PAPER

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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Objective: To determine how cortical compensation occurs in higher cognitive systems during the recovery phase of diffuse axonal injury (DAI).
Design: 12 right-handed patients with a magnetic resonance imaging (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 non-traumatic MRI abnormalities. 12 matched healthy controls were also enrolled. Functional magnetic resonance imaging (fMRI) was used to assess brain activation during a working memory test (Paced Visual Serial Attention Test (PVSAT)).
Results: No significant group differences were observed in reaction times for the PVSAT. Although patients with pure DAI committed a few errors during the PVSAT, controls respond correctly to each probe. Controls showed activations in the left frontal gyrus, left parietal gyrus and right inferior parietal gyrus. Patients with pure DAI showed activations in the left inferior frontal gyrus, right inferior frontal gyrus and right middle frontal gyrus. Between-group analysis of the PVSAT task showed significantly greater activation of the right inferior frontal gyrus (BA 45) and right middle frontal gyrus (BA 9) in patient with pure DAI versus controls.
Conclusions: Patients with pure DAI require compensatory activation of the contralateral (right) prefrontal region to carry out activities similar to healthy controls. These findings provide further evidence for the adaptive capacity of neuronal systems and brain plasticity during the recovery stages of DAI.

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, usually caused by sudden head movement, comprise of classical brief cerebral concussion and more prolonged post-traumatic coma, also called diffuse axonal injury (DAI). DAI is truly a neuropathological 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. Owing to the frequent haemorrhagic component,[3 4] which has been neuropathologically proved, lesions potentially indicative of DAI appear as small hypointense signal changes (traumatic microbleeds (TMBs)).

Patients with DAI often 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-behaviour relationship. Functional imaging studies using positron emission tomography[5] and single-photon emission tomography[6] have provided useful information on DAI-related cognitive decline, showing a relationship between reduced cerebral blood flow and metabolism in specific brain areas, such as the prefrontal cortex, as well as cognitive dysfunction. However, these studies have assessed cerebral blood flow or metabolism at rest, when neural activity does not necessarily correspond to task-related neural activity.

By contrast, functional MRI (fMRI) assays to task-related activity and has sufficient anatomical resolution to accurately localise cerebral function. Recent research has reported fMRI activation patterns during an attention task in patients with multiple sclerosis. 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 reorganisation.

No reports describing fMRI activation patterns were observed in patients with DAI. We aimed to investigate cortical reorganisation in higher cognitive systems during the recovery phase of DAI. To pursue this aim we conducted an 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 patients with DAI. Results were compared with those obtained in a group of 12 healthy controls.

METHODS

Participants

Twelve patients with pure DAI participated in the study. Patients fulfilled the DAI criteria of Gennarelli's[1] classification.

Diagnosis was confirmed by the presence of TMBs in conventional MRI T2* images. Focal brain injury was excluded. The functional status of patients with pure DAI was evaluated using the Wechsler Adult Intelligence Scale Revised, the Trail Making Test-A and B, and the Rivermead Behavioural Memory Test. Twelve education-matched, age-matched, and sex-matched healthy controls were also enrolled. Table 1 showed comparative group characteristics. All participants (patients and controls) were right-handed (70% of Olfield scale[9]), native Japanese speakers. The protocol was approved by the local

Abbreviations: CRT, Choice Reaction Test; DAI, diffuse axonal injury; fMRI, functional magnetic resonance imaging; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; PASAT, Paced Auditory Serial Attention Task; PVSAT, Paced Visual Serial Attention Test; TBI, traumatic brain injury; TMBs, traumatic microbleeds

ethics committee, and all participants gave informed consent to participate.

