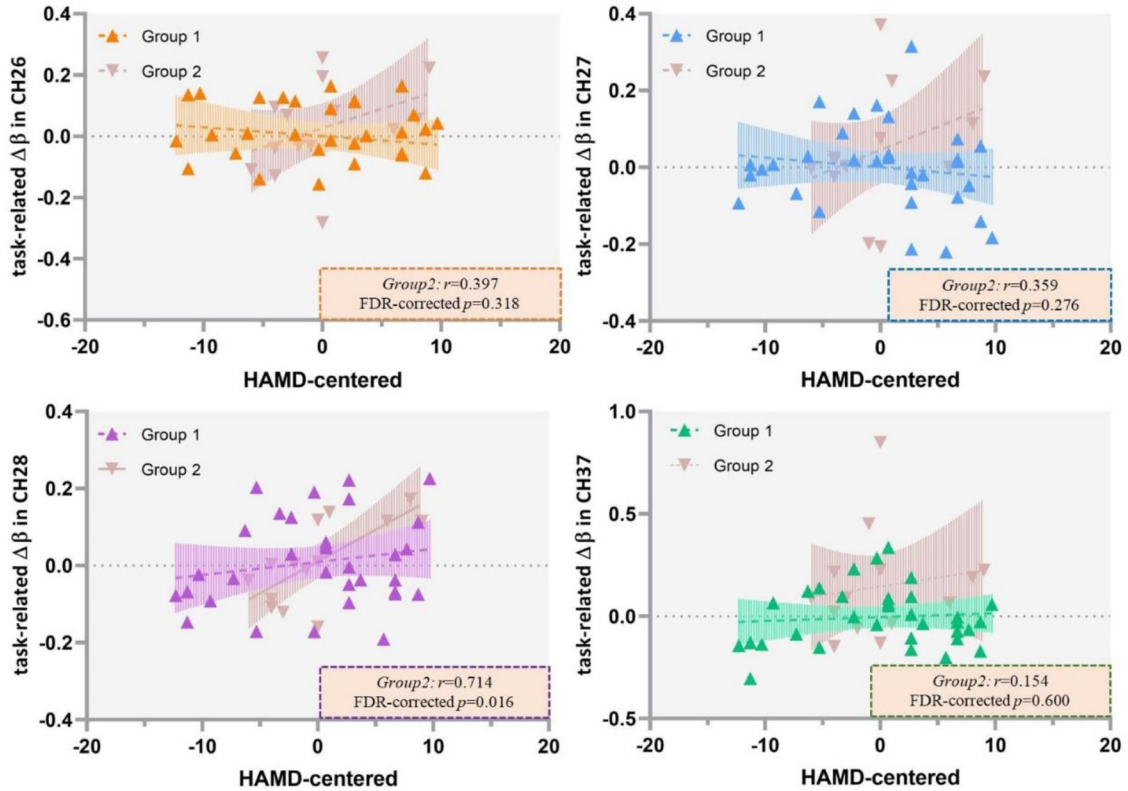

FIGURE 7 | Correlation between HAMD mean centered scores and the VFT-related Δβ ($\beta_{post-}\beta_{pre}$) in patients with mild to moderate depression (Group 1) and severe depression (Group 2). HAMD, Hamilton Depression Rating Scale-24; VFT, verbal fluency task.

which is proposed to be a possible behavioral basis for the development of depressive symptoms (41). The studies with antidepressant medications have thus indicated a correlation between the activation of the left DLPFC and treatment-elicited reduction in depressive symptoms. The activations of the DLPFC and frontopolar areas are of importance in the treatment response to acupuncture. Additionally, further studies should investigate whether antidepressant medications and acupuncture share a common therapeutic mechanism that modulates the PFC.

Furthermore, we found a weak correlation between the neuroplastic response to acupuncture in the left frontopolar area and depressive symptoms scores, which suggests that the severity of the disease may be associated with the modulatory effect of acupuncture on the PFC. This finding is similar to that of a meta-analysis in which the response to antidepressant medications was positively correlated with the baseline severity of depression (4). No such relationship was found in patients with mild and moderate depression. However, a strong positive relationship between the neuroplastic response to acupuncture in the left DLPFC and depressive symptoms scores was observed in this study. Differential effects of treatments for depression have been reported in several previous studies with varying results. A study reported that patients with a high baseline depression severity were unlikely to respond to venlafaxine (42). However, another report showed that patients with severe depression had a similar response slope to that of patients with mild to moderate depression after receiving nefazodone and cognitive behavioral therapy (43). These findings indicate a complex interaction between treatment response and severity of depression, and it is likely that the PFC plays a role in mediating this relationship. To the best of our knowledge, no study has explored the interaction between treatment response to acupuncture, the activation of the PFC, and baseline severity in depression. Although we did not have a clinical outcome, our NIRS data suggested that the patients' selection in acupuncture trials needs to be specific as the baseline severity is likely to influence the treatment response, in view of the potential association between the activation of the PFC area and the treatment response to acupuncture.

Although our sample was limited to young and middle-aged adults, age differences were observed between the disease severity groups. Therefore, we conducted an ANCOVA to account for the potentially confounding effect of age. However, we need to acknowledge that the method is unlikely to fully rule out the effect of the covariable (44). Previous studies have reported an age-related decline in PFC function, although the comparison was mostly made between younger adults and older (>65 years) (45, 46). In addition, the age-related effects on neural activation in response to acupuncture are largely unknown. Future studies need to employ age-matched patient groups with different severities of depressive symptoms to verify the present findings.

LIMITATIONS

The current study had some limitations. First, a sham acupuncture control was not employed in this preliminary investigation because a large sample is required for such a complex study design. Based on the findings from this experiment, further studies should be conducted with a larger sample and sham acupoint controls. Second, we only selected a single acupoint for the treatment. This is in contrast to clinical acupuncture therapy where multiple acupoints are selected. Third, we did not enroll healthy people as controls to investigate whether a unique activation pattern in patients with depression might exist. Finally, our analysis on severity of depression might have been affected by unequal numbers of patients with mild to moderate and severe depression; therefore, these results should be considered preliminary.

CONCLUSION

A single session of acupuncture could not significantly modulate the activities of the PFC in patients with mild to moderate depressive symptoms, but it tended to enhance the activation of the frontopolar area in patients with severe symptoms. Among patients with severe depression, there was a correlation between the activation by acupuncture of left dorsolateral PFC during executive functioning and the severity of depressive symptoms, suggesting that the brain activity induced by acupuncture is likely to be influenced by the baseline disease severity in patients with MDD. The results also highlighted the potential importance of patient selection, in terms of baseline severity of depressive symptoms, when conducting clinical trials using acupuncture in depression treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Human Research Ethics Committee of West China Hospital (Ethical approval number: WCH201801201134). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PW and ZZ conceived and designed the experiments. JH performed the experiments. TZ analyzed the neuroimaging and behavioral data. TZ and JZ drafted the manuscript. PW, ZZ, TZ, and JZ reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.669533/full#supplementary-material

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Left Frontotemporal Region Plays a Key Role in Letter Fluency Task-Evoked Activation and Functional Connectivity in Normal Subjects: A Functional Near-Infrared Spectroscopy Study

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Letter fluency task (LFT) is a tool that measures memory, executive function, and language function but lacks a definite cutoff value to define abnormalities. We used the optical signals of functional near-infrared spectroscopy (fNIRS) to study the differences in power and connectivity between the high-functioning and low-functioning participants while performing three successive LFTs, as well as the relationships between the brain network/power and LFT performance. We found that the most differentiating factor between these two groups was network topology rather than activation power. The high-functional group (7 men and 10 women) displayed higher left intra-hemispheric global efficiency, nodal strength, and shorter characteristic path length in the first section. They then demonstrated a higher power over the left Broca's area than the right corresponding area in the latter two sections. The low-LFT group (9 men and 11 women) displayed less left-lateralized connectivity and activation power. LFT performance was only related to the network topology rather than the power values, which was only presented in the low-functioning group in the second section. The direct correlation between power and connectivity primarily existed in the inter-hemispheric network, with the timing relationship also seeming to be present. In conclusion, the high-functioning

group presented more prominent left-lateralized intra-hemispheric network connectivity and power activation, particularly in the Broca's area. The low-functioning group seemed to prefer using other networks, like the inter-hemispheric, rather than having a single focus on left intra-hemispheric connectivity. The network topology seemed to better reflect the LFT performance than did the power values.

Keywords: connectivity, functional near-infrared spectroscopy (fNIRS), letter fluency task (LFT), power, verbal fluency task (VFT)

INTRODUCTION

Multi-channel functional near-infrared spectroscopy (fNIRS) is an optical neuroimaging that can be used to study regional cortical activity. The technique is based upon so-called neurovascular coupling in which neural activity and vascular responses are closely coupled. Functional NIRS measures brain activity by detecting the hemoglobin concentration changes in the vessels of the underlying cortex. Compared with functional magnetic resonance imaging (fMRI), fNIRS is portable and provides more movement tolerance (1, 2). Moreover, it possesses better temporal resolution due to a higher sampling rate, while also recording brain signals in near real time with less time delay. Previous studies had shown that hemoglobin signals from gray matter recorded by fNIRS offered good concordance with BOLD signals of fMRI (3, 4). Owing to the characteristics described previously, the results of the task can be witnessed in real time as the fNIRS device is running. In contrast, when using fMRI to conduct tasks involving movements and speech, the performance of the participants needs to be re-recorded outside the scanner to avoid artifacts. Therefore, fNIRS has been applied during investigations of several neuropsychiatric disorders (5), including attention deficit hyperactivity disorder (6), depression (7), and schizophrenia (8).

Verbal fluency task (VFT) is a commonly used neuropsychological tool, which measures language (9), executive function (10), and memory (11). According to the properties of the cue, there are two types of VFT: categorical fluency task (CFT) and letter fluency task (LFT). CFT requires a semantic cue, which involves producing words belonging to a given category. LFT uses a phonemic hint, which involves generating words beginning with a specific syllable. Both tasks rely on the same cognitive processes, such as attention and processing speed, but they employ different searching strategies (12). Both types of VFTs had been used to screen for cognitive changes in dementia (5, 13, 14) and traumatic brain injury (15). However, in contrast to the other commonly used tools for screening cognitive function, like Mini-Mental State Examination (MMSE), these two VFTs did not have a definite cutoff score value that can be used to diagnose pathological conditions. Besides, the wide variation is also observed in the normal population.

Both VFTs depend on frontotemporal functions, particularly on the dominant side (16). Previous studies have found that the temporal lobe is of greater importance for CFT, while the frontal lobe is more important for LFT (16, 17). The LFT engages regions extending to the left rolandic operculum and left middle frontal gyrus (18). Functional NIRS showed that the CFT increased power concentrated in the left frontotemporal region (17). LFT activated the left superior and middle frontal gyri, which corresponds to the Broca's area (18). A functional MRI (fMRI) literature revealed that the left superior and anterior temporal regions were primarily activated during CFT, while the left prefrontal cortex and bilateral Broca's areas were mainly activated by LFT (19). Besides, even though declined numbers of appropriate answer and decreased concentrations of the cortical oxygenated hemoglobin had been identified in some pathological conditions (5), the definite network topology of VFTs had only partially been illustrated. The hippocampus was thought as being the component of the networks of CFT, but did not participate in the LFT networks (20). Our previous fNIRS study also identified that the ventral language pathway was used by CFT and the dorsal pathway was used by LFT (21). Measurement of concentration changes of the oxygenated hemoglobulin during VFTs by fNIRS has been found as the possible screening tool for cognitive decline (5). In dementia subjects, the oxygenated hemoglobulin concentration decreased over the right parietal region, while the concentration decreased over the frontopolar prefrontal cortexes in schizophrenia cases.

