A study of persistent post-concussion symptoms in mild head trauma using positron emission tomography

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ost-concussion symptoms are among the most common complaints after mild to moderate head injury. These symptoms include dizziness, headache, sensory sensitivities, impaired attention, poor memory, and executive dysfunction. Irritability, depression, nervousness, discouragement, and anger are also prominent. Most often, objectively measured cognitive functions in most subjects with mild head trauma are not significantly different from normal controls at three months post-injury. Subjective complaints, however, can continue beyond three months. The diagnosis of post-concussion symptoms is largely dependent on the patient’s and family members’ report, with limited corroborative evidence from neuropsychological testing, physical examination, and neuroanatomical imaging such as computed tomography (CT) and structural magnetic resonance imaging (MRI). The lack of objective findings thus makes it difficult to attribute symptoms to documented neuropathological causes, at least in the chronic stage.

Functional imaging in mild head trauma may be more sensitive to physiological defects. For example, single photon emission computed tomography (SPECT) in patients with mild to moderate head trauma has been reported to show a larger number of abnormalities than CT or MRI. However, the lack of large, well controlled studies prompted the therapeutics and technology assessment subcommittee of the American Academy of Neurology to caution against the diagnostic use of SPECT for mild head trauma. Positron emission tomography (PET) using [18F]fluoro-2-deoxy-D-glucose (FDG) in head injured persons with normal neuroanatomical scans has also indicated hypometabolism in frontal and temporal brain regions, with which deficient neuropsychological performance and post-concussion symptoms can be correlated. More recently, resting state FDG uptake in patients with late whiplash syndrome and suspected brain injury showed hypometabolism in the parieto-occipital regions; however, this finding was not replicated by Bick et al., who instead found hypometabolism in the frontal regions that correlated with depression. Radanov et al also failed to show correlations between neuropsychological performance and FDG uptake in late whiplash patients. Studies with functional MRI have shown that working memory evoked activation differed between controls and patients one month after mild head injury.

These studies suggest that functional neuroimaging may detect subtle changes in cerebral physiology. However, not all studies used matched controls, and some included patients who were less than three months post-injury. In this study we investigated resting state regional cerebral metabolism and changes in regional cerebral blood flow (rCBF) during a spatial working memory task in patients with mild head trauma and persistent post-concussion symptoms. The results were then compared with an age and education matched control group. We hypothesised that people with persistent symptoms beyond three months after mild head trauma would have lower FDG uptake in the temporal and frontal brain regions, and a smaller change in rCBF while performing a spatial working memory task.

METHODS

Participants

Five patients and five healthy controls were matched case by case for sex (three women and two men in each group), age (patients 34.4 (11.9) years; controls 34.2 (11.6) years; p = 0.98), handedness (one left handed in each group), and education (patients 14.1 (1.8) years; controls 14.2 (1.5) years; p = 0.85). Controls were excluded if they had a history of neurological and psychiatric diagnoses, including concussion and learning disability.

Abbreviations: CVLT, California verbal learning test; FLOPS, frontal lobe personality scale; PCSC, postconcussion syndrome checklist; ROI, region of interest
Patients were diagnosed with mild head trauma using the American Congress of Rehabilitation Medicine definition; diagnosis of post-concussion symptoms was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM–IV) research criteria. Patients were excluded if there was a history of axis–I psychiatric disorders, learning disability, or previous head trauma, and they were less than three months post-injury (16.6 (11.5) months). None had lesions on clinical CT or MRI, and none showed signs of malingered memory loss on the digit memory test. Such symptoms were both more frequent ($t = 2.33, p < 0.05$) and more intense ($t = 2.60, p < 0.03$) in the patients than in the controls. Neurobehavioural features of frontal lobe injury were quantified using self report forms of the frontal lobe personality scale (FLOPS), on which the patient and control groups did not differ significantly (apathy: $t = 0.84, p < 0.43$; disinhibition: $t = 0.56, p < 0.59$; executive dysfunction: $t = 1.13, p < 0.29$).

**Positron emission tomography**
Participants were imaged in a Siemens 951/31R whole body PET tomograph (6 mm FWHM intrinsic resolution; Siemens Inc, Hoffman Estates, Illinois, USA) in a supine position, with the head aligned approximately 1 cm below the canthomeatal line. A Dermaform® pillow and a hook and loop strap were used to secure the position of the head. Attenuation was corrected by a transmission scan using three internal rod sources before scanning. Dynamic imaging sequences were used within each session. For the resting state study, an intravenous bolus of 10 mCi of FDG was injected. Participants were kept awake during the 60 minute scan by a simple tone monitoring task (pressing a button when a tone sounded, without requiring a quick reaction time). Lights were dimmed during scanning, and the participants were instructed to remain still, eyes open, and ears unplugged.