Image data acquisition

A 1.5-T MRI system (MAGNETOM Symphony, Siemens, Erlangen, Germany) was used to acquire 20 T2*-weighted transverse echo–planar images (FOV, 192×192 mm; matrix size, 64×64 mm; in-plane resolution, 3×3 mm^2; flip angle, 90°; TE 60 ms) with blood oxygenation level-dependent contrast. Echo–planar images represented 6.0-mm thick axial slices obtained every 6 mm, continuously acquired during a 2.5-min session using an interleaf method. An automatic shimming procedure was conducted before each session. Seventy one functional volumes were collected from each participant 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, interpolated synchronously over time to correct for phase advance during acquisition. The images were then normalised to standard stereotactic space using the Montreal Neurological Institute (MNI) template. Normalised images of 3×3×6 mm^3 were spatially smoothed using a Gaussian kernel of FWHM 8–8–15 mm.[10 11] Treating the volumes as a time series, the data were high-pass filtered to 1/128 Hz.

Behavioural tasks

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

Control task (Choice Reaction Test)

The participant was instructed to push a button if the Arabic number presented was the same as that identified beforehand by experimenter (eg, the participant was instructed to push the button when the presenting number was ''8'').

Table 1 Characteristics of pure DAI patients and controls

Characteristics	Patients with pure DAI (n = 12) Mean	SD	Controls (n = 12) Mean	SD	p Value
Total (male/female)	12 (11/1)		12 (11/1)		
Age (years)	26.8	10.5	26.4	4.6	0.79
Education (years)	14.5	2.7	14.1	1.4	0.75
Time from onset (months)	14.3 (3–39)	14.3	NA	NA	
GCS score	5.4	1.2	NA	NA	
Duration of unconsciousness (day)	7.9	7.8	NA	NA	
WAIS-R					
FSIQ	94.3	13.1	NA	NA	
VIQ	94.5	11.6	NA	NA	
PIQ	96.1	13.1	NA	NA	
Trail Making Test-A	79.3	13.2	NA	NA	
Trail Making Test-B	108.4	25.1	NA	NA	
RBMT					
Profile score	18.6	4.6	NA	NA	
Screening score	8.0	3.0	NA	NA	

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

Target task (Paced Visual Serial Attention Test)

The participant 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 (eg, the participant was instructed to push the button if the sum was ''8'').

Both tasks were presented via a projection-mirror system. Randomised numbers between 1 and 9 were presented. The rate at which the same number appeared was 30%. A new stimulus was presented every 2 s, during each trial. Each participant's performance was evaluated based on reaction times and total number of correct responses. The trials were organised into an RABRBA pattern, where R designates, resting with eyes open and A/B designates, performing PVSAT or CRT, each lasting through acquisition of 10 volumes. Paced Auditory Serial Attention Task (PASAT) and CRT were counterbalanced across the 12 patients and 12 controls.

Image data analysis

Data were analysed using SPM2 using a random-effects model implemented in a procedure. Model estimation was convolved with a canonical haemodynamic response function at a fixed effects level based on the General Lineal Model. Random-effects analyses were conducted 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 considerable activation. Contrasts of activation between controls and patients with pure DAI 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 considerable activation.

Anatomical identification was carried out by superimposing the maxima of activation foci on the MNI template and normalised structural images of each participant. Activation foci were labelled using the Talairach atlas.[12]

RESULTS

Behavioural data

The mean reaction time for the patients with pure DAI 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. No considerable group differences were observed in mean reaction times for either (fig 1). In the CRT task, both patients with pure DAI and controls responded correctly in every case. In the PVSAT task, patients with pure DAI made a few incorrect responses (percentage correct 98.2(0.6)%), whereas controls made no incorrect responses.

Neuroimaging data within group analysis

To identify the characteristic activation regions for the PVSAT, we subtracted activation during the control task (CRT) from activation during the target task (PVSAT). Table 2 and fig 2 show the results. 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 patients with pure DAI, 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 both in controls and in patients with pure DAI (fig 3).

