Compensatory cortical activation during performance of an attention task by patients with diffuse axonal injury: a functional magnetic resonance imaging study

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Key words: diffuse axonal injury; working memory; functional magnetic resonance imaging

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Abstract

Objective - To determine how cortical compensation occurs in higher cognitive systems during the recovery phase of diffuse axonal injury (DAI).

Design – Subjects: Twelve right-handed patients with a MRI lesion pattern compatible with pure DAI were identified. Pure DAI was defined as finding of traumatic microbleeds on T2*-weighted gradient-echo images in the absence of otherwise traumatic or nontraumatic MRI abnormalities. Twelve matched healthy control subjects were also enrolled. Methods: Functional magnetic resonance imaging (fMRI) was used to assess brain activation during a working memory test (Paced Visual Serial Attention Test, PVSAT).

Results - There were no significant group differences in reaction times for the PVSAT. While pure DAI patients committed a few errors during the PVSAT, controls respond correctly to each probe. Control subjects showed activations in the left frontal gyrus, left parietal gyrus, and right inferior parietal gyrus. Pure DAI patients showed activations in the left inferior frontal gyrus, right inferior frontal gyrus, and right middle frontal gyrus. Between group analysis of the PVSAT task revealed significantly greater activation of the right inferior frontal gyrus (BA 45) and right middle frontal gyrus (BA 9) in pure DAI patient versus controls.

Conclusions - Pure DAI patients require compensatory activation of the contralateral (right) prefrontal region to perform similarly to healthy controls. These findings provide further evidence for the adaptive capacity of neuronal systems and brain plasticity during the recovery stages of DAI.
**Introduction**

Traumatic brain injury (TBI) is the most common neurological dysfunction in young adults. Gennarelli\(^1\) classified TBI into two categories: focal injuries and diffuse injuries. Diffuse brain injuries, which are usually caused by sudden head movement, comprise classical brief cerebral concussion and more prolonged posttraumatic coma, also called diffuse axonal injury (DAI). DAI is truly a neuropathologic diagnosis. Therefore, the method used for its in vivo assessment is of critical importance. In a previous study\(^2\), it was shown that T2*-weighted gradient-echo magnetic resonance imaging (MRI) is a useful tool for the evaluation of DAI in the chronic stage of TBI. Due to the frequent hemorrhagic component\(^3,4\), which has been neuropathologically proven, lesions potentially indicative of DAI appear as small hypointense signal alterations (traumatic microbleeds [TMBs]).

Patients with DAI frequently present dysfunction of higher cognitive abilities. Neuropsychological impairment in DAI typically consists of deficits in memory, attention, and speed of information processing. Clinical cognitive tests have limited anatomical specificity and are compared with indices of brain function over large pathological lesions; the end-result is modest imaging-behavior relationship. Functional imaging studies using positron emission tomography (PET)\(^5\) and single photon emission tomography (SPECT)\(^6\) have provided useful information on DAI-related cognitive decline, showing a relationship between reduced cerebral blood flow (CBF) and metabolism in specific brain areas, such as the prefrontal cortex, as well as cognitive dysfunction. However, these studies have assessed CBF or metabolism at rest, when neural activity does not necessarily correspond to task-related neural activity.

In contrast, functional MRI (fMRI) assays to task-related activity and has sufficient anatomical resolution to accurately localize cerebral function. Recent research has reported fMRI activation patterns during an attention task in patients with multiple sclerosis (MS). Mainero et al\(^7\) reported that patients with relapsing-remitting multiple sclerosis showed altered patterns of brain activation during an attention task, and suggested that these change might reflect functional reorganization.

There are no reports describing fMRI activation patterns in patients with DAI. In this study, we aimed to investigate cortical reorganization in higher cognitive systems during the recovery phase of DAI. To pursue this aim we performed fMRI in patients with recovery-phase DAI using a conventional Paced Visual Serial Addition Test (PVSAT)\(^8\) as the test paradigm. T2*-weighted MRI images were used to confirm TMBs in all 12 participating DAI patients. Results were compared to those obtained in a group of 12 healthy controls.