However, most studies related to VFTs and cognitions focused on the power activation. The brain network topology had not been well illustrated. Variation of performances in normal population neither been studied. Therefore, we used fNIRS to explore how the LFT network organizes in normal subjects and to identify which parameters are the key components related to their performances. Furthermore, we also analyzed the relationship between cortical activation and its connectivity.

MATERIALS AND METHODS

Participants

The healthy subjects were retrospectively enrolled from the Departments of Neurology and Psychiatry at Taichung Veterans General Hospital during the period 2017–2018. Some were outpatients who were found to be healthy after examinations, while the others were university students studying in these departments. All were native Chinese speakers and right-handed according to the Edinburgh Handedness Inventory, without any history of psychological or neurological diseases. Subjects with any psychological problems identified by a psychiatrist, or any evidence of focal neurological deficits as determined by a neurologist, were excluded. We also excluded cases with histories of cerebrovascular disease, head trauma, or brain surgery, to

remove the possible confounding effect of structural lesions. In total, 37 subjects (16 men and 21 women) were recruited. This study was approved by the Ethics Committee of Taichung Veterans General Hospital (CE18306B).

At present, there is no objective, normalized threshold for LFT scores to define the better or poorer performance. Because we only studied the trend of the LFT performance within the general and normal population, they were solely divided into the relatively better and the relatively worse groups. Because the mean and the median of the summation of LFT scores from the three sections in our study were 12.1 and 12 individually, we chose 12 as the cutoff value. Therefore, participants with a

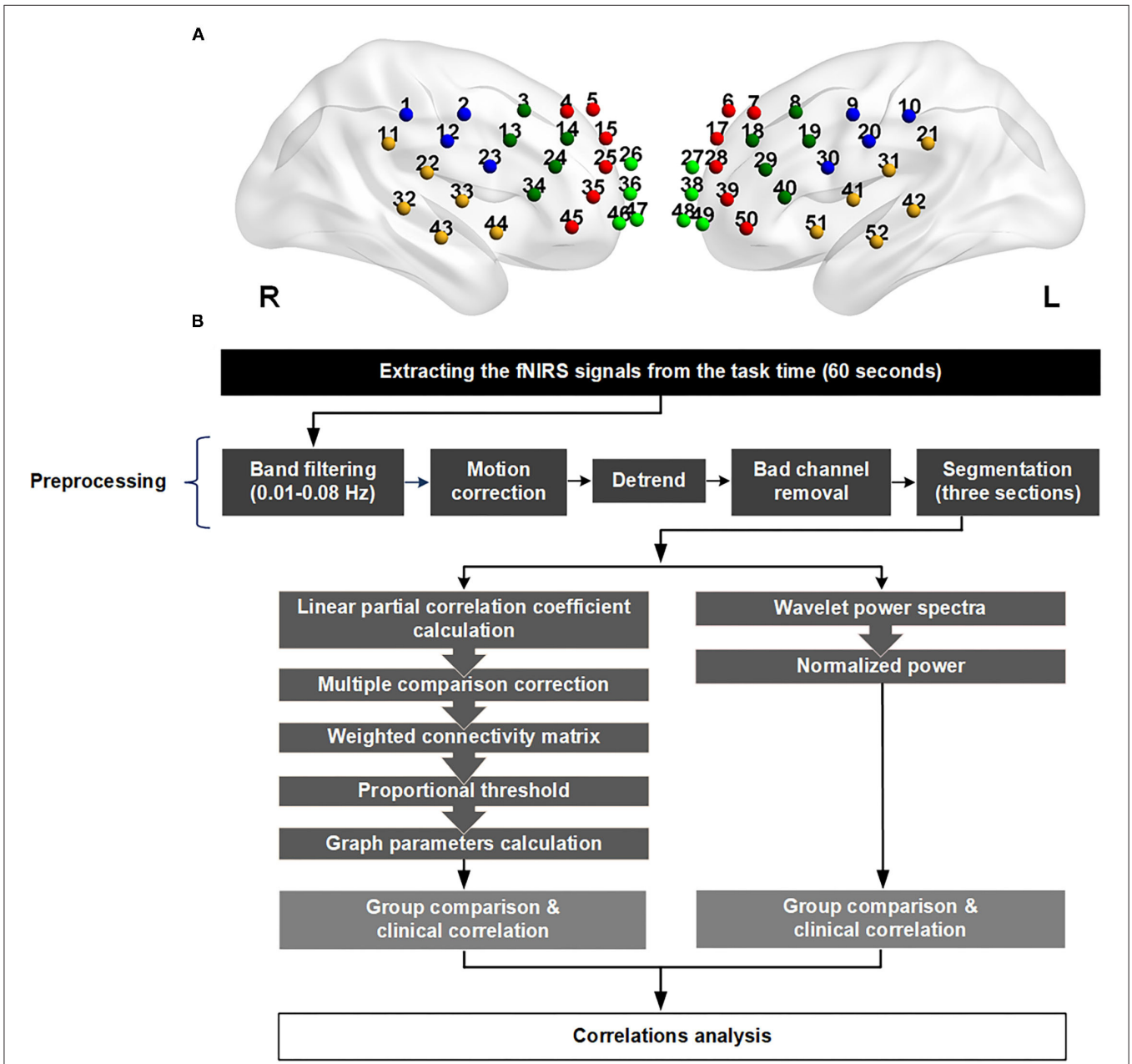

FIGURE 1 | (A) The location of the 52 channels. The channels were divided into 11 parts according to the signals they received from the cortex. The abbreviations and channel numbers are listed below. One color represents one region in any side. Right premotor, motor, and somatosensory cortex (PMS; CH 1, 2, 12, 23): blue; left premotor, motor, and somatosensory cortex (PMS; CH 9, 10, 20, 30): blue; right Broca (CH 3, 13, 14, 24,34): dark green; left Broca (CH 8, 18, 19, 29, 40): dark green; right temporal (CH 11, 22, 32, 33, 43, 44): yellow; left temporal (CH 21, 31, 41, 42, 51, 52): yellow; right frontopolar (CH 26, 36, 46, 47): green; left frontopolar (CH 27, 38, 48, 49): green; right dorsolateral prefrontal cortex (DLPFC; CH 4,5,15,25, 35, 45): red; left dorsolateral prefrontal cortex (DLPFC; CH 6,7,17, 28, 39,50): red; midline (CH 16, 37): gray. **(B)** Flowchart of the data preprocessing and analysis. The source–detector distance of the fNIRS machine is 3.0 cm.

total score of 12 or less were classified as the "low-LFT" or low-functioning group, and consisted of 9 men and 11 women. The other subjects (total LFT score > 12) were classified as the "high-LFT" group or high-functioning group, and included 7 men and 10 women.

Instrument

The hemodynamic changes over the frontotemporal regions were measured using a 52-channel NIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan). The 3 × 11 cell probe with its lowest line at Fp1–Fp2 was based on the EEG international 10–20 system, and extended it laterally to T3 on the left and T4 on the right. The detailed description is mentioned in the **Supplementary Material**.

The 52 channels were grouped based on the standard space of the Brodmann area, and then divided into 11 cortical parcellations, depending on the signal location detected on the scalp (**Figure 1A**): one midline zone, as well as premotor, motor, and somatosensory cortex (PMS), Broca's area, temporal region, frontopolar cortex, and dorsolateral prefrontal cortex (DLPFC) on each side.

Letter/Phonemic Fluency Task

All participants received the Chinese version of the letter fluency task (LFT) with a NIRS probe applied over the anterior head region. A cue using a particular Chinese syllable was given with an audible instruction, and then the participant was asked to generate as many words beginning with that syllable as possible over a span of 20 s (22). In total, the 1-min task period consisted of a series of three sections (**Supplementary Figure 1**), and the detailed process is described in the **Supplementary Material**. The number of produced words in each of the three sections of the task was recorded and summed, representing the subjects' LFT scores.

Data Analysis

We extracted the hemoglobin signal changes during the 60-s task period and analyzed them using MATLAB R2020a (MathWorks, Natick, MA, USA). The NIRS instrument generated two types of values regarding concentration change, oxygenated hemoglobin (HbO), and deoxygenated hemoglobin (HbR). HbO reflects oxygen inflow related to brain activity, while HbR represents oxygen consumption by the tissue (23, 24). HbO has a better BOLD signal correlation and a higher signal-to-noise ratio, and is a better representative of functional connectivity than HbR (24). Therefore, we selected only HbO signals for analysis.

Preprocessing

We discarded any channels presenting as outliers, which were deemed to be bad channels. The remaining signals were preprocessed using a 0.01–0.08 Hz band-pass filter and motion correction, and then detrended for further analysis (**Supplementary Figure 2**). The task period was divided into three 20-s sections, each of which began with a single phonemic cue. The values of regional activation and functional connectivity were calculated individually, and then their correlations were analyzed. The analytic flow chart is depicted in **Figure 1B**.

TABLE 1 | Demographic characteristics of the Low-LFT and High-LFT groups.

	Low-LFT ($n = 20$)	High-LFT ($n = 17$)	p-value*
Age	25.0 (22.3–28.8)	26.0 (25.0–33.5)	0.311
Gender (M:F)	9:11	7:10	1.000
Average LFT scores			
Total	9.0 (7.3–11.0)	15.0 (14.0–17.0)	<0.001
Section 1	3.0 (2.3–4.8)	6.0 (5.0–7.0)	<0.001
Section 2	3.0 (1.3–3.8)	5.0 (4–5.5)	<0.001
Section 3	3.0 (2.0–4.0)	5.0 (4–5.5)	<0.001
Education years	19.0 (16.3–20.0)	19.0 (18.0–20.0)	0.283

Chi-square test or Mann-Whitney U test; Median (IQR).
LFT, letter fluency task; M, male; F, female.
$p < 0.05$.

Regional Power

To define the signal power, we constructed time-frequency spectrograms (with a 0.01-s time resolution and 10^{-4} Hz frequency resolution) of each channel through the use of complex Morlet wavelet transformation (25). The duration of the 5–10 s prior to beginning the task was defined as the baseline period. The power of the individual frequency points within the baseline period was averaged and served as the baseline power. The power during the task was then normalized by subtracting the baseline power individually. The normalized power within the time period of each 20-s section was averaged, and then averaged again by crossing the involved channels within the specific cortical parcellation. Finally, their relationship with the LFT performance and graph theory parameters of connectivity were calculated.

Functional Connectivity

The two midline channels were excluded from the connectivity calculation because they could not be lateralized for analysis. We used the linear partial correlation coefficient to generate the r values between each of the channel pairs. The connections were selected for multiple comparison using false discovery rate (FDR) when their p-values were <0.05. Afterwards, the connection matrix was weighted based on their r values.

We applied proportional (sparsity-based) threshold methods for network measurement, before the network topology was quantified using graph theory. Four parameters were calculated: average node degree, average characteristic path length, global efficiency, and average nodal strength. The connections were divided into intra-hemispheric (LL and RR) and inter-hemispheric. Because there is currently no consensus on network thresholding (26), we performed the test using different cut-off values. The results of the four graph parameters are depicted in **Figures 3–6**. Because the proportional threshold of 0.3 had the smallest p-value among all parameters, we chose 0.3 as the

TABLE 2 | Comparison of the power of each section between the High-LFT and Low-LFT groups.

