PAPER

Functional reorganisation of memory after traumatic brain injury: a study with $H_2{}^{15}0$ positron emission tomography

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J Neurol Neurosurg Psychiatry 2002;**73**:173–181

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Received 20 November 2001
In revised form 16 April 2002
Accepted 30 April 2002

Objective: To study the effects of moderate to severe traumatic brain injury (TBI) on the functional neuroanatomy supporting memory retrieval.
Methods: Subjects were six patients who had sustained a moderate to severe TBI about four years before scanning and had since made a good recovery. Eleven healthy young adults matched to the patients for age and education served as controls. An established $H_2{}^{15}0$ positron emission tomography paradigm was used to elicit brain activations in response to memory retrieval. TBI patients' patterns of brain activation were compared statistically with those of control subjects. Both group and individual case data were analysed.
Results: Both TBI patients and controls engaged frontal, temporal, and parietal regions known to be involved in memory retrieval, yet the TBI patients showed relative increases in frontal, anterior cingulate, and occipital activity. The hemispheric asymmetry characteristic of controls was attenuated in patients with TBI. Reduced activation was noted in the right dorsomedial thalamus. Although local aspects of this pattern were affected by the presence of focal lesions and performance differences, the overall pattern was reliable across patients and comparable to functional neuroimaging results reported for normal aging, Alzheimer's disease, and other patients with TBI.
Conclusions: The TBI patients performed memory tasks using altered functional neuroanatomical networks. These changes are probably the result of diffuse axonal injury and may reflect either cortical disinhibition attributable to disconnection or compensation for inefficient mnemonic processes.

Traumatic brain injury (TBI) is among the most common causes of neurological disability,[1] with an estimated prevalence rate of 2% of the population of the US.[2] The chronic disability of TBI is largely attributable to behavioural and cognitive consequences of brain injury (as compared with physical disabilities),[3] with impaired memory a frequent cognitive complaint.[4] The neural correlates of memory impairment can be studied with structural or functional neuroimaging techniques. Relative to structural neuroimaging (for example, computed tomography (CT) or magnetic resonance imaging (MRI)), cerebral blood flow studies of TBI patients with SPECT or positron emission tomography (PET) yield a greater number of cerebral abnormalities.[5 6] These findings have in turn been related to neuropsychological test performance.[7–9]

Most functional neuroimaging research in TBI has assessed cerebral blood flow at rest, when neural activity does not necessarily correspond to task related neural activity.[10] Cognitive testing is done in a separate session with clinical tests of limited neuroanatomical specificity that are then compared to indices of brain function over large brain regions, resulting in modest imaging-behaviour correlations.

In other populations, $H_2{}^{15}0$ PET or functional MRI have been applied to assess changes in neural circuitry in response to specific tasks with well described functional neuroanatomical characteristics. For example, altered patterns of brain activation during performance of mnemonic tasks have been identified in normal aging[11 12] and Alzheimer's disease.[13 14] In addition to identifying focal metabolic deficits, these techniques have documented regions with metabolism similar to or greater than controls, suggesting preservation in normal task related systems as well as functional reorganisation. Such functional reorganisation is most explicitly seen in studies of patients with focal lesions after recovery from specific neuropsychological deficits,[15–17] who show increased activation relative to controls in areas adjacent to the damaged tissue or in contralateral homologues to damaged regions that would normally mediate task performance.

Similar functional neuroimaging paradigms have been applied in a small number of studies of patients with TBI. In an fMRI study of working memory in patients who sustained a mild TBI one month before scanning, topographical similarity of task related activation was noted between patients and controls, but the mild TBI patients showed greatly increased activations in task specific regions, including the right prefrontal and right parietal cortices.[18] In an earlier retrospective study with mild TBI patients one to five years after injury,[19] patients were scanned with [^{18}F]fluorodeoxyglucose PET during cognitive activation with a continuous performance test. Patients showed hypermetabolism relative to controls in midtemporal cortical and frontal subcortical regions. These subjects, however, were not scanned under a control condition.

These studies were conducted in patients with mild TBI, which causes a brief alteration in consciousness with recovery of mnemonic function occurring over days or weeks. Studies of patients with moderate to severe TBI, in which return of everyday memory is preceded by lengthy period of post-traumatic amnesia and possibly coma, would increase our understanding of functional reorganisation after significant brain injury. Such reorganisation after severe TBI has been studied in single cases with memory,[20] executive functioning,[21] and calculation[22] activation paradigms.

Abbreviations: PET, positron emission tomography; TBI, traumatic brain injury; PASAT, paced auditory serial addition task; DAI, diffuse axonal injury

Table 1 Subject characteristics

	Age	Years of education	Est. IQ*	WAIS-R Vocab.†	WMS-R Verbal Mem. Index‡	Six hour GCS§	PTA (days)¶	Coma length (hr)**	ISS††	TSI‡‡	PET performance§§
TBI patients											
1	41	10	109	13	123	7.5	21	24	22	4.4	0.91
2	24	13	93	11	99	12	2	3	43	4.1	0.80
3	29	17	104	11	111	3	23	48	29	3.9	0.75
4	23	12	105	12	107	11	23	32	43	3.9	0.36
5	28	16	108	12	95	8.5	28	72	26	4.3	0.52
6	30	13	91	7	89	10	16	120	38	4.6	0.27
M	29	13.5	102	11.0	104	8.67	18.8	49.8	33.5	4.20	0.60
SD	5.9	2.4	7.0	1.9	11.2	2.9	8.3	37.9	8.3	0.3	0.23
Healthy controls (n=11)											
M	26	17.8	NA	NA	NA	NA	NA	NA		NA	0.83
SD	4	2.5	NA	NA	NA	NA	NA	NA		NA	0.10

*As determined by the North American Adult Reading Test - Revised[33]. †Standard scores from Wechsler Adult Intelligence Scale - Revised[34]. ‡From Wechsler Memory Scale - Revised[35]. §Glasgow Coma Scale[32]. ¶As determined by two consecutive days of GOAT scores greater than or equal to 75[36]. **Number of hours with GCS <8. ††Injury Severity Score[37]. ‡‡Years from the date of injury to the date of testing. §§Proportion of word pairs correctly recalled during PET study.

