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Reduced prefrontal activation during Tower of London in first-episode schizophrenia: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Cognitive impairments are considered as a core feature of schizophrenia and have been reported in associated with dysfunction of the prefrontal cortex (PFC). The Tower of London (TOL) task is a widely used neuropsychological test to assess the planning ability and the PFC function. In the present study, we examined functional changes in the PFC of 40 first-episode schizophrenia patients and 40 age- and gender-matched healthy controls by means of multi-channel Near-infrared spectroscopy (NIRS) during performance of the TOL task. NIRS is a noninvasive optical method that can measure relative changes in oxygenated ([oxy-Hb]) and deoxygenated ([deoxy-Hb]) hemoglobin in cortical tissue. Compared to the healthy controls, schizophrenia patients exhibited a significant decreased activation in the left PFC and poorer TOL performance. The results confirm the functional deficits of the PFC and impaired planning ability in first-episode schizophrenia patients and suggest that NIRS may be a useful clinical tool for evaluating PFC activation in psychiatric disorders.

Schizophrenia is characterized by a broad range of cognitive impairments, such as abnormalities in attention and information processing, working memory, problem solving, processing speed and memory retrieval [20]. The ability of planning, which involves several subprocesses, including strategy information, coordination and sequencing of mental functions and holding information online, is an essential component of higher order cognitive processes [16,34]. The Tower of London (TOL) task is a widely used test to assess planning ability [28]. The TOL task is an adaptation of the Tower of Hanoi and consists of moving colored balls within a limited number of moves in order to achieve a given target configuration [25]. The prefrontal cortex (PFC) is an important part of the cortical network of planning ability, as suggested by previous studies reported poor TOL performance in schizophrenia patients [17,27]. Therefore, assessing PFC function is essential to elucidate the schizophrenia pathophysiology.

Multi-channel near-infrared spectroscopy (NIRS) is a recently developed optical method that allows noninvasive in vivo measurements of changes in the concentration of oxygenated ([oxy-Hb]) and deoxygenated ([deoxy-Hb]) hemoglobin in brain issue. Since Jobsis [9] first found that useful information in brain could be obtained using light and detected from the scalp, NIRS has been well established as a functional imaging method recently. The technique is based on the principle that near-infrared light (wavelengths from 650 to 900 nm) penetrates biological tissues and is mainly absorbed by the two chromophores [oxy-Hb] and [deoxy-Hb], which have different light absorption spectra in the near-infrared range, then the changes in chromophore concentrations can be detected by measuring changes of the amount of reflected near-infrared light in the skull. Cortical activation found by NIRS suggested an increase in [oxy-Hb] and a corresponding decrease in [deoxy-Hb] [6,7,21]. Compared with other functional neuroimaging methodologies, such as PET, SPECT and fMRI, NIRS is especially suitable for studying psychiatric disorders, due to the following reasons: low susceptibility to movement artifacts, less restrictive and compact, lower cost. Accordingly, multi-channel NIRS has been employed to study the brain functions in many psychiatric disorders, such as schizophrenia, depression, bipolar disorder and post-traumatic stress disorder [10,14,15,29,30]. However, nearly all these studies used verbal fluency test (VFT) as an activation task and only a limited number of reports using the TOL task to assess planning ability by means of multi-channel NIRS.

In the present study, we used multi-channel NIRS to investigate PFC activation during TOL task in first-episode schizophrenia patients. We hypothesized that the schizophrenia patients would differ in their PFC activation patterns from the healthy controls and had a poorer TOL performance.

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Table 1
Clinical characteristics of the schizophrenia group and the control group.

	Schizophrenia patients ($N = 40$)		Healthy controls ($N = 40$)		Group difference P value
	Mean	SD	Mean	SD	
Age (year)	22.8	4.93	24.4	3.63	0.102
Gender (women/men)	20/20	–	22/18	–	0.823[a]
Education (year)	13.29	2.17	14.08	2.22	0.113
Age at onset (years)	20.97	3.27	NA		
Duration of illness (months)	15.48	8.06	NA		
PANSS	73.38	13.99	NA		
Positive	19.33	3.43	NA		
Negative	16.63	4.83	NA		
General psychopathology	33.83	4.91	NA		

PANSS, Positive and Negative Symptom Scale; NA, not applicable.
[a] Chi-square test was used for testing the group difference of the gender. Otherwise, t-test was used.