Region	Section 1					Section 2					Section 3				
	High LFT	***p*†**	**Low LFT**	***p*†**	***p*‡**	**High LFT**	***p*†**	**Low LFT**	***p*†**	***p*‡**	**High LFT**	***p*†**	**Low LFT**	***p*†**	***p*‡**
R_PMS	0.062 ± 0.028	0.1695	0.055 ± 0.039	0.3820	0.8820	0.052 ± 0.056	0.1488	0.047 ± 0.065	0.6165	0.8628	−0.021 ± 0.078	0.4070	−0.010 ± 0.059	0.9700	0.8628
L_PMS	0.088 ± 0.066		0.069 ± 0.062		0.8820	0.111 ± 0.124		0.027 ± 0.103		0.8628	0.022 ± 0.112		0.002 ± 0.103		0.8628
R_Broca	0.049 ± 0.032	0.1695	0.050 ± 0.033	0.5020	0.8820	0.035 ± 0.050	0.0210*	0.040 ± 0.058	0.9400	0.9555	−0.029 ± 0.065	0.0330*	−0.024 ± 0.058	0.9700	0.9555
L_Broca	0.075 ± 0.057		0.053 ± 0.034		0.8820	0.097 ± 0.110		0.043 ± 0.057		0.8628	0.021 ± 0.089		−0.025 ± 0.074		0.8628
R_temporal	0.086 ± 0.064	0.5860	0.053 ± 0.045	0.4695	0.8820	0.093 ± 0.111	0.1488	0.049 ± 0.095	0.6165	0.8628	−0.001 ± 0.103	0.1260	−0.017 ± 0.101	0.7400	0.8628
L_temporal	0.089 ± 0.072		0.065 ± 0.053		0.8820	0.118 ± 0.144		0.062 ± 0.080		0.8628	0.041 ± 0.132		−0.010 ± 0.079		0.8628
R_frontopolar	0.059 ± 0.060	0.1695	0.065 ± 0.070	0.2640	0.8820	0.019 ± 0.088	0.0620	0.047 ± 0.119	0.6165	0.9880	−0.089 ± 0.107	0.1260	−0.022 ± 0.095	0.7400	0.9880
L_frontopolar	0.077 ± 0.076		0.078 ± 0.072		0.9880	0.065 ± 0.126		0.066 ± 0.118		0.9555	−0.048 ± 0.150		−0.003 ± 0.125		0.9555
R_DLPFC	0.053 ± 0.045	0.5860	0.059 ± 0.051	0.5020	0.8820	0.034 ± 0.057	0.2660	0.049 ± 0.066	0.6165	0.9555	−0.041 ± 0.055	0.2952	−0.017 ± 0.046	0.7400	0.9555
L_DLPFC	0.074 ±0.090		0.054 ± 0.044		0.8820	0.079 ± 0.150		0.040 ± 0.073		0.8628	−0.002 ± 0.111		−0.029 ± 0.059		0.8628
midline	0.070 ± 0.070	NA	0.077 ± 0.102	NA	0.8820	0.056 ± 0.095	NA	0.073 ± 0.168	NA	0.9880	0.033 ± 0.080	NA	−0.0003 ± 0.113	NA	0.9880
Right half[a]	0.064 ± 0.041	0.1695	0.057 ± 0.040	0.3000	0.8820	0.051 ± 0.059	0.0120*	0.048 ± 0.067	0.7212	0.9555	−0.033 ± 0.059	0.0240*	−0.018 ± 0.051	0.9700	0.9555
Left half[b]	0.080 ± 0.060		0.063 ± 0.044		0.8820	0.094 ± 0.103		0.055 ± 0.064		0.8628	0.009 ± 0.090		−0.014 ± 0.056		0.8628
All power[c]	0.072 ± 0.047	NA	0.060 ± 0.041	NA	0.8820	0.072 ± 0.078	NA	0.052 ± 0.063	NA	0.8628	−0.013 ± 0.072	NA	−0.015 ± 0.048	NA	0.8628

†*Wilcoxon signed rank test, comparing the powers of the corresponding regions in the left and the right hemispheres, after multiple comparison corrections within each section.*

‡*Wilcoxon signed rank test, comparing the powers of the High-LFT and Low-LFT groups in each section, after multiple comparison corrections within each section.*

**$p < 0.05$, when the difference present is between the left and the right corresponding regions after multiple comparisons using FDR.*

NA, not available.

[a]*Average power of the 25 channels located over the right fronto-temporal region.*

[b]*Average power of the 25 channels located over the left fronto-temporal region.*

[c]*Average power of the all the 52 channels (including midline channels).*

PMS, premotor, motor, and somatosensory cortex; DLPFC, dorsolateral prefrontal cortex (DLPFC).

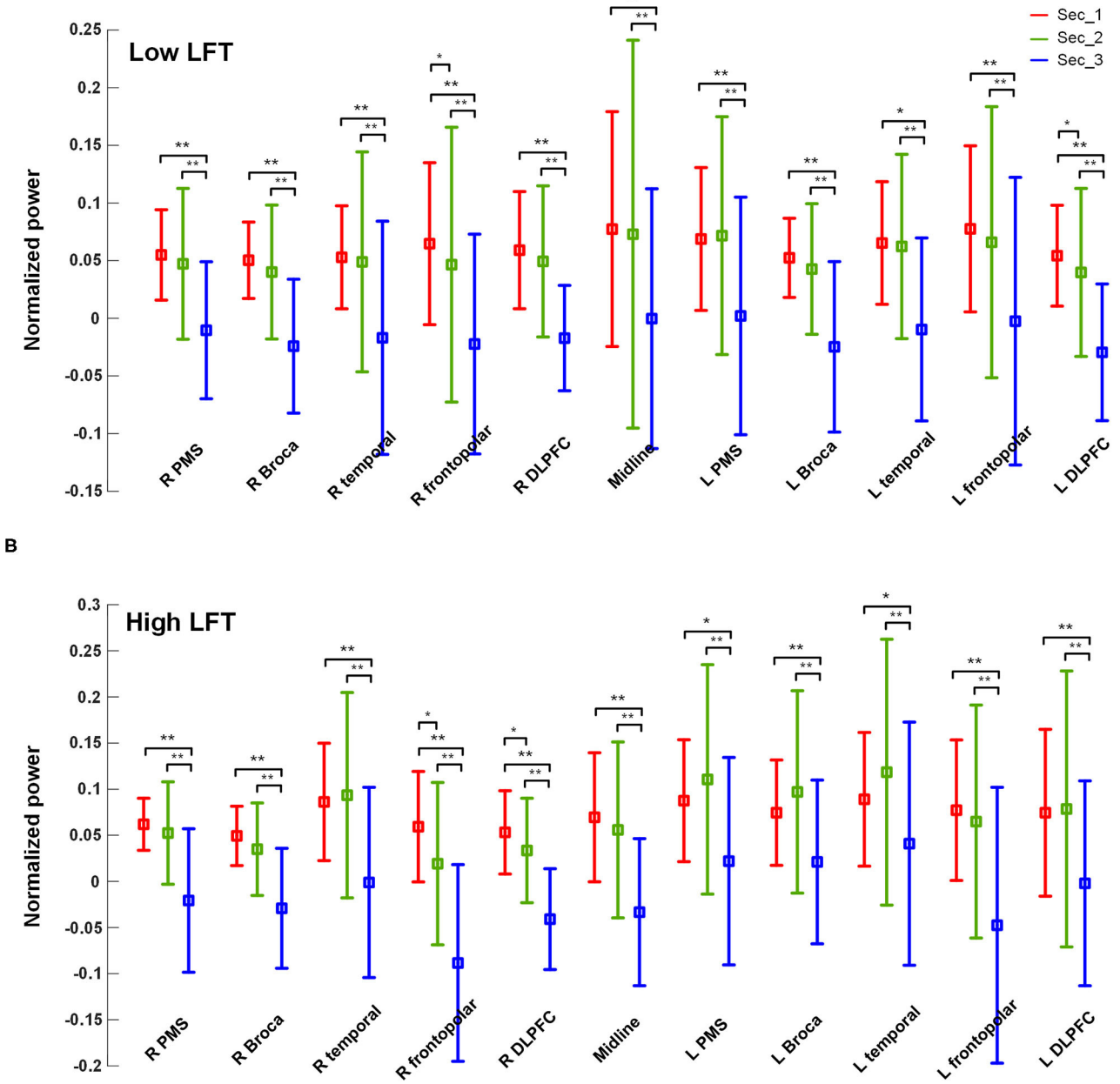

FIGURE 2 | The power values of each of the brain regions within each section in the **(A)** high-LFT and **(B)** low-LFT groups.

network threshold value for subsequent correlation analysis. The detail about selecting the value for network thresholding is described in the **Supplementary Material**.

Statistical Analysis

We used SPSS version 20.0 (IBM, Armonk, NY, USA) and MATLAB R2020a (MathWorks, Natick, MA, USA) for statistical analyses to study the regional power activation and network topology differences between these two groups, as well as their correlation to the LFT scores. The power of each brain region for the individual groups in every section was compared using FDR correction. All graph theory properties were compared using the two-sided Wilcoxon rank-sum test. Statistical significance was set at $p < 0.05$ for correction using multiple comparisons by FDR.

RESULTS

Demographic and Clinical Data

Both groups displayed similar proportions of gender, age, and number of educational years (**Table 1**). The LFT scores in each

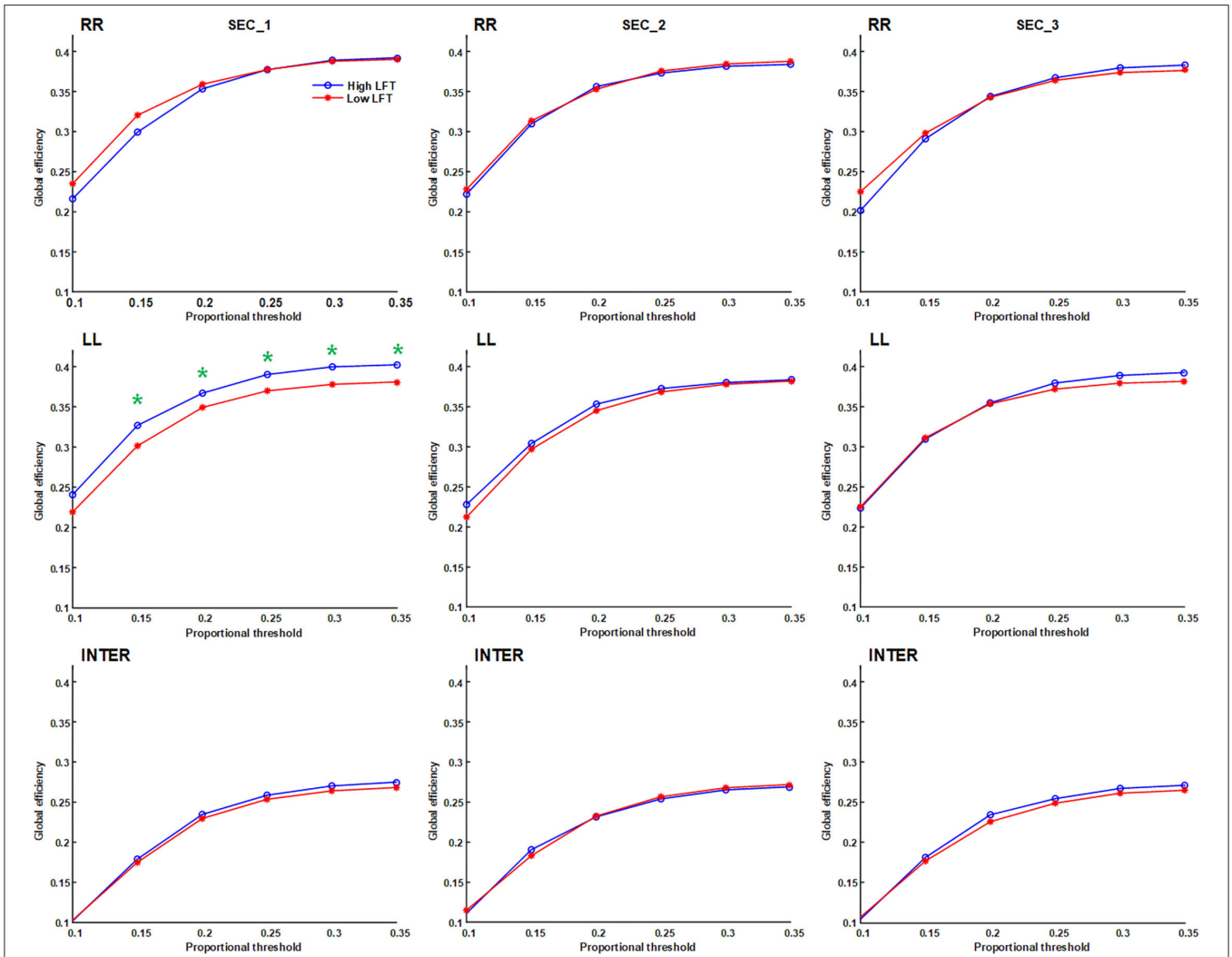

FIGURE 3 | Global efficiency of the inter-hemispheric and the inter-hemispheric networks in each section using different proportional threshold values (*$p < 0.05$).

section showed significant differences. The total LFT score was not correlated with age ($p = 0.850$) or educational years ($p = 0.700$) using Spearman correlation analysis (data not shown in the tables).

