

In Vivo Characterization of Traumatic Brain Injury Neuropathology with Structural and Functional Neuroimaging

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ABSTRACT

Quantitative neuroimaging is increasingly used to study the effects of traumatic brain injury (TBI) on brain structure and function. This paper reviews quantitative structural and functional neuroimaging studies of patients with TBI, with an emphasis on the effects of diffuse axonal injury (DAI), the primary neuropathology in TBI. Quantitative structural neuroimaging has evolved from simple planimetric measurements through targeted region-of-interest analyses to whole-brain analysis of quantified tissue compartments. Recent studies converge to indicate widespread volume loss of both gray and white matter in patients with moderate-to-severe TBI. These changes can be documented even when patients with focal lesions are excluded. Broadly speaking, performance on standard neuropsychological tests of speeded information processing are related to these changes, but demonstration of specific brain-behavior relationships requires more refined experimental behavioral measures. The functional consequences of these structural changes can be imaged with activation functional neuroimaging. Although this line of research is at an early stage, results indicate that TBI causes a more widely dispersed activation in frontal and posterior cortices. Further progress in analysis of the consequences of TBI on neural structure and function will require control of variability in neuropathology and behavior.

Key words: diffuse axonal injury; magnetic resonance imaging, neuroplasticity; neuropsychology

INTRODUCTION

ADVANCES IN THE ACUTE MANAGEMENT of traumatic brain injury (TBI) for reducing mortality and morbidity have not been paralleled by diagnostic or thera-

peutic advances in the chronic stage, where mental and behavioral deficits occur in the areas of memory, executive functioning, and personality. The resulting long-term disability affects millions of Americans, with an economic impact in the billions of dollars (Max et al., 1991).

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Although experimental work has refined the psychological structure of mental and behavioral deficits in TBI, the neuropathology of these deficits is less understood. This review concerns neuroimaging methods used for *in vivo* characterization of TBI neuropathology due to closed head injury at the chronic phase, following stabilization of acute and subacute pathology and evolving cognitive deficits. These deficits can be measured in weeks or months, depending on the severity of the injury.

PRIMACY OF DIFFUSE INJURY IN TRAUMATIC BRAIN INJURY

The most common injuries with the greatest implications for long-term outcome at the chronic phase are focal cortical contusion (FCC) and diffuse axonal injury (DAI) (Gentry et al., 1988a). FCC results from inertial forces causing localized damage in ventral and polar frontal and anterior temporal areas where the brain is confined by bony ridges of the inner skull, regardless of the site of impact (Courville, 1937; Ommaya and Gennarelli, 1974; Clifton et al., 1980). These areas mediate self-regulation, emotional functioning, and social functioning, which are frequently impaired in TBI (Stuss and Gow, 1992; Varney and Menefee, 1993; Levine et al., 2002b). DAI affects interconnected processing in the brain, contributing to the pattern of slowing, inconsistency, distractibility, and impaired top-down control classically observed in patients with TBI. Although FCC is an important cause of TBI-related disability, DAI is more ubiquitous and may account for a greater share of this disability.

DAI is initiated by ionic homeostatic disruption and changed permeability of the axolemma and is terminated hours later by axonal disconnection and demise of the distal axonal segment (and its synaptic field—i.e., deafferentation) (Povlishock and Christman, 1995; Maxwell et al., 1997). Initially, DAI causes confusion, loss of consciousness, or coma due to disruption of ascending fibers involved in arousal (Gennarelli et al., 1982). The degree of this disruption marks the severity of injury, as indicated by measures of coma depth and duration, or duration of post-traumatic amnesia. Initial work characterized DAI as a triad of microscopic and macroscopic lesions in the corpus callosum, dorsolateral quadrant of the rostral brainstem, and cerebral white matter (Adams et al., 1982, 1989). Later work described microscopic DAI pathology 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). The microscopic scale of DAI neuropathology

poses a significant challenge for direct detection by *in vivo* neuroimaging, which traditionally provides structural information on a macroscopic scale (millimeters or greater) to aid in diagnosis.

Although DAI is not directly assessed *in vivo*, its effects can be detected indirectly by structural neuroimaging, measuring volume loss due to axonal demise, and functional neuroimaging, measuring the functional consequences of deafferentation. A recently applied technology, diffusion tensor imaging, provides a more direct measure of the microstructural integrity of white matter. Additional imaging technologies (Garnett et al., 2001), such as magnetic resonance proton spectroscopy, are covered elsewhere in this issue.