**Methods**

**SUBJECTS**
Table 1 Characteristics of Pure DAI Patients and Controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pure DAI patients (n = 12)</th>
<th>Controls (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Total (male /female)</td>
<td>12 (11 / 1)</td>
<td></td>
<td>12 (11 / 1)</td>
</tr>
<tr>
<td>Age</td>
<td>26.8</td>
<td>10.5</td>
<td>26.4</td>
</tr>
<tr>
<td>Education (y)</td>
<td>14.5</td>
<td>2.7</td>
<td>14.1</td>
</tr>
<tr>
<td>Time from onset (mo)</td>
<td>14.3 (3~39)</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>GCS score</td>
<td>5.4</td>
<td>1.2</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of unconsciousness (day)</td>
<td>7.9</td>
<td>7.8</td>
<td>NA</td>
</tr>
<tr>
<td>WAIS-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSIQ</td>
<td>94.3</td>
<td>13.1</td>
<td>NA</td>
</tr>
<tr>
<td>VIQ</td>
<td>94.5</td>
<td>11.6</td>
<td>NA</td>
</tr>
<tr>
<td>PIQ</td>
<td>96.1</td>
<td>13.1</td>
<td>NA</td>
</tr>
<tr>
<td>Trail Making Test - A</td>
<td>79.3</td>
<td>13.2</td>
<td>NA</td>
</tr>
<tr>
<td>Trail Making Test - B</td>
<td>108.4</td>
<td>25.1</td>
<td>NA</td>
</tr>
<tr>
<td>RBMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>profile score</td>
<td>18.6</td>
<td>4.6</td>
<td>NA</td>
</tr>
<tr>
<td>screening score</td>
<td>8.0</td>
<td>3.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

GCS Glasgow Coma Scale,
WAIS-R Wechsler Adult Intelligence Scale-Revised,
FSIQ full-scale intelligence quotient, VIQ verbal IQ, PIQ performance IQ,
RBMT Rivermead Behavioral Memory Test,
NA not available.

Twelve patients with pure DAI participated in the study. Patients fulfilled the DAI criteria of Gennarelli’s classification.

Diagnosis was confirmed by the presence of TMBs in conventional MRI T2* images. Focal brain injury was excluded. The functional status of pure DAI patients was evaluated using the Wechsler Adult Intelligence Scale Revisited (WAIS-R), the Trail Making Test –A & B, and the Rivermead Behavioral Memory Test (RBMT). Twelve education-, age-, and sex-matched healthy control subjects were also enrolled. Comparative group characteristics are presented in Table 1. All subjects (patients and controls) were right-handed (70% of Olfield scale), native Japanese speakers. The protocol was approved by the local ethics committee, and all subjects gave informed consent to participate.

IMAGE DATA ACQUISITION

A 1.5-T MRI system (MAGNETOM SYMPHONY, Siemens, Erlangen, Germany) was used to acquire 20 T *2 -weighted transverse echo–planar (EPI) images (FOV, 192 x192 mm; matrix size, 64 x64; in-plane resolution, 3 x3 mm² ; flip angle, 90; TE 60 ms) with blood oxygenation level-dependent (BOLD) contrast. EPIs represented 6.0-mm-thick axial slices obtained every 6.0 mm, continuously acquired during a 2.5-min session using an interleaf method. An automatic shimming procedure was performed before each session. For each subject 71 functional volumes were collected within a single scanning session, with an effective repetition time (TR ) of 2.2 s/vol. The first volume obtained was discarded to allow for T1 equilibration effects. Image processing was carried out using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; see http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 6.5 (Mathworks, Sherborn, MA). Images were realigned to the first volume by rigid body transformation, sync-interpolated over time to correct for phase advance during acquisition. The images were then normalized to standard stereotactic space using the Montreal Neurological Institute (MNI) template. Normalized images of 3 x3 x6 mm³ were spatially smoothed using a Gaussian kernel of FWHM 8-8-15 mm. Treating the volumes as a time series, the data were high-pass filtered to 1/128 Hz.
BEHAVIORAL TASKS

We designed both a control and target tasks, performed in that order. Subtraction of brain activation during the control task permitted identification of the unique regions activated by the PVSAT task.

