Oxyhemoglobin Changes During Cognitive Rehabilitation After Traumatic Brain Injury Using Near Infrared Spectroscopy

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Abstract

To investigate cerebral reactions to cognitive rehabilitation tasks, oxyhemoglobin changes were compared in 9 patients with cognitive impairments after traumatic brain injury (TBI) and 47 healthy controls using functional near infrared spectroscopy (fNIRS) during nine cognitive rehabilitation tasks employed at Nagoya City Rehabilitation Center. Forty-seven measurement channels were placed on the frontal to temporal cortices, and organized into seven channel regions. Oxyhemoglobin changes were normalized based on the mean oxyhemoglobin value at the resting state, and integrated throughout a task. Statistical analyses of the differences between the TBI patients and controls were performed with the two-sided Mann-Whitney U test. Oxyhemoglobin changes were high for both controls and TBI patients in the lateral frontal regions. Oxyhemoglobin changes in TBI patients tended to be higher than controls in the medial frontal regions for most training tasks, and significant differences (p < 0.05) were seen for two tasks in the medial frontal regions. Different regions were activated during the tasks in TBI patients compared to controls. fNIRS measurement is useful in the evaluation of changes of neuronal activities during rehabilitation tasks in TBI patients.

Key words: traumatic brain injury, cognitive impairment, rehabilitation, near infrared spectroscopy

Introduction

Cognitive impairments after traumatic brain injury (TBI) are important because although the appearance of TBI patients might be normal, their cognitive impairments make it very difficult to return to work or studies. Therefore, rehabilitation of cognitive impairments is very important for TBI patients, and efficient cognitive training tasks for rehabilitation are needed. However, there are few reports on the efficacy of cognitive training tasks based on clinical evidence.

Generally, based on neurovascular coupling,5 functional magnetic resonance (fMR) imaging and positron emission tomography (PET) have been used for measuring cerebral blood flow during cognitive tasks. However, due to limitations such as the fixed and enclosed gantry or artifacts caused by movement, these imaging methods have only been used for simple tasks and cannot be used during actual cognitive training situations. Functional near infrared spectroscopy (fNIRS)9 is a non-invasive optical technique using optical fibers on the scalp which can measure oxyhemoglobin (OxyHb), deoxyhemoglobin, and total hemoglobin changes during tasks that involve a certain amount of movement. OxyHb is mainly associated with cerebral blood flow.7 Thus, we hypothesized that cerebral blood flow would increase during cognitive training tasks, and fNIRS can be used to measure OxyHb changes during such tasks.

This study attempted to compare OxyHb changes...
in TBI patients and normal controls during cognitive training tasks, to investigate any association between the cognitive training tasks and changes in neuronal activities.

Materials and Methods

Nine outpatients, 6 males and 3 females (mean age 28.1 ± 7.4 years), of Nagoya City Rehabilitation Center with cognitive impairments after severe TBI without MR imaging evidence of scar of major cerebral contusion were included in the TBI group. The severity of TBI was classified based on the duration of loss of consciousness, and “severe TBI” was defined as loss of consciousness of 24 hours and longer. The interval since injury was 4.0 to 118.2 months (mean 71.5 months). Clinical characteristics of TBI patients are shown in Table 1. Subjects were evaluated by neuropsychological tests (Wechsler Adult Intelligence Scale-Revised,18) Rey-Osterrieth Complex Figure Test,12 Rivermead Behavioural Memory Test,19 Paced Auditory Serial Addition Task: PASAT6). The definition of cognitive impairments was abnormal score in at least one neuropsychological test and/or the presence of social behavioral disturbance. The criteria for social behavioral disturbance were personality disorder, disinhibition, and inertia. Forty-seven healthy university students, 15 males and 32 females (mean age 20.5 ± 2.2 years) were included in the control group. All subjects were right-handed. The participants gave written informed consent, and the study was approved by the Ethics Committee of Nagoya City Rehabilitation Center.