STRUCTURAL NEUROIMAGING

Magnetic resonance imaging (MRI) is the modality of choice for diagnosis of chronic-phase TBI-related neuropathology (Gentry et al., 1988b; Wilson et al., 1988; Ogawa et al., 1992). A proper TBI imaging protocol should include high resolution T1-weighted, T2-weighted, proton density, and gradient echo 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). The small DAI lesions appreciated on MRI scans represent only the regions where the confluence of DAI is large enough to be visible to the naked eye (Gentry, 1990). Moreover, the clinical significance of these lesions is unclear given the burden of DAI that remains invisible (Scheid et al., 2003). Characterization of classic DAI-related lesions with standard qualitative image analysis protocols therefore does not truly characterize the full extent or consequences of DAI.

Quantified Structural MRI in TBI: A Review

Quantification of the atrophy due to DAI can provide a numerical index that has greater precision than qualitative judgments and that is more amenable to research. Early research focused on enlargement of the lateral ventricles, which reflects brain atrophy and is indicative of a disproportionately greater loss of white matter than gray matter (Anderson and Bigler, 1994). Quantification of lateral ventricular enlargement can be accomplished through simple linear width or planometric measures taken from computed tomography (CT) (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., 1995b). Sev-

eral studies have capitalized on the superior image quality of T1-weighted MRI scans to describe TBI-related changes in easily visualized major nuclei and white matter structures, including the corpus callosum, hippocampus, thalamus, cingulate gyrus, and fornix (Levin et al., 1990; Gale et al., 1993, 1995a; Verger et al., 2001; Yount et al., 2002; Tomaiuolo et al., 2004).

Other studies have focused on tissue compartment segmentation algorithms that take advantage of the relationship between certain properties of the MRI signal and tissue type expressed at the level of the image volume element (voxel), to classify the spatial location of normal tissues and pathology. Several studies of TBI patients have demonstrated the utility of segmentation data in the characterization of TBI-related diffuse damage. Although some have focused on segmentation of CSF from parenchyma (Blatter et al., 1997; MacKenzie et al., 2002), others also included measures of gray and white matter. For example, Thatcher and colleagues (1997) found reduced differentiation between gray and white matter in 31 patients with TBI. This reduction in brain differentiation was related to TBI severity.

Tissue compartment segmentation can be combined with a region-of-interest approach. Berryhill and colleagues (1995) found localized volume loss in prefrontal gray matter and an increased prefrontal CSF in 14 children with severe TBI who did not have focal lesions, as compared to 14 children with mild TBI; white matter changes were not significant. Whole brain volumes were not included in this study. Wilde and colleagues (2005) demonstrated significant whole brain, prefrontal, and temporal volume loss in 16 children with moderate-to-severe TBI relative to 16 normally developing comparison subjects, with differences noted for gray matter, white matter, and CSF. However, some of these effects, particularly those for prefrontal gray matter, were accounted for by the inclusion of patients with focal lesions. Serra-Grabulosa and colleagues (2005) assessed hippocampal, frontal, and whole brain tissue compartments in 16 adolescents with severe TBI and no large frontal lesions. They found reduced white whole brain and prefrontal white matter volumes, increased CSF volumes, and reduced hippocampal volumes among the TBI patients. Only CSF volume was related to memory test performance.

Voxel-based morphometry (VBM), (Ashburner and Friston, 2000) has been widely used to characterize regional changes in tissue composition (usually gray matter) in patient samples. Because this approach analyzes structural brain imaging data at the voxel level (much the same way functional neuroimaging data are analyzed), it makes no assumptions about regional distribution of changes, although it may be biased towards localized and

against spatially complex group differences (Davatzikos, 2004; but see also Friston and Ashburner, 2004). Furthermore, the sensitivity of VBM may not be consistent over all brain areas, as detection decreases for regions with greater anatomical variability (Tisserand et al., 2002).

Two studies used VBM to assess TBI effects on structural MRI data. Gale et al. (2005) reported gray matter loss in frontal, temporal, cingulate, subcortical, and cerebellar regions, some of which were correlated with performance on tests of attention and the Glasgow Coma Scale (GCS). These results, however, are difficult to interpret due to the small sample size ($n = 9$), that included several patients with evidence of focal lesions on acute CT. Using a different algorithm focusing on white matter density in 19 severe TBI patients without focal lesions, Tomaiuolo and colleagues (2005) reported reduced volumes in the corpus callosum, fornix, anterior limb of the internal capsule, superior frontal gyrus, parahippocampal gyrus, and optic radiation and chiasma, although these were not related to injury severity (as indicated by days of coma). Performance on a brief battery of memory tests was unrelated to reduced white matter density, with the exception of immediate short story recall and the mid-body of the corpus callosum.