Regional Power

The power activation of the 11 brain regions was calculated for each section with the results listed in **Table 2**. The serial power changes in the successive sections are presented in **Figure 2**. The power dropped dramatically in section 3 for both groups, while the power in the first two sections was relatively high. In the high-LFT group, most brain regions showed relatively higher power in the high-LFT group than that in the low-LFT group, but did not reach statistical significance. The reverse result was presented in the midline and right frontopolar regions in the second section, where the power was relatively higher in the low-LFT group than that in the high-LFT group. In the high-LFT group, the left Broca's area and left frontotemporal region showed significantly higher power than that in the right corresponding regions of the last two sections. In the low-LFT group, the power of each brain region did not show an obviously left–right asymmetrical pattern.

Functional Connectivity

The network topology was constructed using the proportional threshold with the value of 0.3. The high-LFT group showed higher left intra-hemispheric global efficiency (**Figure 3**), higher average nodal strength (**Figure 4**), and shorter average characteristic path length (**Figure 5**) only in the first section. However, the average nodal degree did not show the differences (**Figure 6**). The RR intra-hemispheric and inter-hemispheric networks showed almost identical topology in these two groups.

LFT Performance Correlation

The sum of the LFT scores were calculated before their relationship with the corresponding network topology was

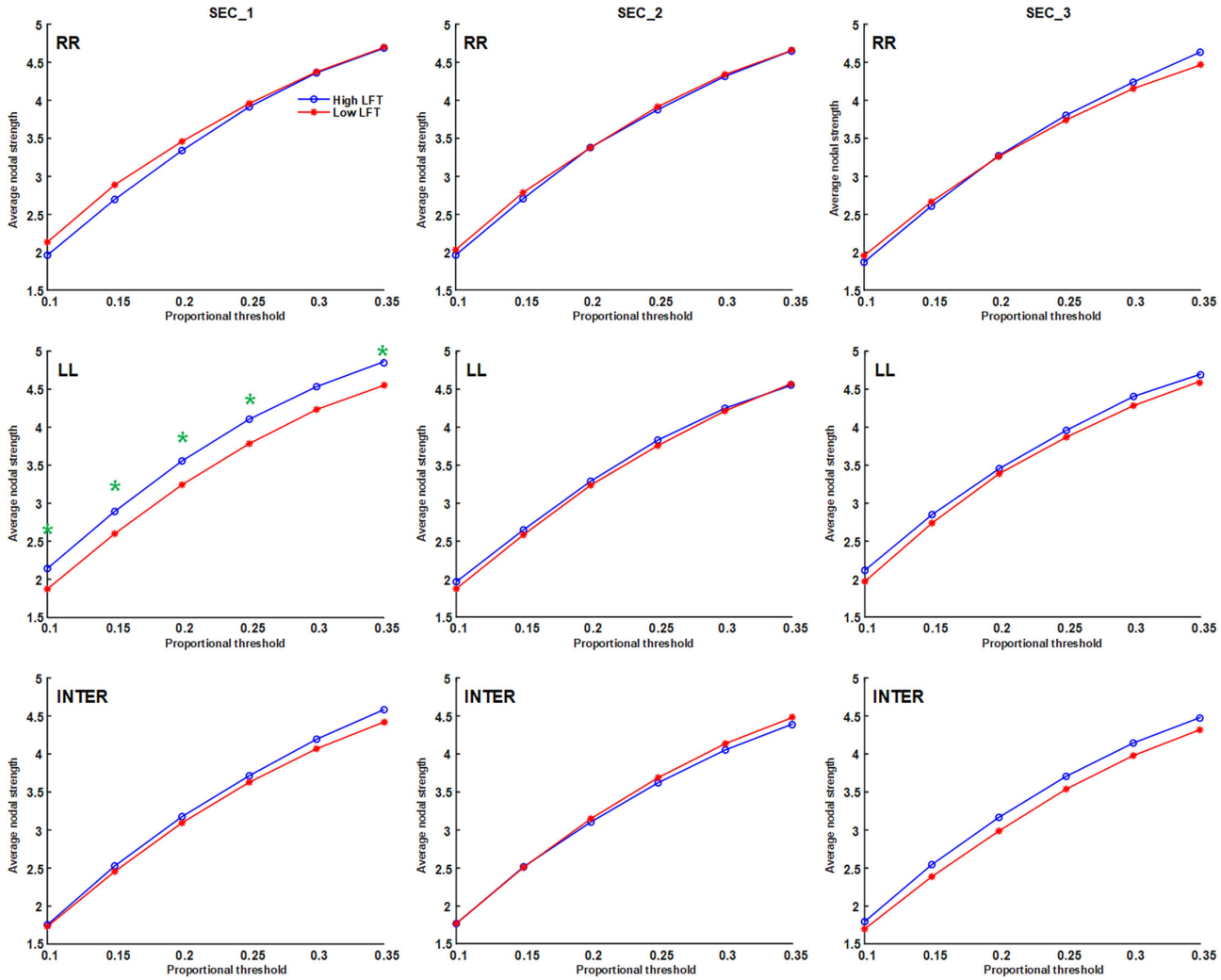

FIGURE 4 | Average nodal strength of the inter-hemispheric and the inter-hemispheric networks in each section using different proportional threshold values (*$p <$ 0.05).

surveyed. The regional brain power for the three sections did not show any obvious correlation with the sum of the LFT scores (**Supplementary Table 1**). However, in terms of connectivity, the total LFT scores were only related to the parameters in the second section of the low-LFT group. They were negatively correlated with the LL intra-hemispheric and inter-hemispheric average characteristic path length, and positively correlated with both sides of the intra-hemispheric global efficiency, as well as the left intra-hemispheric average nodal strength (**Table 3**).

Relationship Between Power and Connectivity

In the high-LFT group, only inter-hemispheric average nodal strength was negatively associated with the average power of 25 channels over the left frontotemporal regions in the first section (**Table 4**). In the low-LFT group, the correlation was only present in the third section (**Table 5**). The average power of the left half channels was positively correlated with the inter-hemispheric average node degree, global efficiency, and average nodal strength. However, the average power of the right half channels was negatively correlated with the LL intra-hemispheric average node degree.

DISCUSSION

This is the first study using fNIRS for establishing the relationship among the frontotemporal connectivity, the regional power activation, and the LFT performance.

The frontal lobe plays an important role in "switching" (27), which is the important component in phonemic word generation, allowing for flexibility during lexical access (27). Moreover, fNIRS studies have revealed relatively greater augmentation of frontal

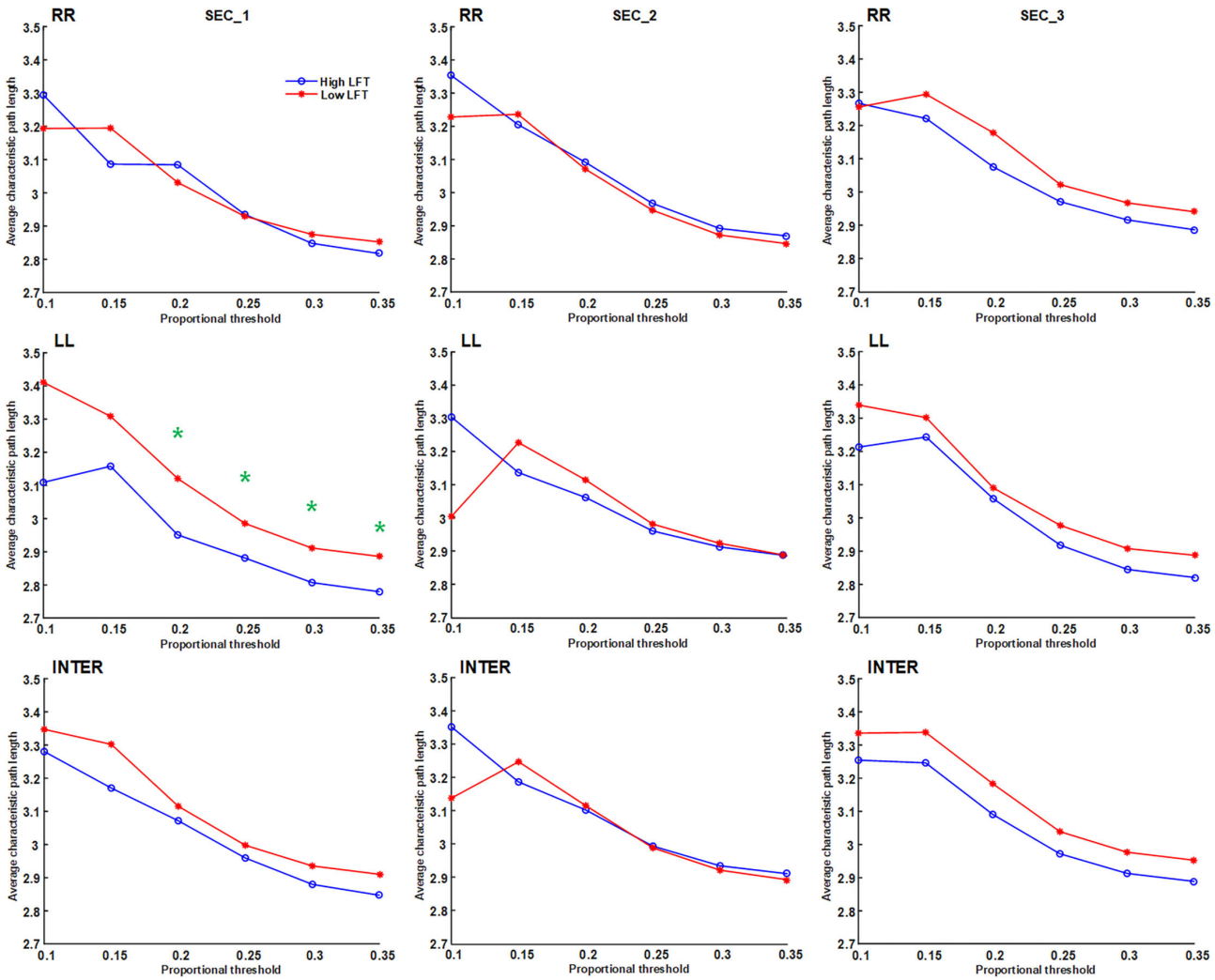

FIGURE 5 | Average characteristic path length of the inter-hemispheric and the inter-hemispheric networks in each section using different proportional threshold values (*$p < 0.05$).

activation when performing LFT as compared with CFT (22, 28). The channels of the fNIRS instrument used in this study mostly covered the frontal and anterior temporal regions, which allowed for a more reliable signal detection of LFT than that of CFT.

