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# Technetium-99m-HMPAO SPECT, CT and MRI in the Evaluation of Patients with Chronic Traumatic Brain Injury: A Correlation with Neuropsychological Performance

Masanori Ichise, Dae-Gyun Chung, Paul Wang, George Wortzman, Bruce G. Gray and William Franks

*Department of Radiology, Department of Psychology, Mount Sinai Hospital, and University of Toronto; and Department of Rehabilitation Medicine, West Park Hospital, Toronto, Canada*

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The purposes of this study were: (1) to compare <sup>99m</sup>Tc-hexamethylpropyleneamineoxime (HMPAO) SPECT with CT and MRI in chronic traumatic brain injury (TBI) patients and (2) to correlate both functional and structural neuroimaging measurements of brain damage with neuropsychological (NP) performance. **Methods:** Twenty-nine patients (minor TBI, n = 15 and major TBI, n = 14) and 17 normal controls (NC) underwent HMPAO SPECT, CT, MRI and NP testing. Imaging data were analyzed both visually and quantitatively. **Results:** Nineteen (66%) patients showed 42 abnormalities on SPECT images, whereas 13 (45%) and 10 (34%) patients showed 29 abnormalities on MRI and 24 abnormalities on CT. SPECT detected relatively more abnormalities than CT or MRI in the minor TBI subgroup. The TBI group showed impairment on 11 tests for memory, attention and executive function. Of these, the anterior-posterior ratio (APR) correlated with six tests, whereas the ventricle-to-brain ratio (VBR), a known structural index of a poor NP outcome, correlated with only two tests. **Conclusion:** In evaluating chronic TBI patients, HMPAO SPECT, as a complement to CT or MRI, may play a useful role by demonstrating brain dysfunction in morphologically intact brain regions and providing objective evidence for some of the impaired NP performance.

**Key Words:** chronic traumatic brain injury; neuropsychological dysfunction; technetium-99m-HMPAO; computed tomography; magnetic resonance imaging; single photon emission computed tomography

J Nucl Med 1994; 35:217-226

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**T**raumatic brain injury (TBI) is the most common of all serious neurologic disorders with incidence and prevalence rates surpassing those for stroke (1). Surviving victims,

who are largely young, often suffer life-long physical, neurologic and psychological effects. Thus, TBI is a significant chronic illness.

During both acute and subacute stages of TBI, CT and MRI play an important role by detecting intracranial lesions which may require surgical intervention (2,3). During the chronic stage, however, the usefulness of these structural neuroimaging techniques appears less dramatic. Although several studies have shown that the late ventriculomegaly, as a result of the brain tissue loss, demonstrated by either CT or MRI is associated with a poor neuropsychological (NP) outcome, there is often no clear-cut relationship between the anatomical and NP findings in these patients (4-9).

On the other hand, functional neuroimaging using PET and SPECT has the potential to probe into the functional consequence of the damaged brain. PET, however, is limited to a small number of research centers due to its high cost and complexity, whereas SPECT, with its widespread availability, is becoming an increasingly utilized clinical tool in the diagnosis of a number of highly prevalent neuropsychiatric disorders (10). The potential usefulness of this technique in the study of TBI was previously shown by several investigators (11-19). Previously, we reported the superior sensitivity of <sup>99m</sup>Tc hexamethylpropyleneamineoxime (HMPAO) brain perfusion SPECT to that of CT in detecting abnormalities in chronic TBI patients (19).

In the present study, we further evaluated the usefulness of HMPAO SPECT in TBI using newly selected groups of normal controls and chronic TBI patients. MRI, which is more sensitive than CT in detecting smaller lesions and white matter changes (3,8), as well as detailed neuropsychological tests were added to the armamentarium. In particular, a new attempt was made to obtain quantitative SPECT measurements of the brain dysfunction based on the pathophysiological mechanisms of TBI in order to correlate both functional and structural neuroimaging measures of brain damage with NP performance.

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Received Jul. 13, 1993; revision accepted Oct. 20, 1993.  
For correspondence or reprints contact: Masanori Ichise, MD, Room 635, Nuclear Medicine, Dept. of Radiology, Mount Sinai Hospital, 600 University Ave., Toronto, Ontario, Canada M5G 1X5.

**TABLE 1**  
Demographic Characteristics of Patients with Traumatic Brain Injury (TBI) and Normal Control Subjects (NC)

Characteristic	TBI (n = 29)	NC (n = 17)
Sex (M/F)	17/12	8/9
Age (yr)	34.1 ± 8.3 (22–49)	27.7 ± 5.3 (22–44)
Education (yr)	13.5 ± 2.7	15.2 ± 2.5
Time after TBI (yr)	2.5 ± 1.1 (0.8–5)	—
Medication	n = 8*	None

Values are expressed in mean ± s.d. and (range).

\*Five patients were on anticonvulsants and three patients on major tranquilizers at the time of study.

## SUBJECTS AND METHODS

### Subjects

TBI patients were selected from referrals to the rehabilitation medicine practice of W.F. Twenty-nine patients participated in the study. Considering the nature of this type of study in which no reference standard can be provided (i.e., no neuroimaging or NP testing prior to the TBI), strict subject selection criteria were adopted to maximize the chance that any detected abnormality is most probably related to a TBI itself. The criteria included (1) at least 6 mo after injury; (2) ages between 20 and 50 yr; and (3) no antecedent history of another TBI, neuropsychiatric disorder, alcoholism or drug abuse. The rationale for the criteria was discussed in detail in our previous study (19).