During the rCBF working memory study, participants performed the Jonides spatial working memory task (fig 1) after an injection of H$_2$O. Inverted mirror goggles were used to visualise the task stimuli directly behind the participants as presented on a PC computer. A single bolus of 50 mCi H$_2$O was injected before each of two three-minute scans. The memory condition was administered during the first injection and the control condition during the second. Participants were given practice sessions before scanning to become comfortable with the task requirements.

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### Table 1 Patient injury characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type of injury</th>
<th>Litigation</th>
<th>Time since injury (months)</th>
<th>LOC reported (minutes)</th>
<th>Estimated PTA (hours)</th>
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</thead>
<tbody>
<tr>
<td>P01</td>
<td>42</td>
<td>F</td>
<td>Blunt object</td>
<td>No*</td>
<td>35</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>P02</td>
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<td>F</td>
<td>Fall</td>
<td>No</td>
<td>10</td>
<td>0.00</td>
<td>0.30</td>
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<tr>
<td>P03</td>
<td>23</td>
<td>M</td>
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<td>No*</td>
<td>14</td>
<td>0.00</td>
<td>0.00</td>
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<tr>
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<td>38</td>
<td>M</td>
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<td>5</td>
<td>0.50</td>
<td>3.00</td>
</tr>
<tr>
<td>P05</td>
<td>21</td>
<td>F</td>
<td>Fall</td>
<td>No</td>
<td>19</td>
<td>2.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean</td>
<td>34.4</td>
<td></td>
<td></td>
<td></td>
<td>16.60</td>
<td>0.50</td>
<td>0.87</td>
</tr>
<tr>
<td>SD</td>
<td>11.89</td>
<td></td>
<td></td>
<td></td>
<td>11.50</td>
<td>0.87</td>
<td>1.26</td>
</tr>
</tbody>
</table>

*Has previously received worker’s compensation but was not in litigation at time of study.
LOC, loss of consciousness; PTA, posttraumatic amnesia.
rCBF changes in the perception control were then subtracted from those in the memory condition. Because the perception control was perceptually similar to the memory condition, the result of the subtraction is rCBF change attributable to spatial working memory.

### Brain imaging
Anatomical MRIs were acquired on a GE Signa, 1.5 Tesla scanner (General Electric Co, Waukesha, Wisconsin, USA) to permit PET-MRI coregistration. One whole brain image series was collected using axial gradient echo T1 image (time of repetition = 24 ms, time of echo = 5 ms (minimum), flip angle = 30°, field of view = 24 cm, slice thickness = 1.2 mm, 256 x 128 matrix, 1 nex).

### Image analysis
#### Resting state study
In-house software was used to analyse PET images. Activity within each region of interest (ROI) was averaged and normalised to the calcarine cortex. ROIs in the frontal and temporal regions were chosen to be the focus of analysis and comparison as these are most likely to be damaged in head trauma. Neuroanatomical landmarks were used to identify the ROIs with the aid of a neuroanatomical reference.

#### Working memory study
The University of Michigan statistical analysis for PET activation software, V3.0 (Minoshima and Koeppe), was used to transform, group, and subtract the activation PET volumes.
stereotactically, normalising individual pixel counts by average whole brain counts. The perception condition was subtracted from the memory condition, and z map images were calculated separately for both patients and controls. A statistical threshold of $z > 3.0$ ($p < 0.001$, one tailed) was used to establish significance of activation.

Two approaches were used in analysing the effects of working memory between the groups. In the first approach, the regions significantly activated in the control group’s z map image (thresholded at $z > 3.0$) were used as the ROIs for analyses of differences between groups. In addition, the spatial distribution of regions activated for both patient and control groups were compared by quantifying the three dimensional differences between regions of activation with the formula:

$$
\text{diff}_{\alpha} = \sqrt{(x_c - x_p)^2 + (y_c - y_p)^2 + (z_c - z_p)^2}
$$

where $x$, $y$, and $z$ are Talairach coordinates, and the subscripts $c$ and $p$ represent controls and patients, respectively. For the second approach, regions that showed significant activation ($z > 3.0$) in the healthy controls studied by Jonides and colleagues were used as the ROIs for analyses of differences between groups.