To our knowledge, there are only two exploratory group studies of cognitive activation functional neuroimaging in patients with moderate to severe TBI.[23 24] In an fMRI study of working memory using an analogue of the paced auditory serial addition task (PASAT), nine moderate to severe TBI patients showed increased recruitment of right frontal regions and generally increased dispersion of activations.[24] In a $H_2{}^{15}0$ PET study of recall and recognition from an earlier studied word list, a sample of five severe TBI patients was noted to have reduced frontal activation relative to four healthy adults during free recall, but increased frontal activation during recognition.[23]

These studies, while providing useful initial data for understanding the functional neuroanatomy of cognition in patients recovered from moderate to severe TBI, also raise certain technical issues stemming from the heterogeneity inherent to this patient population: performance differences and focal lesion effects.[25] In both studies, patients were significantly impaired relative to controls, confounding interpretation of group differences in activation maps. In the working memory studies, structural MRI revealed focal lesions in three of nine patients, but these were not taken into consideration in the analyses. In the verbal learning study, only acute CT scans were available. Acute CT underestimates TBI related findings relative to chronic phase MRI.[26 27]

In this study, we used $H_2{}^{15}0$ PET to assess the effects of moderate to severe TBI and its recovery on patterns of memory related brain activity. Unlike previous studies in patients with moderate to severe TBI that used versions of neuropsychological tests modified for use in the scanning environment TBI,[23 24] we used an established paradigm known to elicit specific activations in healthy young and older adults.[11 28 29] We also conducted supplementary analyses investigating performance differences and focal lesion effects. Given the functional neuroimaging findings from other populations and from studies of patients with TBI, we predicted that the patients would show both reliance on normal functional systems as well as areas of increased activation attributable to injury related changes to neural systems supporting memory.

METHODS

Subjects

The TBI patients were drawn from a well characterised series of consecutive admissions to a level I trauma centre participating in longitudinal studies of the acute and chronic effects of TBI.[30 31] Six men (aged 21–41) who sustained a TBI approximately four years before testing were studied. All patients had sustained a moderate to severe TBI as indicated by Glasgow Coma Scale[32] (GCS) score taken at six hours, coma duration, or duration of post-traumatic amnesia (table 1). At the time of testing, the patients had achieved good neuropsychological and functional recovery, as measured by neuropsychological testing, psychosocial outcome measures, and return to work and school. Patients were free of significant medical or psychological disorders or medication that could affect interpretation of test scores or PET data.

Chronic phase MRI (taken within one month of the PET scans) revealed focal and diffuse neuropathological consequences typical of moderate to severe TBI (see fig 1). Two patients had anterior temporal contusions (one left unilateral, and one bilateral), and one had a left frontal contusion.

The control subjects' PET data had been collected for earlier studies.[29]

Positron emission tomography

The activation PET studies were done on a GEMS-Scanditronix PC2048–15B head scanner. Eight 60 s scans were performed, each preceded by an injection of 40 mCi of $H_2{}^{15}0$. A cued recall task validated in previous PET studies[11 29] was used to elicit brain activations associated with memory retrieval. In brief, semantically related word pairs (for example, penguin-tuxedo) were presented visually at a fixed rate (four seconds, with a one second inter-stimulus interval). In the encoding condition, novel pairs were presented and subjects were instructed to form a meaningful relation between the words in each pair. In the retrieval condition, the first word in previously studied pairs was presented along with "WORD?" and subjects were instructed to recall the second word of the pair. In both conditions, subjects said the second word aloud (or said "PASS" if they could not remember the word in the retrieval condition), equating verbal output across the two conditions. The control subjects performed the tasks during four scans (two encoding, two retrieval) and the TBI patients performed the tasks during eight scans (four encoding, four retrieval—the number of scans in each condition doubled to increase signal to noise in this small sample). The following analyses focus on retrieval, with encoding treated as a baseline. We therefore refer to retrieval minus encoding activations as "retrieval activations".