Summary. Quantitative neuroimaging analysis holds significant promise for clarifying brain behavior relationships in TBI. This brief review indicates that researchers have achieved high anatomical precision in the quantification of TBI-related tissue loss. TBI-related volume loss in the corpus callosum and fornix extend experimental observations of TBI-related white matter degeneration to chronic phase TBI in humans. Further support for this is garnered from segmentation data, although these data also suggest extension of diffuse injury to gray matter, including both deep nuclei such as the thalamus and hippocampus as well as the cerebral cortex. This research, however, is at an early stage; few studies have systematically examined gray and white matter volumes in large samples.

In spite of the advances in quantifying volume loss in TBI, only generalized relationships to clinical outcomes have been consistently demonstrated. As expected, gross classification of outcome is related to volumetric measures of brain parenchyma (Levin et al., 1981; Blatter et al., 1997; MacKenzie et al., 2002; Wilde et al., 2005). With respect to neuropsychological test performance, CSF volumes, particularly in the lateral ventricles, have been associated with neuropsychological outcome, especially memory tests (Levin et al., 1981; Cullum and Bigler, 1986; Gale et al., 1994; Johnson et al., 1994; An-

derson and Bigler, 1995; Blatter et al., 1997; Serra-Grabulosa et al., 2005), reflecting the effects of non-specific white matter degeneration. Corpus callosum volume, also reflecting white matter degeneration, has also been shown to be related to neuropsychological outcome (Verger et al., 2001; Tomaiuolo et al., 2004). The volume of the fornix is related to memory test performance (Gale et al., 1993, 1995a; Tomaiuolo et al., 2004). Otherwise, specific structure-function relationships have been limited (Yount et al., 2002; Serra-Grabulosa et al., 2005; Tomaiuolo et al., 2004, 2005).

Although these findings may simply reflect the diffuse nature of TBI affecting distributed neurocognitive systems, there are also numerous methodological factors that should be taken into consideration. Patient sample sizes vary widely, with large variance for methods of ascertainment, injury severity and time since injury. The presence of focal lesions can interfere with volumetric analyses in patients with TBI. Lesioned tissue contains voxels of varying intensity on structural MRI; some may correctly segment as CSF, others may be isointense with intact gray or white matter. In any case, the inclusion of patients with large lesions introduces a different neuropathology that should not be confounded with diffuse injury effects. In certain segmentation protocols, method variance is introduced by use of slightly different structural MRI protocols, different pre-processing methods (e.g., correction for scan inhomogeneities arising due to the inherent transmission and reception characteristics of radiofrequency coils used in MR scanning) and different post-processing methods for quantifying DAI neuropathology from structural MRI. The variability in patient and imaging methods are compounded by significant variability in behavioral assessment methods, many of which may be insensitive to TBI effects (Levine et al., 2002b).

To illustrate the effects of method variance on structure-function relationships, consider two studies by Tomaiuolo and colleagues. Using a manual region of interest (ROI) method, numerous structure-function relationships were delineated, such as lateralized effects of hippocampal atrophy on verbal and visual memory functioning (Tomaiuolo et al., 2004). Yet many of these relationships did not replicate on voxel-based morphometric interrogation of white matter in the same patients (Tomaiuolo et al., 2005).

Toronto TBI Study

We have attempted to address many of these factors in a recently completed large-scale study of imaging and behavior and the chronic phase of TBI (Levine et al., in

preparation). Sixty-nine patients were assessed, spanning the full range of TBI severity. Patients were recruited from admission lists to Sunnybrook Health Sciences Centre, Canada's largest trauma center. Injury severity was determined from an exhaustive review of admission records. All patients were assessed at least one year post-injury, when neurological recovery has largely plateaued. Patients were assessed on a large battery of contemporary standard and experimental behavioral measures and scanned with a standard TBI protocol on a 1.5-T MRI system (Signa, CV/i hardware, LX software, General Electric Healthcare, Waukesha, WI).

Neuroimaging data were analyzed via an in-house image processing pipeline based on template matching. Following automated removal of non-brain tissue, the voxels on the T1-image were classified as representing gray matter, white matter, or CSF using an automated tissue segmentation method that corrects for radiofrequency inhomogeneity inherent to MR scanning (Kovacevic et al., 2002) (Fig. 1a,b). The CSF compartment was further divided into sulcal and ventricular CSF by outlining the ventricles on the segmented T1 image. A Semi-Automated Brain Region Extraction (SABRE) (Dade et al., 2004) method was used to create 38 ROI's on the template brain. Non-linear registration was used to customize these regions to fit subjects' segmented T1-image (Fig. 1c,d). Although this method lacks the precision of manual tracing, it is completely automated and can be applied reliably to large samples of brains. Regional gray matter, white matter, and CSF volumes were corrected for total intracranial capacity using a regression-based method (Arndt et al., 1991; Raz et al., 2005).

