Title

Active inhibition of task-irrelevant sounds and its neural basis in patients with attention deficits after traumatic brain injury

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Abstract

Primary objective: To examine active inhibition of irrelevant stimuli and evaluate its neural basis using functional near infrared spectroscopy in patients with attention deficits after **traumatic brain injury** (TBI).

Research Design: case control study.

Methods and procedures: Ten patients with TBI and 10 healthy control subjects participated in this study. The Paced Auditory Serial Addition Test (PASAT) was performed with (distracting PASAT) and without (PASAT) distracting Japanese *kana* phonetic characters presented between each number. **A** block design was used. Subjects alternately performed each task three times.

Main outcomes and results: Healthy controls performed better than patients with TBI on both the tasks. When performing the PASAT, healthy controls showed significant activity in every region of interest except the right lateral prefrontal cortex (PFC), but patients with TBI showed significant activity only in the left anterior PFC and left lateral PFC. When performing the distracting PASAT, the right lateral PFC was active in healthy controls, but not in patients with TBI.

Conclusion: These results confirm that patients with moderate-to-severe TBI were affected by distractors that influenced order processing. We suggest that the working memory of patients with TBI was affected by distracting stimuli, whereas that of healthy individuals was not.

Introduction

On a daily basis, we are exposed to a variety of environmental sounds such as conversations, air-conditioning equipment, and cars. These environmental sounds do not cause a salient decline in the performance of everyday tasks, and even if they temporarily capture our attention we can easily return to the ongoing task. This is because, when engaging in a task, humans are insulated against unnecessary information such as noise so that attention can be focused on necessary information. Such control of attention is called active inhibition, and it plays an important role in the maintenance of task performance [1,2]. However, patients with attention deficits after traumatic brain injury (TBI) find it difficult to filter out irrelevant auditory stimuli, even when they must concentrate on a task. Therefore, they are easily distracted by any auditory stimuli in their surroundings and have trouble carrying out tasks [3,4].

Working memory tasks such as serial recall of numbers and words are frequently used in applied psychology, and some studies have reported that performance of these tasks was reduced by task-irrelevant sounds or speech [5,6]. The degree of disruption varied with the task difficulty (cognitive load) and the characteristics of the distraction [5,7]. The effect of distractors on task performance and the neural basis of active inhibition are not necessarily the same in patient populations as in healthy subjects. For instance, Söderlund et al. [8] reported that performance of a short-term memory task improved in the presence of distracting stimuli in patients with attention deficit hyperactivity disorder. The effect of distractors on task performance and the neural basis of active inhibition may also differ between patients with TBI and healthy individuals, but there are no functional brain imaging studies on the effect of auditory distractors on task performance or the neural basis of active inhibition in patients with TBI.

Active inhibition involves two functionally distinct cognitive processes: working memory and order processing [5]. In inhibition processes that involve working memory there is active inhibition of unexpected distractors (e.g., sudden sounds) with attention capture (deviation effect) and of distractors with semantic

information (semantic effect). In inhibition processes that involve order processing there is active inhibition of distractors with the changing sound sequence that appear in a steady rhythm (such as “k l m v r q c”; changing-state effect). It is thought that order-processing inhibition occurs when stimuli have a small distracting effect, and occurs at an early selection stage in the filter model of attention [9,10]. Therefore, the alterations in active inhibition in patients with TBI are consistent with problems in order processing inhibition processes.

Clarification of the mechanisms that underlie active inhibition may lead to better understanding of patients with attention deficits after TBI, and thus contribute to more efficient and effective rehabilitation. The purpose of this research was to examine active inhibition of irrelevant auditory stimuli and evaluate its neural basis in patients with TBI and healthy control subjects.