Seventeen normal control (NC) subjects were recruited by advertisement. They had no history of TBI or any other exclusion criteria described above. The demographic features of all subjects are summarized in Table 1.

Information regarding the TBI was obtained retrospectively from chart review. All 29 patients suffered closed head injuries. Of these, 26 were involved in motor vehicle accidents, 2 sustained falls and 1 was assaulted. The additional information is presented in Table 2. Severity of TBI was inferred from the Glasgow coma scale (GCS) (20) at the time of hospital admission, the duration of loss of consciousness (LOC) and the duration of post-traumatic amnesia (PTA) (21). Based on the criteria described previously (19), patients were classified into minor (n = 15) and major (n = 14) TBI subgroups. This included one patient (GCS = 14, LOC =

20 min, and PTA = 24 hr) who might be considered to have suffered a moderate TBI as judged by the duration of PTA (21) but was included in the minor TBI subgroup based on the GCS score and duration of LOC.

This study was granted ethical approval by the Human Subject Review Committee of the University of Toronto.

### Neuroimaging and NP Testing

After informed consent was obtained, each subject underwent HMPAO SPECT, CT, MRI, and NP testing within a 2-wk period.

### HMPAO SPECT

Technical details were described previously (19,22); hence, only a brief description is given here. Thirty minutes after intravenous injection of HMPAO (740 MBq), a lateral planar image was obtained with two radioactive markers indicating the canthomeatal (CM) line. This was followed by SPECT imaging for 25 min using a truncated single-head rotating gamma camera (Elscent 409 AG, Haifa, Israel) equipped with a high-resolution, parallel-hole collimator. The SPECT data, which were acquired on a 64 × 64 matrix, were attenuation corrected and reconstructed using a modified Hanning backprojection filter. The data set was then reoriented based on the CM line and standardized for brain size, yielding 12 transaxial, 8 sagittal and 9 coronal images (22). These three sets of images were normalized to the maximal pixel count in the respective set and were recorded on film with a lower count density threshold of 30% on a continuous 256 grey scale for visual

**TABLE 2**  
Description of Traumatic Brain Injury

	Minor (n = 15)	Major (n = 14)
Severity of injury		
Glasgow coma scale	14.3 ± 0.8	6.8 ± 2.9
Loss of consciousness	2.7 ± 5.1 min	132 ± 157 hr
Post-traumatic amnesia	—	8.4 ± 10.8 wk
Initial CT findings*		
Normal	7/8	3/12
Intracerebral contusion†	1/8	4/12
Subdural hematoma†	0/8	4/12
Epidural hematoma†,‡	0/8	3/12

\*Initial CT scans were available for 20 of 29 patients, 8 with minor and 12 with major injuries. None showed early hydrocephalus (<2 mo).

†One patient with major injury had all three types of intracranial lesions described.

‡One patient had surgical evacuation of a left temporal epidural hematoma.

interpretation. The FWHM of the system was approximately 14 mm.

## CT

A standard nonenhanced CT (Elscent Exel 2400) of the head was performed providing contiguous 10-mm axial slices parallel to the CM line.

## MRI

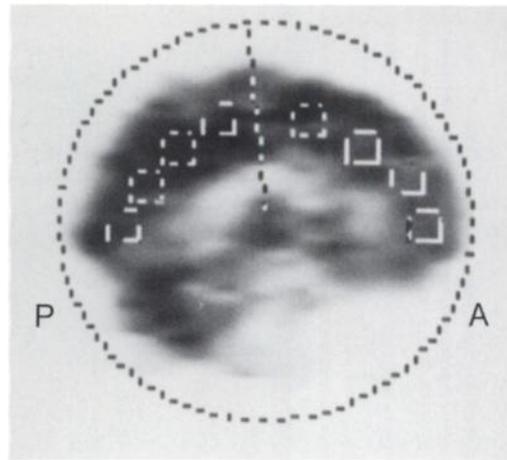
A 1.5-Tesla superconducting unit (Sigma, General Electric Medical Systems, Milwaukee, WI) was used to acquire a standard set of T1-weighted (transaxial and sagittal), proton-density (transaxial and coronal), and T2-weighted (transaxial and coronal) images with spin-echo (SE) pulse sequences of 550 (repetition time in msec)/11 (echo time in msec), 2,500/30, and 2,500/90, respectively. Section thickness was 5 mm, with an intersection gap of 2.5 mm in all examinations. The field of view was 24 cm, with an acquisition and display matrix size of 256 × 256.

### Quantitative SPECT and MRI Measurements

In order to obtain objective neuroimaging indices that can be quantitatively related to NP performance, measurements were made on SPECT and MRI scans. The rationale for obtaining these indices was based on the pathophysiological mechanisms of TBI which suggest that there are two major topographic patterns of brain damage which relate to the severity of injury (4,5,23–25): (1) there is a strong anterior-posterior (AP) gradient, with the most damage being in fronto-temporal regions and (2) the deeper structures within the brain are involved with increasing severity of injury. The mechanisms underlying these observations are related to acceleration-deceleration forces with a “shear-strain” effect (23–25). All of our patients suffered closed head injuries in which such forces were implicated.

Based on the first observation together with SPECT findings in acute TBI patients of a marked fronto-occipital cortical perfusion gradient (11), we decided to measure the AP perfusion gradient in our chronic TBI patients as described below. A mid-sagittal HMPAO SPECT slice including both medial cerebral cortices (15 mm thick) was reconstructed to maximize the volume of cortical tissue within one slice. On this mid-sagittal slice, a circular ROI was placed encompassing the mid-sagittal brain. Its radius was centered on the thalamus and positioned perpendicular to the CM line. The CM line was determined by the technique we described previously (22). Then, a total of eight square ROIs (15 × 15 mm each) were placed in the cortex extending from the frontal to the occipital poles. Four ROIs were anterior and four ROIs were posterior to this radius. Placement of individual ROIs was manually guided so that they represented the main portion of the mid-sagittal cerebral cortex (Fig. 1). The sum of activities in the four anterior ROIs was then divided by that of the remaining four posterior ROIs to generate an AP perfusion ratio (APR).