After realignment, transformation to standard space, and smoothing with an isotropic Gaussian kernel of 10 mm full width at half maximum, changes in rCBF during retrieval were estimated with the Statistical Parametric Mapping software (SPM96, Wellcome Department of Cognitive Neurology, London, UK) using analysis of covariance with global counts

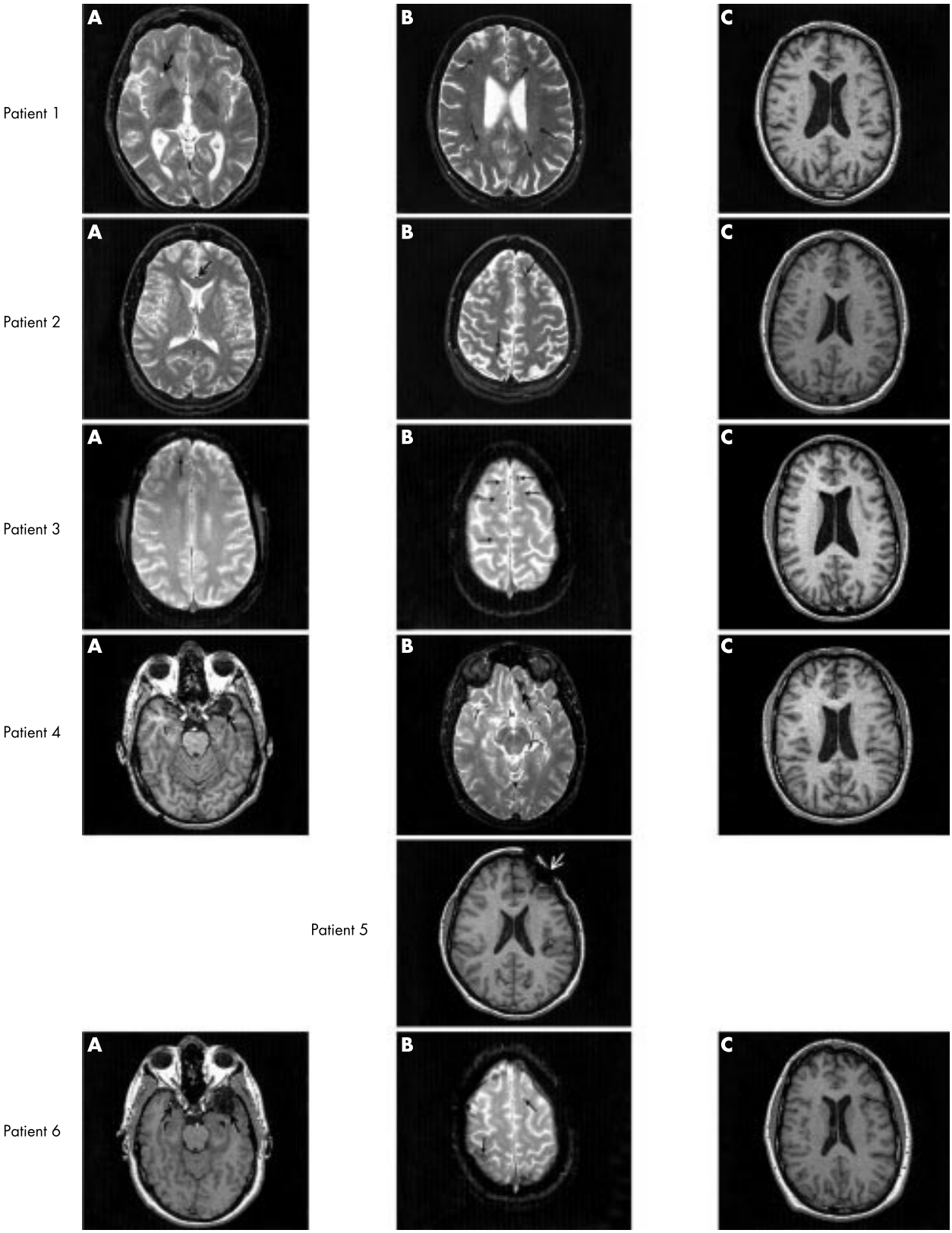

Figure 1 Structural neuroimaging findings as interpreted by a clinical neuroradiologist. Slices from T1 weighted, T2 weighted, or gradient echo T2 images were selected to maximally indicate neuropathology each TBI patient, numbered as in table 1. For each patient, image C shows the body of the lateral ventricles, taken at approximately the same level across patients from the T1 weighted image (the slice of patient number 5 showing left frontal lesion is also at this level). The right side of the brain is depicted on the left side of the image. Patient 1 (A) Small right inferior frontal white matter lesion on T2 weighted image (thick arrow, also hypointense on T1 weighted image, not shown). (B) Multiple hyperintense foci on T2 weighted image. (C) Ventricular enlargement. Patient 2. (A) Frontal lesion adjacent to corpus callosum on T2 weighted image (thick arrow). (B) high parietal, left frontal polar hemosiderin deposits on T2 weighted images (thin arrows). Patient 3. Bilateral frontal hemosiderin deposits on T2 (A) and gradient echo (B) images (thin arrows). (C) Ventricular enlargement. Patient 4. (A) Left anterior temporal gliosis on T1 weighted image (thick arrow). (B) Hemosiderin deposit on T2 weighted image (thin arrow, numerous smaller hemosiderin deposits also observed on other slices). (C) Ventricular enlargement. Patient 5. Left frontal craniotomy, left frontal encephalomalacia, slight dilatation of the left lateral ventricle (ex vacuo effect) on T1 weighted image. Patient 6. (A) Bilateral anterior temporal encephalomalacia on T1 weighted image (left greater than right, thick arrows). (B) Hemosiderin deposits on gradient echo image (thin arrows).