Methods

Subjects

Ten patients with moderate or severe TBI (three females, mean age 34.9 ± 6.9 years, mean duration of education 14.8 ± 2.4 years, mean Glasgow Coma Scale score at the time of injury 9.9 ± 1.6) and 10 age- and education-matched healthy control subjects (three females, mean age 31.6 ± 3.9 years, mean duration of education 15.8 ± 2.0 years) participated in this study. All subjects were right-handed and native Japanese speakers. All patients with TBI exhibited problematic behaviours such as the tendency to overreact to unnecessary stimuli from their surroundings in daily life, restlessness, and difficulties in response inhibition for irrelevant stimuli. In addition, healthy control subjects achieved full marks on the restless/distraction factor of the Moss Attention Rating Scale (Japanese version) [11], indicating the presence of attention deficits. No subjects had hearing impairment or any past medical history that could affect cognitive function, such as a developmental disorder, psychiatric disorder, or other neural disorder. The Ethics Committee of the Faculty of Health Sciences, Hokkaido University approved this study and all subjects provided written informed consent.

Tasks

The Paced Auditory Serial Addition Test (PASAT) was used as the auditory working memory task. The inter-stimulus interval was 2 s to avoid auditory input-output competition that may exist with a shorter inter-stimulus interval [12]. In the distracting PASAT, a randomly selected Japanese *kana* phonetic character (e.g., ‘a’, ‘u’, ‘e’, ‘o’, ‘ka’) was aurally presented between each number in the PASAT (i.e. 1 s after of each number; Figure 1). The duration of each task was 2 minutes. The percentage of correct answers was calculated as an index of task performance.

Experimental protocol

A block design was used (Figure 2). Subjects alternately performed the PASAT and the distracting PASAT three times each. There was a 30 s baseline period before each block. In the baseline period, subjects were asked to read single numbers aloud in order to minimize the effect of factors other than cognitive activity, such as lip movement and contraction of temporal muscles, on brain activity measured during the task period. All subjects received a demonstration of the task before the experiment. The experiment was conducted in a quiet room. Subjects sat at a computer monitor and gazed at a fixation point to reduce eye movements,

task-irrelevant visual distractors, and head movements.

Functional near infrared spectroscopy (fNIRS) instrumentation

fNIRS data were collected using the multichannel fNIRS optical topography system (LABNIRS, Shimadzu Corp. Kyoto, Japan) with three wavelengths of near-infrared light (780, 805, and 830 nm). The sampling rate was 7.4 Hz. fNIRS probes were placed over the prefrontal cortex (PFC) and primary auditory cortex (PAC) in a 3×11 multichannel probe holder that consisted of 17 illuminating and 16 detecting probes arranged alternately at an inter-probe distance of 3 cm, resulting in 52 channels (Figure 3). The R9 probe was placed on Fpz according to the international 10/20 system in order to maintain a consistent measurement location across subjects. Virtual registration [13,14] was used to register fNIRS data to the Montreal Neurological Institute standard brain space. We identified the most likely location of all channels for the group of subjects, then anatomically labeled the estimated locations using a Matlab function that reads anatomical labeling information coded in the Talairach Daemon, a macro anatomical brain atlas [15]. According to this method, brain regions were classified as PAC, premotor cortex (PMC), lateral PFC (LPFC), and anterior PFC (APFC). Regions of interest (ROIs) were formed by combining 4–8 neighbouring channels based on the results of the virtual registration. The ROI were the left PAC (L-PAC; channels 21, 31, 41, 42, 51, and 52), left PMC (L-PMC; channels 9, 10, 20, and 30), left LPFC (L-LPFC; channels 6, 7, 8, 18, 19, 29, 39, and 40), left APFC (L-APFC; channels 17, 28, 38, 49, and 50), right PAC (R-PAC; channels 11, 22, 32, 33, 43, and 44), right PMC (R-PMC; channels 1, 2, 12, and 23), right LPFC (R-LPFC; channels 3, 4, 5, 13, 14, 24, 34, and 35), right APFC (R-APFC; channels 15, 25, 36, 45, and 46), and middle APFC (M-APFC; channels 16, 26, 27, 37, 47, and 48; Figure 3). Signals reflecting the oxygenated hemoglobin (oxy-Hb), deoxygenated hemoglobin, and total hemoglobin concentration were calculated. All analyses utilized the oxy-Hb signals, as this best reflects brain activity [16,17]. To avoid NIRS pathlength issues, oxy-Hb data from each channel were baseline-corrected so that the mean oxy-Hb concentration during the initial 6 s at baseline was zero. Data are expressed as change in oxy-Hb concentration from the mean oxy-Hb concentration during the initial 6 s at baseline.