The second observation is largely related to diffuse axonal injury (DAI) (23) which results from shearing stresses on the deep white matter tracts. DAI can result in late ventriculomegaly as a result of the brain tissue loss, and the ventricle-to-brain ratio (VBR) in these cases has been shown to correlate with NP performance (4,5,26–28). In the present study, this VBR was obtained using a modification of previously described methods (28,29). Instead of CT, T1-weighted transaxial MR images were used to calculate the ratio of the largest area of the body of both lateral ventricles to that of the brain parenchyma on the same image.



**FIGURE 1.** A mid-sagittal HMPAO-SPECT image shows eight square ROIs. A circular ROI is placed encompassing the mid-sagittal brain. Its radius is positioned perpendicular to the cantho-meatal line which has been determined from the planar-lateral image performed prior to SPECT. Two sets of four square ROIs are then placed anterior and posterior to this radius, respectively. A = anterior; P = posterior.

## NP Tests

Tests of memory, attention and executive function are often found to be impaired in chronic TBI patients, whereas tests of general intelligence are usually not compromised (6–8,30). Accordingly, the following tests were selected for administration:

1. Tests of memory and learning: three subsets of the Wechsler Memory Scale (31)—Logical Memory, Associate Learning and Visual Reproduction; and the Consonant Trigram Test to incorporate the Brown-Peterson technique (32,33) of memory testing under interference.
2. Tests of attention, perception and information processing ability: Digit Span (34); three subsets of the Halstead-Reitan NP Battery (35)—Trail Making Test consisting of part A and part B, Speech-Sound Perception Test and Seashore-Rhythm Test; Paced Auditory Serial Addition Task (PASAT) (36); and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale (WAIS) (34).
3. Test of executive function: Wisconsin Card Sorting Test (WCST) (37).
4. Test of general intelligence: Full scale IQ (FSIQ) estimated from the Short Form Wechsler Adult Intelligence Scale-Revised (WAIS-R) (38).

## Data Analysis

SPECT, CT and MRI scans were read on hard copies, independently by two nuclear medicine specialists (SPECT scans) and two neuroradiologists (CT and MRI scans). All were blinded to the results of other imaging, demographic and clinical information, and NP data, except that the subject's age was known in the interpretation of CT and MRI scans. A final interpretation was reached by consensus between the two reviewers in situations where disagreement was encountered. For SPECT studies, regional grey matter perfusion was analyzed and categorized as normal, decreased or increased, with focal or diffuse involvement. Identified perfusion abnormalities were then visually quantified on a scale of 1 to 3 (mild, moderate and severe) and localized to a specific anatomical region of the brain using a stereotaxic atlas of the human brain (22). For both CT and MRI studies, regional

**TABLE 3**

Comparison of Neuropsychological Test Performance between Normal Control (NC) and Traumatic Brain Injury (TBI) Groups by One-way Analysis of Variance

Neuropsychological test	NC (n = 17)	TBI (n = 29)	F (1, 44)	p
Logical Memory*	11.0 <sup>††</sup> (3.6)	8.6 <sup>††</sup> (3.3)	5.5	0.02
Associate Learning	17.9 (1.6), 296 <sup>††</sup> (56)	13.9 (4.4), 230 <sup>††</sup> (121)	5.7	0.02
Visual Reproduction	12.6 (1.3), 153 <sup>††</sup> (33)	9.5 (3.5), 106 <sup>††</sup> (62)	7.6	<0.01
Consonant Trigram <sup>†</sup>	5.8 <sup>††</sup> (1.7)	7.8 <sup>††</sup> (3.0)	6.5	<0.02
Digit Span <sup>‡</sup>	12.0 (1.7)	10.7 (1.9)	5.1	0.03
Trail Making A <sup>§</sup>	24.0 (5.6), 3.17 (0.23)	45.3 (17.6), 3.76 (0.37)	33.0	<0.0001
Trail Making B <sup>§</sup>	51.1 (8.2), 0.140 (0.011)	97.1 (44.1), 0.108 (0.022)	32.5	<0.0001
Speech-Sound Perception <sup>†</sup>	3.2 (1.2), 1.31 <sup>††</sup> (0.54)	6.5 (4.0), 1.72 <sup>††</sup> (0.61)	4.8	0.03
Seashore Rhythm <sup>†</sup>	27.9 (2.7), 633 (182) × 10 <sup>3</sup>	24.9 (4.4), 445 (240) × 10 <sup>3</sup>	7.7	0.01
PASAT <sup>**</sup>	63.3 <sup>††</sup> (20.0)	54.2 <sup>††</sup> (11.9)	3.8	0.06
Digit Symbol <sup>†</sup>	67.1 <sup>††</sup> (13.3)	49.2 <sup>††</sup> (13.3)	25.1	0.0001
Wisconsin Card Sorting <sup>†</sup>	8.7 (4.7), 2.07 (0.58)	26.1 (19.7), 3.00 (0.78)	15.8	0.001
FSIQ	100 <sup>††</sup> (9)	96 <sup>††</sup> (12)	2.0	0.16

Values are expressed in mean (s.d.) and the second set of values when given represents the mean (s.d.) after variable transformation (see Appendix).

