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Novel Approaches to the Assessment of Frontal Damage and Executive Deficits in Traumatic Brain Injury

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Traumatic brain injury (TBI) is a major cause of frontal brain damage. The Centers for Disease Control estimates that 5.3 million Americans are currently living with disability as a result of TBI, with 80,000 to 90,000 people being newly disabled every year (National Center for Injury Prevention and Control, 1999). Traumatic brain injury causes 14 million restricted-activity days per year in the United States, with annual costs estimated at $48 billion annually (Lewin-ICF, 1992). While acute medical care and management of physical symptoms are undoubtedly major contributors to these costs, it is the cognitive and behavioral consequences of TBI that are truly enduring, with a greater impact being on outcome than physical symptoms (Jennett et al., 1981; Brooks et al., 1986; Dikmen et al., 1995).

The long-term cognitive and behavioral impairments in significant TBI are largely determined by damage to the frontal lobes and frontal projections. Deficits that involve capacities governed by prefrontal areas are among the most prominent and ubiquitous after TBI. Despite the well-accepted observations of prefrontal dysfunction and the particular vulnerability of the frontal lobes to traumatic damage, assessment of these impairments is challenging using standard neuropsychological measures, and anatomical–clinical correlations are often elusive. In this chapter, we will describe interrelated streams of research aimed at improving the specificity of behavioral and brain imaging assessment of TBI. We begin with a brief review of TBI neuropathology.

DIFFUSE AND FOCAL NEUROPATHOLOGY OF TRAUMATIC BRAIN INJURY: EFFECTS ON FRONTAL SYSTEMS

The prefrontal areas are highly vulnerable to damage after TBI. Traumatic damage to prefrontal systems may result from a variety of primary and secondary brain processes. Primary processes are best conceptualized in two categories: focal injury and diffuse injury. These two injuries are important determinants of chronic-stage outcome in TBI.

Focal cortical contusions (FCC), the main form of focal injury, result from contact and acceleratory/deceleratory forces. Ventral and polar frontal and temporal regions are particularly prone to contusional damage because of excessive tissue strains in these areas against the ridges and confines of the anterior fossa and middle fossa (Courville, 1937; Ommaya &

Gennarelli, 1974; Gentry et al., 1988a). Other forms of focal damage include large deep hemorrhages from acceleratory disruption of subcortical penetrating vessels. Large deep hemorrhages may involve subcortical white and gray matter (e.g., caudate, dorsomedial, and ventral anterior thalamus), structures involved in frontal–subcortical circuits (Cummings, 1993). Secondary damage to frontal systems after focal injury may result from delayed neuronal injury (as occurs after diffuse injury), herniation syndromes (especially frontal transfalcine herniation that may compromise medial frontal lobes and anterior cerebral artery perfusion), and hypoxic–ischemic injury (including anterior cerebral artery and middle cerebral artery anterior borderzone ischemia from systemic hypotension).

Delayed complications after TBI may also disrupt frontal cortex and projections. Hydrocephalus typically compromises white matter pathways adjacent to the third and lateral ventricles, which include many prefrontal projections. Chronic subdural hematoma frequently occurs in the frontal extra-axial spaces and may cause dysfunction through compression of the underlying frontal cortex.

Diffuse axonal injury (DAI), the main form of diffuse injury, results from acceleratory/deceleratory forces leading to disruption of axonal transport progressing to axonal disconnections and distal axonal degeneration. As a consequence, there is widespread, scattered deafferentation of these axonal projections, including those involving prefrontal systems. Similarly, these forces may disrupt small blood vessels leading to scattered white matter hemorrhages. In addition to the structural damage to axons and blood vessels, DAI is accompanied by a host of other insults including disruption of small subcortical blood vessels (petechial white matter hemorrhages) and secondary neuronal damage from cascades of destructive biochemical cellular processes (e.g., excitotoxicity, membrane lipoperoxidation; see Lyeth & Hayes, 1992; Lynch & Dawson, 1994; Povlishock & Jenkins, 1995).

Elements of prefrontal dysfunction are the most common clinical effects of DAI, especially during later phases of recovery. It has been proposed that DAI may be more concentrated in frontal areas of the brain. Although concomitant petechial hemorrhages are often more concentrated in frontal regions (Wilberger et al., 1990), microscopic DAI pathology can be found throughout the neuraxis at the gray–white matter cortical interface and in subcortical white matter and nuclei in the absence of macroscopic lesions (Povlishock, 1993). Occasionally, petechial hemorrhages involve subcortical structures with critical frontal projections, such as the ventral tegmental area of the midbrain (Goldberg et al., 1989; Adair et al., 1996) and the anterior or medial thalamus. Hypometabolism in prefrontal regions was the only correlate of executive, behavioral, and memory dysfunction in a resting positron emission tomography (PET) study of patients with DAI (Fontaine et al., 1999). It is likely that prefrontal hypometabolism and clinical signs are so prominent with DAI because of the vulnerability of prefrontal systems to any form of diffuse subcortical pathology (Goldberg & Bilder, 1987).

Despite improved understanding of pathophysiologic events after TBI and advances in structural and functional imaging techniques, the precise relationships between brain dysfunction in frontal systems and clinical consequences are not always clear. Part of the problem has been the challenge of parsing out and measuring particular prefrontal cognitive and behavioral deficits in the face of an individually unique combination of focal, diffuse, and secondary pathology associated with TBI.

The clinical effects of TBI on frontal functions are largely determined by the types, severity, and location of these combined pathophysiological events. Computation of clinical–pathological relationships is confounded by several factors: the multiplicity of pathological events; the difficulty of direct measurement of diffuse pathologies; the fact that physiological functional defects usually exceed the structural damage; difficulties in measuring executive and behavioral functions; changes in the proportional contribution of different pathologies and non-injury factors to clinical syndromes as recovery evolves. Interpretation is further compounded by non-injury factors, such as the psychosocial substrate in which the injury occurs.