**RESULTS**

**Resting state study**

There were no significant differences in normalised FDG uptake between patients and controls during the resting state in the ROIs investigated ($p > 0.10$; mean effect size = 0.21). Thus, for cortical regions most likely to be injured in head trauma, the patients had the same range of normalised resting glucose metabolism as the healthy controls. A post hoc analysis using an ROI based on the significant activated centroid (right inferior frontal gyrus) in the working memory task (see below) also did not show the groups to be significantly different ($t = 2.78; p = 0.85$).

**Working memory study**

For the working memory task, accuracy scores of the perception condition showed a statistical trend, with patients scoring slightly lower than controls: 24.0 (1.9) vs 26.6 (3.1) (mean (SD)), $t = 1.59$, $p = 0.09$. Accuracy scores for the memory condition were not significantly different between patients and controls: 16.6 (9.4) vs 18.2 (10.6); $t = 0.24$, $p = 0.41$. There was no statistical difference in perception condition reaction times between patients and controls ($0.32$ (0.59) s vs $0.39$ (0.44) s; $t = 0.75$, $p = 0.23$), nor was there a between group difference in reaction times for the memory condition (patients: $0.32$ (0.50) s; controls: $0.25$ (0.69) s; $t = 0.86$, $p = 0.20$).

The z map image in the healthy controls produced two significant centroids of activation in the right prefrontal regions: the right prefrontal–insular junction (Talairach coordinates, $[−30, 23, 2]$, $z = 4.5$) and the right inferior frontal gyrus (Talairach coordinates, $[−33, 21, 22]$, $z = 3.7$; fig 2A, table 3). One significant centroid of activation was found for the patients in the right prefrontal–insular junction (Talairach coordinates, $[−24, 19, 4]$, $z = 3.0$; fig 2B), the locus of which...
was 7.5 mm in three dimensional space from the same region in the control sample. This spatial difference is within the reconstructed resolution of the PET images, and is therefore likely to be the same region in both groups.

$t$ Test analyses of the ROIs identified from the control group’s $z$ map showed no significant difference in the per cent change in rCBF between the groups for the right prefrontal insular junction: Talairach coordinates, $[-30, 23, 2]$ ($p > 0.17$). However, patients had a smaller percentage change in rCBF than controls in the right inferior frontal gyrus: Talairach coordinates, $[-33, 21, 22]$ ($p < 0.04$) (fig 3). Analysis of the ROIs identified by Jonides and colleagues revealed no significant differences between groups ($p > 0.10$).

**DISCUSSION**

**Resting state study**

Our study did not show that patients with persistent symptoms of mild head trauma have lower resting FDG uptake than carefully matched healthy controls in the anterior temporal and frontal brain regions. This finding is contrary to that of Otte and colleagues, who found hypometabolism in the parieto-occipital regions of six whiplash patients compared with 12 normal controls. These investigators hypothesised that parieto-occipital hypometabolism may be caused by activation of nociceptive afferent nerves from the upper cervical spine. However, post hoc analysis of the parieto-occipital regions in our subjects showed no significant differences ($p > 0.50$).

In a later study by Bicik and colleagues using FDG-PET in 13 whiplash patients and 16 controls, statistical parametric mapping revealed hypometabolism in frontopolar regions, lateral temporal cortex, and putamen, although hypometabolism in the frontopolar regions was correlated with scores on the Beck depression inventory. They also did not find differences in parieto-occipital regions when it was specifically examined. Rather, hypometabolism and cortical thickness measured on MRI were correlated, suggesting partial volume effects. Our non-significant differences in FDG uptake between controls and patients are consistent with the findings of Bicik et al, particularly insofar as we found no between-group differences in depression on the SCL-90-R—that is, if hypometabolism is indeed related to depression, as other studies have also found, then lack of differences in cerebral metabolism between our groups would be expected. Had depression been more prominent in the post-concussion symptoms sample, significant group differences might have emerged.

**Working memory study**

FDG uptake following mild head trauma has been investigated in three other studies while the patients performed sustained attention tasks. Significant differences were reported between patients and controls. Our findings were less dramatic for the working memory task during the $\text{H}_2\text{O}$ study, but partially supported our hypothesis that patients would have a smaller increase in working memory induced rCBF in the right prefrontal brain regions than healthy controls. Using ROIs derived from the healthy controls’ activation map, there...
was no group difference in activation in the right prefrontal-insular junction [−30, 23, 2]. While the patients did not activate this area above the threshold, they had a smaller, sub-threshold activation within 7.5 mm of the controls’ right prefrontal-insular junction region, and within 12.5 mm of Jonides’ right prefrontal region centroid [−35, 19, −2]. Thus patients appeared to activate a similar region during the working memory task, albeit at a lower threshold. Nevertheless, the patients did have a slightly smaller working memory evoked rCBF increase in the right inferior frontal gyrus [−33, 21, 22].

