



ORIGINAL ARTICLE

The functional near-infrared spectroscopy in the diagnosis of schizophrenia



J. Tian^{a,b,1}, J. Wang^{a,b,1}, W. Quan^{a,b,*}, B. Lv^c, J. Liu^{a,b}, C. Hobbie^d, X. Kong^e, W. Dong^{a,b,*}

^a Peking University Sixth Hospital (Institute of Mental Health), Beijing 100191, China

^b National Clinical Research Center for Mental Disorders & Key Laboratory of Mental Health, Ministry of Health (Peking University), Beijing 100191, China

^c China Academy of Telecommunication Research of Ministry of Industry and Information Technology, Beijing, China

^d Carleton College, Northfield, MN 55057, United States

^e Martinos Center of Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129, United States

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Abstract

Background and objectives: Obtaining an objective schizophrenia diagnosis is difficult given current practices. This study aims to evaluate the potential of functional near-infrared spectroscopy (NIRS) in diagnosing individuals with schizophrenia.

Methods: This study recruited 100 subjects with schizophrenia (45 males; 55 females) and 70 healthy controls (36 males; 34 females), and analyzed the spectrum of NIRS signals from ETG-4000 Optical Tomography System while subjects took the Verbal Fluency Test (VFT). Two professional psychiatrists performed the wave analysis.

Results: There was no statistical difference in the number of words produced during the VFT detected between individuals with schizophrenia and the control group. Results demonstrated that NIRS had an 89.0% sensitivity and 88.6% specificity in identifying individuals with schizophrenia.

Conclusion: The results of this study indicated that NIRS spectrums could play a significant role in the diagnosis of schizophrenia by providing an objective index for clinical screening and diagnostic assistance.

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* Corresponding authors.

E-mail addresses: quanwx302@aliyun.com (W. Quan), dongwentian@bjmu.edu.cn (W. Dong).

¹ These authors contributed equally to this work.

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Introduction

Schizophrenia is a common mental illness that has high rates in morbidity, disability, and recurrence.^{1,2} In 2004, the Global Burden of Disease Assessment by the World Health Organization reported that schizophrenia has a prevalence of 2.3% worldwide.³ An epidemiological investigation on mental disorders found that the lifetime prevalence of schizophrenia in China increased from 0.6% in 2012.⁴

Given the subjective nature of a clinical diagnosis of schizophrenia, professional psychiatrists with a great extent of clinical knowledge and experience are required who then diagnose individuals after communicating with and observing behavior of patients. In order to provide a more objective evaluation, research is focusing on neuroimaging, such as PET, SPECT, and fMRI, to identify possible neurobiological markers for schizophrenia.^{5,6} These breakthrough neuroimaging studies provide substantial evidence supporting the use of possible biomarkers as diagnostic tools for schizophrenia in the future.

One challenge of using neuroimaging to study schizophrenia is the difficulty in keeping a patient's head stable, which can be addressed using the near-infrared spectroscopy (NIRS) method. NIRS measurements are currently used in clinical diagnosis and research by detecting functional responses in the brain to cognitive processes. It has benefits of a higher time resolution and anti-interference abilities while allowing for painless and non-invasive detection of brain activity. These advantages were further confirmed by Tomohiro.⁷ Near-infrared light penetrates the cerebral cortex and can be partly absorbed by hemoglobin in the blood. By measuring absorption and reflection of certain wavelengths, we can detect changing levels of oxygenated (Oxy-Hb) and deoxygenated (Deoxy-Hb) hemoglobin.⁸ In 2009, Koike and Fukuda reported that NIRS was approved in Japan as a method to aid in the clinical diagnosis of depression, which was its first approval in the field of psychiatry.^{9,10} Thus, NIRS could be an effective tool for clinical study and diagnosis in psychiatry.

NIRS has been widely used in combination with the Verbal Fluency Test (VFT) to study schizophrenia in individuals.^{11,12} The VFT is a typical task to test cognitive function, and the most commonly used cognitive paradigm to study schizophrenia.^{7,13} The brain's frontal cortex is activated during the complex cognitive activity required by the VFT test.^{14–16} By utilizing VFT methods, differences of functional activity in the frontal cortex, particularly the orbitofrontal area, have been observed in patients with schizophrenia.^{17–20} Also, using Principal components analysis (PCA)-based feature extraction on oxygenated hemoglobin levels and support vector machine (SVM) classifier, several studies found the high accuracy, from 83.37% to 93.33%, on diagnosing schizophrenia.^{21–23} However, machine learning method has its own limitations, for example, they need huge number of data. In this study, based on previously described NIRS methods, we discuss the novel feasibility of using NIRS as an auxiliary method in the diagnosing schizophrenia.