\*Average scores of memory passage 1 and 2.

†Number of errors made.

‡Summed scores of forward and backward span.

§Number of seconds.

†Raw scores.

\*\*Percent correct.

††Covariate (education) adjusted mean.

abnormalities of the brain parenchyma including the white matter and subcortical structures were identified and localized in a manner similar to that for SPECT images.

To eliminate interobserver variation, all SPECT quantitative measurements were made by a single observer and all MRI measurements by another single observer. Both were blinded to any clinical information. To determine intraobserver variation in the measurement of the APR and VBR, ten repeated measurements were made for each ratio in one subject by the same observer. Student's t-test was used for inter-subject group comparisons of the APR and VBR. The Spearman rank correlation was used to correlate the APR with the number of SPECT abnormalities. For those NP tests that yielded more than one score, data were reduced by either selecting certain relevant scores or by calculating compound scores (Table 3). Because parametric statistical tests used in this study require the assumption of normally distributed data, all NP test scores and neuroimaging measures were examined for deviation from normality by the univariate analysis in SAS (a software package by SAS Institute Inc., Cary, NJ). For those variables that did not satisfy the assumption of normality, normalizing transformation was performed. One-way analysis of variance (ANOVA) was performed to compare NP test scores of the subject groups. Pearson correlation coefficients were calculated to relate neuroimaging measures to NP test scores. For the

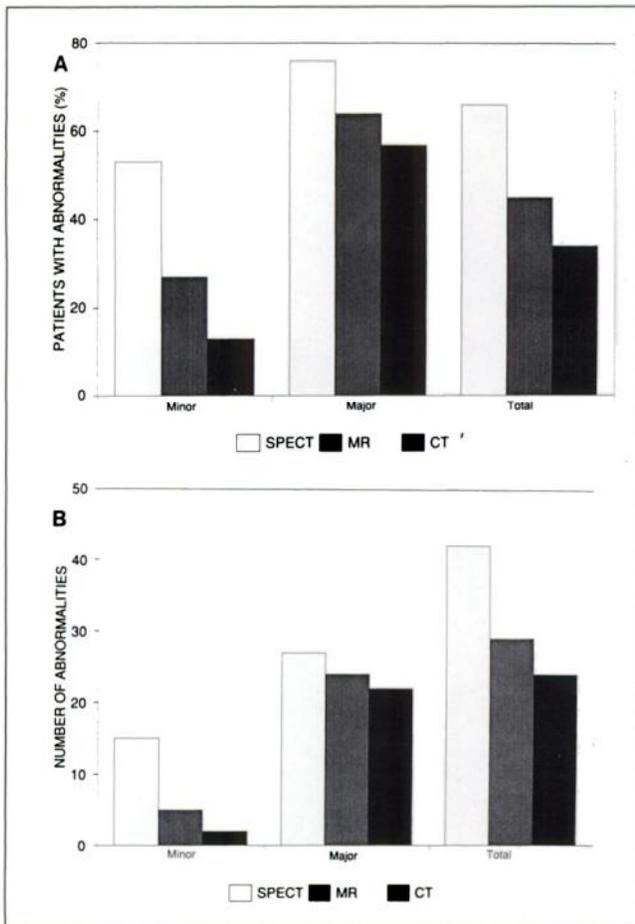
ANOVA and Pearson correlation analyses, all TBI patients were treated as a single group to ensure greater statistical calculation power. Statistical significance was defined as  $p < 0.05$ . Correction for multiple comparisons, which is deliberately conservative, is appropriate only for exploratory types of study design (39). In the present study, mainly those NP tests that were expected to be impaired in the TBI group were selected. Hence, no such correction was made in this study.

## RESULTS

### Neuroimaging

All HMPAO SPECT, CT and MRI scans were technically judged to be adequate in image quality. In the NC group, abnormalities were noted in three subjects. The SPECT scan of one female subject (31 yr) showed an asymmetry of temporal lobe perfusion with the left side being mildly decreased, whereas her CT and MRI scans were both normal. Both MRI and CT scans of one male (29 yr) and another female (22 yr) subject showed mild diffuse cortical atrophy inconsistent with their age, whereas their SPECT scans showed no abnormalities.

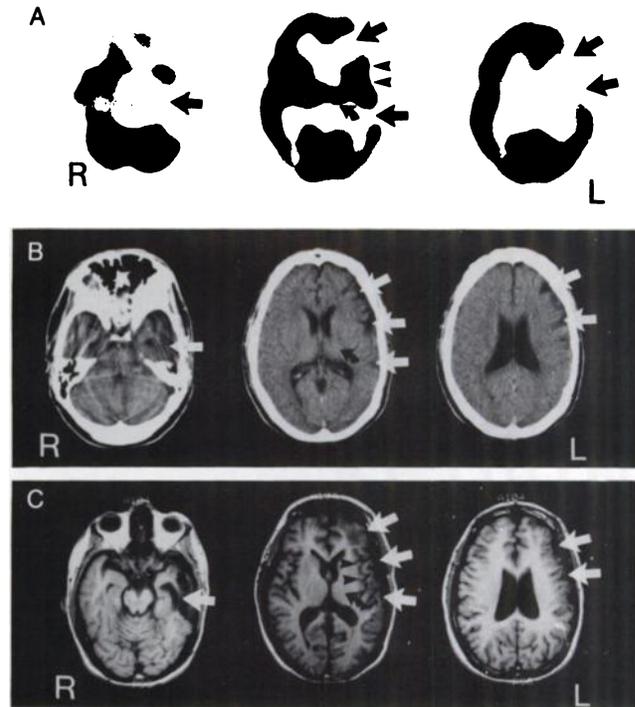
In the patient group, 19 (66%) showed 42 SPECT abnor-