These findings are consistent with a recent functional MRI study in mild head trauma, in which McAllister and colleagues found working memory activation differences in 12 patients and 11 healthy controls in six cortical regions (bilateral middle frontal, bilateral medial parietal, right lateral parietal, and left superior parietal). Their patients performed an n-back task of two difficulty levels (1-back and 2-back) with 0-back as the control condition. Patients showed less intense activation in similar regions than controls when performing the 1-back task. But the patients had significantly more regions of activation and of increased intensity when performing the 2-back compared with the 1-back task. The authors suggested task difficulty as an explanation for the differences in the activation maps. Our study had a relatively simple working memory task analogous to their 1-back task, and this would not evoke performance differences between patients and controls. However, McAllister and colleagues studied their patients at the acute stage of six to 35 days post-trauma, during which changes might more clearly be expected.

**Limitations**

Our findings are not without limitations. The study has a relatively small sample (five patients and five carefully matched controls) and power is an important consideration. However, the mean effect size for the a priori ROIs in the resting state study was 0.21 and extremely small. Thus unrealistically large samples (more than 300 per group) would be needed to identify group abnormalities. Resting FDG appears insensitive to gross abnormalities in key brain regions in patients with mild injuries and persistent complaints.

Our small sample may also not be generalisable to the larger population of mild head trauma, as it was composed of falls and blunt injuries rather than the more common automotive accidents. That said, however, the group is relatively homogeneous in terms of injury mechanism, and each control was carefully selected to match the patient’s demographics. A limitation of the working memory study was the absence of a counterbalanced order of condition presentation. Thus we cannot rule out the presence of uncontrolled carry over effects from one condition to the next, although this is less likely to affect a difference between groups treated in the same manner.

Finally, the patients were relatively free of cognitive impairment as reflected by neuropsychological test performance, both in absolute level and in comparison with the controls. This is an expected state of affairs in the chronic period of a mild head injury. All patients passed a screen for malingering, but they were significantly different in their recognition memory performance on the list learning task. Delayed list recognition is considerably easier than free recall, and poor performance on this task has been described as reflective of malingered cognitive performance on similar paradigms. Although the average recognition performance was higher than that thought to be reflective of malingering, it may be possible that some patients were not exerting full effort. However, accuracy and reaction time during the working memory task were no different between patients and controls during the memory and perception conditions.

**Conclusions**

This study provides potentially useful information for future work. During the resting state, normalised regional cerebral glucose metabolism was similar between patients and controls, but differences emerged in rCBF increases during a spatial working memory task in the inferior right frontal gyrus. Post hoc analysis of this area in the resting state study did not differentiate the groups. In simplistic terms, it is likely that during a more passive state the brain is not using resources required in accomplishing a specific cognitive task.

Mesulam’s model of attention comprises two major operations: the first is a matrix or state function, which serves as an overall information regulator, rendering the person vigilant and ready to act. This is related to the concept of tonic attention and is associated with neural mechanisms in the reticular activating system. The second component is the vector or channel function, which regulates the direction and target of attention. This is similar to selective attention and is associated with neocortical function. Based on Mesulam’s attention model, the resting state paradigm would be considered the “matrix” component of attention, and activation during the spatial working memory task in the current study would be associated with the “vector” component of attention. Therefore, differences between healthy and mildly traumatised brains may not be discernible in resting cerebral metabolism, as cortical tone is not affected postacutely. It is only with the presence of external demands (spatial working memory task) that this mild injury becomes apparent. Hence, this may imply that FDG-PET in the resting state may not be very useful in detecting mild persistent brain injuries; an activation task may be more promising in this regard.

On the other hand, it also remains to be determined how these functional changes relate to clinical outcome. Given that the vast majority of patients recover well from mild traumatic injuries, the validity of any change in brain function needs to be interpreted in terms of its impact on daily life. Were these findings present in patients who recover well from injury, and who do not complain of chronic symptoms, then other mediating factors would need to be sought. Moreover, it is also quite possible that there could be functional changes in how a brain accomplishes a specific cognitive goal, even in the absence of chronic neuronal injury. For example, it was clear that these patients were preoccupied with several persistent symptoms. This preoccupation and subjective discomfort could itself induce changes in cerebral perfusion patterns during task performance. Thus we are cautious in concluding that these changes reflect persistent neuropathological change.

In summary, this study did not reveal significant differences in resting FDG uptake between groups of mildly head injured patients with chronic post-concussion symptoms. Minor differences in rCBF did, however, emerge between groups during a visuospatial working memory task. The specificity and clinical relevance of these differences remains to be established.

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