Studies using structural and functional imaging have been inconsistent in demonstrating clear frontal clinical–pathological relationships. Although atrophy and depth of hemorrhagic lesions on magnetic resonance imaging (MRI) have a fairly clear relationship with overall clinical severity and outcome (Levin et al., 1988; 1990; Wilson et al., 1988), the quantity and location (mostly frontal) of petechial hemorrhages do not correlate well with severity or clinical syndrome (Wilberger et al., 1990; Kurth et al., 1994). A number of studies failed to demonstrate any robust relationship between lesion location (frontal or otherwise) and neuropsychological performance (Levin et al., 1992; Anderson et al., 1995).

Although a consistent picture has not emerged from these larger group studies, certain clinical principles can be useful in projecting natural history for individuals with TBI. Diffuse axonal injury and focal frontal injury differentially relate to outcome depending on stage of recovery. As the clinical course of DAI evolves through unconscious, confusional, and post-confusional phases, the defining cognitive impairment typically undergoes a transition from arousal, attention, and memory to executive functioning. Focal lesion effects are determined by lesion location, depth, and laterality. Delayed secondary complications such as hydrocephalus and chronic subdural hematomas commonly present as persistent or regressive frontal cognitive or behavioral problems. When executive and attentional deficits are due to DAI, they tend to evolve over a more protracted course than the similar deficits from focal injuries. When combined, a severe diffuse injury largely determines the course of recovery and masks the effects of focal pathology in the early stages (Katz & Alexander, 1994; van der Naalt et al., 1999). Focal frontal lesions may cause more persistent and prominent frontal deficits than expected from DAI alone, as recovery evolves.

Recovery depends in part on plasticity and adaptive reorganization of undamaged structures. Prefrontal functions may have more redundancy and less lateralization than some more posterior brain functions, and have a greater capacity for reorganization than other more committed brain systems (e.g., primary visual pathways, motor control of hand, and some language functions). Preservation of subcortical pathways and homologous controlateral areas may be critical factors in adaptive plasticity. For instance, patients with shallow, unilateral frontal lesions may demonstrate substantial clinical recovery and, conversely, patients with bilateral frontal lesions often recover poorly.

SUMMARY AND IMPLICATIONS

The presence of multiple and evolving injuries complicates interpretation of brain–behavior relationships in TBI, which is probably why this disease has not been a popular model for studying frontal lobe dysfunction in the cognitive neuroscience literature. Although TBI patients with focal lesions should not be regarded as equivalent to nontraumatic focal lesion patients, properly conducted TBI research can contribute to the study of frontal lobe function and to our understanding of diagnosis and treatment of TBI-related deficits. Some general guidelines for this research include the following: Large samples should be recruited to overcome the inherent variability of TBI. Smaller subgroups may be analyzed using neuropathologically based diagnosis of injury type and severity. Recovery effects should be dealt with by limiting testing to the chronic phase (e.g., 1 year or longer post-injury) or by serial testing across recovery epochs. As disability in TBI can be influenced by non-injury factors (e.g., compensation seeking), patients should be drawn from hospital admission lists rather than from clinics that attract patients with late-emerging complaints. To minimize confounds related to the psychosocial status of the TBI cohort, matched-control subjects should be drawn from friends and family members of the patients. Concurrent testing of nontraumatic focal lesion patients can be useful in teasing apart focal-lesion from diffuse-injury effects.

The remainder of this chapter describes the application of some novel research technologies designed to increase the specificity of brain–behavior relationships in TBI. For our behavioral work, we have attempted to capitalize on the location of ventral prefrontal

damage in TBI by applying measures designed to be sensitive to this damage. Our imaging work seeks to quantify TBI neuropathology on chronic-phase high-resolution MRI. We will conclude with recent findings from an activation functional neuroimaging study.

ASSESSING COGNITIVE AND BEHAVIORAL CONSEQUENCES OF TRAUMATIC BRAIN INJURY

Research on the cognitive sequelea of TBI indicates a classic pattern of deficits in speeded information processing, attention (Van Zomeren et al., 1984; Stuss et al., 1989), memory (Levin & Goldstein, 1986; Crosson et al., 1989), and executive functioning (Mattson & Levin, 1990; Stuss & Gow, 1992) that corresponds with the frontal, temporal, and diffuse injury of TBI. Although this profile is widely accepted, the complexity of the clinical picture increases as emotional and psychosocial factors are considered. Patients with significant TBI can have profoundly impaired psychosocial outcome as measured by return to work, leisure activities, social and interpersonal relationships, and personality change (Jennett et al., 1981; Rappaport et al., 1989; Crépeau & Scherzer, 1993; Dikmen et al., 1996). The extent of this psychosocial disruption is not fully accounted for by the reported cognitive deficits; many patients with marked real-life disability show only mild cognitive deficits. Conversely, patients with similar cognitive deficits due to other etiologies (e.g., medial temporal lobe amnesics, Parkinson's disease patients) do not report the same degree of psychosocial disruption.

More specific behavioral and imaging measures are necessary to attain laboratory concordance with the patients' real-life disability. A generic "frontal" explanation of the real-life disability in TBI is unsatisfying as tests traditionally considered sensitive to frontal lobe lesions have been inconclusive in studies of patients with TBI (Ponsford & Kinsella, 1992; Anderson et al., 1995; Cockburn, 1995). Performance on these tests corresponds more closely with atrophy than with frontal lobe lesions (Vilkki et al., 1992; Duncan et al., 1997). The insensitivity of standard "frontal" tests such as the Wisconsin Card Sorting Test (WCST) may be related to the fact that these tests were developed and validated in research on the cognitive effects of dorsolateral prefrontal cortical lesions, as opposed to the ventral prefrontal regions that are specifically affected by FCC in TBI (Courville, 1937; Gentry et al., 1988a).

As discussed in detail elsewhere in this volume (see Chapters 3, 21, 22, and 23) ventral prefrontal cortex is intimately connected with limbic nuclei involved in emotional processing (Nauta, 1971; Pandya & Barnes, 1987) and is involved in the acquisition and reversal of stimulus–reward associations (Mishkin, 1964; Fuster, 1997; Rolls, 2000). The involvement of the ventral prefrontal cortex in inhibition, emotion, and reward processing suggests a role in behavioral self-regulation, as shown in numerous case studies of patients with ventral prefrontal lesions (Harlow, 1868; Ackerly, 1937; Eslinger & Damasio, 1985) whose behavior is reminiscent of that observed in patients with TBI (Stuss & Gow, 1992; Varney & Menefee, 1993).