Table 2 Retrieval activations in TBI patients and healthy controls

Side	Region	Brodmann's Area	Size (voxels)	Z	Coordinates x	y	z
TBI patients							
R/L	Anterior cingulate, middle, medial frontal gyri	32, 10	1491	5.04	4	30	28
				5.02	30	52	20
				4.05	–18	54	–4
R	Insula		380	5.03	32	12	–8
R	Medial frontal gyrus	25	141	4.60	12	26	–16
L	Insula		226	4.24	–30	14	–4
R	Inferior temporal gyrus	37	157	3.87	46	–44	–4
				3.33	48	–32	–8
R, L	Cuneus	19, 17	320	3.88	4	–74	32
				3.80	–8	–82	28
R	Globus pallidus		78	4.18	10	2	4
L	Cerebellum		140	3.98	–4	–56	–16
Healthy controls							
R/L	Superior frontal, anterior cingulate, medial frontal gyri	9, 10, 32	970	4.77	10	56	28
				3.60	0	46	12
				3.50	–8	42	24
R	Claustrum, inferior frontal gyrus	45	332	4.55	26	18	–4
				3.46	40	22	4
				3.22	44	28	0
R	Middle frontal gyrus	9	68	3.84	42	16	40
R	Medial frontal gyrus	25	61	3.73	10	22	–16
R	Inferior temporal gyrus	20	182	3.75	58	–36	–16
R	Angular gyrus	39	175	4.60	42	–66	32
R	Posterior cingulate, precuneus	30, 31	178	3.30	4	–52	16
				3.25	10	–64	20
R	Thalamus (medial dorsal nucleus)		167	4.00	4	–10	4
L	Caudate, putamen		88	3.71	–10	22	0
				3.26	–14	12	–8
R	Brain stem		66	3.66	4	–32	–4
L	Thalamus (pulvinar)		26	3.14	–14	–28	8

as covariates. All scans, in particular the TBI patients' scans, were inspected for artefact and normalisation errors. In one TBI patient (number 5), there was no tracer uptake in the left frontal region corresponding to a traumatic contusion. Because normalisation routines would set the corresponding voxels to zero for all subjects' scans included in a group with this patient, we analysed his data separately as a single case study. The other transformed scans were free of normalisation errors, artefact, or detectable lesion effects. Anterior temporal contusions in patients number 4 and number 6 were ventral to PET coverage.

TBI patients' retrieval activations were compared with controls in two analyses. Firstly, retrieval activations were determined for the TBI patients and qualitatively compared with the controls' retrieval activations. Secondly, a quantitative comparison using a two way analysis of covariance in SPM96 with two groups (controls versus TBI patients) and two conditions (encoding versus retrieval) was performed to determine retrieval activations that statistically differed across groups.[38] The threshold for significance in all analyses was $p<0.001$ (uncorrected). Localisation of activations was accomplished with the assistance of the Talairach Atlas[39] and the Talairach Daemon database server on the world wide web (http://ric.uthscsa.edu/projects/talairachdaemon.html).

All subjects gave informed consent. The studies were approved by the ethics committee of Baycrest Centre for Geriatric Care and a University of Toronto committee.

RESULTS

Behavioural data

The TBI patients' performance was below that of the controls (table 1), although this difference did not reach significance, $t(5.77)=2.09$, because of inhomogeneity of variance and low power. The performance of three of the TBI patients was well within the range of control subjects. The remaining three had impaired performance (see table 1). These three subjects had temporal and frontal contusions. Two of the three had substantially longer duration of unconsciousness. As discussed below, the key PET findings are independent of these performance differences and lesion effects.

Imaging data

Within group retrieval minus encoding comparisons indicated a predominantly right lateralised frontotemporal pattern of retrieval related brain activations in both groups that is typically reported in the memory functional neuroimaging literature.[40] This pattern included foci in the frontal pole, inferomedial and ventrolateral frontal cortex, anterior cingulate, inferior temporal gyrus, and medial posterior regions (see table 2).

While the above pattern was broadly similar across the two groups, many of the activations shared across groups were more extensive, had higher maximums, and were less lateralised in patients with TBI. Whereas both groups activated right polar and insular/ventrolateral frontal regions, the TBI patients showed activity in the contralateral homologues of these regions that was not observed in the healthy controls (see fig 2). In comparison with the right posterior cingulate and right medial parietal regions of healthy controls, TBI patients activated bilateral medial occipital regions. TBI patients also activated right lenticular and left cerebellar regions (see table 2). Activations observed in healthy controls but not in TBI patients included the right angular gyrus, bilateral thalami, and left caudate and putamen (see table 2).

Group differences in the extent and foci of the right frontal retrieval activations were reflected in the interaction analyses. The TBI group's retrieval activation was increased in the right anterior cingulate and in area 10 bilaterally, whereas it was significantly reduced in right area 9, the focus of the controls'