Control task (Choice Reaction Test, CRT): The subject was instructed to push the button if the Arabic number presented was the same as that identified beforehand by experimenter (for example, the subject was instructed to push the button when the presenting number was “8”).

Target task (Paced Visual Serial Attention Test, PVSA T): The subject was instructed to add each X consecutive Arabic number presented and push the button if the sum was the number identified beforehand by the experimenter (for example, the subject was instructed to push the button if the sum was “8”).

Both tasks were presented via a projection mirror system. Randomized numbers between one and nine were presented. The rate at which the same number appeared was 30%. A new stimulus was presented every 2 seconds, during each trial. Each subject’s performance was evaluated based on reaction times and total number of correct responses. The trials were organized into an RABRBA pattern, where R designates resting with eyes open, and A/B designates performing PVSA T or CRT, each lasting through acquisition of 10 volumes. PASAT and CRT were counterbalanced across the 12 patients and 12 controls.

IMAGE DATA ANALYSIS

Data were analyzed using SPM2 employing a random-effects model implemented in a procedure. Model estimation was convolved with a canonical hemodynamic response function at a fixed effects level based on the General Lineal Model. Random effects analyses were performed at a second stage for every contrast according to the proposed hypotheses. Task-related group activation tested the null hypothesis to show that patients and controls had identical group means. Clusters of voxels which had a peak Z-score > 3.1 (amplitude threshold uncorrected P < 0.001, extent threshold corrected P < 0.05) were considered to show significant activations. Contrasts of activation between controls and pure DAI patients during the experimental task also tested the null hypothesis to show that patients and controls had identical group means. Clusters of voxels which had a peak Z-score > 3.1 (amplitude threshold uncorrected P < 0.001, extent threshold corrected P < 0.05) were considered to show significant activations.

Anatomical identification was performed by superimposing the maxima of activation foci on the MNI template and normalized structural images of each subject. Activation foci were labeled using the Talairach atlas.

Results

BEHAVIORAL DATA

The mean reaction time for the pure DAI patients was 523 ± 41 ms in the CRT and 802 ± 156 ms in the PVSAT. The mean reaction time for controls was 562 ± 82 ms in the CRT and 812 ± 161 ms in the PVSAT task. There were no significant group differences in mean reaction times for either (Fig. 1). In the CRT task, both pure DAI patients and controls respond correctly in every case. In the PVSAT task, pure DAI patients made a few incorrect responses (percentage correct 98.2 ± 0.6%), whereas controls made no incorrect responses.

NEUROIMAGING DATA

WITHIN GROUP ANALYSISYS
Table 2. Brain Regions Activated by PVSAT vs CRT

<table>
<thead>
<tr>
<th>Brain regions (Brodmann's area)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure DAI patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA 45)</td>
<td>-55</td>
<td>18</td>
<td>19</td>
<td>4.44</td>
</tr>
<tr>
<td>Right inferior frontal gyrus (BA 45)</td>
<td>-48</td>
<td>18</td>
<td>19</td>
<td>4.14</td>
</tr>
<tr>
<td>Right middle frontal gyrus (BA 46)</td>
<td>50</td>
<td>28</td>
<td>19</td>
<td>3.27</td>
</tr>
<tr>
<td>Control Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left precentral gyrus (BA 6)</td>
<td>-46</td>
<td>1</td>
<td>48</td>
<td>4.71</td>
</tr>
<tr>
<td>Left inferior frontal gyrus (BA 44)</td>
<td>-50</td>
<td>7</td>
<td>22</td>
<td>4.37</td>
</tr>
<tr>
<td>Left middle frontal gyrus (BA 46)</td>
<td>-46</td>
<td>26</td>
<td>19</td>
<td>3.71</td>
</tr>
<tr>
<td>Left inferior parietal gyrus (BA 40)</td>
<td>-42</td>
<td>-38</td>
<td>39</td>
<td>4.68</td>
</tr>
<tr>
<td>Left superior parietal gyrus (BA 7)</td>
<td>-32</td>
<td>-49</td>
<td>46</td>
<td>4.51</td>
</tr>
<tr>
<td>Right inferior parietal gyrus (BA 40)</td>
<td>48</td>
<td>-41</td>
<td>40</td>
<td>4.18</td>
</tr>
</tbody>
</table>