A previous fMRI study had demonstrated that both young and old healthy participants had overlapping and different LFT activation patterns (29). The clusters activated in the younger group occurred in the left Broca's area (Brodmann 45), left superior temporal gyrus (Brodmann 22), and left inferior frontal gyrus (Brodmann 9), whereas the group also had relatively higher LFT scores. This result was similar to our findings in the high-LFT group, where the left Broca's area had significantly higher power when compared with the right corresponding region. In the aged group, additional significant clusters were detected in the right frontopolar area (Brodmann 10). However, their participants were older than our low-LFT group cases (64–88 years old vs. 17–53 years old), even though both groups had relatively lower LFT scores. These two results were not closely comparable. Relatively higher power over the midline, as well as the left frontopolar and temporal regions was also noted in our low-LFT group, even though it did not reach statistical difference. Such phenomenon suggests that better LFT performance is primarily related to activation of the left Broca's area. Our high-functioning group cases showed a more prominent left lateralization activation pattern than the low-functioning group. We suggest those who were unable to concentrate firmly to activate the Broca's area showed lower LFT scores. This further indicates that activation of the frontopolar, temporal, and midline areas serves as an alternative pathway and is related to weaker competence.

The regions with relatively higher power had been reported as having roles in language production and executive function in previous literatures. The Broca's area of the dominant hemisphere

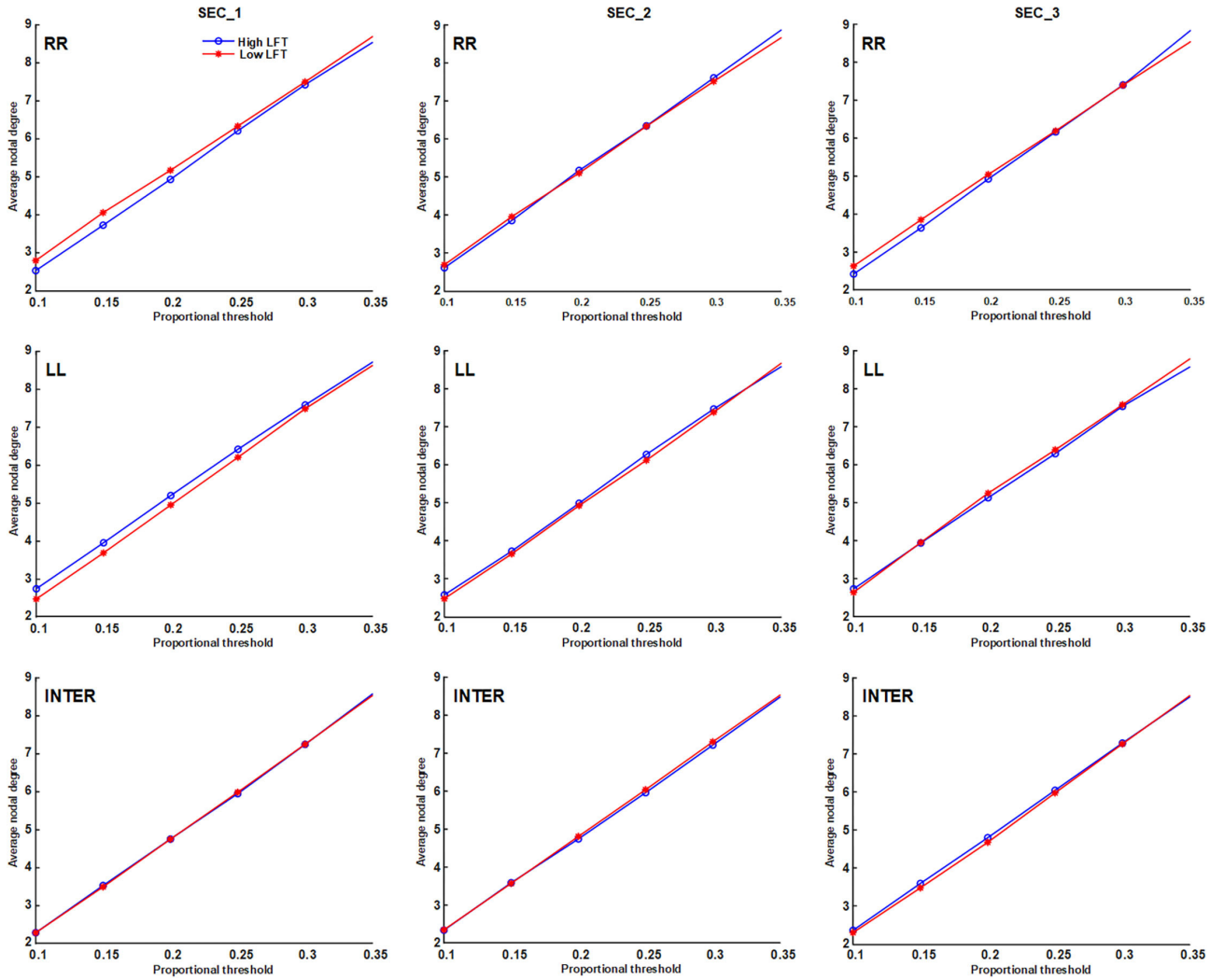

FIGURE 6 | Average node degree of the inter-hemispheric and the inter-hemispheric networks in each section using different proportional threshold values.

manages language production and has also been reported to be the primary activated area when performing LFT (17). The temporal area is a part of the ventral language pathway according to the dual language stream hypothesis, and mediates lexical concepts and comprehension (30). The midline channels represent the frontopolar region, which integrates cognitive information to re-disperse activity toward the action (31). Bilateral frontopolar activation has been reported when LFT is carried out (32).

The power reflects the amount of regional neuronal activation, and the connectivity indicates the correlations between frequency fluctuations in the separate brain regions. In our study, the strongest power occurred in the first two sections of both groups. Power dropped dramatically in the third section, where most of the values were lower than those in the baseline values. This phenomenon was also noted in previous fMRI studies and was interpreted as the "practice effect" (33–35). Repetition of working memory tasks attenuates activation, which is thought to be due to an improvement in efficiency, where the behavior of the performance is maintained. Another explanation is that persistent activation-related exhaustion of oxygenated hemoglobin possibly occurs, as according to the results of a previous fNIRS study (36).

Network thresholding assists in the elimination of spurious connections, which in turn strengthens the characteristics of the network topology (26). We used proportional thresholds for network measurements with step-wise increasing values. Although their values regarding the graph theory parameters differed, the results showed a consistent trend. The main differences between the high-LFT and low-LFT groups manifested in the first section, and presented similar in the following two sections. The most differentiating factor between the high-LFT and low-LFT groups was network topology rather than the activation power. High-functional cases displayed higher global efficiency and nodal strength, as well as shorter path length in the first section. This suggests that the initial

TABLE 3 | Correlation between the sum LFT scores and graph theory parameters using the proportional threshold 0.3.

		Section 1		Section 2		Section 3	
		Low LFT†	High LFT†	Low LFT†	High LFT†	Low LFT†	High LFT†
Average node degree	RR	0.0905 (0.7126)	0.1243 (0.6466)	−0.0233 (0.9246)	0.0208 (0.9391)	0.0905 (0.7126)	−0.2026 (0.4518)
	LL	−0.3161 (0.1874)	−0.0374 (0.8905)	0.1707 (0.4848)	−0.0517 (0.8492)	−0.3161 (0.1874)	0.1921 (0.4761)
	INTER	0.2052 (0.3994)	−0.1883 (0.4850)	−0.2027 (0.4054)	−0.1577 (0.5597)	0.2052 (0.3994)	−0.1424 (0.5989)
Average characteristic path length	RR	0.1262 (0.6066)	0.1810 (0.5022)	−0.4194 (0.0739)	−0.0465 (0.8643)	−0.2221 (0.3608)	0.4170 (0.1081)
	LL	0.0165 (0.9464)	0.1661 (0.5387)	−0.4743 (0.0402)*	0.1830 (0.4976)	0.1446 (0.5548)	0.0885 (0.7446)
	INTER	−0.0107 (0.9653)	0.1323 (0.6253)	−0.4632 (0.0458)*	0.0400 (0.8832)	−0.0541 (0.8260)	0.2637 (0.3237)
Global efficiency	RR	−0.1932 (0.4281)	−0.0103 (0.9698)	0.4577 (0.0488)*	0.1005 (0.7112)	0.1997 (0.4125)	−0.4008 (0.1240)
	LL	−0.0991 (0.6864)	−0.0543 (0.8418)	0.4988 (0.0297)*	−0.1139 (0.6746)	−0.1474 (0.5472)	−0.1989 (0.4602)
	INTER	−0.0881 (0.7199)	−0.0566 (0.8352)	0.4295 (0.0665)	−0.2622 (0.3266)	0.1751 (0.4733)	−0.2846 (0.2854)
Average nodal strength	RR	−0.0106 (0.9655)	0.1005 (0.7112)	0.4167 (0.0760)	0.0925 (0.7334)	0.1971 (0.4187)	−0.3875 (0.1381)
	LL	−0.2111 (0.3856)	−0.0226 (0.9337)	0.5019 (0.0286)*	−0.0296 (0.9135)	−0.2258 (0.3527)	−0.1140 (0.6741)
	INTER	0.1243 (0.6121)	0.0087 (0.9744)	0.3578 (0.1326)	0.0771 (0.7764)	0.1318 (0.5907)	−0.2552 (0.3402)

†*Spearman partial correlations (p-value), with age as the covariant.*
RR, LL, intra-hemispheric connections in right or left side; INTER, inter-hemispheric connections.
*$p < 0.05$.

TABLE 4 | Correlation between power and connectivity in the High-LFT group.

		Left power			Right power		
		Sec 1	Sec 2	Sec 3	Sec 1	Sec 2	Sec 3
Average node degree	RR	−0.155 (0.554)	−0.043 (0.870)	−0.028 (0.914)	−0.103 (0.694)	−0.105 (0.689)	0.037 (0.888)
	LL	0.383 (0.130)	0.025 (0.925)	−0.314 (0.220)	0.097 (0.711)	−0.007 (0.978)	−0.134 (0.609)
	INTER	−0.168 (0.518)	0.213 (0.411)	0.396 (0.116)	0.093 (0.722)	0.317 (0.215)	0.218 (0.400)
Average characteristic path length	RR	0.365 (0.149)	0.157 (0.548)	−0.179 (0.492)	0.265 (0.305)	0.083 (0.751)	−0.132 (0.613)
	LL	0.044 (0.866)	0.061 (0.815)	−0.113 (0.667)	0.284 (0.269)	−0.025 (0.926)	−0.306 (0.232)
	INTER	0.458 (0.064)	0.314 (0.220)	−0.203 (0.434)	0.390 (0.122)	0.238 (0.358)	−0.284 (0.269)
Global efficiency	RR	−0.433 (0.083)	−0.356 (0.161)	0.143 (0.583)	−0.432 (0.084)	−0.266 (0.302)	0.141 (0.589)
	LL	−0.072 (0.782)	−0.155 (0.554)	0.121 (0.643)	−0.258 (0.318)	−0.070 (0.790)	0.330 (0.196)
	INTER	−0.433 (0.082)	−0.098 (0.707)	0.413 (0.100)	−0.354 (0.163)	−0.022 (0.933)	0.346 (0.173)
Average nodal strength	RR	−0.412 (0.101)	−0.245 (0.343)	0.130 (0.619)	−0.404 (0.107)	−0.179 (0.492)	0.123 (0.639)
	LL	0.110 (0.673)	−0.137 (0.599)	0.105 (0.687)	−0.108 (0.680)	−0.100 (0.701)	0.331 (0.195)
	INTER	−0.495 (0.043)*	−0.348 (0.171)	0.397 (0.115)	−0.326 (0.202)	−0.284 (0.269)	0.358 (0.158)

Spearman correlation: Spearman's ρ (p-value).
$p < 0.05$.
RR, LL, intra-hemispheric connections in right or left side; INTER, inter-hemispheric connections.

network topology is more asymmetrical and more left-lateralized in high-functioning LFT, even becoming similar in the second and the third sections.