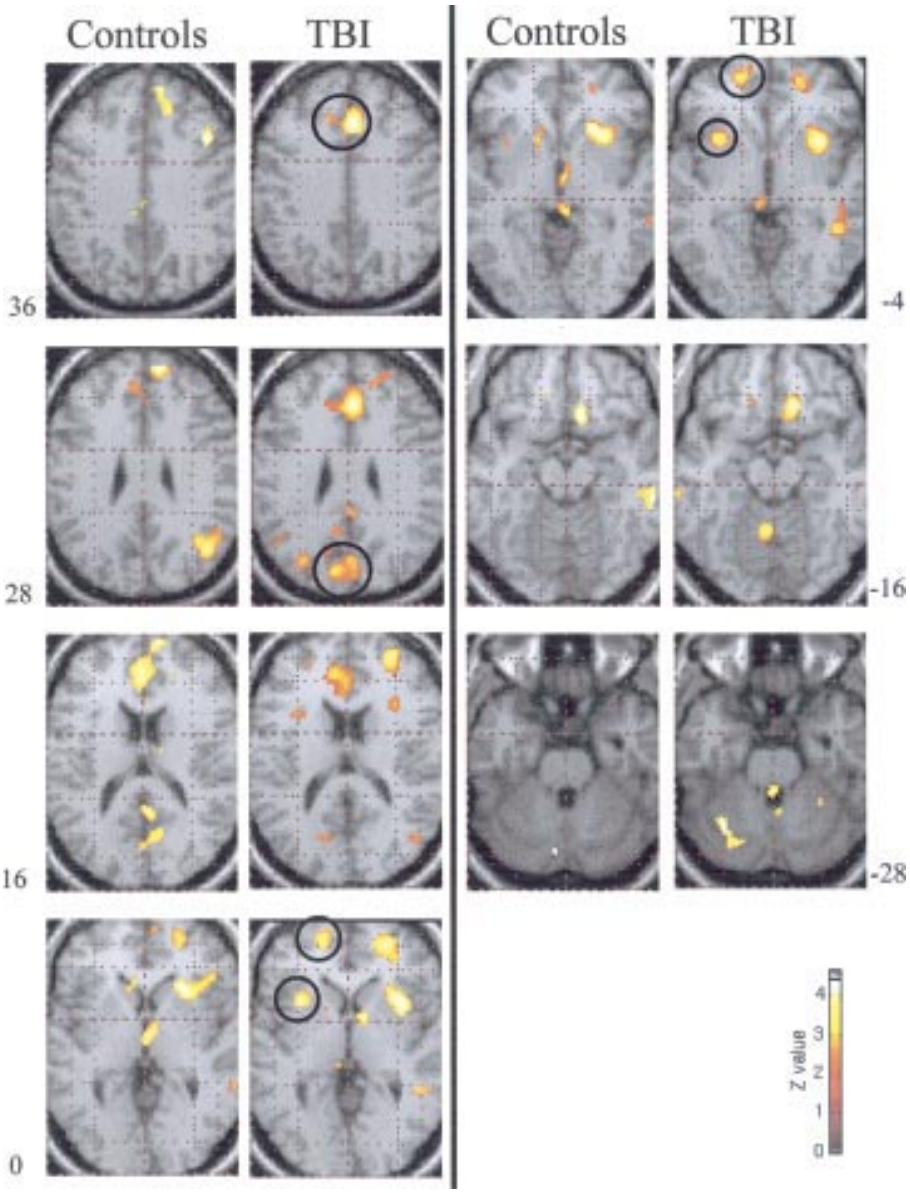

Figure 2 Retrieval activations in healthy young adults and traumatic brain injury (TBI). Activations are displayed in standard space on axial brain images provided with the SPM96 software at slices indicated by coordinates on the z plane.[38] The right side of the brain is depicted on the right side of the image. Activations are thresholded at p<0.01 for the purposes of display. The scale in the bottom right corner indicates the colour coded degree of activation in standard units. Both healthy adults and patients with TBI show a right lateralised pattern of' retrieval related brain activations in frontal polar, lateral temporal and parietal regions, and bilaterally in the anterior cingulate gyrus. Patients with TBI, however, show additional activations (circled) in anterior cingulate gyrus (Z=36), cuneus (Z=28), left insula and frontal pole (Z=0 and –4), and left cerebellum (Z=–28) (see tables 2 and 3).

right frontal polar retrieval activation (see table 3). This analysis also indicated greater retrieval activation for the TBI group in bilateral occipital regions; right medial occipital activation was present in this interaction analysis but fell short our significance threshold (Z=3.02). Less retrieval activation in the TBI group relative to controls was observed in right ventrolateral frontal, superior temporal, thalamic, and cerebellar regions.

Single case study

As noted above, one TBI patient (number 5 in table 1) was not included in the group analysis because of signal drop out in the area of his left frontal lesion. His retrieval activations, however were very similar to the other TBI patients, including peaks in the right frontal pole and insula (*x, y, z*=16, 46, 28 and 30, 14, –8; Z=4.47 and 3.70), anterior cingulate gyrus (*x, y, z*=6, 36, 16; Z=3.87), inferior temporal gyrus (*x, y, z*=46, –44, –8; Z=2.92), bilateral cuneus (*x, y, z*=6, –72, 24 and –4, –78, 28; Z=4.60 and 3.96), and right globus pallidus (*x, y, z*=6, –4, –4; Z=3.66). The one exception to the pattern, consistent with the location of his structural damage, was a lack of additional left frontal activation observed in the other TBI patients.

DISCUSSION

Functional neuroimaging studies in the chronic phase of recovery in TBI emphasise reductions in metabolism or blood flow at rest.[5 7–9] While such studies are sensitive to functional neuroanatomical deficits that in turn bear modest relations to neuropsychological test performance, they are complicated by the variability of mental activity during rest as well as the questionable specificity of the neuropsychological tasks and perfusion deficits in patients with TBI.[41 42]

In contrast, activation functional neuroimaging paradigms with $H_2^{15}0$ PET or functional MRI capitalise on cognitive tasks with known functional neuroanatomical patterns in control subjects. These paradigms have proved fruitful in exploring the functional neuroanatomical changes associated with normal aging,[11 12] Alzheimer's disease,[13 14] and mild TBI,[18] but research of this sort in patients with significant TBI involving recovery from extended consciousness alteration has been limited to case or exploratory group studies.[20–24]