**FIGURE 2.** Frequency (A) and number (B) of neuroimaging abnormalities according to imaging modality and subgroup of TBI patients.

malities, whereas 13 (45%) and 10 (34%) showed 29 MRI and 24 CT abnormalities, respectively. Figure 2 depicts the frequency and number of neuroimaging abnormalities according to the imaging modality and subgroup of TBI patients. SPECT detected relatively more abnormalities than CT or MRI in the minor TBI subgroup (Fig. 2). SPECT abnormalities were found predominantly in the frontal (43%) and temporal (40%) lobes, and much less frequently in the parietal lobe (5%), occipital lobe (2%), cerebellum (5%) and subcortical grey matter (5%). These consisted of areas of decreased grey matter perfusion (Fig. 3A). Both CT and MRI demonstrated brain parenchymal atrophy, encephalomalacia or gliosis, with focal and/or diffuse involvement, ventricular enlargement (Figs. 3B and C), and also foci of white matter hyperintensities on MRI. Mass lesions such as subdural hematomas, typically found in both acute and subacute stages of TBI, were not identified.

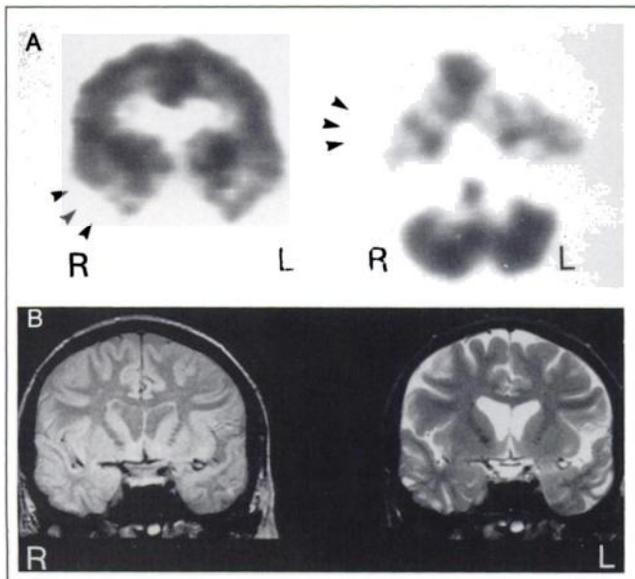
There was significant discordance of visually detected abnormalities between SPECT and structural neuroimaging. Of the 42 SPECT abnormalities, 33 (79%) SPECT abnormalities, which were mostly focal cortical perfusion deficits of mild to moderate severity, shared no CT or MRI abnormalities in the corresponding anatomical regions



**FIGURE 3.** A 26-yr-old male 4.4 yr after major head injury (GCS = 6, LOC = 7 days and PTA = 7 wk) following a motor vehicle accident. His neuropsychological findings at the time of the study included impaired performance in tests of logical memory, attention, auditory perception (both verbal and nonverbal), and executive function. (A) HMPAO-SPECT scan. Transaxial images at the levels of the inferior temporal lobes (left), basal ganglia and thalami (center), and superior fronto-parietal lobes (right). Severe perfusion deficits are seen involving the left fronto-temporal region (straight arrows). The perfusion of the left insular cortex (arrowheads) appears intact. The perfusion of the thalami is asymmetrical; the left side has less perfusion (curved arrow). (B) CT scan. Corresponding images show mild ventricular enlargement, cortical atrophy and subcortical gliosis of the left fronto-temporal region (straight white arrows) and slight asymmetry of the thalami (curved black arrow). It is difficult to assess the region of the left insular cortex. (C) Corresponding T1-weighted (SE 550/11) MRI scans. The ventriculomegaly is the same as on CT. The left fronto-temporal cortical atrophy and subcortical gliosis (straight white arrows) are delineated more clearly than on CT and the insular cortex appears intact (black arrowheads). Slight asymmetry of the thalami is also seen (curved black arrow).

(Fig. 4). Of the remaining nine SPECT abnormalities with CT and/or MRI abnormalities in the corresponding anatomical regions, six (67%) showed partial concordance; namely, areas of involvement on SPECT were judged to be larger than anatomical involvement, or vice versa.

Both CT and MRI detected diffuse cortical atrophy in seven patients with no corresponding findings on SPECT, and ventricular enlargement in eight patients. (The ventricular size was not assessed on SPECT for reasons described below.) There were five lesions detected by MRI but not by CT or SPECT. These included one small focal encephalomalacia (Fig. 5) and four lesions characterized by white matter hyperintensities. Conversely, all CT lesions were detected by MRI which overall delineated the abnormalities more clearly than did CT.

