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# Cerebral blood flow in chronic symptomatic mild traumatic brain injury

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**Abstract**

Patients with mild traumatic brain injury (MTBI) (Journal of Head Trauma and Rehabilitation, 8, 1993, 83–84) challenge physicians' skills and test their patience. Their manifold symptomatology is often not supported by objective neurological findings. We sought to compare regional cerebral blood flow (rCBF) between symptomatic subjects with longstanding MTBI and healthy controls, and to examine the correspondence between neuropsychological deficit and rCBF compromise. Twenty-eight clinically symptomatic male subjects with MTBI and twenty matched controls underwent neuropsychological testing and Tc-99m-HMPAO brain SPECT imaging. Neuropsychological test data were used to categorize subjects into sub-groups according to the presumed location of lesions based on their neurobehavioral deficits. Image subtraction comparisons were made between controls, all MTBI subjects and sub-groups. MTBI patients demonstrated regions of hypoperfusion in frontal, pre-frontal and temporal cortices, and sub-cortical structures. Hypoperfusion in 'frontal', 'left posterior' and to a lesser extent 'sub-cortical' sub-groups was concordant with neuropsychological localization. This was not the case for the 'right posterior' group, where no concordance was found. The rCBF is reduced in symptomatic patients with longstanding MTBI and unremarkable structural brain imaging. Although group analysis is appropriate for the generation of statistically significant differences, the clinical application of brain SPECT imaging in MTBI calls for a capability to associate clinical examination, neuropsychological assessment and cerebral perfusion at the individual subject level. Such competence is still to be attained.


*Keywords:* Neuropsychological testing; SPECT; Statistical parametric mapping; MTBI

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## 1. Introduction

Mild traumatic brain injury (MTBI, 1993) is a common and often severely debilitating condition, predominately affecting young males. Of 2 000 000 estimated traumatic brain injuries occurring yearly in the USA (Borczuk, 1997), 50–80% fit this category. No precise universal definition of 'mild' TBI exists in the literature. Prevailing definitions usually involve reference to a brief loss of consciousness or alteration in mental state, often based on the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), a brief anterograde or retrograde amnesia, and sometimes focal neurological deficits that may or may not be transient (DeKruijk et al., 2001).

A certain portion of individuals sustaining MTBI will exhibit long-lasting psychological and cognitive symptomatology (Adams and Victor, 1993). The clinical picture typically includes headache, dizziness, blurred vision (an early sign), fatigue/lethargy, anxiety/irritability, emotional instability, explosiveness, insomnia/hypersomnia, sensitivity to noise (hyperacusis), and deficits in memory, information processing, cognitive flexibility, problem solving and attention/concentration (Lezak, 1995). This manifold symptomatology and severe disability is generally not supported by objective neurological findings. Monetary issues are often involved and add an additional confound to the management of such cases (Binder and Rohling, 1966).

Imaging data regarding MTBI were derived mainly from structural imaging (computed tomography (CT) and magnetic resonance imaging (MRI) studies (Klauber et al., 1998; Stein and Ross, 1992; Duus et al., 1994; Miller et al., 1996). Functional brain imaging in MTBI has not yet been extensively explored. Intra-cerebral pathology was usually (Gray et al., 1992; Ichise et al., 1994; Abdel Dayem et al., 1998), but not always (Mitchener et al., 1997; Hofman et al., 2001), better detected by functional compared with structural imaging techniques in the acute as well as longer-term setting. Initial negative SPECT study was a predictor of favorable outcome in cases of mild and moderate head trauma (Jacobs et al., 1996), and in severe head injury. Baulieu et al. (2001) concluded that brain SPECT can be valuable in predicting neuropsychological deficit. Kant et al. (1997) reported a high prevalence of SPECT abnormalities in subjects with disturbances in behavior after head trauma, although no correlation with neuropsychological (NP) test scores or other clinical variables could be substantiated. Likewise no correlation was found between cognitive performance and detectable morphological or functional brain damage in the late whiplash syndrome (Radanov et al., 1999). A retrospective study of 20 patients with MTBI (Gross et al., 1996) showed local cerebral metabolic rates decrease in midtemporal, anterior cingulate, precuneus, anterior temporal and frontal regions. These decreases were significantly correlated with overall clinical complaints and overall NP test results. Ichise et al. (1994) examined a group of 29 subjects with mild and moderate TBI, and reported perfusion abnormalities in two thirds of these subjects, with a significant correlation between the antero-posterior perfusion ratio (APR) and some NP test scores. Varney et al. (1995), in a SPECT study, found anterior mesial temporal and left orbitofrontal hypoperfusion in cognitively competent mild head injury subjects with normal structural imaging but poor psychosocial and vocational function. Hofman et al. (2001) compared early MR images and SPECT scans after MTBI, and found an association between hypoperfusion seen on acute SPECT and brain atrophy after 6 months, yet with little correlation to general neurocognitive outcome. Finally, McAllister et al. (2001) studied working memory load effects after MTBI in a group of 18 patients using functional MRI (fMRI) and concluded that MTBI patients show a different pattern of allocation of processing resources despite similar task performance, suggesting an underlying anatomical correlation to memory complaints after MTBI.

The debate of generalized function (holism) vs. localization of function has a considerable foundation dating from the beginning of the study of brain-behavior relationships. The basic orientation of modern neuropsychology is to assume localization of function, although not a strict one in the sense that there is rarely a one-to-one correspondence between a region and a cognitive function.

Rather, networks of regions that operate around critical epicenters, act together to perform cognitive functions (e.g. Mesulam, 2000). Thus, significant deficits in a particular cognitive function most likely reflect a lesion related to one of these epicenters which link distributed information from other portions of the network into a coherent multimodal assembly that is critical for performance. Converging evidence from different behavioral tests (see below) can lead to more definite determination of the location of lesion.