In this study, a previously validated cued recall paradigm was used to assess the effects of moderate to severe TBI on the functional neuroanatomy of retrieval. We found that the overall pattern of frontal, temporal, occipital, subcortical, and cerebellar brain regions engaged by the TBI patients was similar

Table 3 Regions of interaction in retrieval activations between patients with TBI and controls*

Side	Region	Brodmann's Area	Size (voxels)	Z	Coordinates x	y	z
Increased retrieval activation relative to controls							
R	Middle frontal gyrus	10	160	4.53	30	52	20
R	Cingulate gyrus	32	66	3.94	12	10	44
L	Superior, middle frontal gyri	10	124	3.25	–26	46	20
R	Middle occipital gryus	19	77	3.21	46	–70	8
L	Middle occipital gyrus	19	127	3.62	–46	–76	12
Decreased retrieval activation relative to controls							
R	Inferior frontal gyrus	45	68	3.12	48	30	8
R	Superior frontal gyrus	9	48	3.98	12	56	28
L	Superior temporal gyrus	22	43	3.39	–58	2	0
R	Thalamus		31	3.41	4	–10	0
R	Cerebellum		63	3.85	14	–46	–12

*Group differences in retrieval activations were determined by interactions in a two way analysis of covariance with two groups (controls versus TBI patients) and two conditions (encoding versus retrieval).

to that reported in previous functional neuroimaging research with healthy controls,[40 43] yet they showed larger areas of activation, including contralateral homologues of activated regions, in addition to areas of hypoactivation in relation to controls. These findings suggest that TBI and its recovery cause functional reorganisation of memory systems.

Interpretation of regional effects

Both right frontal polar and ventrolateral regions are commonly activated in association with retrieval,[40 43 44] with the polar region involved in establishing a cognitive set for retrieval ("retrieval mode")[45] or internal monitoring and guidance of retrieval[46] and the right ventrolateral frontal region activated in response to specific retrieval cues.[46] The TBI patients' right frontal polar activation was lateral to that of controls and extended more inferiorly, where it was accompanied by activation of the homologous left frontal pole (not seen in controls).

While left frontal foci can be seen in healthy adults during memory retrieval,[44] the expected hemispheric profile of frontal lobe retrieval activations is strongly biased towards the right (that is, the Hemispheric Encoding/Retrieval Asymmetry or HERA pattern[47]). The reduction in frontal asymmetry observed in TBI patients is notable in light of similar findings in older adults,[11 48] patients with medial temporal lobe epilepsy and hippocampal sclerosis,[49] patients with Alzheimer's disease,[13 14 50] healthy adults genetically at risk for Alzheimer's disease,[51] and TBI.[18 23] Supplementary recruitment of left frontal regions in these diverse groups has been attributed to compensation for mnemonic impairment. It may reflect altered strategies, such as reliance on semantic associations[11] or a response to increased task complexity in TBI patients relative to controls.[52]

Both groups activated the anterior cingulate gyrus during retrieval, although the TBI patients did so to a significantly greater degree than controls. The anterior cingulate gyrus is involved in response initiation, selective attention, and effort.[53] It is activated in response to increased task difficulty,[54] and increased task related activation of this region has been noted in other groups.[11 50 51]

Significant interactions in auditory and visual association cortices indicate group differences in the use of perceptual processes during encoding or retrieval. TBI patients showed greater retrieval activations in bilateral lateral occipital cortices and less retrieval activation in left superior temporal cortex. This may reflect greater reliance on visual rather than auditory processes at retrieval in patients with TBI. Under the subtraction logic of PET, an alternative encoding based interpretation would suggest a TBI related bias towards auditory rehearsal processes during encoding, as compared with a more elaborated visual associative encoding strategy (capitalising on the highly imageable word pairs) in controls.

The most intriguing among TBI patients' decreased retrieval activations was the right dorsomedial thalamus, which is strongly interconnected with both ventrolateral and dorslateral frontal cortex.[55] Thalamic damage causes memory deficits[56], and reduced thalamic blood flow in this region has been related to behavioural impairment in studies of CBF at rest in TBI.[7 57] Our patients were free of swelling or herniation in the acute stage that could produce thalamic dysfunction. Neuropathological studies of TBI in humans have shown specific excitotoxic effects on thalamic reticular GABAergic neurons critical to mediodorsal thalamic/frontal relay.[58] A resulting thalamofrontal gating deficit may in turn cause hyperactivation of intact frontal cortex such as that observed in this study.

To summarise, patients with moderate to severe TBI and controls showed topographically similar task related patterns of activation in response to memory retrieval demands. TBI patients, however, showed relatively high activation of frontal polar and anterior cingulate regions, including recruitment of left frontal regions. Such regional effects have been associated with compensation for mnemonic inefficiency, increased effort, and increased internal monitoring. They engaged additional occipital regions involved in lower level perceptual processes, and they showed reduced activation in several regions, including the right dorsomedial thalamus. The controls showed less widespread activation, possibly aided by increased activation of subcortical nuclei.