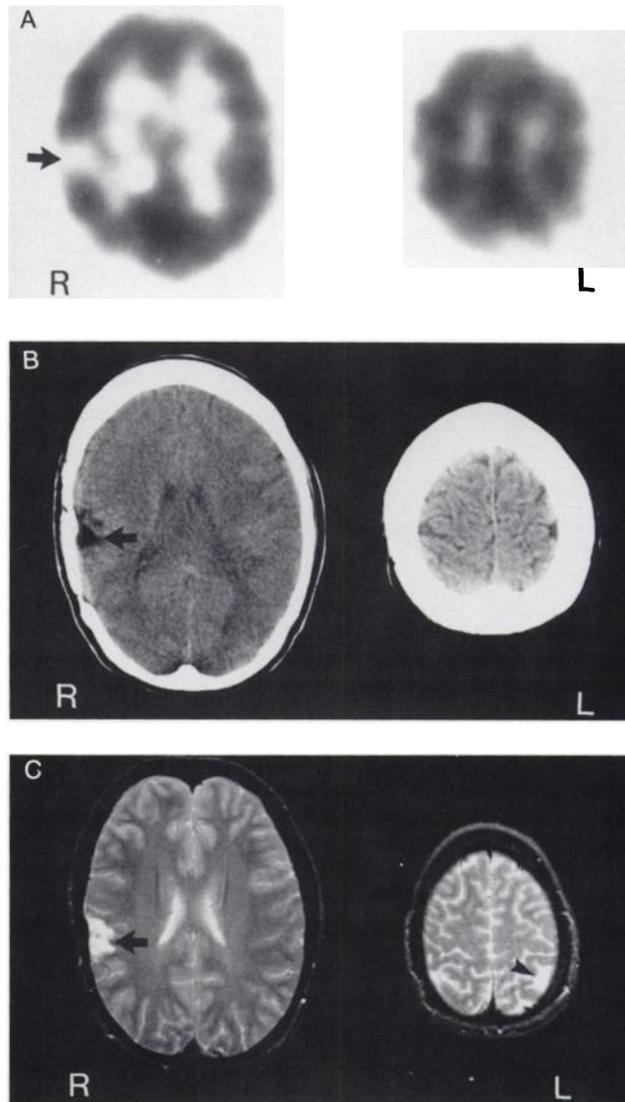


**FIGURE 4.** A 40-yr-old female 2.4 yr after major head injury (GCS = 7, LOC = 5 days and PTA = 6 wk) caused by falling on concrete stairs. Neuropsychological findings at the time of the study included impaired performance in memory under interference (Consonant Trigram Test), information processing ability and attention. (A) HMPAO-SPECT scan. A coronal image through the basal ganglia (left) and a transaxial image at the inferior temporal lobe level (right). The perfusion of the right inferior temporal lobe is decreased (arrowheads). (B) Corresponding coronal MRI scans. Both proton-density (SE 2,500/30) (left) and T2-weighted (SE 2,500/90) (right) images show mild ventricular enlargement but no other abnormalities. Neither T1-weighted MRI nor CT showed any focal cortical abnormalities.

#### Quantitative Neuroimaging Measures and NP Tests

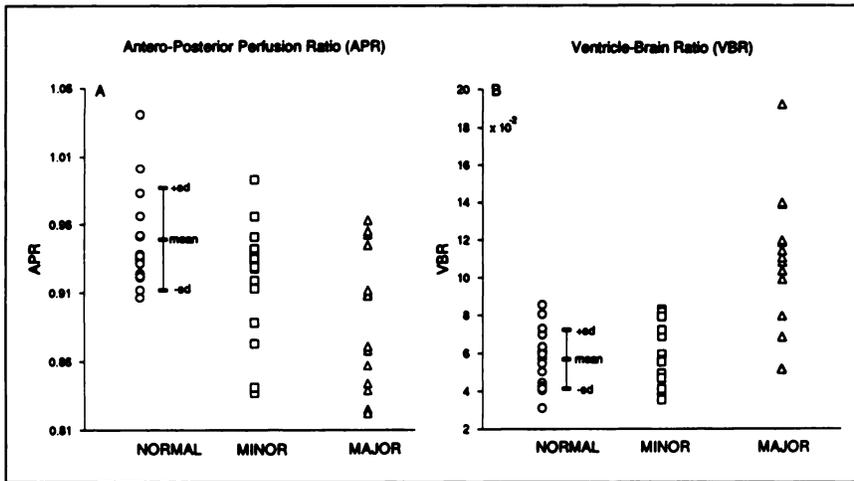
The coefficients of intraobserver variation in the determination of the APR and VBR were both less than 1%. The APR (mean  $\pm$  s.d.) was decreased in both minor ( $0.920 \pm 0.044$ ,  $p < 0.05$ ) and major ( $0.891 \pm 0.037$ ,  $p < 0.001$ ) TBI subgroups compared with the NC group ( $0.950 \pm 0.037$ ) with a more marked decrease in the major TBI subgroup, whereas the VBR (mean  $\pm$  s.d.) was increased in the major TBI subgroup ( $0.107 \pm 0.037$ ,  $p < 0.001$ ) but was normal in the minor TBI subgroup ( $0.057 \pm 0.017$ ) compared with the NC group ( $0.057 \pm 0.016$ ) (Fig. 6). Examples of the mid-sagittal SPECT image with a normal and a decreased APR are illustrated in Figure 7. The APR was inversely correlated to the number of SPECT abnormalities ( $n = 29$ ,  $r = -0.54$ ,  $p < 0.003$ ).