Behavioral syndromes in TBI may be conceptualized in relation to a two-dimensional organization of cortical functions (Lezak, 1995). The longitudinal axis divides the cortex into the anterior or frontal (i.e. pre-rolandic) area that may be roughly characterized as responsible for motor/response functions, while the posterior cortical region deals with perceptual functions. The frontal area also includes the prefrontal region, which is involved in higher cognitive functions, such as linking and integrating components of behavior (Fuster, 1996; Mesulam, 2000). The behavioral consequence of lesions to prefrontal regions can generally be described as a defect in the temporal organization of behavior, defective monitoring of ongoing activity, and a deficit in planning. Other than the cerebral cortex itself, NP deficits in TBI may also be caused by damage to sub-cortical structures such as the thalamus and basal ganglia and white matter lesions. Broadly speaking, these injuries may cause alterations in arousal, attention and affect as well as basic sensory and motor functions, and more complex functions such as the encoding and retrieval of memories, procedural learning, certain language skills and more.

The lateral organization of the brain describes the distribution of functions across a dominant/non-dominant distinction, usually left/right, respectively. The left hemisphere is usually involved in linear, sequential and more detailed processing, as opposed to configurational large-scale global processing that characterizes the right hemisphere (Bradshaw and Nettleton, 1981). The left hemisphere also seems to be more proficient in processing familiar information, as opposed to the handling of novelty, which is better carried out by the right hemisphere.

The present study was conducted to test the hypothesis that regional cerebral blood flow (rCBF) abnormalities will be detected by SPECT imaging in clinically symptomatic subjects with chronic mild traumatic brain injury. A second hypothesis tested in the study was that the location of these rCBF abnormalities would be in agreement with the locations of cognitive deficit as indicated by an integrative analysis of NP testing.

## 2. Materials and methods

### 2.1. Subjects

Twenty-eight relatively young (mean $37 \pm 7.1$; range 22–49), clinically symptomatic male subjects were recruited into the study from the Unit for the Treatment and Rehabilitation of Head Trauma Victims. All had suffered MTBI no less than 2 years before examination (mean $5.2 \pm 2.3$ years).

Subjects were included in the study if their Glasgow Coma Scale score following trauma was no lower than 13, loss of consciousness (if present) lasted no longer than 20 min, and structural imaging (26 CT; 8 MRI) revealed no abnormality. Additional DSM-IV axes I and II pathology was excluded using the Structured Clinical Interview for DSM-IV (First et al., 1995). Twenty subjects had incurred motor vehicle accidents (MVA), four were injured at work (W) and four sustained combat injuries while in army service (Table 1, left-hand side).

All subjects were free of medication at the time of examination. Twenty age- and sex-matched healthy controls (paid volunteers) were recruited to the study. Control subjects all underwent psychological testing to exclude latent cognitive deficit. Control subjects were free from psychopathology, as were their first-degree relatives. Symptomatic and control subjects were all right-handed.

### 2.2. Neuropsychological testing battery

The following NP tests were used; where normative data other than those published in the manual were used, this is indicated in parentheses:

Table 1
Etiologies, imaging data and categorization by neuropsychological profile

| Patient | Etiology | Imaging | | | Neuropsychological deficits | | | |
|---|---|---|---|---|---|---|---|---|
| | | EEG | CT | MRI | Right posterior | Left posterior | Frontal lobe | Sub-cortical |
| HD | MVA | v | v | | | | v | |
| TM | MVA | | v | v | v | v | | |
| PM | W | | v | | v | v | | |
| MG | MVA | v | v | | v | | v | v |
| MT | MVA | v | v | v | | | v | |
| DM | CI | v | v | | | | v | v |
| MA | MVA | | v | | | v | v | |
| RD | MVA | v | v | | | v | v | |
| TH | W | v | v | v | v | v | | |
| LY | MVA | | v | | v | | v | v |
| BY | MVA | v | v | | | | v | |
| PA | MVA | v | v | | | v | v | |
| IA | CI | v | v | | | | v | |
| DY | MVA | | v | v | | | v | v |
| ST | MVA | v | v | | | | v | |
| CM | MVA | v | v | | | v | | v |
| LY | W | | | | v | v | v | |
| TR | MVA | | v | v | v | | | |
| GM | MVA | v | v | | | | v | |
| NA | MVA | v | v | v | v | | | |
| FM | CI | | v | | v | v | | |
| AR | MVA | | v | | | | v | |
| ZY | MVA | v | v | | v | | v | v |
| BY | W | | | | v | | v | |
| AE | CI | v | v | v | | | v | |
| AA | MVA | v | v | | v | | v | |
| Aar | MVA | | v | | | v | | |
| BS | MVA | v | v | v | v | | v | |

*Note*: MVA = Motor vehicle accident. W = Work accident. CI = Combat injury.

*Visuo-spatial and constructional ability*. Measures comprise subtests from the Wechsler Adult Intelligence Test-Revised (WAIS-R) (Wechsler, 1981): Block Design, Object Assembly and Picture Completion; Hooper Visual Organization Test (HVOT) (Hooper, 1981); Benton Visual Retention Test (BVRT) (Benton, 1974)-copy trial; Rey Osterrieth Complex Figure Test (ROCFT) (Osterrieth, 1993; Norms: Meyers and Meyers, 1995)-copy trial.