Emerging schizophrenia studies focus on the frontal cortex, the main area for higher cognitive functions such as executive function and working memory.^{24,25} A large number

of studies have correlated changes in Oxy-Hb concentrations with schizophrenia.^{26,27} Yamamuro et al. found that Oxy-Hb changes in the prefrontal cortex were significantly smaller in individuals with schizophrenia.²⁷ Thus, the neural activities of patients can be observed by detecting the relative concentration curves of Oxy-Hb. In this novel study, we discerned the concentration curve of Oxy-Hb that can predict the diagnosis of Chinese patients with schizophrenia.

Materials and methods

Participants

Participants for this study consisted of inpatients from November 2012 to August 2013 with schizophrenia, who had been diagnosed following criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).²⁸ All 100 patients (45 males; 55 females) aged 18–60 years old were right-handed. All patients used antipsychotic medication in conventional dosages (daily chlorpromazine equivalent of 579.72 ± 34.24 mg). 56 patients exhibited positive symptoms such as hallucinations and thought disorders. 19 patients exhibited extrapyramidal symptoms and received dosages of Trihexyphenidyl (Table 1). The exclusion criteria was: schizophrenia accompanied with mental retardation and organic brain disease; severe physical ailments; current alcohol or drug abuse; uncooperative patients; currently pregnant or lactating. 70 psychiatrically healthy control subjects (36 males; 34 females) were recruited from July 2011 to July 2012 (see Table 1). This study was approved by Peking University Sixth Hospital Ethics Committee. All participants were provided informed consent before enrollment.

Procedures

VFT task

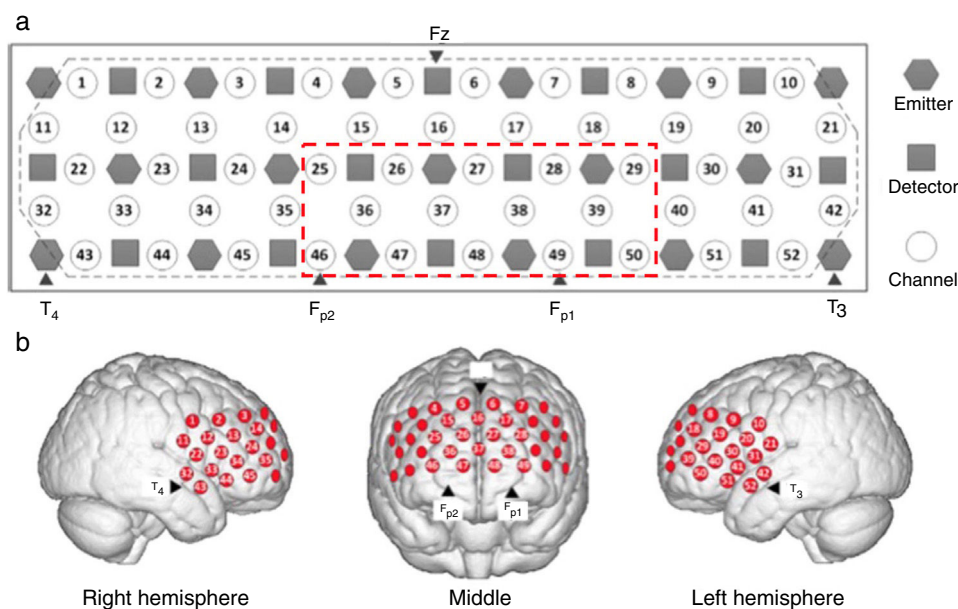
The VFT was performed in a quiet examination room. Subjects were asked to sit in a relaxed position and focus their eyes on a cross (5 cm × 5 cm) on the screen with a distance of 75 cm between eyes and screen. They were informed to keep their head and body stable for the following 3 min of test. The VFT task was phonological VFT in Chinese version, it was developed by Quan,^{29,30} it consists of four stages: first, 10 s of pre-scanning; second, 30 s of a waiting stage where subjects were asked to count from 1 to 5 repeatedly in a low voice; third, 60 s of stimulation time in which subjects were asked to produce as many words as possible that start with a character offered verbally by the psychiatrist (three characters, 20 s for each one). The three high frequency Chinese characters were '白', '天', and '大' (meaning 'white', 'sky', and 'big' respectively), they are commonly used in daily life; fourth, 70 s of a resting stage where, as in stage two, subjects were asked to count from 1 to 5 repeatedly in a low voice.