Seven NP variables did not satisfy the assumption of normality. After transformation of these variables as described in the Appendix, they were all normally distributed. The validity of such variable transformations has been described previously (40). Age ( $F(1, 44) = 9.6$ ,  $p < 0.005$ ) and education ( $F(1, 44) = 6.6$ ,  $p = 0.01$ ) were different between the NC and TBI groups; hence, these variables were treated as covariates in the analysis. Age, however, turned out not to be a significant covariate in any NP analysis, whereas education was a significant variable for



**FIGURE 5.** A 27-yr-old female 1.3 yr after minor head injury (GCS = 14, LOC = 20 min, and PTA = 24 hr) due to a motor vehicle accident. Neuropsychological findings at the time of the study included impaired performance in memory under interference (Consonant Trigram Test), auditory perception (verbal), attention and executive function. (A) HMPAO-SPECT scan. Two images through the superior fronto-parietal lobes. There is a focal perfusion deficit in the anterior aspect of the right parietal lobe (arrow). The image on the right that corresponds to the MRI scan with a small focal encephalomalacia (C) shows no definite focal defects. (B) Corresponding CT scan images show a focal encephalomalacia corresponding to the site of the perfusion deficit (arrow). No other abnormalities are seen. (C) Corresponding T2-weighted (SE 2,500/90) MRI scans show a concordant focal defect corresponding to the SPECT and CT abnormalities (arrow). In addition, there is a small focal encephalomalacia in the supero-posterior aspect of the left parietal lobe (arrowhead). No corresponding defect was seen on either SPECT or CT.

the Logical Memory, Associate Learning, Visual Reproduction, Consonant Trigram, Seashore Rhythm, PASAT and FSIQ tests. Thus, for these variables, linear effects of education were adjusted. Neither age nor education was a significant covariate for neuroimaging measures. A sum-



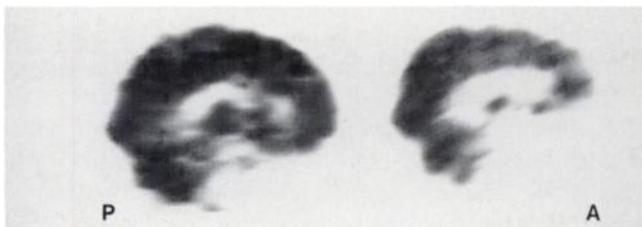
**FIGURE 6.** The APR (A) and VBR (B) plotted according to subject group.

mary of ANOVA results on NP performance of the NC and patient groups is presented in Table 3. The TBI patient group showed impaired NP performance in the areas of memory, attention and executive function. Of the 13 tests, the TBI group was impaired on 11 ( $p < 0.05$ ) and borderline on one (PASAT,  $p = 0.06$ ). As expected, only FSIQ showed no significant difference ( $p = 0.16$ ).

The APR correlated with six of the 12 tests that measured the performance in all three areas of memory, attention, and executive function. These included Logical Memory ( $r = 0.33$ ,  $p < 0.03$ ), Visual Reproduction ( $r = 0.32$ ,  $p = 0.04$ ), Consonant Trigram ( $r = -0.33$ ,  $p < 0.03$ ), Trail Making Test A ( $r = -0.39$ ,  $p < 0.01$ ) and B ( $r = 0.42$ ,  $p = 0.005$ ), Digit Symbol ( $r = 0.35$ ,  $p < 0.02$ ) and WCST ( $r = -0.39$ ,  $p = 0.01$ ). In contrast, the VBR correlated with only two tests: Logical Memory ( $r = -0.33$ ,  $p = 0.02$ ) and Consonant Trigram ( $r = 0.36$ ,  $p < 0.02$ ).

## DISCUSSION

Given the strict subject selection criteria and significant differences in our findings between the NC and TBI groups, both neuroimaging and NP abnormalities in the TBI group in this study were considered to be most probably related to the TBI. The causes for a few neuroimaging abnormalities in the NC group are unclear but they might be related to undocumented traumatic incidence or some other occult neurological conditions.



**FIGURE 7.** Two mid-sagittal HMPAO-SPECT images with normal (0.950, left) and decreased (0.886, right) antero-posterior perfusion ratios. A = anterior; P = posterior.

Despite being significantly inferior in its spatial resolution compared with CT or MRI, HMPAO SPECT was more sensitive in detecting brain abnormalities, particularly in our minor TBI patients. This is because HMPAO SPECT can detect perfusion abnormalities in morphologically normal brain regions. This superior sensitivity of HMPAO SPECT to that of CT or MRI together with the significant discordance between the functional and structural findings in the present study confirm our previous findings (19) and those of others (12,16). Slightly differing sensitivities of neuroimaging techniques in detecting abnormalities between this study and others may be related to the differences in the patient population studied and/or the methodology used. It must be noted that the patients in this study were selected from referrals for assessment and they do not represent a consecutive series of TBI patients. Future studies may be warranted which would include a TBI subject group without any measurable neuropsychological sequelae.

Compared with CT, MRI was more sensitive and delineated lesions more clearly in our chronic TBI patients. However, MRI has been shown by others to be significantly more sensitive than CT during the subacute stage (24,25). This difference may be explained by the observation made by others that MRI lesions including both mass lesions and parenchymal "hyperintensities" can show considerable morphological recovery within several months after TBI (8).

Only a few studies have previously looked into the issue of the relationship between functional imaging findings and neuropsychological performance in chronic TBI patients (12,17). Wiedman et al. (12) were able to show a consistent relationship between the location of SPECT abnormalities based on visual assessment and NP performance in a small group of head injury patients. However, Goldenberg et al. (17) in their SPECT study could not confirm this relationship based on their "relative" quantitative regional perfusion analysis, except that they did note some correlation between thalamic perfusion and NP performance. They

suggested that the thalamic hypoperfusion may reflect an underlying significant effect of diffuse injury.