*Memory and Learning*. Measures comprise Logical Memory I (LMI) and Logical Memory II (LM II) from the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987); Learning index and delayed memory index from Rey's Auditory Verbal Learning Test (Rey AVLT) (Norms: Vakil and Blachstein, 1997); BVRT-immediate retention (Benton, 1974); ROCFT- delayed recall (Osterrieth, 1993; norms: Meyers and Meyers, 1995).

*Manual Speed and Dexterity*. These tests are sensitive to subcortical damage and can provide important information about lateralization (Spreen and Strauss, 1998). They comprise the Purdue Peg-Board (Tiffin, 1968): Right hand, Left hand and Assembly; Digit Symbol from the WAIS-R; Symbol-Digit Modalities Test (SDMT) (Smith, 1982); Trail Making Test-part A (TMT-A, public domain; norms: Spreen and Strauss, 1998).

*Executive Functions*. Measures comprise the Similarities sub-test from the WAIS-R; Raven's Progressive Matrices (RPM) (Raven 1982); Controlled Oral Word Association (COWA; Hebrew

Norms: Kempf-Sherf, O., unpublished norms); Trail Making Test-part B (TMT-B; Norms: Spreen and Strauss, 1998).

The presence of language disorders was derived from the clinical evaluation of the patient's speech and the performance on tests that also require language skills such as naming ability on the HVOT.

### 2.3. Neuropsychological test analysis

Test performance was interpreted by preparing a summary profile sheet of test results for each patient. Test raw scores were translated into percentile ranks by using age-corrected scores and where available education-corrected percentile. Where the normative data does not provide actual score distributions, deviations from the age-appropriate mean were converted into percentile ranks. The summary profile for each of the participants, together with qualitative reports of test performance and behavior, were inspected by two neuropsychologists who evaluated the patterns of cognitive strengths and deficits. Based on this integrative interpretation, they classified each patient into one or more of the groups (see below) that best reflected their neurobehavioral syndrome.

Three primary reasons support the employment of an integrative interpretation of test data based on pattern analysis, rather than a cut-off score classification for determining cognitive deficits. First, the use of cut-off scores on their own to separate 'normal' from 'abnormal' test performance has numerous potential pitfalls (Lezak, 1995). These include limited reference in normative data regarding base rates of diagnostic classifications and unsatisfactory adjustments for age, education, pre-morbid ability, etc., within the sample. These potential hazards make cut-off scores questionable tools for determining group membership in research settings and may generate cases of false-positive and false-negative misdiagnoses. Second, cut-off scores do not take into account meaningful discrepancies in test performance within a subject as well as test score patterns, two dimensions of performance without which any description of a patient's deficit is inappropriate. Integrated interpretations, which provide diagnostically more meaningful information, are more efficient in identifying organic impairments and minimizing false-positives than rigid cut-off scores. Finally, the use of a large number of neuropsychological tests and the application of cut-off scores for each of them may give rise to statistical error that would inflate the perception of clinically significant deficit due to multiple comparisons. However, the use of multiple tests in an integrative way is considered a powerful tool for assessing multiple dissociations between tests and test scores based on the logic of double dissociations that directs cognitive neurology and neuropsychology (e.g. Russell, 1984).

Neuropsychological test performance, analyzed as described above, was then used to categorize MTBI subjects into one or more of the following sub-groups, defined according to the major hypothesized cerebral locations of impairment: (1) 'right posterior', (2) 'left posterior', (3) 'frontal', and (4) 'sub-cortical' (Table 1 right-hand side). Since lateralization of cognitive functions is not as marked in the frontal lobe as it is in more posterior regions, 'frontal' dysfunction was not sub-divided into left and right syndromes. Most patients demonstrated multiple deficits, and were categorized accordingly into multiple diagnostic groups (Table 1).

The correlation between damaged neuroanatomical structures and behavioral functions is not straightforward, and localization of dysfunction based on neuropsychological performance is by nature hypothetical. However, neuropsychological performance can be the basis for quite accurate educated guesses regarding the site of lesion based on abnormal patterns of behavior, in particular when a syndrome approach is employed (Damasio and Damasio, 1989; Lezak, 1995).

### 2.4. SPECT imaging

SPECT images were obtained with a double-headed gamma camera (Elscint-Helix), which has two rectangular $540 \times 400$ mm field-of-view detectors, equipped with a low energy, ultra-flared fan-beam collimator. Resolution of the system is given at 8 mm (full width half maximum). Five group comparisons were made, comparing all MTBI patients together and each of the four sub-groups

of MTBI patients (categorized according to their cognitive deficit profile), to normal control subjects. Patients were placed in the SPECT gantry with head immobilized in a head holder (with Velcro straps), positioned in the center of the detectors' field-of-view in order to ensure coverage of the entire brain. Twenty mCi (740 MBq) of Technetium-99m hexamethylpropyleneamineoxime (Tc-99m HMPAO) were injected into each subject, while resting supine in a quiet, darkened room with eyes open and ears unplugged. Immediately after the end of the acquisition, corrections for center of rotation, isotope decay, sensitivity and scanning velocity were implemented. Reconstruction of the transaxial data sets was performed with 1 pixel-thick (3.655-mm) slices using ramp filtered back-projection. Attenuation correction was done by the Chang method.

### 2.5. Data analysis

Data were analyzed using statistical parametric mapping (SPM), as subsequently modified and augmented for data analysis by Friston et al. (1995) within the MEDx (Sensor Systems Inc., 1998) software. All images were realigned to a standard stereotactic (Talairach et al., 1988) brain atlas using the AIR algorithm (Woods et al., 1998) and normalized to an average global blood flow of 50. The alignment had a mean error of 2 mm, well within the SPECT system resolution. Voxels with counts of less than 80% of the average blood flow were considered white matter or external regions and removed from the sample (as is the convention in SPM–in addition, confines were lowered to 70% with no effect upon results). The normalized images were smoothed using a 10-mm (full width at half maximum) isotropic Gaussian kernel.