Statistical analysis

Unpaired *t* tests were used to compare the performance on the PASAT and the distracting PASAT between groups (TBI, control). In addition, the relation between PASAT performance and the distracting effect, which was defined as the difference between the performance on the PASAT and the performance on the distracting PASAT, was evaluated using Pearson's product moment correlation coefficient. Practice effects on the PASAT and distracting PASAT performance were analysed by repeated-measures ANOVA.

Change in oxy-Hb concentration was calculated every second during each task for each ROI using LABNIRS. Unpaired *t* tests were used to compare change in oxy-Hb concentration between groups. A one-way repeated-measures ANOVA was performed to compare change in oxy-Hb concentration across tasks (baseline, PASAT, distracting PASAT) within each group. Bonferroni tests were used for post-hoc analysis. All statistical analyses were performed with SPSS 19.0 and statistical significance was set at $p < 0.05$.

Results

Task performance

The percentage of correct answers was higher in the healthy control group than the TBI group for both the PASAT (69.9 ± 16.2% vs. 40.3 ± 14.6%, $p < 0.001$) and the distracting PASAT (65.0 ± 19.4% vs. 27.6 ± 17.8%, $p < 0.0001$) tasks. The healthy control group had similar performance on the PASAT and the distracting PASAT ($p = 0.130$), whereas the TBI group performed significantly worse on the distracting PASAT than on the PASAT ($p < 0.001$). The information is tabulated in Table I.

There was no correlation between PASAT performance and the distracting effect in the healthy control group (r = -0.155, $p = 0.675$), but there was a significant negative correlation in the TBI group (r = -0.645, $p = 0.032$). Repeated-measures ANOVA showed that the percentage of correct answers was similar across the three repetitions of the task for both tasks in both groups, indicating that there was no practice effect.

fNIRS data

In the healthy control group, repeated-measures ANOVA showed a significant main effect of task in all ROIs. Post-hoc tests indicated that change in oxy-Hb concentration in all ROIs except the R-LPFC was significantly higher during the PASAT task than during the baseline period, and change in oxy-Hb concentration in the L- and R-PAC and the R-LPFC was significantly higher during the distracting PASAT task than during the baseline period (Figure 4A). When comparing the PASAT to the distracting PASAT, change in oxy-Hb concentration in the M-APFC was significantly lower during the distracting PASAT than during the PASAT and change in oxy-Hb concentration in all ROIs except for the L- and R-PAC and the R-LPFC had a tendency to be lower during the distracting PASAT than during the PASAT.

In the TBI group, repeated-measures ANOVA showed a significant main effect of task in the L-APFC and L-LPFC. Post-hoc tests indicated that change in oxy-Hb concentration in the L-APFC and L-LPFC was significantly higher during the PASAT than during the baseline period (Figure 4B), but was similar during the distracting PASAT and the baseline period. There were no significant differences between the PASAT and the distracting PASAT.

During the PASAT, the change in oxy-Hb concentration in the L- ($p = 0.011$), and R- ($p = 0.008$) PAC, L- ($p = 0.009$), and R- ($p = 0.022$) PMC, and the R-LPFC ($p = 0.028$) was significantly higher in the healthy control group than in the TBI group (Figure 4). During the distracting PASAT, the change in oxy-Hb concentration in the L- ($p = 0.019$) and R- ($p = 0.025$) PAC, the R-PMC ($p = 0.044$), and the R-LPFC ($p = 0.033$) was significantly higher in the healthy control group than in the TBI group (Figure 4). In both tasks, the change in oxy-Hb concentration in all ROIs tended to be higher in the healthy control group than in the TBI group.

Discussion

In this study we found that PASAT performance was lower in the TBI group than in the healthy control group, which is in line with previous studies [6,18]. However, we did not find a significant practice effect, which is in contrast to previous studies [19,20].