The mean proportional score on the retrieval task in our TBI group was lower than that of controls (although this difference was not significant because of low power). It is therefore possible that our findings are simply an artefact of impaired performance.[25] This issue affects interpretation in other activation functional neuroimaging studies of patients with TBI.[23 24] In other populations, however, similar effects have been observed when performance is equated across groups.[11 14 18]

Although we did not do so by design, we did have three TBI patients with performance well within the range of controls. Replication of the group's TBI pattern when the analysis was restricted to these three patients would suggest that the pattern could not be attributed to performance differences. The bilateral frontal (x, y, z=30, 52, 20 and –28, 32, 36; Z=4.09 and 2.83), occipital (x, y, z=46, –70, 12 and –46, –76, 12; Z=3.75 and 3.63), and thalamic (x, y, z=–14, –4, 12, Z=2.92) interactions reported in table 3 held (although the left frontal and thalamic effects fell short of our significance threshold

and the lateralisation of the thalamic effect shifted from right to left). These findings suggest that the right frontal and occipital increased activation could not be accounted for by performance differences. Effects involving the left frontal pole and thalamus may also be considered performance independent, but larger samples of patients with spared performance are necessary to establish the reliability of these observations. There was no evidence of increased anterior cingulate activation relative to controls. This aspect of the pattern was therefore unique to the patients with poor retrieval performance, possibly because of the increased difficulty of the task for these patients.[54]

Neuropathological consequences of TBI on task related brain activation

Although various aspects of the TBI related functional neuroanatomical changes may be related to specific lesion effects or poor performance, the overall pattern of reduction in specificity of brain activation was consistent across patients and replicates previous findings in TBI patients.[18 19 24] A common feature across patients that can account for the consistent findings is diffuse axonal injury (DAI), the primary neuropathology and cause of coma in TBI.[59–61] Microscopic DAI pathology in humans can be observed throughout the neuraxis at the grey/white matter cortical interface and in subcortical white matter and nuclei.[62]

DAI has functional consequences for the intact receptive fields of axotomised neurons, with cortical dysregulation resulting from both excitatory and inhibitory deafferentation. Neuronal function is further affected by the resulting neuroplastic changes (that is, axonal sprouting and synaptogenesis) that may occur in these fields as part of the recovery process.[63–65] While our findings do not permit the disambiguation of these and other complex processes, they do suggest that DAI is involved in the feature of the activation pattern that is common across patients (that is, a reduction in the focus of cortical activation). Aging and Alzheimer's share with TBI both diffuse neuronal changes and, as noted above, more widespread task related activation.

Many authors interpret functional neuroanatomical changes such as those observed here as evidence of compensation.[11 12 14 51] This interpretation is most transparent in cases of focal damage in which activation of contralateral homologues and other task related regions is seen concurrent with behavioural recovery.[15–17] In cases of diffuse injury, however, adaptive compensation, alteration in strategic approach to the task, or a maladapative consequence of the brain's response to injury can conceivably result in similar activation. While good task performance may support the compensation hypothesis, it does not rule out underlying mnemonic disorganisation or disinhibition that is not measured by task performance, but is associated with TBI.[66]

Methodological considerations

TBI causes focal and diffuse injury, both of which have morphological effects that can influence image processing. Indeed, focal frontal injury in one subject caused decreased uptake at the lesion site and reduction in left frontal retrieval activation. We do not, however, believe that focal injury can account for the reduced cortical focus in this group study. As is typical in TBI, most of the lesions detected on MRI were small markers of diffuse axonal injury and below the spatial resolution of PET (see fig 1). In two cases with larger contusions, the anterior temporal location was outside the PET slice coverage.

In this context, it is instructive to examine the retrieval activations of patient ML, a severe TBI patient with a right frontotemporal disconnection syndrome who was scanned under this same cued recall PET paradigm,[20] achieving a high proportional score of 0.81. Although focal pathology resulted in right frontal polar retrieval deactivation (accompanied by left hippocampal hyperactivation), the remaining retrieval activations described in the TBI sample (right inferior frontal, the anterior cingulate gyrus, medial parietal/occipital regions, and left cerebellum) were present in ML.[20] Therefore, although focal lesions disrupt local aspects of the TBI retrieval pattern described here (that is, left frontal effects in patient number 5, right frontal effects in patient ML), global features of the TBI functional neuroanatomical profile were reliably detected each of seven patients we have examined despite diversity in focal pathology.

Yet another morphological effect important in functional image processing is atrophy,[67] an expected consequence of diffuse injury in moderate to severe TBI that was present in our patients (see fig 1). Atrophy causes partial volume effects that can artefactually reduce signal intensity. In this study, partial volume effects, if present, would have been matched across retrieval and encoding conditions. In any case, our main findings involve hyperactivation as compared with the reduction in signal changes expected from atrophy.

When stimuli are presented at a fixed rate, increased duration of neural processing attributable to response slowing (a known effect of TBI) can cause signal increases (even when neural processing intensity does not differ across groups).[68] In this study, TBI related response slowing, if present, would have occurred in both the encoding and retrieval conditions, providing some experimental control for this effect. Furthermore, as we observed both increases and decreases in TBI patients' retrieval activation, increased duration of neural processing attributable to slowing cannot fully account for the results.

As noted above, we interpreted retrieval activations in relation to an encoding baseline. One problem with this subtraction logic is that significant effects could be attributable to encoding deactivations in addition to or rather than retrieval activations. While a lower level baseline such as reading that was originally used for our cued recall task[29] may be preferable, the encoding condition used here is similar to baseline conditions in other studies of episodic retrieval[69] and can be viewed as a more conservative match to the mnemonic demands of the retrieval task. Accordingly, we previously reported that use of this baseline for the current cued recall task does not alter the overall pattern of retrieval activations in comparison to reading[20]; also see Nyberg *et al*.[70] Although encoding deactivations cannot be entirely ruled out, these seem unlikely given the consistency of our results with other retrieval studies using a variety of different baseline conditions.