To identify the characteristic activation regions for the PVSAT, we subtracted activation during the control task (CRT) from activation during the target task (PVSAT). Results are shown in Table 2 and Figure 2. For the control group, subtraction indicated activations in the left frontal (precentral, inferior frontal, and middle frontal) gyrus, left parietal (inferior parietal and superior parietal) gyrus, and right inferior parietal gyrus. In the pure DAI patients, activation was found in the left inferior frontal gyrus and right frontal (inferior frontal and middle frontal) gyrus. Direct comparisons of cerebral blood flow in the bilateral parietal region showed a signal increase in the CRT and PVSAT task in both in controls and pure DAI patients (Fig. 3).

**BETWEEN GROUP ANALYSIS**

Between-group analysis of brain activation during the PVSAT task (Fig. 4) revealed significantly greater activation of the right inferior frontal gyrus (BA 45, 52 20 28, z = 3.54) and the right middle frontal gyrus (BA 9, 40 42 22, z = 4.03) in pure DAI patients versus controls. No foci were significantly more active in controls versus pure DAI patients.

Raw data of the percent increase of activities in the right inferior frontal gyrus (BA 45, 52, 28) in each subject and PVSAT measurement are shown in Figure 5. The pure DAI patients who made a few errors tended to show a stronger activity than those who made no errors.

**Discussion**

This study offers the first demonstration that pure DAI patients show a compensatory cortical activation during the recovery phase of the condition. We performed fMRI of 12 patients with pure DAI showing TMB in T2*-weighted gradient-echo images in the absence of other traumatic or nontraumatic MRI abnormalities and compared the result to that for 12 control subjects of the same age and sex. During the PVSAT task pure DAI patients showed cortical activations in the bilateral prefrontal region, while control subjects showed only left prefrontal activation. Activation of the right prefrontal region (BA 45 and 9) was statistically different between the 2 groups. At the behavioral level, pure DAI patients had a slightly lower percentage of correct responses than control subjects during the PVSAT. These findings suggest that compensatory activation of the contralateral (right) prefrontal cortical region was necessary in order for pure DAI patients to perform similarly to control subjects.

The results of recent studies on cognitive disability of DAI are inconsistent. Scheid et al proposed that the reason for this inconsistency was that diagnosis of DAI relies on cranial computed tomography, although DAI is in fact a neuropathologic diagnosis. To further clarify the relationship between DAI and cognitive deficit, they defined pure DAI as the presence of TMBs on T2*-weighted
gradient-echo images and the absence of other traumatic or nontraumatic MRI abnormalities, and calculated correlations with detailed neuropsychological test findings for pure DAI. Pure DAI was confirmed in all patients with impairment of one or more cognitive subfunction, while there was no correlation between the number of TMBs and specific or global cognitive performance. Scheid et al\(^{15}\) suggested that functional reorganization affected performance, such that performance and TMB load were no longer correlated. The same phenomenon has been reported in fMRI studies of other diseases. In patients with MS, cognitive decline was determined to be unrelated to lesion load, reportedly because the patients differed in the ability to recruit resources from brain areas not primarily required for the task. Several recent fMRI studies have shown that during working memory tasks MS patients exhibited a higher degree of brain activation than do healthy controls\(^{7,16-21}\), revealing that MS patients and healthy controls use different brain areas to perform the same cognitive task.