We used a multi-channel fNIRS instrument (FOIRE-3000; Shimadzu Corporation, Kyoto) to measure relative changes in OxyHb, deoxyhemoglobin, and total hemoglobin. The fNIRS instrument calculates the changes in cerebral hemoglobin levels from absorbance at three wavelengths (780 nm, 805 nm, and 830 nm) in the near infrared. The sampling intervals were 100 msec. The cerebral hemoglobin changes were measured continuously between the start of the resting state (gazing at a fixation point for 30 seconds) and the end of the task. An array of 3 × 10 probes (15 pairs of light emitters and detectors) were placed on a fiber holder at intervals of 3 cm. The fiber holder covered the frontal to temporal cor-

Table 1 Clinical characteristics of 9 patients in the traumatic brain injury group

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Interval since injury (months)</th>
<th>LOC</th>
<th>MR imaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>M</td>
<td>114.9</td>
<td>25 days</td>
<td>DAI</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>M</td>
<td>92.8</td>
<td>1 month</td>
<td>DAI</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>M</td>
<td>25.1</td>
<td>2 weeks</td>
<td>DAI</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>F</td>
<td>47.3</td>
<td>1 week</td>
<td>DAI</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>F</td>
<td>118.2</td>
<td>10 days</td>
<td>DAI</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>M</td>
<td>102.0</td>
<td>1 month</td>
<td>DAI</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>M</td>
<td>76.7</td>
<td>3 days</td>
<td>nothing</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>F</td>
<td>40.9</td>
<td>1 week</td>
<td>DAI</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>M</td>
<td>4.0</td>
<td>2 weeks</td>
<td>minor contusion, DAI</td>
</tr>
</tbody>
</table>

ties, and the bottom center of the array was located at the electrode position Fpz according to the international 10–20 system.\(^1\)\(^2\)\(^3\)\(^4\) Figure 1 shows the location of the near infrared laser light emitters, detectors, and measurement channels used in this study. Taking into account alleviation for individual differences in probe position caused by the variations of head shapes, we selected seven channel regions as shown in Fig. 1 for analysis. These channel regions could facilitate comparison of individual subjects. The channel regions were the right and left lateral frontal regions (LF regions), right and left anterior frontal regions (AF regions), and right, mid, and left medial frontal regions (MF regions).

The measured data without marked artifacts (e.g., body movement) confirmed by the technologist were smoothed using a nine point Savitzky-Golay filter\(^14\) three times, and only the OxyHb changes were extracted into the text files. In order to compare the relative changes of OxyHb between the channels, subjects, and tasks, the OxyHb changes were normalized according to the procedure of Matsuda and Hiraki.\(^11\) In the normalization calculation, the mean OxyHb value at the resting state was subtracted from the measurements, and then the results were divided by one standard deviation of the OxyHb value at the resting state. Therefore, the mean of the normalized measurements was 0, and the standard deviation was 1. The normalized measurements, called the z-score, represented the difference from the average by the standard deviation. The normalized OxyHb changes were integrated throughout a task, and divided by the required time for the task to exclude the effects of the engaged time.

SPSS statistics 17.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses of the acquired normalized integral value of OxyHb changes per unit time. Since some variables were not normally distributed, we decided to use non-parametric analyses. Statistical analyses comparing the TBI group and control group were performed with a two-sided Mann-Whitney U test.

In this study, we used nine cognitive tasks employed for training at the clinical psychological department of Nagoya City Rehabilitation Center. The orders of the nine tasks were randomized, and the answer time for each task was limited to at most one minute. Between the end of a task and the start of the next task, participants took a rest and gazed at a fixation point until the OxyHb changes returned to almost the same level as at the start. The tasks are listed below.

1. Arithmetic cryptogram: pairs consisting of a letter and an easy calculation problem (one or two digits) are shown sequentially. The participants write down the letter when the answer to the problem is an even number. Finally, the letters make a sentence.
3. Message taking: memorize a telephone message while taking notes, and convey the message to an examiner.
4. Figure rotation: reproduce the presented figure while mentally rotating the figure toward the specified heading.
5. Direction: leap the specified number of squares in the specified directions (e.g., 4E, 2NW, . . . ), and fill in the square reached. Finally, some hidden letters are found.\(^10\)
6. Comparison: find the difference between three similar groups of characters.
7. Development of a solid figure: draw the development of a presented solid figure precisely.
8. Dictation of numerals: memorize six-digit numerals which are sequentially read out a digit per second, and write down those numerals if the first and the last numerals are the same.
9. Anagram: make a word by changing the order of the presented letters.