We have used the term *self-regulatory disorder* (SRD) as shorthand for the syndrome exhibited by these patients (see Chapter 25). Self-regulatory disorder is defined as the inability to regulate behavior according to internal goals. It arises from the inability to hold a mental representation of the self on-line and to use this self-related information to inhibit inappropriate responses (Levine et al., 1998a, 1999; Levine, 1999). It therefore involves sustained attention, inhibition, and self-awareness.

This disorder is most apparent in unstructured situations (e.g., child rearing, making a major purchase, or occupational decision making), where patients fail to inhibit inappropriate responses. This is contrasted with structured situations in which environmental cues or overlearned routines determine the appropriate response, which is often the case for standard neuropsychological tests (Shallice & Burgess, 1993). As a result, many patients with SRD appear unimpaired in overlearned, structured situations, in spite of significant real-life

upheaval (Mesulam, 1986; Stuss & Benson, 1986; Shallice & Burgess, 1991).

Until the last decade or so there were very few studies that quantified real-life SRD in clinical samples (as opposed to patients preselected for their highly specific lesions and clear SRD). In 1991, Shallice and Burgess attained laboratory concordance of real-life SRD in patients with ventral prefrontal damage using naturalistic multiple subgoal tasks, setting a quantitative standard for deficits that had previously been limited to qualitative description. Subsequent studies in our laboratories and elsewhere have further established the use of similar unstructured tasks in the study of patients with focal lesions (Bechara et al., 1994; Goel et al., 1997; Burgess et al., 1998, 2000; Levine et al., 1998b; Schwartz et al., 1998) and TBI (Whyte et al., 1996; Robertson et al., 1997; Levine et al., 1998b, 2000; Schwartz et al., 1999).

Our paper-and-pencil Strategy Application Test, modeled on one of the measures from the Shallice and Burgess 1991 study (the Six Element Test), requires the selection of targets with high payoff to the exclusion of readily available but lesser-valued targets. In our original study with various patient groups (Levine et al., 1998b), patients tested at 1 year post-injury were significantly impaired relative to socioeconomic- and age-matched controls. Consistent with our hypothesis that the TBI deficit was due to ventral prefrontal damage was the finding that concurrently tested patients with nontraumatic focal ventral prefrontal lesions were uniformly impaired on this task, although they were preserved on other tests sensitive to dorsolateral prefrontal damage (Levine et al., 1995, 1997). The test was also sensitive to right hemispheric damage in both patients with TBI and those with nontraumatic focal lesions. Given similar findings in patients with right-lateralized pathology (Schwartz et al., 1999) and the right lateralization of the sustained attention system (Posner & Petersen, 1990), this finding indicated a role for sustained attention in strategy application.

We subsequently revised the test to increase its sensitivity to ventral prefrontal damage (Levine et al., 2000; see also Levine et al., 1999). This was accomplished by fostering a response pattern (completion of all items in a sequential manner) applicable early in the task but not as the task progressed, forcing a shift in strategy (selective completion of certain items to the exclusion of other items) to maintain efficiency (see Fig. 28–1). In other words, efficient performance depended on inhibition or reversal of the response pattern reinforced at the beginning of the test. Unlike the original measure, this revised Strategy Application

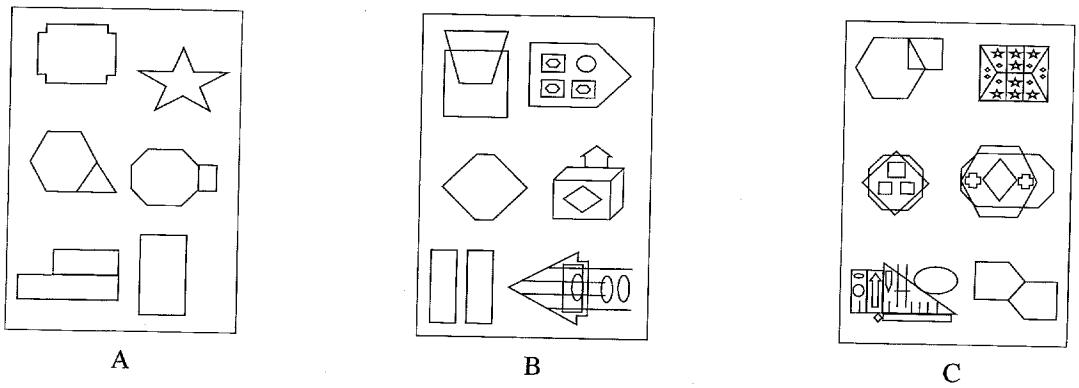


Figure 28–1. Sample items from the revised Strategy Application Task (R-SAT; Levine et al., 1999, 2000). On the early pages (*A*), all items can be traced in 5–10 seconds. As the subject progresses through the task, items increase in duration to completion but not in difficulty of completion (*B, C*). Given limited time and an equal amount of points per item, the best strategy is to inhibit the tendency to do all items (established on early pages) in favor of selective completion of brief items on later pages. The test is constructed such that brief items are always available. Subjects are also to complete similarly constructed sentence copying and simple counting items (not shown).

Test (R-SAT) was sensitive not only to TBI in general but also to the degree of TBI severity as measured by the 6-hour Glasgow Coma Scale (GCS) score (Levine et al., 2000). The R-SAT performance was related to patients' health-related quality of life on the Sickness Impact Profile (SIP; Bergner et al., 1976), suggesting that SRD as measured by this laboratory task is related to real-life SRD effects. This relationship held even after variance attributable to standard neuropsychological measures (including the WCST) was controlled.