Our healthy participants demonstrated a wide distribution of LFT performance, which was quantified by their total LFT scores, but not related to age or educational years. Most left intra-hemispheric parameters of the second section were related to LFT performance only in the low-functioning group. In addition, some right intra-hemispheric and inter-hemispheric network topologies in the second section were also related to their LFT performance. Therefore, we suppose that the low-functioning group dispersed their LFT network into other pathways, instead of only the left intra-hemispheric connectivity, which decreases LFT competency. This result also suggests that the cognitive and executive function in normal population may be better interpreted by the network topology rather than the power activation, like dementia and schizophrenia (5).

In addition, we even found that high-LFT groups had the higher efficient and dense network topology in the first section, as well as higher power over both the Broca's area and the left frontotemporal region in the last two sections. Neither power nor current network parameters had directly reflected the LFT scores in the high-functioning group. We speculate that network connectivity of the left hemisphere used by the high-LFT group was more concentrated in a small area, like the Broca's area. Its

TABLE 5 | Correlation between power and connectivity in the Low-LFT group.

		Left power			Right power		
		Sec 1	**Sec 2**	**Sec 3**	**Sec 1**	**Sec 2**	**Sec 3**
Average node degree	RR	0.072 (0.762)	−0.132 (0.580)	−0.101 (0.671)	0.042 (0.860)	−0.140 (0.556)	0.172 (0.468)
	LL	−0.137 (0.563)	0.186 (0.432)	−0.393 (0.087)	−0.211 (0.373)	−0.014 (0.954)	−0.468 (0.037)*
	INTER	0.032 (0.895)	0.165 (0.486)	0.497 (0.026)*	0.094 (0.693)	0.375 (0.103)	0.306 (0.189)
Average characteristic path length	RR	−0.200 (0.398)	0.259 (0.269)	−0.298 (0.202)	−0.120 (0.613)	0.272 (0.245)	−0.200 (0.398)
	LL	−0.316 (0.175)	0.029 (0.905)	0.023 (0.922)	−0.213 (0.368)	0.147 (0.535)	0.310 (0.184)
	INTER	−0.320 (0.169)	0.273 (0.244)	−0.433 (0.056)	−0.211 (0.373)	0.305 (0.192)	−0.156 (0.510)
Global efficiency	RR	0.275 (0.240)	−0.253 (0.282)	0.192 (0.418)	0.166 (0.486)	−0.199 (0.399)	0.139 (0.560)
	LL	0.198 (0.403)	−0.167 (0.482)	−0.050 (0.833)	0.093 (0.696)	−0.290 (0.214)	−0.194 (0.412)
	INTER	0.429 (0.059)	−0.202 (0.394)	0.500 (0.025)*	0.363 (0.116)	−0.281 (0.230)	0.207 (0.381)
Average nodal strength	RR	−0.038 (0.875)	−0.195 (0.409)	0.134 (0.574)	0.164 (0.490)	−0.212 (0.369)	0.235 (0.319)
	LL	−0.197 (0.405)	−0.078 (0.743)	−0.092 (0.701)	0.092 (0.701)	−0.198 (0.402)	−0.280 (0.232)
	INTER	−0.033 (0.890)	−0.304 (0.193)	0.559 (0.010)*	0.323 (0.164)	−0.305 (0.191)	0.287 (0.220)

Spearman correlation: Spearman's ρ (p-value).
$^{*}p < 0.05$.
RR, LL, intra-hemispheric connections in right or left side; INTER, inter-hemispheric connections.

effect may be diluted by using the graph theory when the whole left frontotemporal area was counted.

The network topology in our study showed similar inter-hemispheric and intra-hemispheric values, and presented almost the same throughout the three sections. The only exception was in global efficiency, whose values were relatively lower in the inter-hemispheric than intra-hemispheric aspects during all three sections (**Figure 3**), regardless of the thresholding values used. Inter-hemispheric global efficiency was only one half of intra-hemispheric connectivity. This suggests that performance of the letter fluency task primarily depends on the intra-hemispheric network, and less on inter-hemispheric connectivity (21), which is reflected in their use of the dorsal language pathway (19).

The changes in power and connectivity were not parallel. The relationship between the left frontotemporal power and their functional connectivity mostly existed in the inter-hemispheric networks of both groups. In the high-functioning group, higher inter-hemispheric nodal strength was related to lower left-side power, which indicates that the left frontotemporal region possesses sufficient efficiency and requires less additional efforts in the first section. In the low-functioning group, the higher left-side power was associated with higher inter-hemispheric nodal degree, nodal strength, and global efficiency in the third section. This suggests that considerable efforts and supports from left frontotemporal activation are needed to maintain the average level of inter-hemispheric connections. In addition, the right frontotemporal power required less activation when the left intra-hemispheric nodal degree was achieved in the third section. Therefore, this indirectly echoes that the left frontotemporal region remains the important area for LFT. Low-functioning cases also used less left intra-hemispheric but relatively more inter-hemispheric connectivity to perform LFT.

Some fMRI studies have reported that task-evoked activation and connectivity are not usually correlated (37–39), and a fNIRS study also found a similar outcome (40). These results depended on the parcellation of brain regions and the analytic methods that were employed. The connectivity was still present even when the activation pattern was not evident (37), which was also observed in our study. The network topology was maintained in the third section, although the power had dropped. One study discovered that the more activated brain regions exhibited significantly greater connectivity changes than those seen in the non-activated regions (39). The authors concluded that hubs and activation patterns modify the network topology (39). Our study found the possible timing relationship between the connectivity and the power activation. The left intra-hemispheric nodal strength and efficiency increased initially during the first section in the high-functioning group, with the power of the left Broca's area asymmetrically increasing in the latter two sections. This disclosed the elevated power that could result from an increase in network efficiency and nodal strength. However, to firmly establish the definite relationship between power and connectivity, further studies must be explored.

Our studies had some limitations. First, only cortical neuronal signals could be detected, while signals from deep structures could not be obtained. This is an inevitable shortcoming of the fNIRS instrument. Second, only the frontal lobes and part of the temporal lobes could be covered by the electrodes. As a result, signals from the posterior head region might have been missed. Third, our data were collected retrospectively and the sample size was relatively small. Finally, no other comprehensive neuropsychiatric examinations were conducted. Therefore, further studies involving a larger sample size are still necessary.

CONCLUSION

The performance of LFT varies greatly even in a normal population. The activation power surged in the first two sections and dropped dramatically during the third. The

main differentiating factor between high-functioning and low-functioning groups was network topology rather than activation power. The high-functional group displayed higher left intra-hemispheric global efficiency and nodal strength, but decreased characteristic path length in the first section, which suggested a greater left lateralized connectivity pattern in the high-LFT group. In addition, the high-LFT group demonstrated higher power over the left Broca's area than it did in the right corresponding area in the latter two sections. The low-LFT group displayed less left-lateralized connectivity and activation power, which suggested other networks were used by them, including inter-hemispheric connectivity, rather than just the single left intra-hemispheric network.

The network topology seemed to better reflect the LFT performance than the power values. We found that the well-constructed left intra-hemispheric connectivity and the well-activated left Broca's area seemed to be related to the more excellent LFT performance.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the original datasets are inquiries can be directed to the corresponding author. Requests to access these datasets should be directed to S-JP, sjpeng2019@tmu.edu.tw.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Taichung Veterans General Hospital (CE18306B). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HT and S-JP: work conception, study design, and final approval of the version. W-HL, T-HL, and PH: examination enrollment. W-HL: conducting NIRS examination. S-JP: data processing and analysis. HT: clinical data analysis and drafting the work. HT, T-HL, M-CC, and Y-YL: interpretation of data. Y-YL and S-JP: revising the work for valuable intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.810685/full#supplementary-material

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rTMS Therapy Reduces Hypofrontality in Patients With Depression as Measured by fNIRS

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Multichannel functional near-infrared spectroscopy (fNIRS) is a tool used to capture changes in cerebral blood flow. A consistent result for depression is a decrease in blood flow in the frontal cortex leading to hypofrontality, which indicates multidomain functional impairment. Repetitive transcranial magnetic stimulation (rTMS) and elective convulsive therapy (ECT) are alternatives to antidepressant drugs for the treatment of depression but the underlying mechanism is yet to be elucidated. The aim of the current study was to evaluate cerebral blood flow using fNIRS following rTMS treatment in patients with depression. The cerebral blood flow of 15 patients with moderate depression after rTMS treatment was measured using fNIRS. While there was clear hypofrontality during pre-treatment (5 ± 2.5), a notable increase in oxygenated hemoglobin was observed after 30 sessions with rTMS (50 ± 15). This increased blood flow was observed in a wide range of channels in the frontal cortex; however, the centroid values were similar between the treatments. Increased blood flow leads to the activation of neuronal synapses, as noted with other neuromodulation treatments such as electroconvulsive therapy. This study describes the rTMS-induced modulation of blood oxygenation response over the prefrontal cortex in patients with depression, as captured by fNIRS. Future longitudinal studies are needed to assess cerebral blood flow dynamics during rTMS treatment for depression.

Keywords: cerebrovascular circulation, depression, functional near-infrared spectroscopy, oxyhemoglobins, prefrontal cortex, repetitive transcranial magnetic stimulation

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INTRODUCTION

Brain activity assessed by functional near-infrared spectroscopy (fNIRS) *via* blood oxygen change has been utilized to distinguish psychiatric disorders, such as depression, bipolar disorder, and schizophrenia (1, 2). In particular, a number of reports have repeatedly shown reduced cerebral blood flow during the verbal fluency task (VFT) in patients with psychiatric disorders compared to healthy controls (3–6). Since the classification of psychiatric disorders is currently based on expressed symptoms, clinicians urgently need relevant biological markers to add persuasiveness to their practice. Multichannel fNIRS is a non-invasive neuroimaging technique

for observing the living brain during tasks; therefore, it has a strong potential to distinguish major psychiatric disorders. Repetitive transcranial magnetic stimulation (rTMS) is efficacious for treating depression (7). A meta-analysis of the efficacy of rTMS reported its robustness in reducing the severity of depression (8). Moreover, this technique is easier to adopt in practice compared to electroconvulsive therapy (ECT), which requires general anesthesia and an operating room (9). These two treatment techniques are similar in terms of the direct electrostimulation of the brain (10). While the underlying mechanism of action for neuromodulation therapies (ECT and rTMS) is yet to be determined, the role of medication therapies in increasing monoamine levels at the synapse has been suggested (11, 12). Since neuromodulation and medication therapies have different durations of response, different modes of action are postulated.

A recent finding suggested that fNIRS is a trait marker, which refers to alterations in functioning that persist in those who have experienced major depression when they are no longer depressed, rather than a state marker, which is characteristic of the clinical status, because it reveals consistent hypofrontality during antidepressant medication in drug-naive patients with major depressive disorder (MDD) (13). Measuring oxygenated hemoglobin (oxy-Hb) in the VFT showed the same activation between pre-and post-drug treatment despite the significantly improved severity of MDD (14). However, to date, only a few studies have used fNIRS to evaluate rTMS as a treatment for MDD, probably because rTMS has been developed primarily in North America, whereas fNIRS has been mainly studied in Japan and other South Asian countries. The main aim of the current study was to evaluate hypofrontality using fNIRS, for the comparison of the pre- and post-rTMS treatment of depression.

MATERIALS AND METHODS

Participants

We noticed the enrollment to rTMS therapy in community patients, therefore the recruited participants were from other outpatient clinics. Fifteen patients with moderate MDD were included in this study (seven men and eight women). These participants had received more than two antidepressant medication treatments before rTMS; however, a satisfactory response was not achieved. MDD diagnosis was based on an interview with the Structured Clinical Interview for DSM (SCID) (15) by blinded clinical psychologists. Patients with intellectual disability, impaired language disability, or difficulty speaking Japanese were excluded in this study. The demographic data are presented in **Table 1**; the mean years of medication was 6.9 (SD ± 4.9). All patients were right-handed. The mean equivalent dose of imipramine (antidepressant), chlorpromazine (antipsychotic), and diazepam (benzodiazepine) was 192 ± 122, 67 ± 108, and 10.2 ± 8.6 mg, respectively. During the rTMS procedure, the medication was not changed. Ethical approval for this research was obtained from the committee of the Osaka Medical College (IRB-approval number: 970-1). All participants gave oral approval and written informed consent.