Forty schizophrenia patients and forty age- and gender-matched healthy controls participated in the study. The patients were recruited from outpatients and inpatients in the Psychiatry Department of the Renmin Hospital of Wuhan University from January 2009 to November 2009. Schizophrenia was diagnosed according to the Structured Clinical Interview of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [1] with less than 2 years duration of illness. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) [11]. All patients were receiving antipsychotic medication as follows: risperidone ($n = 23$, 3.10 ± 1.60 mg/d), aripiprazole ($n = 6$, 16.67 ± 10.33 mg/d), ziprasidone ($n = 6$, 86.67 ± 45.02 mg/d), quetiapine ($n = 3$, 466.67 ± 152.75 mg/d) and olanzapine ($n = 2$, 12.50 ± 3.54 mg/d). The healthy controls had no personal or family history of neuro-psychiatric illness and were free of medication. The exclusion criteria for both groups were a history of electroconvulsive therapy, alcohol or substance abuse, neurological disorders and head trauma. All the participants were right-handed as determined by the Edinburgh Handedness Scale [22] and gave written informed consent after complete explanation of the procedures. This study was approved by the Medical Ethics Committee of Wuhan University. The demographic and clinical characteristics of the subjects are summarized in Table 1.

The present version of the TOL task consisted of five conditions: a zero-move control condition and four planning conditions ranging from one to four moves. In the planning condition, subjects were presented a start configuration (in the upper half of the screen) and a target configuration (in the lower half) (see Fig. S1B). In both configurations, three colored balls (blue, green, red) on three pegs, which could accommodate 1, 2, and 3 balls each. One ball could be moved at a time and only when there was no other ball on top. Subjects were requested to determine the minimum number of moves necessary to reach the target configuration and whisper the solution. Verbal responses were recorded by the investigators. In the control condition, subjects were presented a series of pictures that consisted of zero-move problems (i.e. the two configurations presented were identical), with the aim of preventing planning activity (see Fig. S1A). The cognitive task was presented in a block design using the Presentation software (http://nbs.neuro-bs.com/) running on a PC. Two blocks of 60 s of control condition alternated with two blocks of 120 s of TOL planning condition. Presentation order of the stimuli in the planning condition was pseudo-random with a distribution frequency of the four stimulus types derived from van den Heuvel et al. [34].

NIRS measurements were conducted with a 28-multi-channel continuous wave optical instrument CW5 (TechEn Inc, American). The CW5 measures changes of concentration of [oxy-Hb] and [deoxy-Hb] using near-infrared light at two wavelengths 690 and 830 nm based on the modified Beer–Lamberd law [13]. In this study, we used two 14-channel arrays of probes for bilateral frontal regions. Each array was consisted of four optical source-probes and eight detector probes. The distance between the pair of source-detector probes was 3.0 cm, and it was considered that the machines measure points at 2–3 cm depth from the scalp, that is, the surface of cerebral cortices [10]. Each measurement point between one source and its neighbor detector was defined as a channel. Therefore each array allows to measure the relative changes in [oxy-Hb] and [deoxy-Hb] at 14 channels and covered an area of 5.7 cm × 5.8 cm on the scalp. The probes were mounted on two plastic helmets that were held by adjustable straps over the subject's bilateral frontal lobes, with the most inferior and former probe positioned Fp1 (left) or Fp2 (right), according to the international 10/20 system used in electroencephalography [8]. The measurement points, which were labeled as Ch1–14 for right frontal channels and Ch15–28 for left frontal channels, were approximately covered the anterior and ventrolateral PFC and superimposed on a template brain for schematic illustration (cf. Fig. 1).

Demographic and behavioral data were analyzed using SPSS 11.0 software (SPSS Inc., Chicago, Illinois). The NIRS data was analyzed by the open source software Homer (http://www.nmr.mgh.harvard.edu/PMI/) which is implemented in Matlab (Mathworks, Natick, MA). First, the data were band-pass filtered within the range 0.01–0.5 Hz to eliminate slow drifts and the blood pressure variations. Then the optical signals for the two wavelengths were translated to hemoglobin concentrations using the modified Beer–Lambert equation with a differential path length correction of 6 and a partial volume correction of 50 for both wavelengths. The waveforms of [oxy-Hb] and [deoxy-Hb] changes were acquired from all the subjects in all 28 channels. For statistical analyses, the data were averaged according to the task condition (control or planning condition). Thereby, we got one mean value of each condition for each NIRS channel of each participant. Four-way repeated measures analysis of variance (RMANOVA) with three between-groups factors (2 diagnoses × 2 hemispheres × 14 channels) and one within-subjects factor (2 task conditions) was applied to [oxy-Hb] and [deoxy-Hb] data separately. Student's paired t-test was performed to specify the characteristic patterns of activation for the TOL planning task in contrast to the control task in each group. Furthermore, at each channel, the mean hemoglobin changes during the TOL task period were compared between two groups using two-sample Student's t-test. The correction of multiple comparisons by False Discovery Rate (FDR) was used.

Additionally, Pearson's correlation coefficients were calculated for the relationships among the PFC activation during the TOL task, the PANSS scores and the task performances for each channel in the schizophrenia group. A P value < 0.05 was considered to be statistically significant.