Statistical variation in rCBF between MTBI and control subjects at each voxel was estimated according to the general linear model. A *t*-statistic image (SPM($t$)) denoting the contrast condition effect was constructed. The resulting set of $t$ values for each group comparison constitute the statistical parametric map SPM($t$). The SPM($t$) values were transformed to the unit normal distribution (SPM($Z$)). $Z$ scores were further analyzed using random field theory within SPM, and thresholded at 2.35 (or $P=0.01$). Clusters of voxels surpassing this contingency were further thresholded according to size, with minimal cluster size set at 50 voxels. In order to further account for multiple comparisons, only clusters with a maximal $Z$ value higher than 3.75 ($P=0.0005$) were considered significantly different.

## 3. Results

*All patients* ($n=28$) (Fig. 1a): A comparison of all patients with healthy controls revealed several areas of reduced relative blood perfusion in head trauma subjects, incorporating both the cerebral cortex and sub-cortical structures. The most prominent regions included: (i) an area with the left pre-central gyrus at its center (BA: 4, 6), extending forward to the left inferior frontal gyrus (BA: 44,45), backwards to the left superior and mid-temporal gyrus (BA: 43, 40) and up to the lateral sulcus. (ii) A region on the right extending from the medial aspect of the frontal lobe and cingulate gyrus (BA: 9, 32) back through peri-ventricular longitudinal fasciculi and striatal structures to right transverse temporal gyrus and sub-cortical structures. This region extended as low as the orbito-frontal and inferior temporal regions (BA: 10 to 41) and inferior frontal gyrus (BA: 13). No brain regions with significantly higher rCBF in subjects with MTBI were found.

Comparisons were then performed between subgroups of patients with MTBI (defined according to neuropsychological profile as described above) and healthy controls.

Since subgroups included the same subjects that made up the whole patient group, and since all groups were compared with the same healthy subjects, some overlap exists between the whole group comparison and that of subgroups. This is particularly seen in large subgroups (with a considerable overlap with the 'all patients' group), such as the group with frontal lobe deficit. Nevertheless, division of patients into subgroups according to cognitive deficit reveals the unique contribution of each subgroup (with the exception of the 'right posterior' group, see below) to the full picture.