Attempts to measure "absolute" regional brain perfusion with HMPAO SPECT have so far met with limited success (41). Alternatively, a variety of "relative" quantitative techniques have been employed successfully for an objective analysis of the brain perfusion SPECT scan in clinical studies of neuropsychiatric disorders (41). With these techniques, regional perfusion measurements are normalized to those of a reference region(s). However, we previously commented on the difficulty we encountered in our attempt to choose an optimal common reference region(s) in TBI patients because of the fact that any part of the brain may be affected in these patients (19). In the study by Goldenberg et al., each ROI was normalized to the mean value of a total of 32 ROIs taken together (17). Such a technique may be insensitive in detecting regional abnormalities when a large area of the brain is abnormal. Statistical analysis can be also problematic when dealing with a large number of variables in a limited number of subjects (41,42). Furthermore, given the limited spatial resolution of SPECT systems, the regional perfusion analysis of subcortical structures such as the thalamus or white matter may be less accurate in cases of underlying ventricular enlargement. This is because of the partial volume averaging effect from the adjacent nonvascular fluid-containing ventricles. Therefore, no attempt was made to make quantitative measurements of subcortical regions on SPECT in this study.

In this study, an attempt was made to obtain a single "relative" quantitative SPECT measure of brain dysfunction based on the pathophysiological mechanisms of TBI, namely, the APR. A reduction in the APR may be largely explained by the fact that focal cortical contusions primarily involve antero-inferior aspects of the fronto-temporal regions (23-25). This study confirms that perfusion deficits are still found in these regions in the chronic stage even without any apparent morphological abnormalities.

In contrast to the focal damage, DAI involves the white matter of the fronto-temporal lobes and the corpus callosum (23-25,43). DAI has been demonstrated to occur through the full spectrum of severity of TBI including minor injuries (44). Although the primary damage is to axons, DAI may affect regional cortical perfusion by deafferentation (45). This may indirectly contribute to the reduction in the APR.

An increase in the VBR as a result of the neuronal tissue loss from DAI, has been shown by others to reflect morphological consequences of the diffuse brain damage and to correlate with NP outcome (25-28). The values of the VBR in our NC and TBI subjects are consistent with those found by others (25-28). However, the VBR appears to be a useful measurement only for patients with major TBI. The VBR was entirely within normal limits for the minor TBI subgroup in this study. In contrast, the APR was decreased in both minor and major subgroups and overall correlated better with NP performance than did the VBR.

As an index of functional consequences of the brain

damage, the usefulness of the VBR may be limited in the following situations: (1) as implicated above, there is usually no ventriculomegaly in minor TBI patients; (2) the VBR would be abnormal in patients who show early ventriculomegaly, i.e., as a result of subarachnoid hemorrhage in the absence of DAI; and (3) ventriculomegaly may be found with normal aging (46). Thus, the APR may be a more useful index of the underlying cerebral dysfunction than the VBR in TBI patients.

In the present study, the APR correlated with the NP performance in the areas of memory, attention and executive function. These included (1) memory for verbal contextual material, grapho-motor memory and memory for consonant trigrams; and (2) performance on tasks that demand sustained attention, divided attention and flexibility in shifting of mental sets. These functions require the integrity of frontotemporal lobe systems and the impairment of these functions has been shown to occur characteristically in TBI patients (6-8,30).

However, these correlations were relatively weak. Only six out of the 12 NP tests were significant. This may be due to the fact that the APR is a rather crude index of brain dysfunction and may not reflect all of the focal and/or diffuse brain damages in a given patient. In addition, the reduction in the APR may not be specific for TBI. Depression may, for instance, reduce frontal lobe perfusion as reported by some investigators (47), which could affect APR. Thus, depression secondary to the long-term disability in these patients may be a contributing factor to the frontotemporal lobe dysfunction. Further studies, preferably longitudinal studies which would include rigorous prospective neuropsychiatric assessments, might be warranted to investigate this possibility.

The use of a state-of-the-art SPECT system with higher spatial resolution of 6-9 mm in FWHM (10) should improve the sensitivity by detecting smaller focal abnormalities. It should also allow a more accurate quantitative analysis of smaller ROIs. However, the clinical significance of those additional small focal lesions might be difficult to demonstrate, particularly in the presence of underlying diffuse brain damage.

To address the issue of the contribution of the effect of focal versus diffuse brain injuries and its relationship with the NP performance (48), further studies may be needed which would employ some other innovative quantitative techniques in a larger number of patients, preferably with near identical focal SPECT lesions without any underlying diffuse brain damage, or vice versa. However, the likelihood of obtaining such pure subgroups of TBI patients might be difficult.

In conclusion, HMPAO SPECT, as a complement to CT or MRI, may play a useful role in evaluating chronic TBI patients by demonstrating brain dysfunction in morphologically intact brain regions and providing objective evidence for some of the impaired NP performance. However, it must be remembered that the correlation between neuroimaging findings and NP performance may not be simple

when effects of both focal and diffuse injuries are contributing to the overall brain dysfunction.

## APPENDIX

Seven variables were transformed as follows:

Association Learning (AL) →  $AL^2$ ;  
Visual Reproduction (VR) →  $VR^2$ ;  
Trail Making A (TA) →  $\text{LOG}(TA + 0.5)$ ;  
Trail Making B (TB) →  $1/\text{SQRT}(TB + 0.5)$ ;  
Speech-Sound Perception (SS) →  $\text{LOG}(SS + 0.5)$ ;  
Seashore Rhythm (SR) →  $(SR)^4$ ;  
Wisconsin Card Sorting (WC) →  $\text{LOG}(WC + 0.5)$ .

## ACKNOWLEDGMENTS

The authors thank Joanne Garrie for her assistance in this study and Janice Pogue at Rotman Research Institute Baycrest Center for her assistance in statistical data analyses. This work was supported by Sterling-Winthrop Imaging Research Institute grant RP1015. This work was presented at the 40th Annual Meeting of the Society of Nuclear Medicine in Toronto, Canada, June 1993.

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