Twenty-three of the patients had focal lesions (i.e., with volume greater than 0.5 cm³). By coincidence, nearly all of these lesions were right lateralized or bilateral. They otherwise followed the typical frontotemporal distribution. These lesions were manually traced. This lesion mask was incorporated into the analysis to enable separation of volume loss due to focal lesions from that due to DAI. A set of 12 age-matched healthy adults was included as a comparison sample.

Given the large number of regional volumes, data were analyzed with partial least squares (PLS) (McIntosh et al., 1996), a multivariate method that operates on the covariance between the regional volumetric data and one or more measures to identify a limited number of components (latent variables [LVs]) that optimally relate the two. This method has been used extensively in analysis of both functional (McIntosh et al., 2004) and structural (Gilboa et al., 2005) brain imaging data.

Our initial analyses examined the relationship of regional gray and white matter volume loss to injury sever-

ity, coded as mild, moderate, severe, or none (in the case of comparison subjects), in the patients *without* large focal lesions (Levine et al., in preparation). The findings confirmed that regionally-specific volume loss is related to TBI severity in a large sample of TBI patients. Gray and white matter volume loss was observed in ventral prefrontal regions previously shown to be affected in patients both with and without focal lesions, but volume loss was not limited to these regions. Volume loss was noted in both rostral and caudal sectors of the cingulate gyrus, within subcortical nuclei, and dorsal prefrontal, posterior temporal, parietal, and occipital cortical regions. Whereas earlier studies emphasized white matter as determined by ventricular expansion or measurement of specific fiber tracts (Levin et al., 1990; Anderson and Bigler, 1994), our data are in accord with those from later studies in which both gray and white matter volumes were systematically evaluated (Serra-Grabulosa et al., 2005; Wilde et al., 2005).

We next applied the same analysis technique to the full sample of 71 patients to examine the effects of TBI severity on regional volume loss in a sample of TBI patients with combined focal and diffuse injury. In this analysis, additional ventral prefrontal and medial temporal gray and white matter volumes emerged as significantly related to TBI severity, particularly in the right hemisphere. This finding was expected given the encroachment of lesions on these regions. Had we run the analysis without discriminating between patients with and without focal lesions, these effects could not have been separated from those related to DAI.

We next examined covariance patterns between the volumetric data and a set of standard neuropsychological tests of memory and speeded information processing commonly affected by TBI. This analysis was restricted to patients. Test performance was robustly related to gray matter volume loss in patients with and without large focal lesions, particularly in the cingulate, temporal, parietal, and ventral prefrontal regions. White matter volumes were not consistently related to test performance, except in patients with focal lesions. Tests of speeded information processing—i.e., the Symbol-Digit Modalities Test (Smith, 1978) and the Trail Making Test (Army Individual Test Battery, 1944)—tended to have stronger relationships to structural changes than did non-speeded tests, such as the Wisconsin Card Sorting Test (Grant and Berg, 1948).

We have also begun to investigate the relationship of these same brain imaging data to more refined, experimental tests. We reported that the Iowa Gambling Test (Bechara et al., 1994), a widely researched test of decision making, was unrelated to whole-brain measures of gray matter, white matter, or CSF, although the presence

of focal lesions was associated with impaired performance (Levine et al., 2005). In a subsequent study, PLS was used to examine covariances between three behavioral measures—the Iowa Gambling Test, Smell Identification (Doty et al., 1984), and Object Alternation (Freedman et al., 1998)—and regional atrophy using the same image analysis procedures described above (Fujiwara et al., submitted). The three behavioral measures have all been associated with ventral prefrontal function in experimental animal or human studies. Performance on Smell Identification and, to a lesser extent, Object Alternation, was related to the integrity of ventral prefrontal regions in patients with and without large focal lesions, but volume loss in medial and lateral temporal regions also emerged as related to behavior. The Iowa Gambling Test was not significantly associated with patterns of volume loss.

