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

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ARTICLE INFO

Article history:
Received 19 March 2010
Received in revised form 20 April 2010
Accepted 3 May 2010

Keywords:
Schizophrenia
Multi-channel near-infrared spectroscopy (NIRS)
Tower of London (TOL)
Prefrontal cortex (PFC)

ABSTRACT

Cognitive impairments are considered as a core feature of schizophrenia and have been reported in association 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.
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 \( (n = 23, 3.10 \pm 1.60 \text{ mg/d}) \), aripiprazole \( (n = 6, 16.67 \pm 10.33 \text{ mg/d}) \), ziprasidone \( (n = 6, 86.67 \pm 45.02 \text{ mg/d}) \), quetiapine \( (n = 3, 466.67 \pm 152.75 \text{ mg/d}) \) and olanzapine \( (n = 2, 12.50 \pm 3.54 \text{ mg/d}) \). 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.

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Schizophrenia patients ((N = 40))</th>
<th>Healthy controls ((N = 40))</th>
<th>Group difference (P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(22.8 \pm 4.93)</td>
<td>(24.4 \pm 3.63)</td>
<td>(0.102)</td>
<td></td>
</tr>
<tr>
<td>Gen (women/men)</td>
<td>(20/20)</td>
<td>(22/18)</td>
<td>(0.823^a)</td>
</tr>
<tr>
<td>Education (year)</td>
<td>(13.29 \pm 2.17)</td>
<td>(14.08 \pm 2.22)</td>
<td>(0.113)</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>(20.97 \pm 3.27)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td>(15.48 \pm 8.06)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PANSS</td>
<td>(73.38 \pm 13.99)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>(19.33 \pm 3.43)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>(16.63 \pm 4.83)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>General psychopathology</td>
<td>(33.83 \pm 4.91)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

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.

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 \([\text{oxy-Hb}]\) and \([\text{deoxy-Hb}]\) 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 \( \times 2 \) hemispheres \( \times 14 \) channels) and one within-subjects factor (2 task conditions) was applied to \([\text{oxy-Hb}]\) and \([\text{deoxy-Hb}]\) 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.
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control subjects ($N=40$)</th>
<th>Schizophrenia patients ($N=40$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correct responses</td>
<td>Performance scores (%)</td>
</tr>
<tr>
<td>1 Move</td>
<td>8.82 ± 1.48</td>
<td>100 ± 0.0</td>
</tr>
<tr>
<td>2 Moves</td>
<td>8.38 ± 1.59</td>
<td>97.25 ± 6.04</td>
</tr>
<tr>
<td>3 Moves</td>
<td>7.68 ± 1.47</td>
<td>84.72 ± 11.78</td>
</tr>
<tr>
<td>4 Moves</td>
<td>3.73 ± 1.71</td>
<td>75.62 ± 21.07</td>
</tr>
</tbody>
</table>

Student’s $t$-test was used for testing the group difference.

\* $P<0.05$.

\* $P<0.01$.

\* Data are given as mean ± SD.
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 [5,28,33]. 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-naive 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.

Acknowledgements

This study was supported by the Stanley Medical Research Institute (SMRI, Grant ID: 06T-776) and the National Nature Science Foundation of China (NSFC, Grant ID: 30300108). We thank two anonymous reviewers for their thoughtful and helpful comments regarding the manuscript. We also want to thank Dr. Richard Keefe for providing the manual of Tower of London and Alex Johnson for editing and English language assistance.

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.

References