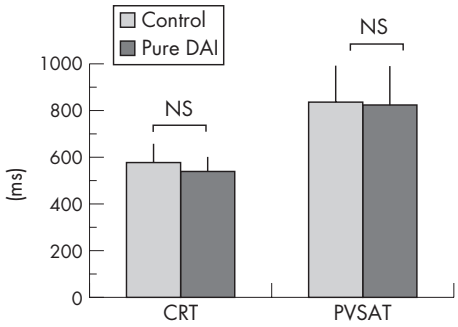

Figure 1 Reaction times of the patients with pure DAI and healthy controls were not significantly different in the CRT or the PVSAT.

Between group analysis

Between-group analysis of brain activation during the PVSAT task (fig 4) showed considerably 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 patients with pure DAI versus controls. No foci were considerable more active in controls versus patients with pure DAI.

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

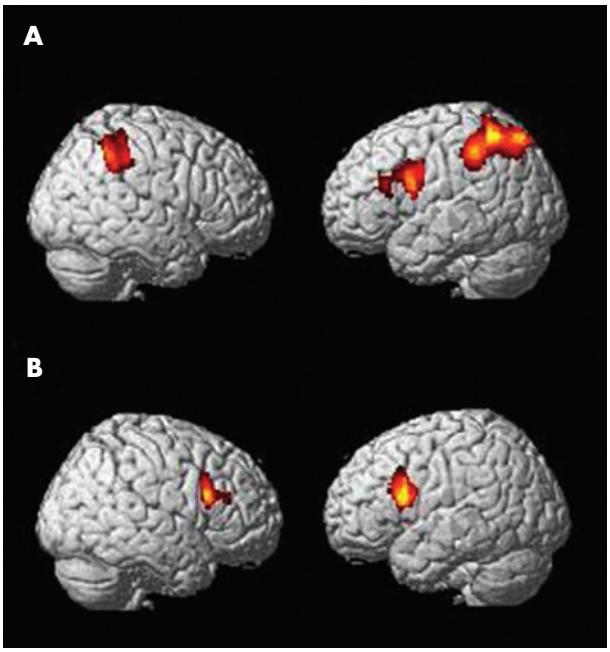

Figure 2 Averaged activation maps showing considerable task-related increases in the blood oxygenation level-dependent contrast signal (amplitude threshold uncorrected $p<0.001$, extent threshold corrected $p<0.05$, for multiple comparisons). Data are from to a group analysis of 12 participants, and are displayed on a reference brain (MNI) with the indicated Talaraich coordinates. (a) Subtracted activation during CRT from activation during PVSAT 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 PVSAT in the patients with pure DAI indicated target-task-related activation in the left inferior frontal gyrus and right frontal (inferior frontal, middle frontal) gyrus.

DISCUSSION

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

The results of recent studies on cognitive disability of DAI are inconsistent.[13 14] Scheid *et al*[15] proposed that the reason for this inconsistency was that diagnosis of DAI relies on cranial computed tomography, although DAI is in fact a neuropathological 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 they calculated correlations with detailed neuropsychological test findings for pure DAIs. Pure DAI was confirmed in all patients with impairment of one or more cognitive subfunction, whereas there was no correlation between the number of TMBs and specific or global cognitive performance. Scheid *et al*[15] suggested that functional reorganisation 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 multiple sclerosis, 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, patients with multiple sclerosis exhibit a higher degree of brain activation than do healthy controls,[7 16–21] showing that patients with multiple sclerosis and healthy controls use different brain areas to carry out the same cognitive task.

Some of the studies designed to investigate compensatory cortical mechanisms have used the PVSAT task, but there have been no studies of compensatory cortical activation in patients with pure DAI. 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, about 50% 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 dealing with functional compensatory mechanisms that included both focal and diffuse injuries was suspected to be inconsistent.