NIRS data collection

The NIRS measurements were conducted throughout the VFT with an ETG-4000 Optical Tomography System (Hitachi, Japan) with 52 channels. In this study, 11 channels were utilized to collect data from the prefrontal cortex, especially in the frontopolar and orbitofrontal areas,^{31,32} including CH25,

Table 1 Characteristic comparisons between the neurotypical and patient groups including gender, age, years of education, and words produced in VFT.

	Neurotypical group	Patient group	χ^2/t	p
Gender (male/female)	36/34	45/55	0.68	0.44
Age, year	37.4 ± 1.38	34.76 ± 1.05	1.596	0.112
Years of education, year	14.16 ± 0.41	13.64 ± 0.28	1.092	0.276
Number of words	10.19 ± 0.43	9.62 ± 0.44	0.895	0.372
Duration of illness, year	–	8.66 ± 0.74		
Onset age, year	–	25.17 ± 0.98		
BPRS	–	34.44 ± 0.92		
Chlorpromazine equivalent dose, mg/day	–	579.72 ± 34.24		
Trihexyphenidyl, mg/day	–	4.74 ± 1.52		

**Figure 1** Schematic diagram of near-infrared spectroscopy probe and channel settings. (a) The emitters, detectors and channels are shown as hexagon, square and circle respectively. The channels in the rectangle are in the frontopolar and orbitofrontal areas. (b) The location of channels according to the international 10–20 system. The probe array is centered in the NASION–INION line and its lowest boundary is positioned along the Fp1–Fp2 line.

CH26, CH27, CH28, CH36, CH37, CH38, CH46, CH47, CH48, and CH49.¹⁴ The 11 channels used are typical channels of the frontopolar and orbitofrontal area³⁰ and atypical activity in this area is positively correlated with schizophrenia.^{19,20} In addition, this area is in the middle of the frontal lobe and not covered by hair, rendering measurements therefrom superior to other locations. The orbitofrontal area is the proper place for NIRS measurement to diagnose schizophrenia. The location of these channels is provided in Fig. 1. The wave analysis was performed by two professional psychiatrists (Quan WX and Tian J) who were blind to the patient condition and had worked in the NIRS Lab for more than 5 years.

NIRS data analysis

Data were analyzed using the integral mode of the ETG-4000 machine. A linear fit was applied to the data between baseline levels. The pre-task and post-task baselines were defined as the mean value of the 10-s period just prior to the

task and at the end of the 70-s post-task period, respectively. A 5 s moving average was calculated to remove any short-term motion artifacts.^{33,34}

Previous studies have found that the spectrum consists of a stationary wave under baseline resting conditions and a fluctuating wave under test conditions.

Spectrum in neuro-typical individuals:

The average oxy Hb concentration increases rapidly at the beginning of the VFT task period, and then begins to decline after peaking. The peak of the spectrum is located at the frontal position. Concentrations then decline to baseline levels after the VFT task has concluded^{13,35} (Fig. 2a).

Spectrum in individuals with schizophrenia:

The average oxy Hb concentration increases moderately during the task period and begins to decrease immediately after the end of the task period. Concentrations then increase again (re-ascend) during the post-task period^{7,13} (Fig. 2b).

