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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