The development of clinical tests of SRD has significant implications for patients whose disability is overlooked in standard exams. To date, however, the precision of lesion–behavior relationships in group studies of SRD in TBI is constrained by the use of computed tomography (CT) scanning, which is less sensitive than MRI in documenting TBI effects (Levin et al., 1987; Gentry et al., 1988b; Ogawa et al., 1992). Moreover, because of the evolving nature of TBI, scans acquired during the acute phase only partially indicate chronic-phase pathology (Wilson et al., 1988; Blatter et al., 1997). In our studies, for example, TBI patients' R-SAT performance was not related to lesion location along the anterior–posterior gradient as documented by acute CT. From these data alone, we could not tell if the lack of effect was due to insensitivity of the R-SAT or insensitivity of acute CT to chronic-phase frontal damage. The following section describes improved neuroimaging analysis technology that can be used to address such questions.

NEUROIMAGING ASSESSMENT OF TRAUMATIC BRAIN INJURY NEUROPATHOLOGY

Greater precision in brain–behavior relationships in studies of TBI patients requires, at minimum, chronic-phase MRI. A proper TBI imaging protocol should include high-resolution T1-weighted, T2-weighted, proton density, and gradient echo recalled images taken at least 70 days post-injury (Blatter et al., 1997). Even with state-of-the-art images, however, qualitative interpretation does not adequately describe TBI neuropathology, especially DAI effects. Skilled radiologists have been shown to underestimate DAI pathology on MRI (Gentry, 1990). Moreover, the small DAI lesions represent only the regions where the confluence of DAI is large enough to be visible to the naked eye (Gentry, 1990). Thus even perfect agreement among raters on DAI lesions would not truly characterize the full extent of DAI. Interpretation of focal lesions is more straightforward, but detection of focal damage due to localized atrophic changes in the absence of large lesions is subject to the same limitations as those in interpreting generalized DAI (Berryhill et al., 1995). These problems in measurement of traumatically damaged brain tissue contribute substantially to the poor precision of brain–behavior relationships in many studies of TBI.

Although axonal degeneration and cellular loss caused by DAI are microscopic, the quantification of the resultant atrophy can provide a numerical index that has greater precision than qualitative judgments and that is more amenable to research. Ventricular enlargement has been shown to reflect brain atrophy and is indicative of a disproportionately greater loss of white matter than of gray matter (Anderson & Bigler, 1994). Quantification of ventricular enlargement can be accomplished through simple linear width measures taken from CT (corrected for head size; Levin et al., 1981; Bigler et al., 1992) or by tracing of the ventricles across multiple scan slices to obtain ventricular cerebrospinal fluid (CSF) volumes (Gale et al., 1995).

More modern methods have focused on tissue compartment segmentation algorithms that capitalize on a relationship between certain properties of the MRI signal and tissue type expressed at the level of the image voxel. These quantitative analyses involving segmentation of brain volume into its constituent divisions of gray matter, white matter, and CSF have been successfully applied in the study of normal brain development (Blatter et al., 1995) as well as in the study of neurological and psychiatric disorders (Shenton et al., 1992; Reiss et al., 1993).

Several studies of TBI patients have demonstrated the utility of segmentation data in the characterization of TBI-related diffuse damage (Berryhill et al., 1995; Blatter et al., 1997; Thatcher et al., 1997). The *k*-nearest-neighbor technique used in these studies, however, is based on user sampling of the tissue compartments and does not correct for scan inhomogeneities that arise as a result of the inherent transmission and reception characteristics of radiofrequency coils used in MR scanning. Additional steps must be taken to correct for this type of error. Newly developed automated methods for MRI tissue segmentation using T1-weighted images apply local model fitting to account for inhomogeneities, and increase reliability by removing dependence on a user to identify gray matter, white matter, and CSF points (Grabowski et al., 2000). These methods are also able to accommodate variations in scan contrasts.

We have developed and validated a segmentation protocol similar to that described by Grabowski and colleagues (2000) for the purposes of rapid and reliable assessment of gray matter, white matter, and CSF compartment volumes in patients with TBI (Kovacevic et al., submitted). The following study describes preliminary data from our application of this method in our ongoing series of TBI patients.

METHODS

Imaging Parameters

Subjects were scanned on a GE Signa 1.5T MRI scanner. Sagittal T1-weighted three-dimensional (3D) volume images (TR/TE/flip angle = 35 ms/5 ms/35°, 1.0 NEX, acquisition matrix = 256 × 256; 124 slices, slice thickness = 1.3 mm; FOV = 22 cm) were acquired. Proton density/T2-weighted images were acquired using an interleaved sequence (TR/TE/flip angle = 3000 ms and 80 ms/30 ms/35°, 0.5 NEX, acquisition matrix = 256 × 256; 56 slices, slice thickness = 3 mm; FOV= 22 cm).

Image Preprocessing

Prior to segmentation of the T1 image, the skull and tissue surrounding the brain were masked out of the image, preventing the misclassification of nonbrain tissues as parenchyma. Rather than rely on fully automated software that is error-prone, we used a semi-automated process in which an automated brain–nonbrain classification on the PD/T2 weighted images was followed by manual editing, slice by slice. This was followed by a second semi-automated step in which ventricular CSF and the cerebellum were demarcated. This presegmentation procedure can be completed in less than 30 minutes per scan by a trained operator. Interrater reliability is high, as indicated by intraclass correlation coefficients of 98%–99%. The result is a mask of total brain tissue without the inclusion of skull and dura matter, and separate classifications of cerebellar tissue and ventricular CSF. This mask is then transferred onto the T1 image for tissue compartment segmentation (see Figure 28–2).

Tissue Compartment Segmentation

Four gaussian curves were fit to a two-dimensional histogram of the masked T1 image, modeling the image intensity. This information was used to find appropriate cutoff values between gray matter and CSF compartments, and between gray and white matter. To compensate for inhomogeneity of intensity values across the T1 image, segmentation was done over small regions of 50 × 50 × 30 voxels. Only the central portion of each region was segmented with overlap occurring on the outer edges of each region, so that the segmentation can occur locally yet vary smoothly across the image. All voxels were assigned gray, white, or CSF values (ventricular or sulcal as determined by the masking procedure; see Fig. 28–2). The total number of voxels in each category was then calculated as a percentage of the total intracranial capacity. Our algorithm (Kovacevic et al., submitted) is similar to that of Grabowski and colleagues (2000), but it is faster, providing the advantage of very quick computational processing time of under 1 minute for the skull-extracted T1 image.