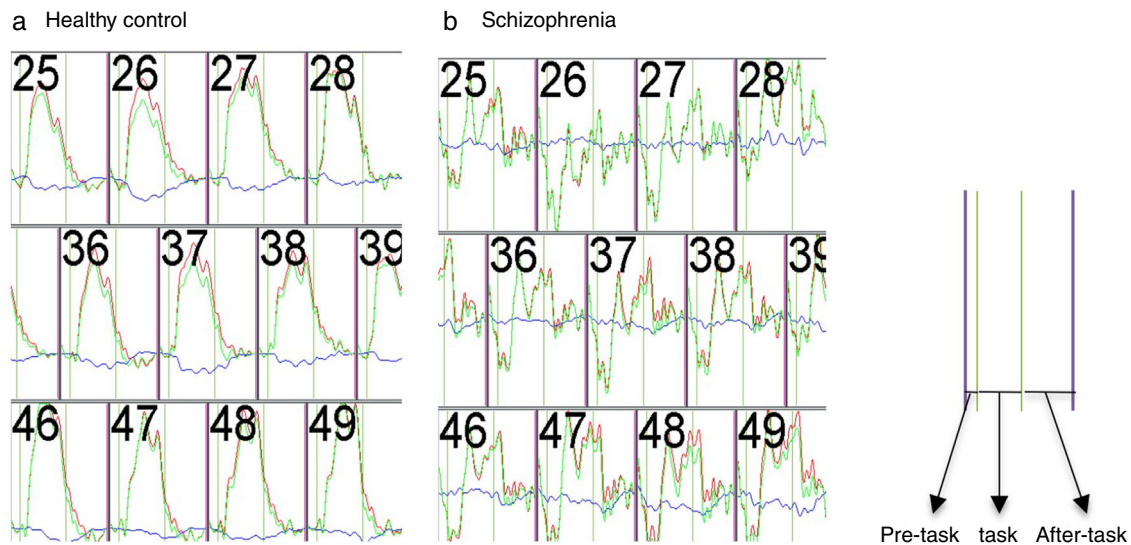


Figure 2 The average oxy Hb concentration in the prefrontal cortex of representative schizophrenia and control subjects during VFT. (a) Healthy control related spectrum. (b) Schizophrenia-related spectrum. Red, Oxy-Hb; blue, Deoxy-Hb; green, total Hb.

Table 2 Latency of peak waves (mean/SD) in patient groups.

	Early peak(<i>n</i> = 11)	Late peak(<i>n</i> = 18)	Re-ascending(<i>n</i> = 11)
Mean	682.37	862.95	1074.65
SD	101.98	18.33	108.74
Range	502–796	820–892	906–1319

A minimum value of 0.1 was necessary to identify a peak. If the peak appeared after the VFT task, it was considered re-ascending. If a peak appeared before 50 s (early peak wave) during the task period and there was no re-ascending peak after the VFT task (latency ≤ 80 s), the spectrum was considered neurotypical. If a peak appeared after 50 s (late peak wave) during the task period (latency > 80 s), or there was re-ascending peak after the VFT task (latency > 90 s), the spectrum was considered schizophrenia-related. The peak latencies of three waves are shown in Table 2. The peak detection methodology used was also previously described in Japanese studies.^{13,36}

Sensitivity and specificity

Sensitivity, reflects true positive rates in patients, was calculated by: “true positive number”/ (“true positive number” + “false negative number”) $\times 100\%$. Specificity, reflects true negative rates in neuro-typical subjects, was calculated by: “true negative number”/ (“true negative number” + “false positive number”) $\times 100\%$.

Clinical symptoms

The Brief Psychiatric Rating Scale (BPRS) was used to evaluate severity of psychotic symptoms. BPRS comprises of 18 items that can be scored from 1 (not present) to 7 (very severe). Ratings were given based on clinical interviews with and behavioral observations of patients over the 1–3 days

before the start of the study. Global scores were used to indicate the severity of clinical symptoms.³⁷

Data analysis and statistics

SPSS 20.0 was used for the data and statistical analysis using Chi-squared tests and *t* tests. Pearson’s correlation was employed to calculate correlation coefficients between Oxy-Hb peak detection and clinical symptoms.

Results

General information

No statistical differences ($\chi^2 = 0.68$, $p > 0.05$; $t = 1.60$, $p > 0.05$; $t = 1.09$, $p > 0.05$) were found between the control and patient groups in terms of gender, age (37.4 ± 1.38 vs. 34.76 ± 1.05), and years of education (14.16 ± 0.41 vs. 13.64 ± 0.28) (Table 1). The average treatment dose taken by patients with schizophrenia in this study was 579.72 ± 34.24 mg/d (dose conversion was subject to chlorpromazine). The average score of BPRS in schizophrenia was 34.44 ± 0.92 . The average onset age of the disease was 25.17 ± 0.98 years old with a duration of 8.66 ± 0.74 years. No statistical difference ($\chi^2 = 0.04$, $p > 0.05$; $t = -0.15$, $p > 0.05$) were found between 56 patients with positive symptoms and 44 patients without positive symptoms in terms of re-ascending wave and peak latency. No statistical difference ($\chi^2 = 1.51$, $p > 0.05$; $t = 0.66$, $p > 0.05$) was found

Table 3 Classification of spectrums between control and patient groups.