Our data included only patients with pure DAI. No previous reports demonstrating functional mapping of pure DAI were shown. Although patients and controls were matched on age, sex and handedness, cognitive function of the pure DAI patients was slightly inferior to that of controls. Cognitive function could not be matched because all patients with pure DAI showed impairments of one or more cognitive subfunctions.[2]

The PVSAT[8] sustained attention task, adapted from the PASAT, served as the paradigm during fMRI. This test requires rapid information processing, working memory and arithmetic

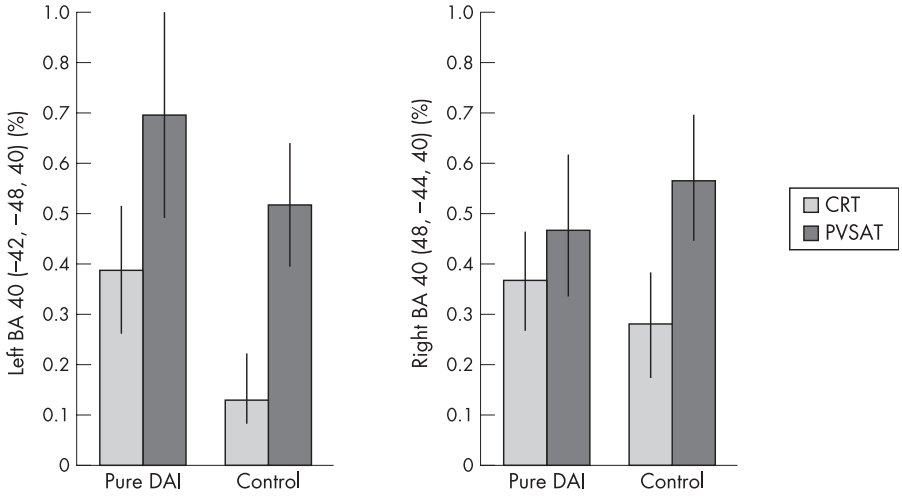

Figure 3 Averaged responses of the left and right inferior parietal region (BA 40) during the PVSAT and CRT. The difference in activation during the PVSAT and CRT was greater in controls than in patients with pure DAI.

abilities, and thus can be considered as a test of dual processing. Neither healthy controls nor patients in the early stage of chronic cognitive diseases, such as HIV[26 27] or multiple sclerosis,[28] have substantial difficulties with the PVSAT.[16] We found that patients with pure DAI completing the PVSAT had equal reaction times and only slightly lower 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 most of the participants, an indication of limited interindividual variation. Brain activation during the PVSAT in these participants 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 oral 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 with 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 showed right prefrontal activation. We interpret this bilateral activation of the prefrontal region as a cortical compensatory mechanism.[18] One of the most important aspects was that the control group outperformed the pure DAI group in the PVSAT. In addition, the patients with DAI who made a few errors tended to show a greater 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 (oral or spatial).[32] On the basis of 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 multiple sclerosis, the primary activation was detected in the right frontal cortex (BA 6, 8, and 9); in addition, the left BA 39

Table 2 Brain regions activated by Paced Visual Serial Attention Test versus Choice Reaction Test

Brain regions (Brodmann's area)	MNI template X	Y	Z	Z score
Patients with pure DAI				
Left inferior frontal gyrus (BA 45)	−55	18	19	4.44
	−48	18	18	4.14
Right inferior frontal gyrus (BA 45)	51	18	19	4.23
Right middle frontal gyrus (BA 46)	50	28	19	3.27
Controls				
Left precentral gyrus (BA 6)	−46	1	48	4.71
Left inferior frontal gyrus (BA 44)	−50	7	22	4.37
Left middle frontal gyrus (BA 46)	−46	26	19	3.71
Left inferior parietal gyrus (BA 40)	−42	−38	39	4.68
	−46	−35	46	4.51
Left superior parietal gyrus (BA 7)	−32	−49	60	4.51
Right inferior parietal gyrus (BA 40)	48	−41	40	4.18