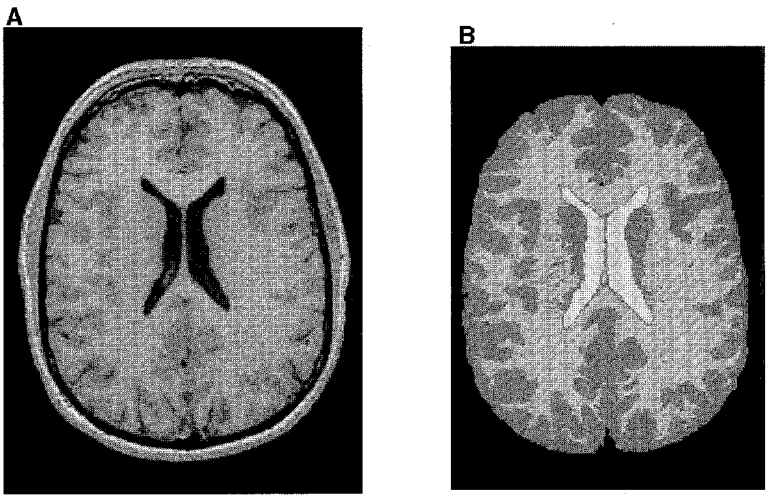


Figure 28–2. *A:* T1-weighted image from a healthy control subject. *B:* Same slice as *A*, with skull and nonbrain tissue masked out and voxels color coded to represent gray matter, white matter, sulcal cerebraspiral fluid (CSF), and ventricular CSF on the basis of a tissue compartment segmentation algorithm.

Neuropsychological Tests

We administered a small battery of standard neuropsychological tests of memory, attention, and executive functioning to 21 of the patients. These included the WCST; Trail Making, Parts A and B; phonemic word list generation; the Hopkins Verbal Learning Test, Revised (Benedict et al., 1998); and the Symbol Digit Modalities Test (Smith, 1978).

SUBJECTS

Twenty-six patients with TBI participating in our TBI research program were recruited from consecutive admissions to Sunnybrook and Women's Health Sciences Centre, Toronto, Canada's largest trauma center. According to the GCS score taken at 6 hours post-injury, six had mild TBI (GCS = 13–15), eight had moderate TBI (GCS = 9–12), and nine had severe TBI (GCS = 3–8). Clinical radiologic interpretation of these patients' MRIs taken at approximately 1 year post-injury indicated multiple tiny lesions in 70% of the patients. Thirty percent of the patients had evidence of larger focal lesions, mostly in the anterior temporal and frontal regions. Seventeen percent of the clinical reports mentioned atrophy.

Twelve healthy adults, age matched to the TBI patients, served as controls. For both groups, subjects with prior TBI, neurological disorders, psychiatric or substance abuse disorders, and medical conditions or medications affecting brain functioning were excluded.

RESULTS

Relation to Traumatic Brain Injury Severity

The presence and degree of TBI was significantly related to tissue compartment volumes. Gray matter, white matter, and sulcal and ventricular CSF volumes were all reliably discriminated among groups, with total parenchymal volume being the most sensitive and specific. As seen in Figure 28–3, there was a significant main effect of TBI group on brain parenchyma (expressed as a percentage of total intracranial capacity; F (3,36) = 11.02, $P <$ 0.0001). By this measure, all TBI groups had significantly lower corrected parenchymal volumes than controls, and severe TBI patients had significantly lower volumes than mild TBI patients. This dose–response relationship is also apparent in the significant correlation between corrected parenchymal volume and GCS (r (26) = 0.45, $p < 0.05$). Analysis of individual compartments revealed that ventricular CSF was more closely related to GCS than sulcal CSF (r's (26) = −0.48, $P < 0.05$; −0.35, $P < 0.08$, respectively), and that white matter volume was more closely related to GCS than gray matter volume (r's(26) = 0.40,

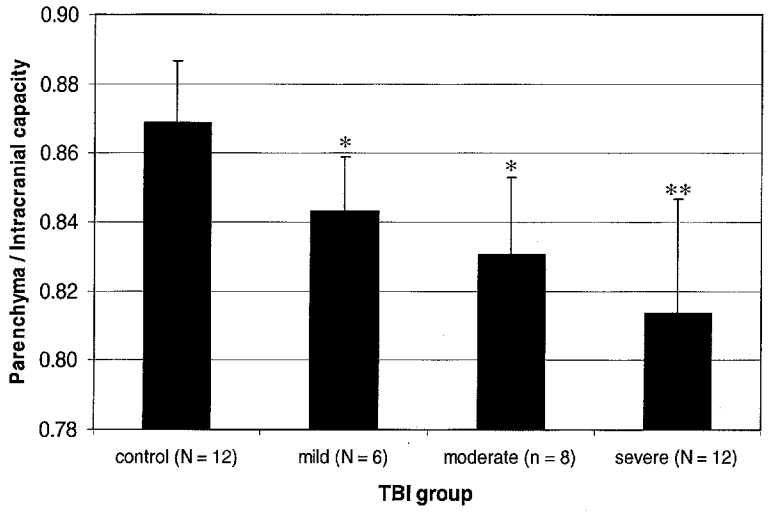


Figure 28–3. Dose–response relationship between traumatic brain injury (TBI) severity and parenchymal change. Brain parenchyma (gray + white matter, adjusted for total intracranial capacity) is plotted for controls and patients with TBI of varying levels of severity. Asterisk indicates significant atrophy relative to controls. Double asterisk indicates significant atrophy relative to controls and to mild TBI. Group differences were assessed with the Student-Newman-Keuls Test, $P < 0.05$.

$P < 0.05$; 0.25, not significant (NS), respectively).