	Early peak wave and no re-ascending	Late peak wave or re-ascending	Total
Control group	62	8	70
Patient group	11	89	100

between 19 patients with extrapyramidal symptoms and 81 patients without extrapyramidal symptoms in terms of re-ascending wave and peak latency.

Results of VFT

No statistical difference in number of words produced during the VFT was observed ($t = 0.90$, $p > 0.05$) between the control (10.19 ± 0.43) and patient groups (9.62 ± 0.44).

NIRS

Two psychiatrists assessed the spectrum separately, there were inconsistent diagnosis in 5 data, 3 persons in control group and 2 persons in schizophrenia group, for the reason of low spectrums and two equal peaks. They discussed inconsistencies to provide a final result.

Sensitivity and specificity were calculated based on Table 3 and were 89.0% and 88.6%, respectively. Correlational analyses were conducted comparing peak detection of Oxy-Hb and BPRS scores. The correlation coefficient was -0.078 and not significant ($p = 0.448$).

Discussion

In this study, based on the diagnosis of clinical psychiatrists using DSM-IV, the NIRS spectrum played a great role in diagnosis of schizophrenia. Furthermore, there was no correlation between a change NIRS measurements and clinical symptoms. These results suggest that using NIRS is an effective and feasible tool to diagnose schizophrenia.

In Japan, related studies showed that the sensitivity and specificity of NIRS in diagnosing schizophrenia is 58.9% and 94.6%, respectively.¹³ Our study found a higher sensitivity, 89.0%. This improved sensitivity could be attributed to a larger sample size in our Chinese study. Alternatively, different languages and populations may have caused this difference. Despite these differences, the two studies indicate that NIRS is an emerging and promising technology for psychiatry.

VFT is the most common cognitive paradigm used in schizophrenia.^{7,13} There are two common versions of the VFT task: the administrator either provides a letter or a category, with the letter version inducing overall stronger brain activation than the category version.¹² In this study, we used a revised Chinese letter version of the VFT task widely used in our previous studies,^{29,30} and showed that it has potential for combining with NIRS to diagnose schizophrenia.

After analyzing the VFT results, we found no statistical difference between neurotypical and patient groups (10.19 ± 0.43 vs. 9.62 ± 0.44). Differences in behavioral patterns are not easily observed in such a short test time (20 s

for each character). However, differences did appear in the NIRS spectrum between the two groups after the VFT. Thus, by detecting the concentration of Oxy-Hb and Deoxy-Hb, the NIRS method is much more sensitive than the behavioral test.

In this study, we have shown that individuals with schizophrenia may possess their own unique spectrum from NIRS measurement, which has potential as a diagnostic tool.

This study was limited by a few factors. For one, all of the patients had taken psychiatric drugs, the effects of which on data measurements could not be totally ruled out. Second, further research with a larger sample size following this preliminary study needs to be performed. Third, this study only examined patients with schizophrenia and did not include those with depression and other psychiatric illness. This is important, because in psychiatry, a differential diagnosis is the most difficult, but also most needed. Fourth, using peak latency of NIRS spectrum to ascertain the diagnosis of schizophrenia in this study may be not comprehensive. Futures studies should investigate whether other features of NIRS spectrum should be used either alone or in addition to peak analysis. Finally, this study only analyzed 11 channels in the orbitofrontal cortex and more channels in the prefrontal cortex may be useful. This is another potential avenue for expansion into future research.

This research is a primary study to provide a new perspective highlighting the potential role for NIRS in the diagnosis of schizophrenia. Going forward, more effort should be focused on the sensitivity and specificity of NIRS in differential diagnosis of other disease in psychiatry, such as depression and bipolar disorder. The utilization of NIRS will benefit patients as well as psychiatrist to diagnose and cure psychiatric diseases.

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Conflict of interest

The authors declared that they have no conflicts of interest to this work.

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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