In this study, Japanese *kana* phonetic characters were used as distractors and were placed between numbers in the PASAT. This kind of distraction influences order processing and should be filtered out at the perceptual processing level [21]. However, our results indicated that patients with TBI did not effectively filter out the

distractors at the perceptual processing level, and the distractors may have reached the late selection stage of the attentional filter model [9,10,22]. Therefore, the distractors competed with attentional resources for the cognitive load, exhausting the attentional resources necessary to resolve the distracting effect. Recent studies demonstrated that there is a limited amount of attentional resources available for the active inhibition that takes place in the background of working memory [23,24]. On the other hand, studies in healthy subjects have reported that there was no correlation between the effect of distractors that influenced order processing and working memory [25,26]. In this study we found no correlation between the distracting effect and the PASAT score in healthy subjects, but we did find a negative correlation in patients with TBI. These results suggest that patients with TBI did not filter out the distractors at an early stage (i.e. at the perceptual processing level), thus working memory capacity was overloaded. In support of this, a previous study reported that attention was easily captured by task-unrelated information, and this information was allowed to enter the perceptual processing stream when working memory capacity was overloaded [27]. These behavioural data suggest that, in patients with TBI, task performance was disrupted by the distracting stimuli because of the increased load on working memory. Additionally, the data suggest that lower-order active inhibition, which works to filter out task-unrelated information, was impaired in the patients with TBI.

It has been reported that the left superior temporal gyrus, anterior cingulate cortex, and extensive brain regions from prefrontal to parietal cortices are active during the PASAT [28]. In this study, we found significant activity in every ROI except the R-LPFC in healthy subjects, but only in the L-APFC and L-LPFC in patients with TBI. In healthy subjects, the pattern of brain activity was different in the PASAT and the distracting PASAT, as only the L- and R-PAC and the R-LPFC were active during the distracting PASAT. It has been reported that R-LPFC, especially the right inferior frontal gyrus, was activated in various types of inhibitory tasks [29,30], and Dolcos et al. [31] reported that activation of the right inferior frontal gyrus correlated with the load of the distracting stimuli. These reports suggest that activation of the R-LPFC in this study may have contributed to filtering out the distractors at the perceptual processing level. In healthy subjects, all brain regions except the L- and R-PAC and the R-LPFC tended to be less active in the distracting PASAT than in the PASAT. In particular, the M-APFC exhibited significant deactivation, which is consistent with a previous report [32]. In patients with TBI there was no significant activation during the distracting PASAT but there was significant activation of the L-APFC and L-LPFC in the PASAT, indicating that L-APCF and L-LPFC had a tendency to be less active in the distracting PASAT than in the PASAT. This pattern of deactivation is thought to be induced when attentional resources have reached their limit, i.e., during an overflow state, as occurs with increases in task difficulty [33].

The L- and R-PAC, the L- and R-APFC, and the R-LPFC were more active in healthy subjects than in patients with TBI during the PASAT, and the L- and R-PAC, the R-PMC, and the R-LPFC were more active in healthy subjects than in patients with TBI during the distracting PASAT. These areas of activation are consistent with a previous study using the PASAT [28], and it therefore appears that activity in these brain regions is required for the task we used. These results suggest that working memory is necessary for the PASAT, and that the active inhibition required to filter out the distracting stimuli was impaired in the patients with TBI.

Two limitations of the present study should be noted. First, we studied young patients with chronic and moderate-to-severe TBI, therefore our results may not generalize to other patients with TBI, particularly those

with mild TBI. Second, fNIRS has poor spatial resolution and cannot provide information on the activity of deep brain regions.

In conclusion, the differences in brain activation and task performance indicate that patients with severe or moderate TBI were easily affected by distractors that influenced order processing and that should have been filtered out at the perceptual processing level. As a result, their working memory capacity was overloaded. We suggest that the working memory of patients with TBI was affected by low interference stimuli that did not influence healthy individuals.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table Ⅰ. Comparison of the PASAT and the Distracting PASAT score (percentage of correct answers) between groups

Task No.	Control	TBI	*P*
1 PASAT(%)	66.0±16.4	36.4±12.9	<0.001
2 Distracting PASAT(%)	58.2±23.1	23.9±19.3	<0.001
3 PASAT(%)	71.5±13.7	43.2±15.0	<0.001
4 Distracting PASAT(%)	65.5±16.0	27.9±17.3	<0.001
5 PASAT(%)	72.3±18.4	41.4±16.0	<0.001
6 Distracting PASAT(%)	71.3±19.1	30.9±16.9	<0.001
PASAT(1.3.5)	69.9±16.2	40.3±14.6	<0.001
Distracting PASAT(2.4.6)	65.0±19.4	27.6±17.8	<0.001