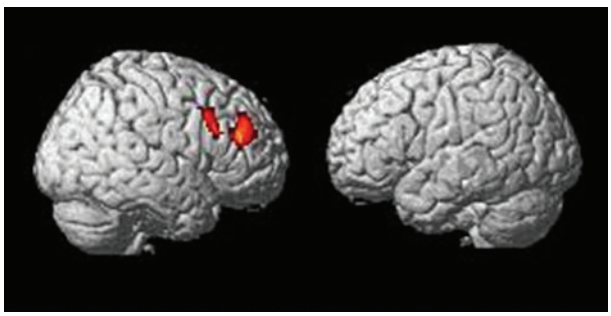

Figure 4 Between-group analysis of brain activation during the PVSAT task, patients with pure DAI showed greater activation of right inferior frontal gyrus (BA 45, 52 20 28, z = 3.54) and right middle frontal gyrus (BA 9, 40 42 22, z = 4.03) than did controls (amplitude threshold uncorrected $p<0.001$, extent threshold corrected $p<0.05$, for multiple comparisons). Data are displayed on a reference brain (MNI) with the indicated Talaraich coordinates.

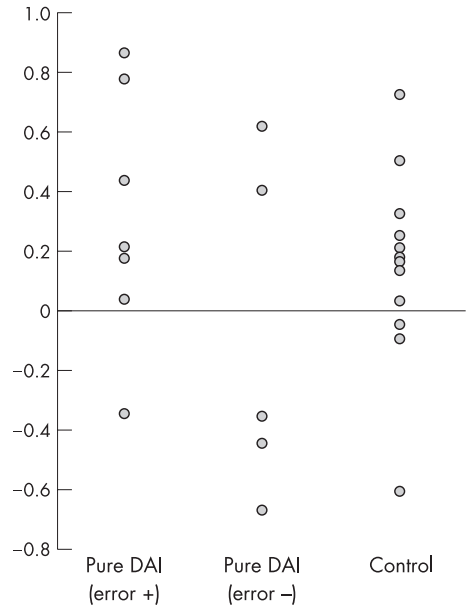

Figure 5 Raw data of the percent increase of activities in the right inferior frontal gyrus (BA 45, 52, 28) in each participant and PVSAT measurement, showing variability within the patients with pure DAI. The patients who made a few errors tended to show strong activity.

was active.[15] In healthy volunteers, tool use activated the right BA44, whereas simple stick use activated only the left BA 44. The right premotor cortex appears to play a greater part than its left-sided counterpart in sequence production when sequences are performed or learnt using the right hand.[33] Maruishi *et al*[34] showed that the right ventral premotor cortex plays an important part 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 patients with pure DAI needed greater parietal activation of storage processes during CRT than did the controls. As a result, subtraction of brain activation during CRT from brain activation during PVSAT did not show a significant difference in parietal activation in patients with pure DAI. Specifically, during the PVSAT task, cerebral blood flow in the left parietal region was increased more in patients with pure DAI than in controls.

Our study improved the methods of the fMRI task.[7 16–18] As in most previous studies, we 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.[12] 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.[35] A second relevant difference between this study and previous studies was the control task. In the studies by Audoin *et al*[17 18] the control task was repetition, whereas in others it was rest.[7 16] Several researchers have criticised the use of rest as a control task based on the notion that it may increase the likelihood of participants engaging in unsolicited cognitive activities that may confound results.[36] The third relevant difference from previous studies was the required response. Like Staffen *et al*,[16] we preferred not to directly control task performance and instructed participants to carry out the task silently. Mainero *et al*[7] instructed participants to carry out the task silently and raise their finger whenever the sum equalled 10. This approach avoided the problems associated with participants 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*[17 18] instructed participants to respond aloud. Clearly, allowing participants to verbalise in the scanner rather than carry out a motor response would be very desirable when seeking to obtain high-quality fMRI. However, the risk of movement and magnetic susceptibility artefacts has made the use of oral response prohibitive.

In conclusion, we interpret the differences in brain activation of patients with pure DAI 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.

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