TABLE 1 | Demograhic data.

Subjects	15
Age (years)	42.87 ± 8.93
Gender	Male 7 Female 8
WAIS-III (Full IQ)	96.40 ± 19.60
Age of onset	41.2 ± 8.86
Treatment period (month)	18.17 ± 14.15
MT level	1.12 ± 0.20
DSM-IV (SCID)	
Major depressive disorder, single episode	
296.21 Mild	1
296.22 Moderate	4
296.23 Severe without psychotic features	1
Major depressive disorder, recurrent	
296.32 Moderate	5
296.35 In partial remission	4
Comorbid disorders	
300.02 Generalized anxiety disorder	1
300.23 Social anxiety	2
300.82 Somatoform disorder NOS	1
Medication Equivalent dose (mg/day)	
Antidepressants (Imipramine-E.D.)	192 ± 122
Antipsychotics (Chlorpromazine-E.D.)	67 ± 108
Benzodiazepines (Diazepam-E.D.)	10.2 ± 8.6
E.D. = equivalent dose	
Dominant hand	Right 15 Left 0

rTMS

The NeuroStar® device (16) (Neuronetic Inc., Pennsylvania, USA) was used for 30 days of stimulation. In the current protocol design, 5 days of continuous stimulation per week were performed for 6 weeks. A 10-Hz pulse sequence for 4 s followed by a 26-s quiet period at a 120% motor threshold was the generated stimulation. A daily session lasted 37.5 min in total, including 40 pulses per train, with 75 trains in 1 day (3,000 pulses) (17, 18) (**Figure 1A**). Stimulation was set at the left dorsolateral prefrontal cortex (DLPFC), placed 5.5-cm anterior to the motor threshold location (19, 20). All rTMS treatment procedures were performed according to the guidelines provided by the working group to formulate a policy for the proper usage of rTMS in the Japanese Society of Psychiatry and Neurology (21).

Clinical Outcome Assessment and the Medication During the rTMS Course

The Hamilton Depression Scale (HAM-D) (22) was used to assess the severity of depression. The assessment was performed by clinicians before starting the rTMS treatment (pre; blue in **Figure 3**) and after treatment (post; red in **Figure 3**). Antidepressant medication was not changed during the rTMS treatment, although sleeping pills were allowed as needed only a few times during the entire course. A 15-channel fNIRS (OEG-17ME; Spectratech Inc., Tokyo, Japan) with recording

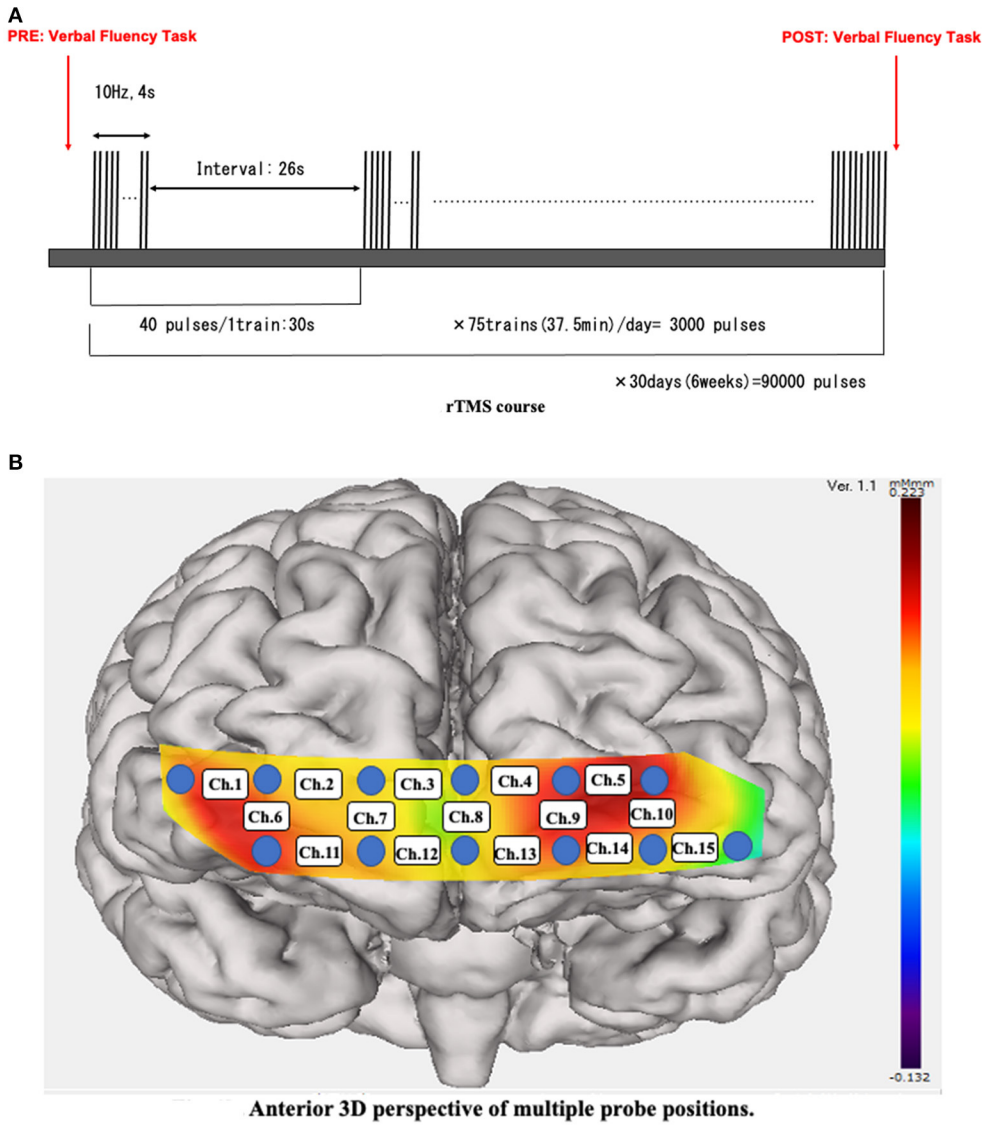

FIGURE 1 | (A) rTMS course. A 10-Hz pulse sequence was applied for 4 s followed by a 26-s interval. We applied 3,000 pulses per train for 75 trains per day over the course of hospitalization. rTMS, repetitive transcranial magnetic stimulation. **(B)** Anterior 3D perspective of multiple probe positions. Twelve probes (lowest probes according to the Fp1–Fp2 line) were placed on the anterior brain. The 15 channels were divided into temporal (Ch. 1, 6, 10, and 15) and frontal (the remaining channels) positions.

using a 12-probe device was used to assess changes in oxy-Hb and deoxy-Hb in the brain during the VFT. The full VFT procedure included a 30 s pre-task baseline, a 60 s VFT, and a 70 s post-task baseline. For the pre- and post-task baseline periods, participants were instructed to repeat aloud the five Japanese vowels ("a," "i," "u," "e," "o"). The subtraction method (task minus pre- and post-task baseline) minimized vocalization effects during the VFT. During the task, participants were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (1. /to/,/se/,/o/; 2. /a/,/ki/,/ha/; 3. /na/,/i/,/ta/) were presented in counterbalanced order among the subjects, and each syllable changed every 20 s during the 60 s task (23, 24). Briefly, the fixed fNIRS probes were 3 × 11 thermoplastic shells, and we set the lowest probes according to the Fp1–Fp2 line, along the international 10–20 system used in EEG (**Figure 1B**). Participants sat comfortably in a quiet, day-lit room. The task procedures were explained by a clinical laboratory technician who subsequently monitored head movement during the procedure. To avoid the effect of motion artifacts, data with clear evidence of head movement were omitted from further analysis. Similar to a widely used assessment method (2), the integral value of oxy-Hb and the centroid value of oxy-Hb were calculated for the frontal and temporal lobes using

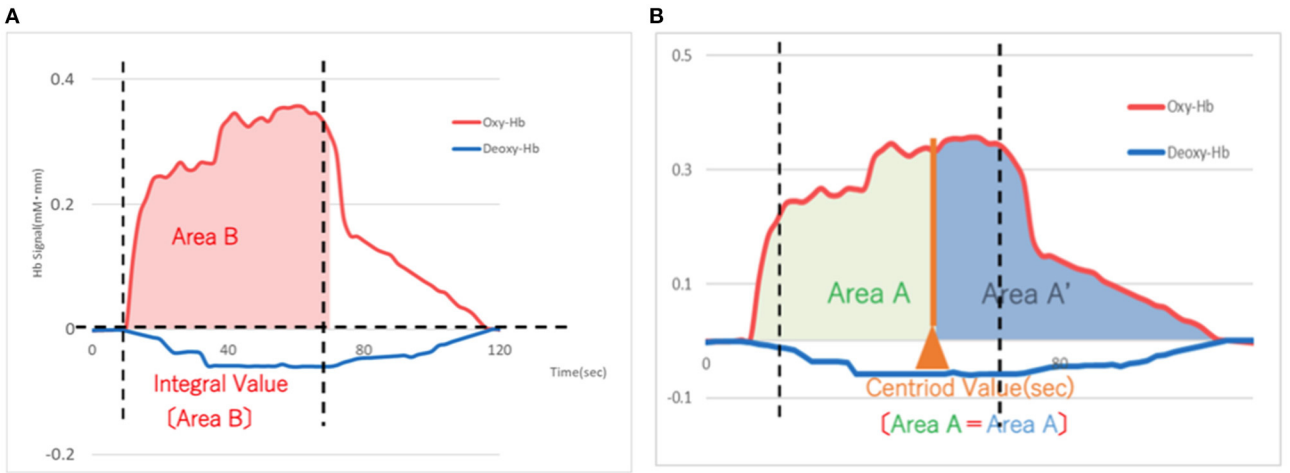

FIGURE 2 | (A) Schema of the integral value of blood flow (Area B) based on the means of 15 patients with depression after rTMS treatment. The integral value of oxygenated hemoglobin (red) represents an increase in blood flow for each probe. X-axis: time (sec), Y-axis: Hemoglobin signal (mM-mm) rTMS, repetitive transcranial magnetic stimulation. **(B)** Schema of the centroid value (timing of activation) based on the means of 15 patients with depression after rTMS treatment. The centroid value of oxygenated hemoglobin (red) is the timing of activation on each probe. X-axis: time (sec), Y-axis: Hemoglobin signal (mM-mm) rTMS, repetitive transcranial magnetic stimulation.