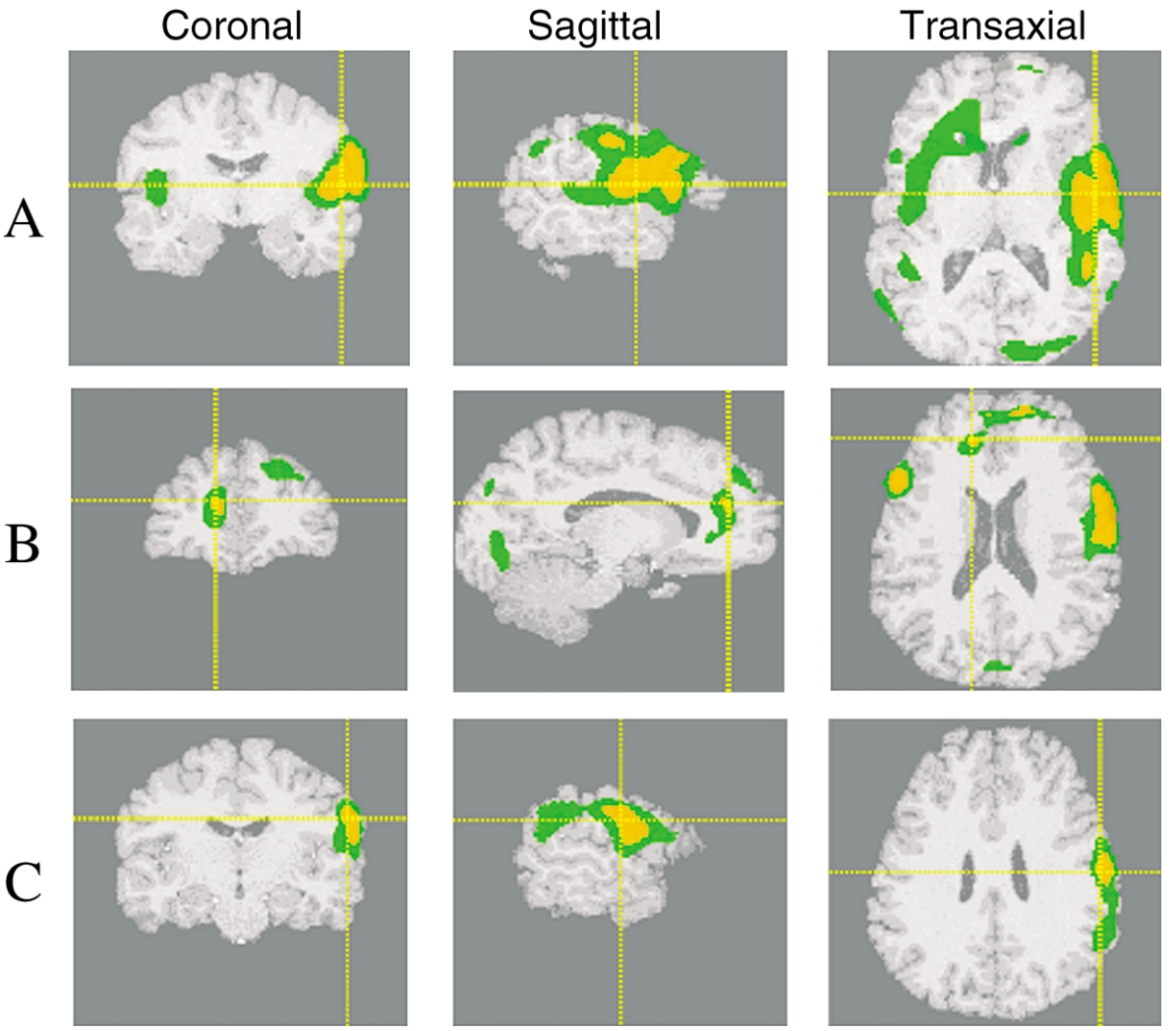


Fig. 1. Regions demonstrating compromised cerebral perfusion ratios in the comparisons between the following groups: (a) All patients with MTBI compared to healthy controls (Talairach coordinates −52; −4; 12). (b) Patients with neuropsychological profile suggestive of frontal lobe deficit, compared with healthy controls (Talairach coordinates 14; 41; 22). (c) Patients with neuropsychological profile suggestive of left-posterior deficit, compared with healthy controls (Talairach coordinates −56; −15; 29). Color scale: Green: *Z* score 2.35–4; Orange: *Z* score 4–6.

*Frontal* ($n=20$) (Fig. 1b): (i) The left pre-central gyrus was still prominent, extending forward to the inferior and medial frontal gyri (areas 6, 44, 45). However, it does not extend as far back and down into parietal and temporal cortices. (ii) Bilateral medial frontal gyrus, extending to right and left superior frontal gyri (BA: 9, 10). On the left, this area extends back to the left anterior cingulate gyrus (BA: 32, 24). (iii) Right inferior frontal gyrus, extending back to pre-central gyrus (BA: 45, 44, 6) and up to the medial frontal gyrus and frontal eye field (BA: 8).

*Left posterior* ($n=10$) (Fig. 1c): (i) A region beginning at the left pre-central gyrus (BA: 6, 4), extending back to the post-central gyrus (BA: 3, 1, 2). (ii) The left inferior parietal lobule and

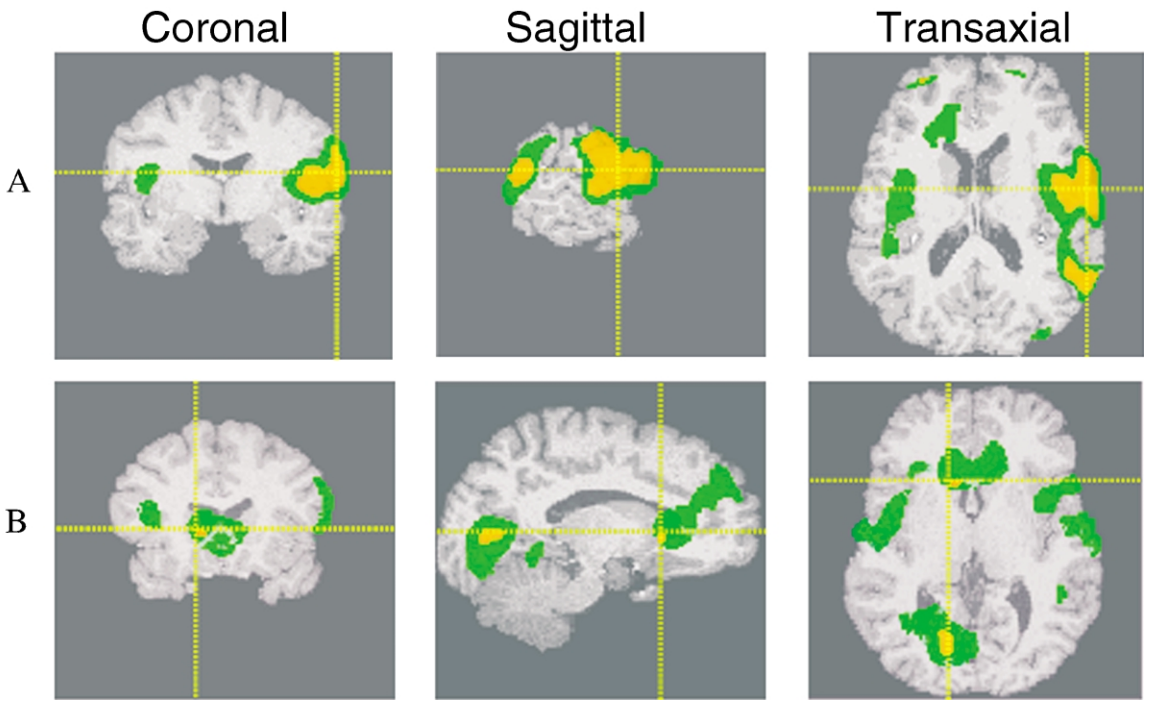


Fig. 2. Regions demonstrating compromised cerebral perfusion ratios in the following comparisons: (a) Patients with neuropsychological profile suggestive of right-posterior deficit, compared with healthy controls (Talairach coordinates −59; −6; 16). (b) Patients with neuropsychological profile suggestive of sub-cortical deficit, compared with healthy controls (Talairach coordinates 12; 22; 10). Color scale: Green: *Z* score 2.35–4; Orange: *Z* score 4–6.

supra-marginal gyrus (BA: 40) ending at the superior temporal gyrus (BA: 39).

*Right posterior* ($n=13$) (Fig. 2a): (i) A large region on the left, beginning at the pre-central gyrus (BA: 6) and extending backwards along the surface of the cortex to the superior and medial temporal gyri (BA: 42, 22, 21, 37). This region also extends inwards along the insula and the operculum. In contrast to all other subgroups, where neuropsychological and scintigraphic findings were largely compatible, in this subgroup neuropsychological and scintigraphic findings were incongruent.