**Results**

Figure 2 shows box-whisker plots of the differences in the normalized integral values of OxyHb changes (abbreviated OxyHb changes) between the control and TBI groups for the nine cognitive tasks. OxyHb changes in the LF regions were high in both control and TBI groups. OxyHb changes of the TBI group tended to be higher, particularly in MF regions, compared to the control group for most tasks. OxyHb changes were significantly higher in the TBI group than in the control group for the average of all tasks in the mid MF, right MF (p < 0.01), and left MF (p < 0.05) regions (Fig. 2J), for the letter pick-out task in the mid MF and right MF regions (p < 0.05) (Fig. 2B), and for the direction task in the left MF and mid MF regions (p < 0.05) (Fig. 2E). Therefore, the OxyHb changes appeared to increase in the TBI group for all MF channel regions. On the other hand, OxyHb changes in the left LF (p < 0.05) and right LF (p < 0.01) regions were significantly higher in the control group than in the TBI group for the average of all tasks (Fig. 2J).

**Discussion**

The OxyHb changes were higher in the LF regions for both control and TBI groups in all tasks. The LF regions include part of the primary motor cortex.
Fig. 2 Differences in the normalized integral value of oxyhemoglobin (OxyHb) changes during different tasks in the control group (white boxes) and the traumatic brain injury group (gray boxes). Horizontal axis shows seven channel regions (LF: lateral frontal, AF: anterior frontal, MF: medial frontal). A: Arithmetic cryptogram, B: letter pick-out, C: message taking, D: figure rotation, E: direction, F: comparison, G: development of a solid figure, H: dictation of numerals, I: anagram, J: averages of all tasks. *p < 0.05, **p < 0.01, significant differences with two-sided Mann-Whitney U test.

(Brodmann area [BA] 4), supplementary motor cortex (BA 6), auditory cortex, and superior temporal gyrus (BA 41, 42, and 44). Participants wrote answers for all tasks used in this study, so the primary and supplementary motor cortices in both hemispheres were activated. Whereas the arithmetic cryptogram, letter pick-out, message taking, dictation of numerals, and anagram tasks clearly include linguistic processes, the other tasks (figure rotation, direction, comparison, and development of a solid figure) seem to include no linguistic processes. However, we verbally explained the task at the beginning of each task. Thus, the auditory cortex might be activated by understanding and recalling the problem. PET and fMR imaging studies\textsuperscript{1,20} have shown that the left hemisphere correlates with phonological processing, and tone and pitch of the speech are judged within the right hemisphere in speech recognition. Therefore, it may be reasonable to assume bilateral activation of the LF regions.

The OxyHb changes were higher in the MF regions in the TBI group except for the figure rotation task. The MF regions include part of the anterior prefrontal cortex (BA 10) and dorsolateral prefrontal cortex (BA 9). It is thought that this area is engaged in episodic memory retrieval and integration function,\textsuperscript{13,15} and activated when using internally generated information like past memories or hints about the solution produced by the participants themselves.\textsuperscript{3}

To investigate the working memory of TBI patients, executive control processing tasks and a modified PASAT have been used to compare TBI patients with normal controls using fMR imaging.\textsuperscript{2,17} TBI patients showed right medial frontal gyrus activation during the modified PASAT,\textsuperscript{2} and bilateral prefrontal cortex and left parietal lobe activation during heavy tasks.\textsuperscript{17} In our study, OxyHb changes were significantly higher for the MF regions in the TBI group, consistent with these previous results. On the other hand, OxyHb changes were mainly higher in the LF regions in the control group, suggesting that different regions may be activated to compensate for the decline of processing efficiency in TBI patients.

On the basis of neurovascular coupling\textsuperscript{5} and the previous results,\textsuperscript{17} which suggested a relationship between the load of the task and activation of the prefrontal cortex, cerebral blood flow should increase with the load of the task. OxyHb changes in the lateral prefrontal cortex were also associated with the load of the working memory task using fNIRS.\textsuperscript{16} These reports suggest that brain activation is correlated to the OxyHb changes reflecting the load of cognitive tasks. Therefore, assuming that activation of the brain is effective in the rehabilitation of cognitive functions, training tasks which increase OxyHb might be better for rehabilitation of TBI patients. This hypothesis will be the subject for further study.

fNIRS has a lower spatial resolution but better temporal resolution than fMR imaging or PET, and
can detect rapid activation changes. fNIRS also has fewer restrictions on the measuring environment than fMR imaging or PET. Thus, fNIRS is better for real time measurements of cerebral activation during cognitive training tasks. The present study found that different regions of the brain were activated during cognitive tasks in TBI patients compared to normal controls. fNIRS measurement could be useful in the evaluation on changes in neuronal activities during rehabilitation tasks for TBI patients.

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Conflicts of Interest Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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