The number of correct responses and performance scores of the schizophrenia patients were statistically less than the control group

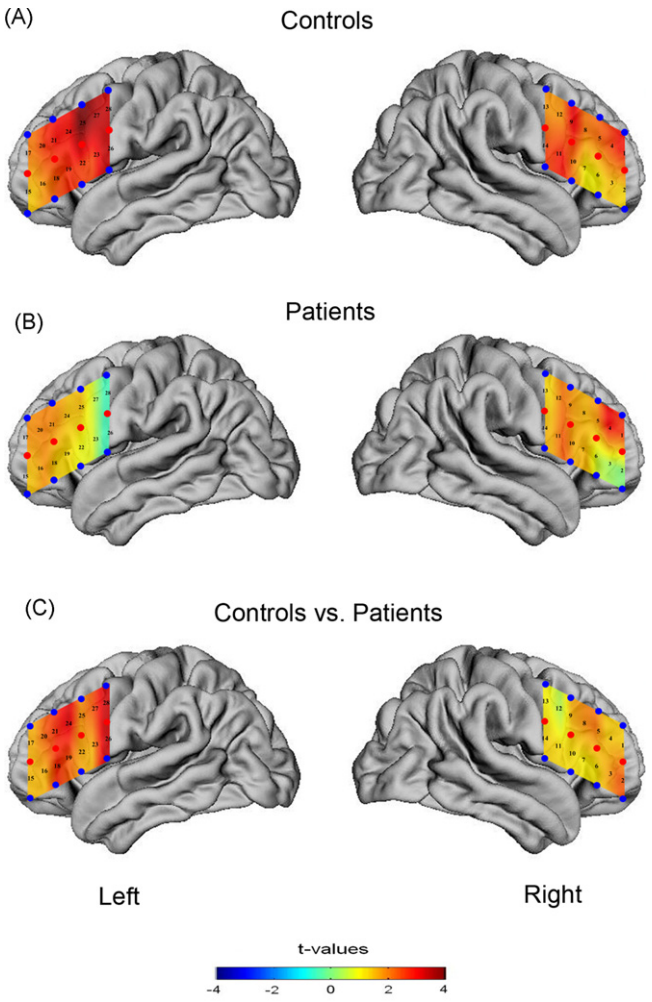

Fig. 1. Topographical presentation of *t* value of [oxy-Hb]. (A) PFC activation pattern of the healthy controls during the TOL task. (B) PFC activation pattern of the schizophrenia patients during the TOL task. (C) The comparison between the control and the schizophrenia group. The sources (red) and detectors (blue) are superimposed on a template brain. The numbers between the optodes indicate the measurement channels. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

at all task levels (see Table 2), and there was a significant negative correlation between the task performance and the negative symptom scores in schizophrenia (see Supplementary materials for details).

The grand averaged waveforms of [oxy-Hb] and [deoxy-Hb] during cognitive activation in the healthy controls and schizophrenia patients were shown in Fig. S2 and S3.

As for [oxy-Hb], there was a significant main effect of task condition, diagnosis and a significant interaction between task condition and diagnosis ($F = 185.32$, $df = 1$, $P < 0.001$; $F = 67.03$, $df = 1$, $P < 0.001$; $F = 21.186$, $df = 1$, $P < 0.001$, respectively) by the analysis of RMANOVA. For [deoxy-Hb], analysis by RMANOVA revealed a significant main effect of task condition and a significant interaction between task condition and diagnosis ($F = 22.48$, $df = 1$, $P < 0.001$; $F = 3.89$, $df = 1$, $P < 0.05$, respectively). There were no significant main effect of hemisphere and no interaction of hemisphere and task or hemisphere and diagnosis.

When comparing the TOL planning task and the control task, the results demonstrated significant activation caused by the TOL task: in 16 channels for [oxy-Hb] (Ch1, Ch4, Ch9, Ch11, Ch14 and Ch18–28; FDR-corrected $P < 0.05$) and in 13 channels for [deoxy-Hb] (Ch1–6 and Ch15–21; FDR-corrected $P < 0.05$) in the healthy controls and in 9 channels for [oxy-Hb] (Ch1–4, Ch16–18, Ch20 and Ch21; FDR-corrected $P < 0.05$) and in 2 channels for [deoxy-Hb] (Ch11 and Ch12; not corrected $P < 0.05$) in the schizophrenia patients. Parts of the results are shown in Fig. 1A and B.

The results of the *t*-test for the between-group comparison of the [oxy-Hb] changes during the TOL planning task showed that the schizophrenia patients had decreased activation than healthy subjects in 5 channels (Ch18, Ch21, Ch24 Ch26 and Ch28; FDR-corrected $P < 0.05$), but no significant difference in the [deoxy-Hb] data, as outlined in Table S2 and shown in Fig. 1C in the form of topographs.