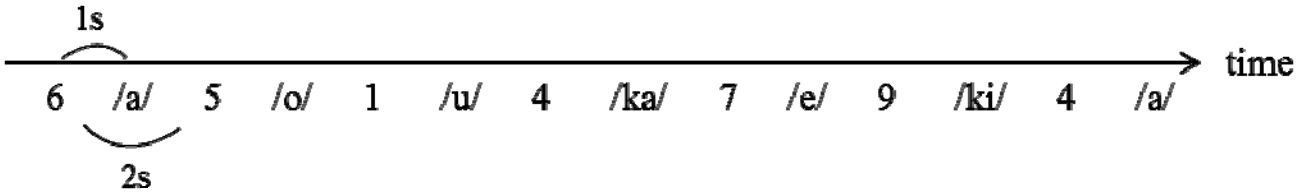

Figure 1. A sample of the distracting PASAT. Japanese *kana* phonetic characters (e.g. ‘a’, ‘u’, ‘e’, ‘o’, ‘ka’) were aurally presented in a random order in between each number.

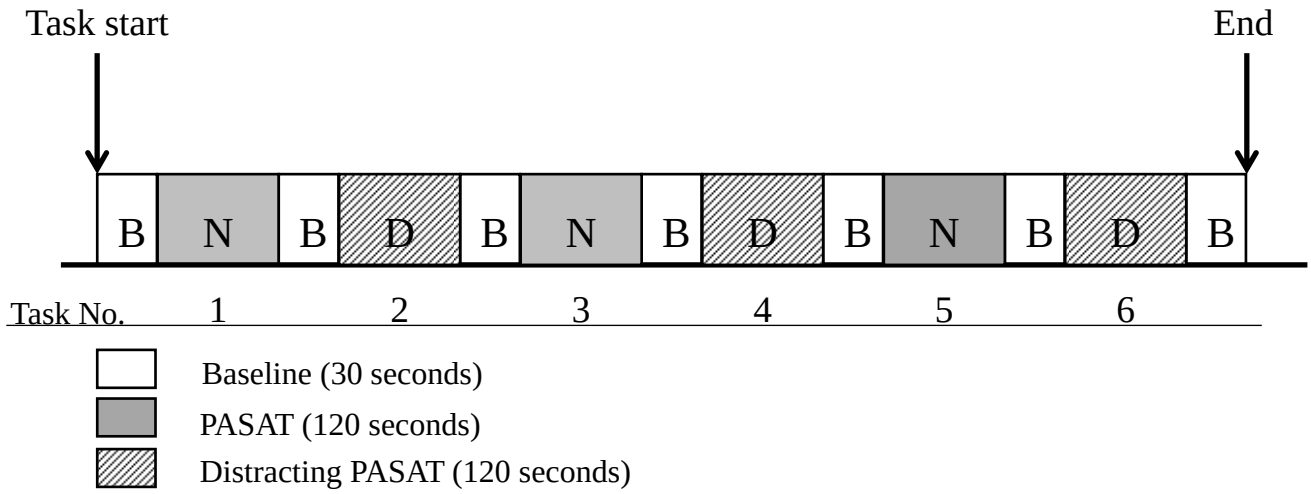

Figure 2. Representation of time course of the experiment protocol. A block design was used. Subjects alternately performed the PASAT and the distracting PASAT three times each.