Relation to Behavior

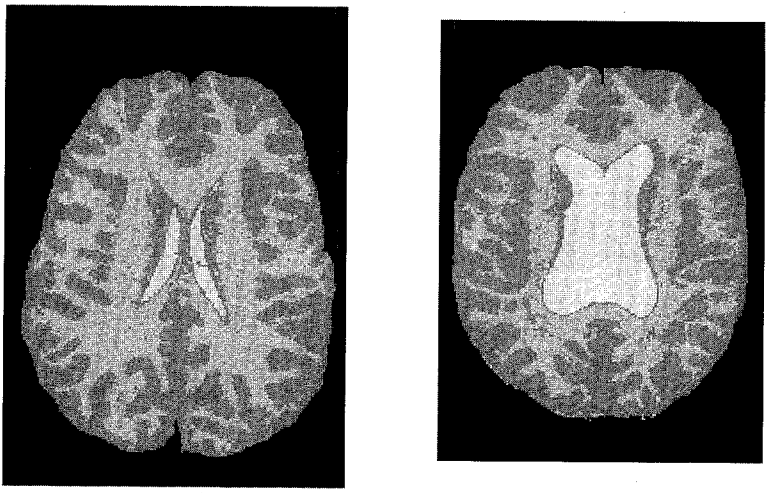
The tests with the strongest relation to segmentation measures were those involving speeded information processing, such as the Symbol Digit Modalities Test (speeded digit transcription, related to ventricular CSF; $r(20) = -0.63$, $P < 0.005$) and Trail Making Test, Part B (speeded alternating letter–number connection, related to parenchymal volume; $r(20) = -0.49$, $P < 0.05$). No significant relationships emerged for other tests of executive functioning and memory.

DISCUSSION

These results support the validity of our tissue compartment segmentation protocol. Although only four patients in this series were diagnosed with atrophy from standard radiologic interpretation, over half had significant atrophy as assessed by percent parenchyma > 2 standard deviations less than controls. The analysis of individual tissue compartments, while preliminary, suggests that white matter is more affected by increasing severity of TBI than gray matter. The correlation of severity with ventricular as opposed to sulcal CSF is consistent with this interpretation, as ventricular expansion would be an expected consequence of white matter loss (Levin et al., 1990; Anderson & Bigler, 1994).

Parenchymal volume was moderately related to injury severity as assessed by the GCS. In using the GCS as a criterion measure in this analysis, it is important to keep in mind that it is a measure of coma depth at the time of injury. It was not designed to measure later outcome. Consciousness alteration at the time of injury can be caused by many factors, not all of which are associated with later atrophy. Figure 28–4 displays segmented images from two patients, both of whom received GCS scores of 3, but demonstrated markedly different atrophy at 1 year post-injury. Patient A had a thalamic hemorrhage at the time of injury, possibly causing altered consciousness in the absence of major DAI. Patient B, at age 58, may have been more vulnerable to DAI effects due to aging (patient A was age 19 at the time of injury). It should be noted that the degree of atrophy in this patient was far greater than that seen in age-matched controls. Whatever the explanation for the discrepancy, these patients illustrate the importance of chronic-phase brain imaging in the assessment of TBI-related brain damage as opposed to relying strictly on acute clinical signs.

Diffuse axonal injury affects the speed and efficiency of mental operations. Accordingly, DAI as indexed by tissue compartment volumes was significantly and specifically related to measures of speeded information process-



A B

Figure 28–4. *A, B:* Two traumatic brain injury patients with severe consciousness alteration (prorated GCS = 3), but dissimilar parenchymal volumes. Tissue compartment segmentation indicated 88% parenchymal volume for patient A (in the range of controls, see Fig. 28–3), whereas patient B's percent parenchyma was 78%.

ing, but not other untimed tests. This finding suggests that these volumetric measures could be used to model the cognitive effects of general parenchymal loss.

The next step in this research program is to analyze the effects of focal damage. Chronic-phase, three-dimensional image acquisition facilitates localization and characterization of lesions. Using the Analyze software system (Biodynamic Research Unit, Mayo Foundation, Rochester, MN, USA), and comparing regions across the PD, T2, and T1 scans, areas of contusion, encephalomalacia, and hemosiderin deposits may be quantified volumetrically and localized in standard space, greatly increasing the precision of lesion classification over acute CT (e.g., Levine et al., 1998a).

A second approach to assessing focal damage in TBI is through measurement of regional atrophy, which can reveal localized effects in the absence of focal lesions (Berryhill et al., 1995). These data may be extracted from the whole-brain segmentation by co-registering a parcellated mask to the segmented image. This mask is defined by specialized algorithms that use manually and automatically identified landmarks identified on each brain to create a standard but individually customized grid (see Fig. 28–5). Segmentation data can then be derived individually for each region of interest and used to model the effects of focal tissue loss. Greater precision in lesion identification and quantification of focal atrophy should increase brain–behavior correlations with respect to the elusive behavioral and neuropsychological deficits described above.

In summary, a properly obtained structural MRI contains a wealth of information about TBI effects that is only partially utilized in the standard radiologic examination. Quantification of atrophy can be accomplished with several different methods. Our tissue compartment segmentation algorithms provide these data rapidly and reliably, with the benefit of extension to assessment of focal atrophy. Additionally, three-dimensional acquisition in the chronic phase allows for greater precision in lesion characterization. Combining these methods with novel behavioral measures should improve the sensitivity and specificity of brain–behavior relationships in TBI.

FUNCTIONAL NEUROIMAGING

Even the most sophisticated structural imaging analysis is not informative about the functioning of brain tissue. Functional brain imaging techniques can be used to study changes in cerebral blood flow (CBF) or cerebral metabolism resulting from TBI. Most contemporary functional brain imaging studies of chronic-stage TBI effects have used single