*Sub-cortical* ($n=6$) (Fig. 2b): (i) A region which includes the anterior part of the head of the caudate nucleus, extending forward into the cingulate gyrus (BA: 24). (ii) Regions on the left and on the right which include the temporal operculum and some of the neighboring insular and parietal cortex. (iii) A medial occipital region with the cuneate gyrus (BA: 17) at its center.

## 4. Discussion

These results are consistent with prior studies that revealed SPECT abnormalities in chronic/post-acute stages of MTBI, despite scanty or altogether absent findings in structural imaging (e.g. Gray et al., 1992).

The rCBF abnormalities detected by SPECT in our subject group were particularly marked in the medial and lower aspects of the temporal and frontal regions. Since skull fractures were absent in all patients, it is reasonable to assume that most of the neurological damage is a result of the rotational, rather than the linear, component of TBI. The rotational component of TBI often induces contusions of orbitofrontal surfaces, cortical

areas above the Sylvian fissures, temporal poles and inferior aspects of the temporal lobes (Adams and Victor, 1993). It also produces diffuse axonal injury (DAI), which typically occurs at the junction between gray and white matter (Adams et al., 1980; Gennarelli, 1993; McAllister, 1995), affecting the parasagittal regions of the frontal lobes and the periventricular regions of the temporal lobes (Adams et al., 1985).

Our findings are similar to those of Kant et al. (1997), who reported a predominance of frontal and temporal lobe SPECT abnormalities, as well as to those of Gross et al. (1996), who report decreases in cerebral glucose metabolism in mid-temporal, anterior cingulate, precuneus, anterior temporal and frontal regions, both studies examining similar subjects. In Jacobs et al.'s (1996) follow-up study, SPECT abnormalities in frontal regions were more persistent than in other locations. Varney et al. (1995) reported that anterior mesial temporal hypoperfusion was common among MTBI patients, although their conclusions regarding orbitofrontal regions are less conclusive. Conversely, in a review of 228 patients, Abdel Dayem et al. (1998) report that basal ganglia and thalami abnormalities are more common than either frontal lobe or temporal lobe abnormalities. More than half the patients were imaged within 3 months of their injury. The authors do not distinguish between short- and long-standing lesions, deeming it difficult to judge the association between chronicity of insult and cerebral perfusion.

The general pattern of rCBF abnormalities also demonstrates a moderate degree of correspondence between neuropsychologically determined sub-groups and regions of decreased cerebral perfusion. Neuropsychological classification produced the expected large group of patients characterized by 'frontal' cognitive dysfunction ($n=20$). The most conspicuous behavioral outcome of traumatic brain injury, irrespective of the exact location of insult, is frontal lobe dysfunction (Miller et al., 1996; Benson and Miller, 1997). This was also the case in the present group of patients. 'Right posterior' and 'left posterior' cognitive dysfunction, i.e. dysfunction related to occipital, parietal and/or temporal lobes, was present in 13 and 10 of the patients, respectively. Only six patients were characterized by sub-cortical related cognitive deficits. This is compatible with the fact that only short periods of loss of consciousness were present in this cohort, rendering deeper (and manifest by sub-cortical deficit) DAI unlikely.

It should be noted that the typology according to neuro-behavioral syndromes was not exclusive, i.e. patients most often exhibited patterns of test-behavior that corresponded to more than one syndrome. Hence, one cannot expect the pattern of blood perfusion deficits to be exclusive (e.g. compatible with only one neuro-behavioral syndrome), and the classification to groups should yield a pattern where the expected region is prominent, but not preclusive of other regions.

In three of the four groups, i.e. 'frontal', 'left posterior' and 'sub-cortical' groups, this indeed was the case. In the frontal group an attunement was observed between SPECT abnormalities and test performance, as most regions of hypoperfusion were confined to frontal lobe cortex, and more posterior regions of hypoperfusion demonstrated by the group as a whole were not as prominent. The group that was characterized as having 'sub-cortical' cognitive deficits was the only one there was with hypoperfusion of the basal ganglia (head of the caudate), possibly reflecting the fact that this group represented a minority within the group as a whole, as discussed above. Mental slowness and motor speed deficits that characterized this group can be attributed to diffuse axonal injury (Richardson, 1999), which may explain why this group did not show more extensive perfusion deficits. Importantly, these patients did not show marked perfusion abnormalities in frontal and posterior neocortical cortices, as had characterized the other neurobehaviorally determined sub-groups. The differentiation between the two posterior groups was less conclusive. While the 'left posterior' group indeed presented with primarily left parietal and temporal regions of hypoperfusion, the 'right posterior' sub-group did not present the expected pattern of blood perfusion abnormalities. In fact, the pattern of blood perfusion in that group was very similar to the one exhibited by the 'left posterior' group, with right posterior regions of hypoperfusion not meeting the stringent statistical threshold ($Z$ score $>3.75$). Given that any attempt

to explain this finding will be entirely hypothetical, we make note of this fact and suggest that further research is needed to determine the relationship between perfusion indices and posterior neocortical cognitive functions in mild TBI.

Only a few studies have undertaken to investigate the relationship between functional imaging and performance on NP tests in chronic MTBI. These were characterized by mixed results. Ichise et al. (1994) investigated 29 patients, of whom 15 were classified as MTBI. An antero/posterior blood perfusion ratio was weakly correlated with 6 of 12 NP test measures, including memory, attention and executive function. The association between NP function and cerebral perfusion in chronic MTBI was also investigated by Umile et al. (1998) in a SPECT study that examined four patients approximately 19 months post-injury. Composite data regarding impaired test performance was correlated with qualitative interpretations of SPECT images. Test performance predicted SPECT findings on most occasions while rCBF abnormalities often had no corresponding behavioral deficit on testing. Kant et al. (1997), in another SPECT study, could not substantiate a relationship between NP test scores and SPECT qualitative visual inspection.