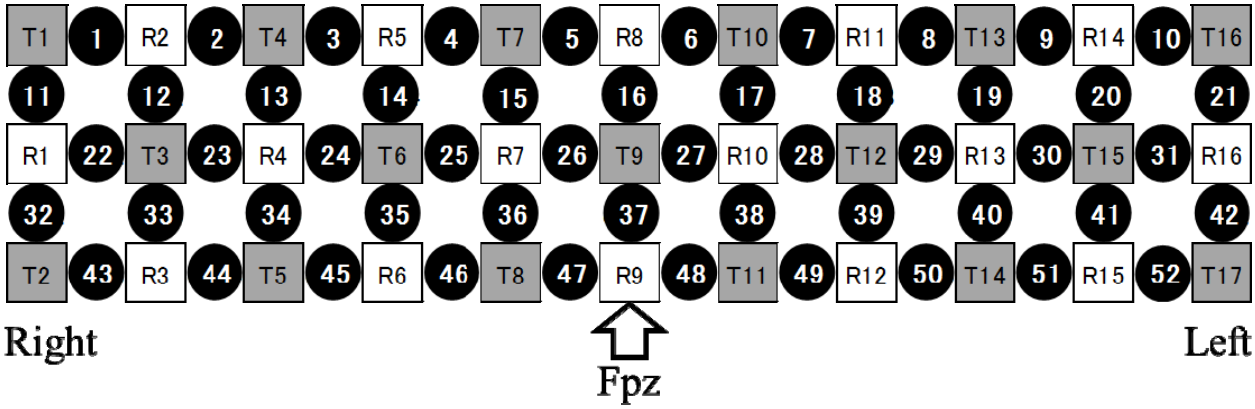

Figure 3. fNIRS channel orientation. Illuminators are shown as gray squares, detectors are shown as white squares, and channels are shown as black circles. The R9 probe was placed on Fpz according to the international 10/20 system.

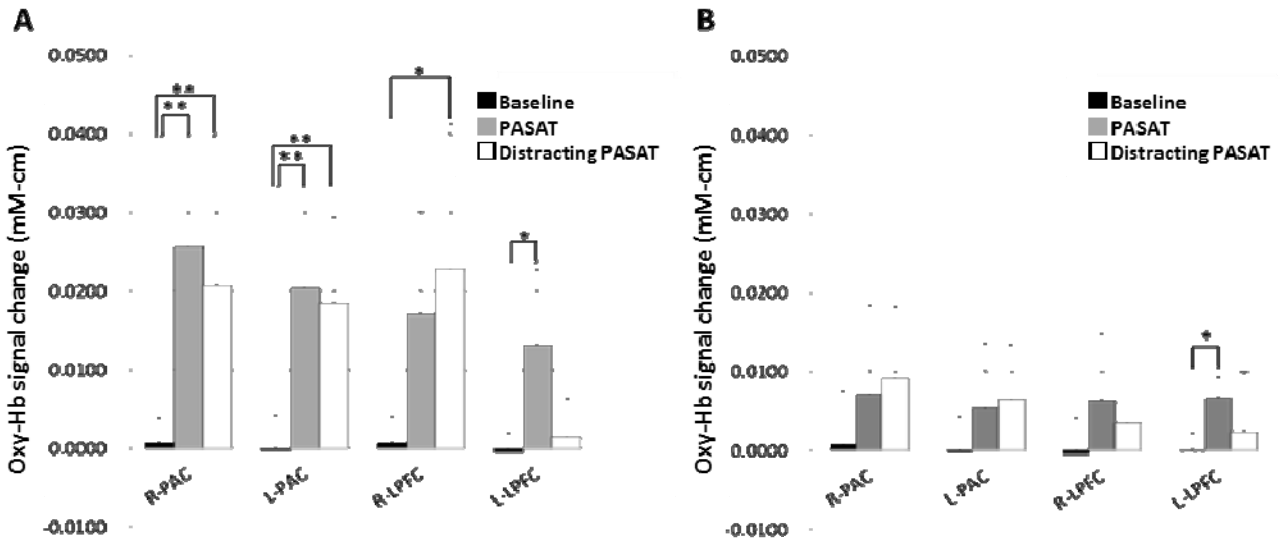

Fig 4. The change in oxy-Hb concentration from the initial 6 s of baseline to the entire baseline period and the PASAT and distracting PASAT tasks in healthy control subjects (A) and TBI patients (B). Only ROIs with a prominent difference in oxy-Hb concentration change between healthy control subjects and TBI patients are shown. * $p < 0.05$, ** $p < 0.01$. Error bars indicate standard error.