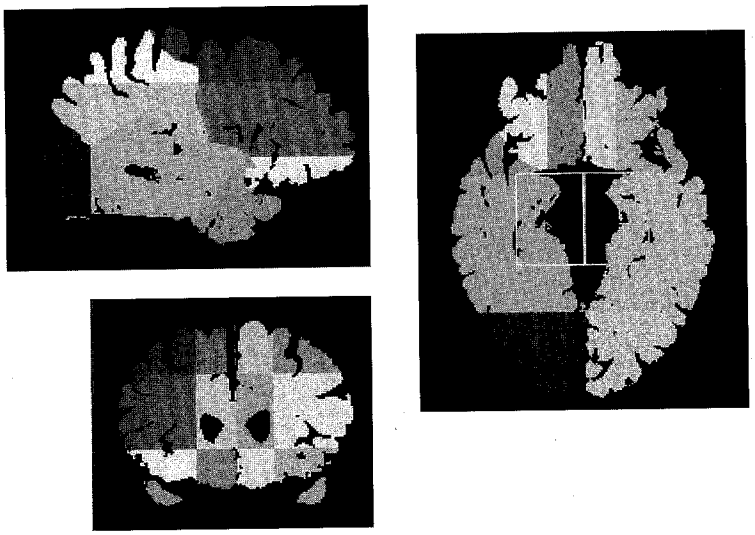


Figure 28–5. Color-coded regional parcellation mask superimposed on a healthy older adult's T1-weighted image shown in three planes. The box indicates the medial temporal region (including amygdala and hippocampus).

photon emission computed tomography (SPECT, usually with hexamethyl propyleneamine oxime [HMPAO] labeled with technetium-99m) and positron emission tomography (PET, usually with fluorodeoxyglucose [FDG]). Given the cost-effectiveness and wide availability of SPECT, it is more commonly used. It yields a greater number of cerebral abnormalities than concurrent structural imaging studies (Gray et al., 1992; Newton et al., 1992; Abdel-Dayem et al., 1998). These findings have in turn been related to neuropsychological test performance (Goldenberg et al., 1992; Ichise et al., 1994). Like SPECT, FDG PET is sensitive to functional abnormalities not appreciated by structural neuroimaging (Langfitt et al., 1986; Alavi et al., 1997), again with a meaningful relationship to neuropsychological test performance (Fontaine et al., 1999).

This functional neuroimaging research, while providing useful supplementation to structural neuroimaging findings, is still wanting with respect to elucidating brain–behavior relationships in chronic TBI. These studies are typically done with the patient in a resting state, when neural activity does not necessarily correspond to task-related neural activity (Duara et al., 1992). Cognitive testing is done separately from scanning with clinical tests of limited neuroanatomical specificity that are then compared to indices of brain function over large brain regions. The resulting modest imaging–behavior correlations are of heuristic clinical value, but are limited in their contribution to knowledge of brain–behavior relationships in TBI. Additionally, measures of resting metabolism reflect general functional status that can be affected by factors other than brain injury (Alexander, 1995; Ricker & Zafonte, 2000)

Rather than study the relationship of these functional neuroanatomical changes at rest, when mental activity is highly variable, it makes sense to study them in response to specific tasks with reliable functional neuroanatomical properties that tap mental processes affected by TBI. $H_2{}^{15}O$ PET and functional MRI reflect task-related changes in regional cerebral blood flow (rCBF). There has been an explosion of cognitive functional neuroimaging research in the last decade, probing neural circuitry in response to specific tasks in all major domains of human cognition (Cabeza & Nyberg, 2000). This body of research provides useful templates against which to interpret functional imaging findings in special populations such as patients with TBI (Grady et al., 1995; Becker et al., 1996; Woodard et al., 1998). In addition to identifying focal metabolic deficits, these techniques have documented regions in patients with metabolism similar to or greater than controls, thus indicating preservation in normal task-related sys-

tems as well as reorganization in response to injury. Such functional reorganization is most explicitly seen in activation studies of patients with focal lesions following recovery from specific neuropsychological deficit, who show increased activation relative to controls in areas adjacent or homologous to damaged regions (Engelien et al., 1995; Weiller et al., 1995; Buckner et al., 1996).

Activation functional neuroimaging paradigms have been applied in a small number of cases and group studies of patients with TBI (Gross et al., 1996; Kirkby et al., 1996; Levin et al., 1996; Levine et al., 1998a; McAllister et al., 1999; Ricker et al., 2001). In a functional magnetic resonance imaging (fMRI) study of working memory in patients who sustained a mild TBI 1 month prior to scanning, McAllister and colleagues (1999) noted topographic similarity of task-related activation between patients and controls. Consistent with the findings described above, however, was the finding that the mild TBI patients showed greatly enhanced activations in task-specific regions, including the right prefrontal and right parietal cortices.

Mild TBI causes a brief alteration in consciousness, with recovery of mnemonic function occurring over days or weeks. Assessment patients with moderate to severe TBI, in which return of everyday memory is preceded by a lengthy period of post-traumatic amnesia and possibly coma, would be more informative for the study of the functional neuroanatomical correlates of mnestic recovery. Case studies in the literature have focused on focal lesion effects (Kirkby et al., 1996; Levin et al., 1996; Levine et al., 1998). In an exploratory $H_2{}^{15}O$ PET study, a sample of five patients with severe TBI was noted to have reduced frontal activation relative during free recall, but enhanced frontal activation during recognition (Ricker et al., 2001). However, the memory activation paradigm had not been previously validated and there were only four control subjects. Additionally, structural neuroimaging data for the patients was taken from acute CT rather than chronic-phase MRI.

In a recent study with $H_2{}^{15}O$ PET, we demonstrated reorganization of neural systems supporting memory in patients with moderate-to-severe TBI (Levine et al., submitted). The patients, who had sustained their TBI an average of 4 years prior to the PET study, were scanned while performing a simple cued recall task that had been previously validated in studies of healthy young and older adults (Cabeza et al., 1997a; 1997b). Consistent with the functional neuroimaging findings from other populations and from studies of patients with TBI, our patients showed both reliance on normal functional systems as well as areas of increased activation (see Fig. 28–6). In particular, they showed relatively more activation of ventrolateral and dorsolateral frontal and anterior cingulate regions, including increased recruitment of left frontal regions relative to controls. We were able to relate the functional neuroimaging data to patterns of diffuse and focal injury as revealed by high-resolution structural MRI taken close in time to the PET scans. Although focal frontal lesions affected local aspects of the activation patterns, the remaining areas of increased activation were unaffected. With the exception of the anterior cingulate increase (likely associated with task difficulty in poor-performing patients; Barch et al., 1997), the overall pattern was unaffected by performance differences.