In contrast to the above-mentioned studies, the present study took an integrative approach to NP functioning, in which both normative data and intra-subject cognitive profile, i.e. both absolute and relative measures of cognitive deficit, were considered in generating subjects' overall neurobehavioral deficit. Furthermore, SPECT analysis in the present study utilized SPM for comparing subjects' perfusion patterns with those of a reference group of healthy matched controls. Regions of significant difference between groups were thus identified in the absence of any preconceived demarcation of putative regions of interest.

The results of the present SPECT investigation support the presence of residual organic brain damage following even slight craniocerebral injury in carefully chosen symptomatic subjects. Our data further suggest that the location of perfusion deficits may be foreseeable by careful interpretation of NP test results. However, it should be borne in mind that our imaging findings were derived from between-group comparisons, not interpretation of single patient scan data. Hence, clinical application of brain SPECT imaging in MTBI still calls for a capacity to associate clinical examination, neuropsychological assessment and cerebral perfusion at the individual subject level. We believe this and similar studies will aid in lending credibility to complaints voiced by subjects suffering from sequelae of MTBI. We further hope that future research will aid in making valid diagnosis and providing appropriate treatment to the individual patient.

## References

Abdel Dayem, H.M., Abu Judeh, H., Kumar, M., Atay, S., Naddaf, S., El Zeftawy, H., Luo, J.Q., 1998. SPECT brain perfusion abnormalities in mild or moderate traumatic brain injury. Clinical Nuclear Medicine 23, 309–317.

Adams, J.H., Scott, G., Parker, L.S., Graham, D.I., Doyle, D., 1980. The contusion index: a quantitative approach to cerebral contusions in head injury. Neuropathlogy and Applied Neurobiology 6, 319–324.

Adams, J.H., Doyle, D., Graham, D.I., Lawrence, A.E., McLellan, D.R., Gennarelli, T.A., Pastuszko, M., Sakamoto, T., 1985. The contusion index: a reappraisal in human and experimental non-missile head injury. Neuropathology and Applied Neurobiology 11, 299–308.

Adams, R.D., Victor, M., 1993. Craniocerebral trauma. In: Adams, R.D., Victor, M. (Eds.), Principles of Neurology. McGraw-Hill, New York, pp. 749–775.

Baulieu, F., Fournier, P., Baulieu, J.L., Dalonneau, M., Chiaroni, P., Eder, V., Potteir, J.M., Legros, B., 2001. Technetium-99m ECD single photon emission computed tomography in brain trauma: comparison of early scintigraphic findings with long-term neuropsychological outcome. Journal of Neuroimaging 11 (2), 112–120.

Benson, D.F., Miller, B.L., 1997. Frontal lobes: clinical and anatomic aspects. In: Feinberg, T.E., Farah, M.J. (Eds.), Behavioral Neurology and Neuropsychology. McGraw-Hill, New York, pp. 401–408.

Benton, A.R., 1974. The Revised Visual Retention Test. 4th ed. Psychological Corporation, New York.

Binder, L.M., Rohling, M.L., 1966. Money matters: a meta-analytic review of the effects of financial incentives on recovery after closed-head injury. American Journal of Psychiatry 153, 7–10.

Borczuk, P., 1997. Mild head trauma. Emergency Medicine Clinics of North America 15, 563–579.

Bradshaw, J.L., Nettleton, N.C., 1981. The nature of hemispheric specialization in man. Behavioural Brain Science 4, 51–63.

Damasio, H., Damasio, A.R., 1989. Lesion Analysis in Neuropsychology. Oxford University Press, New York.

De-Kruijk, J.L., Twijnstra, A, Leffers, P., 2001. Diagnostic criteria and differential diagnosis of mild traumatic brain injury. Brain Injury 15 (2), 99–106.

Duus, B.R., Lind, B., Christensen, H., Nielsen, O.A., 1994. The role of neuroimaging in the initial management of patients with minor head injury. Annals of Emergency Medicine 23, 1279–1283.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders. Biometrics Research Department, New York State Psychiatric Institute, New York.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.B., Frith, C.B., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging. A general approach. Human Brain Mapping 2, 189–210.

Fuster, M.Y., 1996. Frontal lobe syndromes. In: Fogel, B.S., Schiffer, R.B., Rao, S.M. (Eds.), Neuropsychiatry. Williams and Wilkins, Baltimore, pp. 407–413.

Gennarelli, T.A., 1993. Mechanisms of brain injury. Journal of Emergency Medicine 11 (Suppl), 5–11.

Gray, B.G., Ichise, M., Chung, D.G., Kirsh, J.C., Franks, W., 1992. Technetium-99m-HMPAO SPECT in the evaluation of patients with a remote history of traumatic brain injury: a comparison with X-ray computed tomography. Journal of Nuclear Medicine 33, 52–58.

Gross, H., Kling, A., Henry, G., Herndon, C., Lavretsky, H., 1996. Local cerebral glucose metabolism in patients with long-term behavioral and cognitive deficits following mild traumatic brain injury. Neuropsychiatry and Clinical Neuroscience 8, 324–334.

Hofman, P.A., Stapert, S.Z., VanKroonenburgh, M.J., Jolles, J., De Kruijk, J., Wilmink, J.T., 2001. MR imaging, single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. American Journal of Neuroradiology 22 (3), 441–449.