In this study, we evaluated PFC activation during the TOL task in first-episode schizophrenia patients using multi-channel NIRS. The major finding is that the schizophrenia patients exhibited a significant hypoactivity in PFC in contrast to the control subjects, with a significant difference in behavioral performance between the two groups.

In the present study, the task performance of the first-episode schizophrenia patients was poorer than that of the controls. It suggested that the schizophrenia patients had impairment in planning and problem-solving capability at the initial stage of the disease, which is in accordance with previous researches [17,27]. Moreover, the task performance of patients showed a negative correlation with the negative symptoms scores of PANSS, and this result confirms that cognitive impairments were associated with the negative symptoms in schizophrenia patients [31].

With regard to the NIRS results, the TOL planning task recruited widespread regions of the PFC in healthy subjects, which is in line with other brain imaging studies [2,12,23]. During the TOL task, the participants were asked to calculate the minimum number of moves by comparing a start configuration with a target configuration. Thus, the TOL task required the participants to "look ahead" and map out a plan to solve the problem [32]. This characteristic of the task demands may recruit the anterior and ventrolateral PFC [28,32]. This result confirms that the PFC plays a crucial role in the solution of TOL tasks which requires high-level executive function, such as the ability of planning and solving problems and underlines the usefulness of multi-channel NIRS in monitoring brain activation associated with these cognitive progresses.

Table 2
The number of correct responses and performance scores.[a].

Condition	Control subjects ($N = 40$)		Schizophrenia patients ($N = 40$)	
	Correct responses	Performance scores (%)	Correct responses	Performance scores (%)
1 Move	8.82 ± 1.48	100 ± 0.0	7.35 ± 1.94**	94.99 ± 9.64**
2 Moves	8.38 ± 1.59	97.25 ± 6.04	7.30 ± 2.53*	90.54 ± 17.10*
3 Moves	7.68 ± 1.47	84.72 ± 11.78	6.58 ± 2.53*	76.13 ± 21.20*
4 Moves	3.73 ± 1.71	75.62 ± 21.07	2.90 ± 1.89*	62.29 ± 32.14*

Student's *t*-test was used for testing the group difference.
[a] Data are given as mean ± SD.
* $P < 0.05$.
** $P < 0.01$.

In comparison with the healthy controls, the schizophrenia patients showed a significant attenuation of activation in the PFC during the TOL planning task. This result is consistent with several previous studies using other executive tasks [4,24,30]. Takizawa et al. found slower and smaller [oxy-Hb] changes in schizophrenia patients during the VFT [30] and Quaresima et al. also found PFC dysfunction during a visual spatial working memory task in schizophrenia [24]. Our results in the current study suggest that the schizophrenia patients failed to recruit enough prefrontal cortical resources associated with the task and did not show the expected activation of the task-related areas exhibited by the control subjects. Further study is needed to investigate whether these findings can be extended to the individual level using discriminative analysis. These results confirm the PFC dysfunction in the first-episode schizophrenia patients and suggest that NIRS could be a useful clinical tool for the diagnosis and treatment of psychiatric disorders by monitoring the PFC activity.

In this study, we did not find any hemispheric differences during the TOL task in both groups. To our knowledge, there are inconsistencies with respect to hemispheric specialisation during the TOL planning task. Newman et al. indicated predominantly left PFC activation in association with processing TOL task [18], while other neuroimaging data reported either bilateral or predominantly right PFC activation [5,26,33]. This controversy across various functional brain imaging studies may be explained by task variations and sample bias. More research is needed to resolve this question.

Some limitations of the present study must be mentioned. First, all of our schizophrenia patients were taking antipsychotic medication, which makes it difficult to disentangle drug effects from disease effects, although we could not find a significant correlation between [oxy-Hb] change and dose of medication. A review suggested that treatment with antipsychotic medication seemed to normalize brain function and to make the brain function of schizophrenia patients more similar to that of healthy individuals [3]. Therefore, the results of our study were likely primarily because of this disease rather than the medication, although we cannot eliminate completely the medication effects. Future studies with drug naïve patients are required to discard the medication effects and confirm the findings of this study. Second, because of the limited number of channels, the area of measurement in NIRS was restricted to the prefrontal cortex. Simultaneous measurements by NIRS and other neuroimaging methodologies might be used to clarify the association of the PFC with other brain regions [19].

In summary, this is the first study that applied the TOL planning task to evaluate prefrontal dysfunction in individuals with schizophrenia using multi-channel NIRS. The results confirm the functional deficits of the PFC and impaired planning ability in first-episode schizophrenia patients and suggest that NIRS may be a useful clinical tool for evaluating PFC activation in psychiatric disorders.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2010.05.003.

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