Conclusions

In contrast with neuroimaging studies of TBI effects emphasising structural or functional metabolic deficits, activation functional neuroimaging paradigms can reveal effects in intact or altered tissue in relation to focal or diffuse brain injury. Consistent with prior work in patients with TBI and other aetiologies, we documented a reduction in focus of cortical activation in patients with moderate to severe TBI in response to a memory retrieval task with known functional neuroanatomical properties. While local features of this pattern were affected by focal injury and performance differences, the overall pattern was consistent across patients. This alteration in task related brain function probably occurs as a result of DAI. Further research is necessary to determine the adaptiveness of these changes.

ACKNOWLEDGEMENTS

We thank Gordon Cheung for assistance with MRI interpretation, Michael Schwartz for assistance with early clinical information, and Doug Hussey and Kevin Cheung for assistance in conducting the PET scans, and Helen Mayberg for valuable advice on an earlier draft.

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Funding: this research was supported by the Canadian Institutes of Health Research, the Ontario Mental Health Foundation, and the Rotman Research Institute.

Competing interests: none declared.

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NEUROLOGICAL PICTURE

Diffusion weighted magnetic resonance imaging in a case of acute Wernicke's encephalopathy

A 71 year old man was transferred to our hospital with a two week history of gait disturbance and disorientation. He had no apparent history of malnutrition, surgery of digestive tract, or alcoholism. Eye movements were limited vertically. Deep tendon reflexes were absent in the lower limbs. Vibration sensation was absent at ankles. His score on the Mini Mental State Examination was 14. Diffusion weighted magnetic resonance imaging (DW-MRI) revealed hyperintense lesions in periaqueductal region of the midbrain and medial thalami (fig 1(A)). Signal of these regions was also intensified on T2 weighted imaging (fig 1 (B)), but less markedly.

The MRI findings in Wernicke's encephalopathy in the acute phase reportedly include hyperintense areas around the third ventricle and aqueduct on T2 weighted and FLAIR imaging.[1 2] Characteristic topographical distribution of abnormal signal intensity on DW imaging in the setting of disorientation and polyneuropathy suggested that our patient had Wernicke's encephalopathy. Plasma vitamin B1 level was later revealed to be reduced to 8 μg/ml (20 to 50 μg/ml).

The diagnosis of Wernicke's encephalopathy can be difficult in the absence of apparent history of chronic alcohol intake or malnutrition. Detection of reduced plasma thiamine level may be crucial, however, it takes time to obtain the value. Magnetic resonance imaging is convenient measure to detect the characteristic topographic distribution. Of particular interest, our patient showed the hyperintense on DW imaging in these locations. Because the apparent diffusion coefficient of the lesion is not reduced as was reported by Oka *et al*,[3] the hyperintense appears to be derived from T2 shine through effect and may represent vasogenic oedema. Diffusion weighted magnetic resonance imaging can be obtained sooner than T2 weighted or FLAIR imaging. Thus, we emphasise that DW-MRI is superior to conventional MRI in depicting the lesion of acute Wernicke's encephalopathy, which enables early diagnosis of the disease.

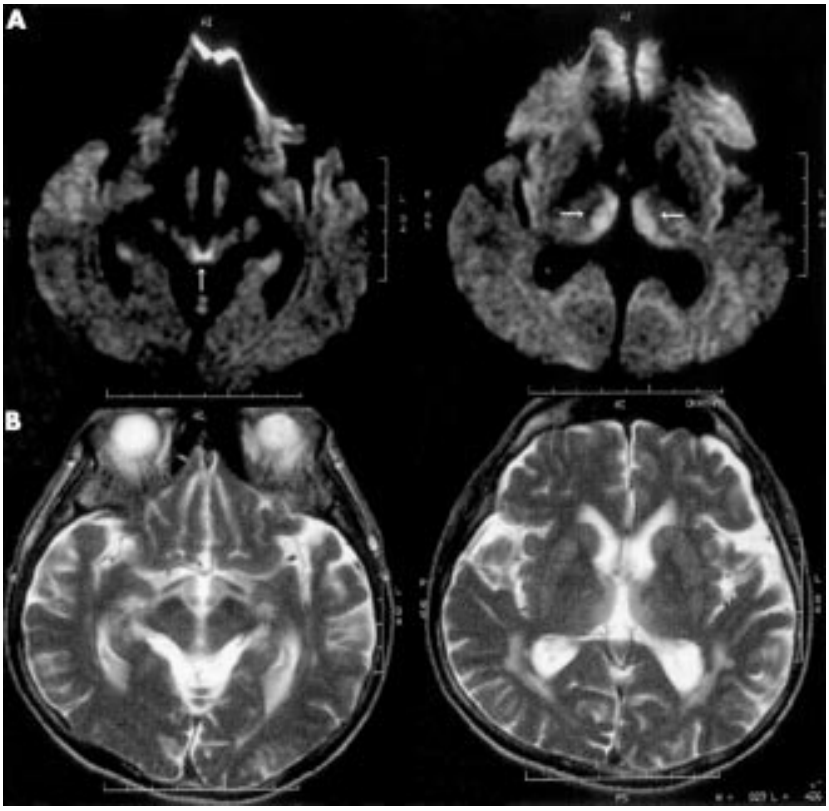

Figure 1 Axial magnetic resonance imaging. (A) Diffusion weighted imaging reveals symmetrical hyperintense in periaqueductal region of the midbrain and medial thalami (arrows). (B) T2 weighted imaging of these regions also shows hyperintense, but less pronounced.

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