Clinical functional neuroimaging studies of chronic-stage TBI patients typically focus on hypofunctioning, interpreted within a lesion-focused framework as reduced brain activity due to focal or diffuse injury. Our findings suggest an alternative injury effect: task-related hyperactivation. Similar findings in aging and dementia have been interpreted as evidence of compensatory recruitment of additional brain areas to maintain performance (Grady et al., 1995; Cabeza et al., 1997a; Woodard et al., 1998; Bookheimer et al., 2000). Another interpretation relates to the neuropathology of DAI as described above. Widespread DAI as occurs in moderate-to-severe TBI and the resulting neuroplastic changes have functional consequences for the intact receptive fields of axotomized neurons, with functional reorganization resulting from both excitatory and inhibitory deafferentation. Neuronal function is further affected by the resulting neuroplastic changes (i.e., axonal sprouting and synaptogenesis) that may occur

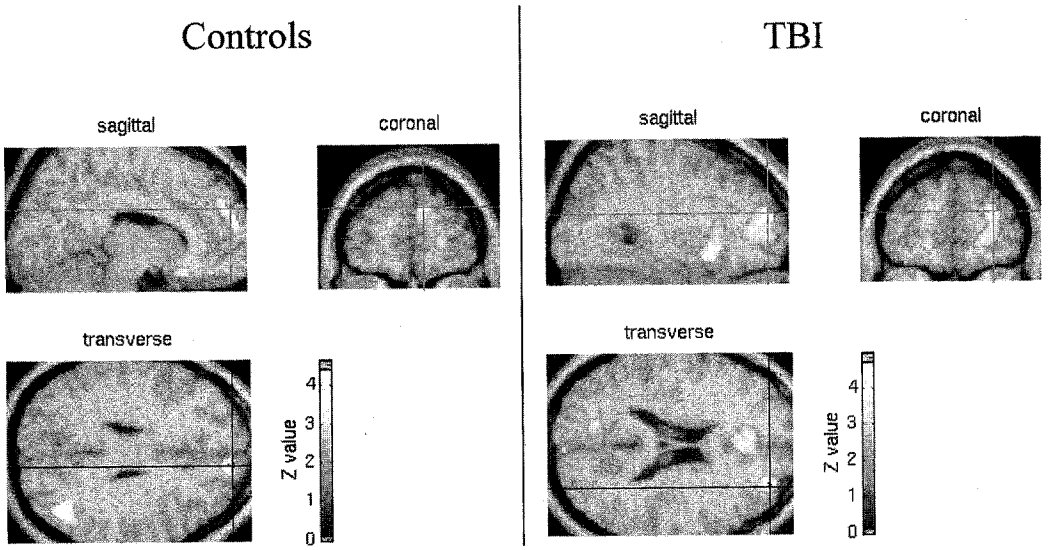


Figure 28–6. Retrieval activations (relative to an encoding baseline) in healthy controls and patients with traumatic brain injury (TBI) as displayed on a standard brain image in three planes. Activations are displayed in white in standard space on axial brain images provided with SPM96. Activations are thresholded at $P < 0.01$ for the purposes of display. Both healthy adults and patients with TBI show a right lateralized 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 in anterior cingulate gyrus, cuneus, left insula, and left frontal pole. These additional activations were statistically significant in Group × Condition interaction analyses, $P < .001$.

in these fields as part of the recovery process (Povlishock et al., 1992; Christman et al., 1997). The increased spread of cortical activation observed in this study may result from such neuroplastic changes. Aging and Alzheimer's disease share with TBI both diffuse neuronal changes and, as noted above, more widespread task-related activation.

CONCLUSIONS

The advances in the acute management of TBI that have reduced mortality and morbidity have not been paralleled by diagnostic or therapeutic advances in the chronic stage, when mental and behavioral deficits predominate, including memory loss, impaired executive functioning, and personality changes. The resulting long-term disablement affects millions of North Americans, with an economic impact in the billions of dollars. While it is acknowledged that certain deficits may have a higher base rate in the cohort of individuals who sustain TBI (Dikmen et al., 1995), it is nonetheless widely accepted that the neuropsychological profile of moderate to severe TBI is related to brain damage.

The mechanisms governing these brain damage effects, including their trajectory over the recovery process, their rehabilitation, and their high variability across patients with similarly severe TBIs, however, are not well understood. While structural and functional neuroimaging measures do show correlations with behavioral and cognitive outcomes, the relationships tend to lack psychological and anatomic specificity. This state of affairs could be improved by increasing the specificity of psychological and anatomic measures.

Standard neuropsychological assessment procedures are more effective at assessing speeded information processing deficits and cognitive-executive effects of dorsolateral prefrontal cortical damage than at assessing ventral prefrontal cortical effects on emotion-related information processing (Stuss & Levine, 2002; see Chapter 25), yet in patients with

TBI, it is often the ventral prefrontal effects that determine negative outcomes. Neuropsychological assessment of these patients should include measures capable of revealing the SRD (such as our strategy application tests) that characterizes this population. It should further incorporate analysis of patients' real-life functioning, as assessed through psychosocial outcome questionnaires. These measures may reveal lesion–behavior effects not observed in laboratory assessment. A corollary point is that studies of TBI can contribute to the understanding of the human ventral prefrontal cortex, which is otherwise not a common site of frontal neuropathology.

Magnetic resonance imaging is the modality of choice for chronic-phase TBI structural neuroimaging. Not only does MRI have greater sensitivity to TBI-related focal damage, but it can also provide quantification of parenchymal loss useful in both research and clinical contexts. Such data are more appropriate to the description of chronic stage injury characterization than are acute injury data.

*Functional neuroimaging studies usually in*volve assessment of brain metabolism at rest. Studies of task-related brain activation may show injury effects not predicted by standard clinical imaging studies. Early data have revealed task-related activation increases as an effect of DAI (and other diffuse pathologies), possibly due to deafferentation and neuroplasticity leading to reorganization in response to injury.

The future care and treatment of patients with TBI will depend on improving neuropsychological and imaging assessment with novel approaches such as those described in this chapter. Furthermore, TBI is unique for its effects on ventral frontal cortex and diffuse axonal injury. The study of the effects of these injuries provides unique insights into the function of frontal systems.

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Principles of Frontal Lobe Function

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