Some of the studies designed to investigate compensatory cortical mechanisms have employed the PVSAT task, but there have been no studies of compensatory cortical activation in pure DAI patients. Many fMRI studies of TBI have focused on mild TBI\(^{22,24}\). Although Christodoulou et al\(^{25}\) reported fMRI data for patients with severe TBI, but approximately half of their sample was patients with focal brain contusion. Correlation of cognitive function and traumatic load was inconsistent, because traumatic load included both focal and diffuse injuries. Therefore, the data addressing functional compensatory mechanisms that included both focal and diffuse injuries was suspected to be inconsistent.

Our data included only pure DAI patients. There are no previous reports demonstrating functional mapping of pure DAI. Although patients and controls were matched on age, sex, and handedness, cognitive function of the pure DAI patients was slightly inferior to that of control subjects. Cognitive function could not be matched because all pure DAI patients showed impairments of 1 or more cognitive subfunctions\(^{2}\).

The PVSAT\(^{26}\) sustained attention task, adapted from the Paced Auditory Serial Attention Task (PASAT), served as the paradigm during fMRI. This test requires rapid information processing, working memory, and arithmetic abilities, and thus can be considered as a test of dual processing. Neither healthy controls or patients in the early stage of chronic cognitive diseases, such as HIV\(^{26,27}\) or MS have substantial difficulties with the PVSAT\(^{16}\). We found that pure DAI patients completing the PVSAT had equal reaction times and only slightly lesser performance than control subjects. On average, brain activation in healthy controls during the PVSAT occurred primarily in the frontal and parietal lobes, and these areas were activated in the majority of subjects, an indication of limited inter-individual variation. Brain activation during the PVSAT in these subjects depended mainly on left frontal (BA 6 and 9) and parietal areas (BA 7 and 40), with some important activations in the right hemisphere (BA 6) as well. These areas are relevant to performance of verbal working memory tasks. The left prefrontal –dorsal region (BA 9) is recruited during the maintenance of information in working memory. Both areas have previously been reported to be components of the central executive system of working memory\(^{29,30}\). Left parietal cortex (BA 7 and 40) has been proposed to be involved in storage processes, in contrast to the maintenance and rehearsal-related functions thought to be subserved by the prefrontal cortex. Specifically, the posterior parietal cortex participates in phonological storage\(^{31}\), while the left ventral prefrontal cortex (BA 44, Broca’s area) is involved in subvocal rehearsal. Moreover, parietal BA 7 has also been found to be active during arithmetical tasks\(^{17}\).

In our study, healthy controls showed patterns of cortical activation during the PVSAT task similar to those previously reported. The patients with pure DAI also demonstrated right prefrontal activation. We interpret this bilateral activation of the prefrontal region to be a cortical compensatory mechanism\(^{16}\). One of the most important aspects was that the control group outperformed the pure DAI group in the PVSAT. In addition, the DAI patients who made a few errors tended to show more of an increase in activities of the right prefrontal region. In healthy volunteers, BA 6 has been reported to show bilateral activation during tasks of selective and sustained attention. Likewise, this area has been found to be bilaterally activated in relation to the decision making subprocess of working memory, independent of the specific nature of the task (verbal or spatial)\(^{32}\). Based on the superior performance of the control group in the PVSAT task, we believe that the differences in activation of
the right prefrontal cortex are an indication of compensatory mechanisms. Bilateral activation during a sustained task has been observed in other diseases and conditions. In patients with MS, the primary activation was detected in the right frontal cortex (BA 6, 8, and 9); in addition, the left BA 39 was active. In healthy volunteers, tool use activated the right BA44, while simple stick use activated only the left BA 44. The right premotor cortex appears to play a greater role than its left-sided counterpart in sequence production when sequences are performed or learned with the right hand. Maruishi et al. demonstrated that the right ventral premotor cortex plays an important role in manipulating the electromyographic prosthetic hand. In addition, neuroplasticity, neural changes in response to the disease processes, is also an explanatory factor.

A possible explanation for the difference in parietal activation between patients and controls is that the pure DAI patients needed greater parietal activation of storage processes during CRT than did the control subjects. As a result, subtraction of brain activation during CRT from brain activation during PVSAT did not demonstrate a significant difference in parietal activation in pure DAI patients. Specifically, during the PVSAT task cerebral blood flow in the left parietal region was increased more in pure DAI patients than in control subjects.