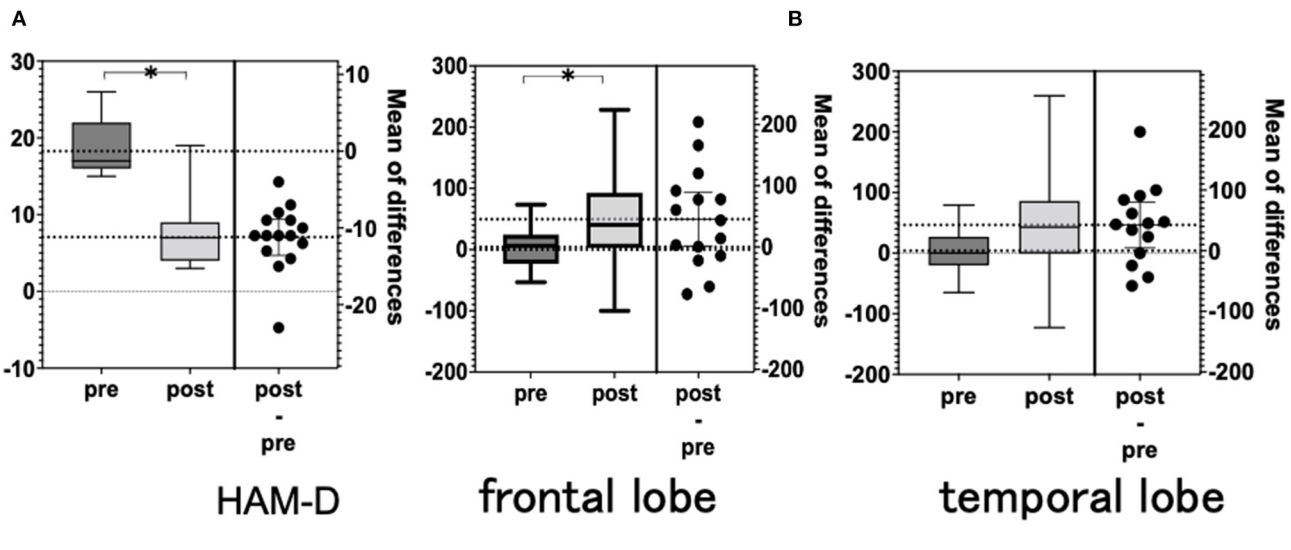

FIGURE 3 | (A) Hamilton Depression Scale (HAM-D). **(B)** NIRS integral values (average). NIRS, near-infrared spectroscopy.

channel 2–14 and channel 1 and 15, respectively (**Figures 2A,B**). These were captured between pre- and post-VFT (**Figure 1A**). On the healthy controls measured by fNIRS, the oxyhemoglobin concentration is generally more pronounced in response to the VFT, increasing during VFT execution and reaching a peak value at the end of the VFT. Oxyhemoglobin then gradually returns to baseline values (25).The integral value of oxy-Hb is the value of frontal brain activation, whereas the frontal centroid value is the timing of activation and is often used to distinguish psychiatric disorders. A *t*-test was used to compare pre- and post-treatment values to detect the significance.

RESULTS

HAM-D

The total HAM-D score was significantly lower after rTMS than before rTMS. The total HAM-D score decreased in 14 of the 15 patients but remained unchanged in 1 patient (**Table 2** and **Figure 3**).

fNIRS

There was a significant difference in the mean integral value at the frontal and temporal cortices when comparing pre- and

TABLE 2 | The difference between pre- and post-rTMS treatment regarding the severity of depression (HAM-D) and fNIRS assessment.

	Pre		Post		*t*-stats	*p*-value		df
	Mean	SD	Mean	SD				
HAM-D	18.27	3.75	7.07	4.03	−10.14	<0.001	**	14
Integral value at frontal cortex	4.18	33.67	49.64	89.67	2.19	0.05	*	14
Centroid value at frontal cortex	57.61	21.18	51.63	41.28	−0.45	0.66	n.s.	14
Integral value at temporal cortex	4.01	41.32	46.44	90.75	2.42	0.03	*	13
Centroid value at temporal cortex	58.89	27.14	69.16	15.88	1.22	0.21	n.s.	13

*$p<.05$ **$p<.01$

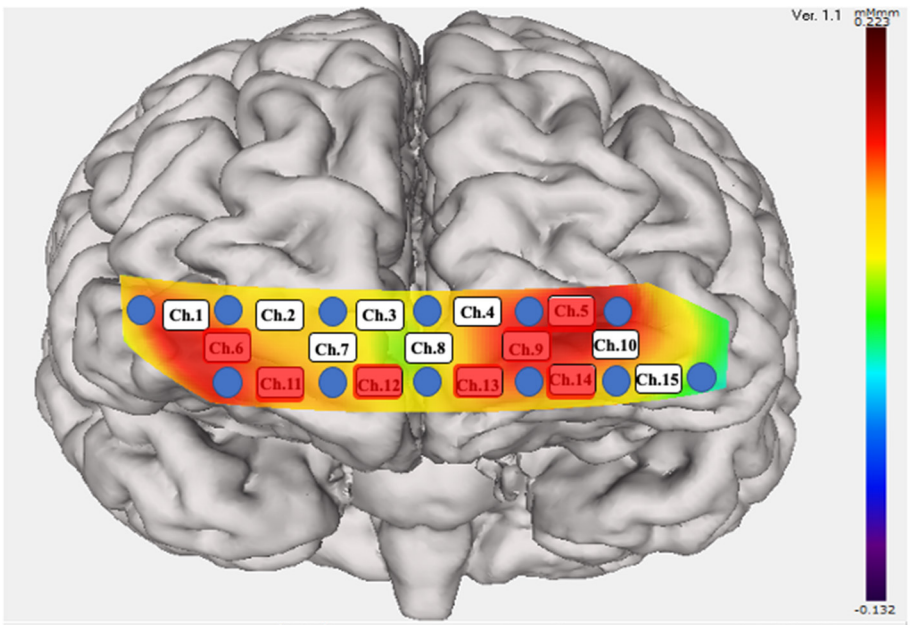

FIGURE 4 | Significant increase in the integral value of blood flow. Twelve probes (lowest probes according to the Fp1–Fp2 line) were placed on the anterior brain. Fifteen channels were divided into temporal (Ch. 1, 6, 10, and 15) and frontal (the remaining channels) positions. A significant increase in blood flow was seen in the red colored probes.

post-rTMS (**Figures 3A,B**). However, there was no significant difference in the mean centroid values for both the frontal and temporal regions. The analysis of each channel showed a significant increase in the integrated values of frontal channel 5, 9, 11, 12, 13, and 14 and temporal channel 6 (**Figure 4**). A similar analysis of the centroid values showed significant increments at frontal channel 5, 11, 12, 13, and 14, and temporal channel 1 and 10.

DISCUSSION

Fourteen of 15 depressed patients showed improvement in symptoms after rTMS treatment. In addition, the integral value of NIRS measurements of cerebral blood flow before and after treatment showed an ∼10-fold increase (5 ± 2.5 vs. 50 ± 15). Our previous research found that the severity of various psychiatric disorders was correlated with the integral value of the frontal lobe with fNIRS ($n = 43$) (23). The current data consisting of MDD showed symptomatic improvement; therefore, it is possible that this marked increase in the integral value in the frontal lobe was due to these effects.

Earlier Studies

Initial studies utilizing both rTMS and fNIRS attempted to determine the physiological mechanisms underlying MDD. fNIRS observed simultaneously or immediately after rTMS demonstrated a significant change in the time course of oxy-Hb (26, 27). In those studies, researchers attempted to reveal the most beneficial conditions for brain stimulation. The combination of rTMS coil and fNIRS probes confirmed an intensity-dependent increase in oxy-Hb (27). However, in the current study, fNIRS assessment was compared between pre- and post-30 days of rTMS treatment at a 120% motor threshold intensity. This

is because our primary aim was to observe dynamic oxy-Hb changes after successful rTMS treatment in patients with MDD. Fifteen patients with moderate MDD showed significant improvement in their depression symptoms without major adverse events. Several patients experienced scalp discomfort during early stimulation, although the discomfort disappeared within 10 stimulations.

Eschweiler et al. conducted a pilot study utilizing fNIRS and rTMS to reveal whether the putative therapeutic effect of rTMS depends on the hemodynamic dysfunction of the left DLPFC in patients with depression ($n = 12$) (28). To date, this is the only previous study that assessed rTMS with fNIRS at the DLPFC in the brains of depressed patients based on a recent systematic review (29). Their design differed significantly from that of the current study in terms of stimulation patterns, strength of stimulation, interval days, task during the procedures of fNIRS, the existence of sham controls, and instruments; therefore, it is impossible to precisely compare their findings with ours, although total Hb increased on the mirror drawing task at the position next to the coil position. This is partly similar to the current study, although future research is required to shed light on the complexity of fNIRS and rTMS in patients with depression. In contrast, a recent study demonstrated fNIRS recordings during stimulation (30). They analyzed 15 patients with depression. Their fNIRS device had only one channel; thus, it was difficult to detect detailed locations in the brain, but they suggested that an increase in hemoglobin at the end of treatment would improve the treatment effect.

Hypofrontality and the Differences Between rTMS and Antidepressant Treatment

The main finding of the present study is the significant increase in the integral value of oxy-Hb during the rTMS consisting of 30 sessions. Of note, the integral value of oxy-Hb was increased during measurements of the VFT. Compared to a study utilizing antidepressant medication (13) (paroxetine, milnacipran, or mirtazapine), rTMS was different in terms of consistent hypofrontality despite similar improvements in depressive symptoms. Although they are similar MDD treatment options, direct electrical stimulation *via* ECT or rTMS (31) differ from monoaminergic (especially by serotonergic) reactions resulting from antidepressant medication. Our rTMS finding is in accordance with the ECT study (32) in terms of the increase in cerebral blood flow after treatment, unlike for the study utilizing antidepressant medication (13). More than 85% of cerebral glucose is used mainly by neuronal synaptic activity (33); therefore, the difference in blood flow between the two treatments indicates altered activity in the synapse. While antidepressant medication simply increases the monoamine (especially serotonin and noradrenalin) levels in the synapses, it has been suggested that neuronal connectivity *via* the reconstitution of synapses occurs in these two stimulation treatments (33). In particular, when cortical- limbic connectivity is measured, the functional connection increases rapidly (34). The left DLPFC was the region where rTMS was stimulated in this study, and we found a marked increase in blood flow as assessed by fNIRS. This suggests that much of the reconstitution of synapses occurs in the course of rTMS treatment, although we did not measure the connectivity assessed by fMRI in the current study. Moreover, it is known that the penetration depth by fNIRS stays close to the surface (typically in the range of 10–40 mm from the skull) (35). Meanwhile stimulation by rTMS reaches relatively deep into the brain. This is because the mechanism of action of rTMS is due to the generation of a magnetic field, which is known to have an effect as deep as the DLPFC (typically 20–40 mm from the surface of the brain) (36, 37). In the future, we aim to simultaneously observe blood flow and connectivity during rTMS treatment.

Comparison Between rTMS and ECT

Generally, rTMS and ECT are the treatment options for treatment-resistant depression, which is defined as non-response to adequate doses of two different antidepressants taken for a sufficient duration of time. This may indicate that the two modulation treatments were differentially effective compared to the antidepressant medications. A meta-analysis of high-frequency left DLPFC rTMS for treatment-resistant depression yielded a weighted mean difference of 2.31, and an effect size of 0.33, compared to sham stimulations (38, 39). For patients with one or more unsuccessful antidepressant drug therapy, a recent guideline recommended rTMS as a first-line alternative treatment option rather than ECT based on more than 30 systematic reviews and meta-analyses (39). Another systematic review concluded that ECT was the most efficacious but least tolerated option, while rTMS was the best tolerated treatment for MDD. It is because of the side effect due to ECT, such as transient cognitive impairment, which could be induced by a massive increase in CBFV (cerebral blood flow velocity). The amount is increased by about a 100% (40, 41) while an increase of 3.6–5.6% of CBVF in the hemisphere is stimulated by rTMS (42).

LIMITATIONS AND CONCLUSION

This study had several limitations. First, our data were solely derived from two points within a short duration. Another potential limitation is the small sample size and the lack of a sham control design. In conclusion, this study described the rTMS-induced modulation of the blood oxygenation response over the DLPFC in patients with depression, as captured by fNIRS. Future longitudinal studies and the comparison between the sham controls are warranted to assess cerebral blood flow dynamics during rTMS treatment for depression.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Osaka Medical

and Pharmaceutical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YKa: study design, data acquisition, data interpretation, data analysis, and writing the first draft. S-iI and KM: study design, data acquisition, and data interpretation. KT: data interpretation and critics on the first draft. MK and SK: data acquisition, data interpretation, and critics on the first draft. YKu: data interpretation and data analysis. YN: data acquisition and data interpretation. TK: study design, data interpretation, data analysis, and writing the final manuscript. All authors have approved the final article should be true and included in the disclosure.

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