Hooper, H.E., 1981. Hooper Visual Organization Test (VOT). Western Psychological Services, Los Angeles.

Ichise, M., Chung, D.G., Wang, P., Wortzman, G., Gray, B., Franks, W., 1994. Technetium-99m-SPECT, CT and MRI in the evaluation of patients with chronic traumatic brain injury: a correlation with neuropsychological performance. Journal of Nuclear Medicine 35, 217–226.

Jacobs, A., Put, E., Ingels, M., Put, T., Bossuyt, A., 1996. One-year follow-up of technetium-99m-HMPAO SPECT in mild head injury. Journal of Nuclear Medicine 37, 1605–1609.

Kant, R., Smith-Seemiller, L., Isaac, G., Duffy, J., 1997. Tc-HMPAO SPECT in persistent post-concussion syndrome after mild head injury: comparison with MRI/CT. Brain Injury 11, 115–124.

Klauber, M.R., Marshall, L.F., Luerssen, T.G., Frankowski, R., Tabaddor, K., Eisenberg, H.M., 1998. Determinants of head injury mortality: importance of the low risk patient. Neurosurgery 24, 31–36.

Lezak, M.D., 1995. Neuropsychological Assessment. Oxford University Press, New York.

McAllister, T.W., 1995. Neuropsychiatric sequelae of head injuries. Psychiatric Clinics of North America 15, 395–413.

McAllister, T.W., Sparling, M.B., Flashman, L.A., Guerin, S.J., Manourian, A.C., Saykin, A.J., 2001. Differential working memory load effects after mild traumatic brain injury. Neuroimage 14 (5), 1004–1012.

Mesulam, M.M., 2000. Principles of Behavioral and Cognitive Neurology. 2nd ed. Oxford University Press, New York.

Meyers, J., Meyers, K., 1995. The Meyers Scoring System for the Rey Complex Figure and the Recognition Trial: Professional Manual. Psychological Assessment Resources, Odessa, FL.

Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine, 1993. Definition of mild head injury. Journal of Head Trauma and Rehabilitation 8, 83–84.

Miller, E.C., Derlet, R.W., Kinser, D., 1996. Minor head trauma: is computed tomography always necessary? Annals of Emergency Medicine 27, 290–294.

Mitchener, A., Wyper, D.J., Patterson, J., Hadley, D.M., Wilson, J.T., Scott, L.C., Jones, M., Teasdale, G.M., 1997. SPECT, CT, and MRI in head injury: acute abnormalities followed up at six months. Journal of Neurology, Neurosurgery and Psychiatry 62, 633–636.

Osterrieth, P.A., 1993. Le test de copie d'une figure complexe. Clinical Neuropsychologist 7, 9–15. Translated by J. Corwin and F.W. Bylsma.

Radanov, B.P., Bicik, I., Dvorak, J., Antinnes, H., Von-Schulthess, G.K., Buck, A., 1999. Relation between neuropsychological and neuroimaging findings in patients with late whiplash syndrome. Journal of Neurology, Neurosurgery and Psychiatry 66 (4), 485–489.

Raven, J.C., 1982. Revised Manual for Raven's Progressive Matrices and Vocabulary Scale. NFER, Nelson, Windsor, UK.

Russell, E.W., 1984. Theory and development of pattern analysis methods related to the Halstead–Reitan battery. In: Logue, P.E., Schear, M. (Eds.), Clinical Neuropsychology A Multidisciplinary Approach. Charles C Thomas, Springfield, IL.

Richardson, J.T.E., 1999. Clinical and Neuropsychological Aspects of Closed Head Injury. 2nd ed. Psychology Press, Hove.

Smith, A., 1982. Symbol Digit Modalities Test (SDMT) Manual (Revised). Western Psychological Services, Los Angeles.

Spreen, O., Strauss, E., 1998. A Compendium of Neuropsychological Tests: Administration, Norms and Commentary. Oxford University Press, New York.

Stein, S.C., Ross, S.E., 1992. Mild head injury: a plea for routine early CT scanning. Journal of Trauma 33, 11–13.

Talairach, J., Zilkha, G., Tournoux, P., Prosalentis, A., Bordas-Ferrier, M., Covello, L., Iacob, M., Mempel, E., 1988. Atlas d'Anatomie Stereotactique du Telencephale. Masson, Paris.

Teasdale, G., Jennett, B., 1974. Assessment of coma and impaired consciousness: a practical scale. Lancet 2, 81–84.

Tiffin, J., 1968. Purdue Peg Board Examiner's Manual. London House, Roisemont, IL.

Umile, E.M., Plotkin, R.C., Sandel, M.E., 1998. Functional assessment of mild traumatic brain injury using SPECT and neuropsychological testing. Brain Injury 12, 577–594.

Vakil, E., Blachstein, H., 1997. Rey AVLT: developmental norms for adults and the sensitivity of different memory measures to age. Clinical Neuropsychologist 4, 356–369.

Varney, N.R., Bushnell, D.L., Nathan, M.E., 1995. Neuro-SPECT correlates of disabling mild head trauma: preliminary findings. Journal of Head Trauma Rehabilitation 10, 18–28.

Wechsler, D., 1981. Wechsler Adult Intelligence Scale-Revised. The Psychological Corporation, San Antonio, TX.

Wechsler, D., 1987. Wechsler Memory Scale-Revised. The Psychological Corporation, San Antonio, TX.

Woods, R.P., Grafton, S.T., Holmes, C.J., Cherry, S.R., Mazziotta, J.C., 1998. Automated image registration: I. General methods and intrasubject, intramodality validation. Journal of Computer Assisted Tomography 22, 141–154.