Our study improved the methodology of the fMRI task. As in most previous studies, they used an auditory version of the PASAT that resembled the original task. However, the first study used a visual version of the PASAT, called PVSAT. As the authors noted, use of the visual modality had the advantage of suppressing interference between scanner noise and auditory stimuli. However, the PVSAT was an easy task because visual presentation of stimuli removed the interference between output and input modalities, leading to better performance. A second relevant difference between this study and previous studies was the control task. In the studies by Audoin et al. the control task was repetition, whereas in others it was rest. Several researchers have criticized the use of rest as a control task based on the notion that it may increase the likelihood of subjects engaging in unsolicited cognitive activities that may confound results. The third relevant difference from previous studies was the required response. Like Staffen et al., we preferred not to directly control task performance and instructed participants to perform the task silently. Mainero et al. instructed subjects to perform the task silently and raise their finger whenever the sum equaled 10. This approach avoided the problems associated with subjects responding aloud but increased the difficulty of the task, converting it to a dual-task situation. Using a strategy more similar to the PASAT, Audoin et al. instructed subjects to respond aloud. Clearly, allowing subjects to verbalize in the scanner rather than perform a motor response would be very desirable when seeking to obtain high-quality fMRI images. However, the risk of movement and magnetic susceptibility artifacts has made the use of verbal response prohibitive.

In conclusion, we interpret the differences in brain activation of pure DAI patients and healthy controls during intact performance of a sustained attention and dual processing task as the consequence of compensatory mechanisms. These findings provide further evidence of the adaptive capacity of neuronal systems and brain plasticity during the recovery stages of DAI.

Acknowledgment
This research was supported in part by grants from the General Insurance Association of Japan.

References


**Figure Legends**

**Figure 1.** Reaction times of the pure DAI patients and healthy controls were not significantly different in the CRT nor the PVSA T.

**Figure 2.** Averaged activation maps showing significant task-related increases in the BOLD contrast signal (amplitude threshold uncorrected P < 0.001, extent threshold corrected P < 0.05, for multiple comparisons). Data are from a group analysis of 12 subjects, and are displayed on a reference brain (Montreal Neurological Institute; MNI) with the indicated Talaraich coordinates. (a) Subtracted activation during CRT from activation during PVSA T in the controls indicated target-task-related activation in the left frontal (precentral, inferior frontal, and middle frontal) gyrus, left parietal (inferior parietal and superior parietal) gyrus, and right inferior parietal gyrus. (b) Subtracted activation during CRT from activation during PVSA T in the pure DAI patients indicated target-task-related activation in the left inferior frontal gyrus and right frontal (inferior frontal, middle frontal) gyrus.

**Figure 3.** Averaged responses of the left and right inferior parietal region (BA 40) during the PVSA T and CRT. The difference in activation during the PVSA T and CRT was greater in controls than in pure DAI patients.
Between-group analysis of brain activation during the PVSAT task, pure DAI patients showed greater activation of right inferior frontal gyrus (BA 45, 52 20 28, z = 3.54) and right middle frontal gyrus (BA 9, 40 42 22, z = 4.03) than did controls (amplitude threshold uncorrected P < 0.001, extent threshold corrected P < 0.05, for multiple comparisons). Data are displayed on a reference brain (Montreal Neurological Institute; MNI) with the indicated Talaraich coordinates.

Raw data of the percent increase of activities in the right inferior frontal gyrus (BA 45, 52, 28) in each subject and PVSAT measurement, showing variability within the pure DAI patients. The patients who made a few errors tended to show strong activity.
Figure 1

[Graph showing comparison between Control and Pure DAI in CRT and PVSAT tests.]

- CRT: Control group shows lower values compared to Pure DAI group.
- PVSAT: No significant difference (n.s.) between Control and Pure DAI groups.

Y-axis: (msec) 0 to 1000
X-axis: CRT and PVSAT
Figure 4
Figure 5
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