Summary. The Toronto TBI study is unique for its large sample size and for its application of advanced image analysis and behavioral assessment techniques. Preliminary findings replicate and extend earlier findings that parenchymal volume loss can be documented and quantified *in vivo* in patients with TBI even in the absence of large focal lesions (Berryhill et al., 1995). The results are also consistent with recent findings suggesting that DAI affects both gray and white matter to a similar degree when both tissue compartments are systematically assessed. Increased severity of TBI was associated with volume loss in numerous regions, including prefrontal regions classically associated with TBI-related damage. Standard neuropsychological tests typically used in clinical assessments of patients with TBI were robustly related to volume loss, particularly for gray matter. Certain refined tests, particularly Smell Identification, showed evidence of specificity, although even here the significant structure-function relationships were not limited to the hypothesized ventral prefrontal regions. We are currently investigating patterns of additional experimental test performance against these same brain imaging data.

Functional Neuroimaging in TBI

Even the most sophisticated structural imaging analysis lacks information about the functioning of intact tissue. Functional brain imaging techniques can be used to study changes in cerebral blood flow (CBF) or cerebral metabolism as a result of TBI. In the acute phase, these techniques are important for the study of disturbances in cerebral circulation (ischemia or hyperemia) (Overgaard and Tweed, 1974; Langfitt et al., 1977; Obrist et al., 1979; Sakas et al., 1995) or metabolism

IMAGING TRAUMATIC BRAIN INJURY

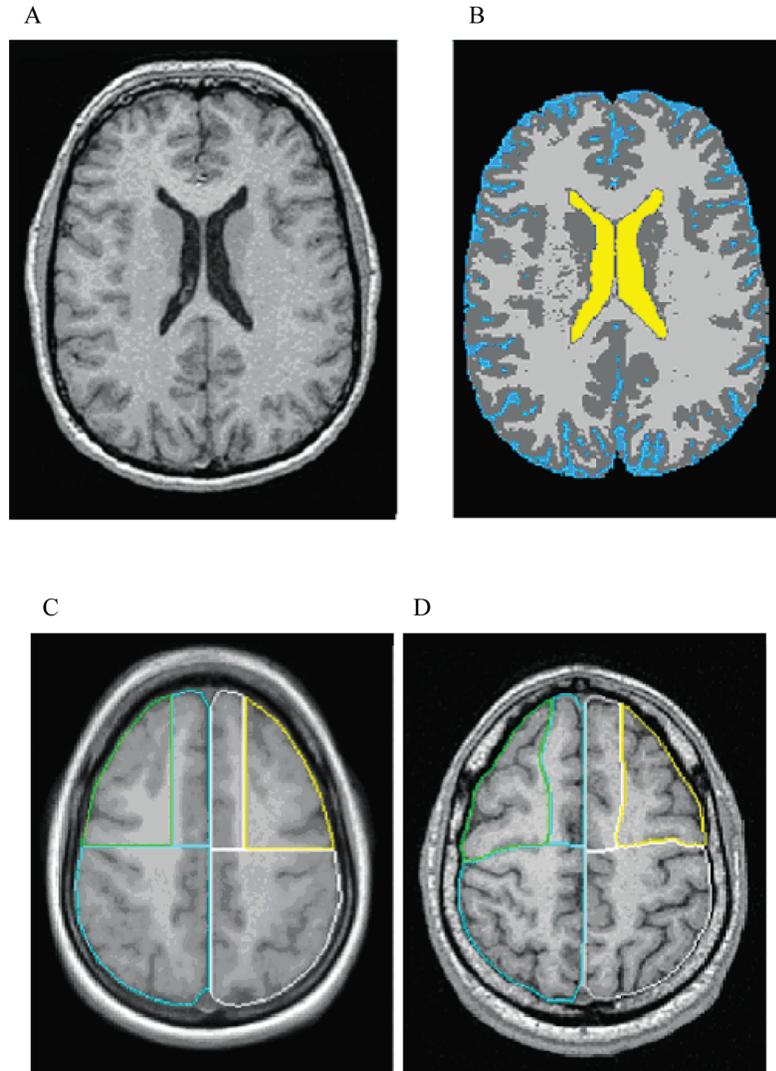


FIG. 1. (A) T1-weighted image. (B) T1-weighted image with skull removed and tissue classified as gray, white, ventricular cerebrospinal fluid (CSF), or sulcal CSF. (C) Regional mask applied to averaged reference image. (D) Regional mask fit to registered to an individual subject's image

(Yamaki et al., 1996; Bergsneider et al., 1997) that may occur as secondary TBI effects. Functional neuroimaging studies of brain-behavior relationships must await the resolution of these abnormalities for measures of CBF and metabolism to resume their expected coupling with each other and their assumed relationship with neuronal activity.

The majority of contemporary functional brain imaging studies of chronic-stage TBI effects have used single photon emission computed tomography (SPECT—usually with hexamethyl propylene-amine oxime [HMPAO] labeled with technetium-99m) and positron emission tomography (PET—usually with [^{18}F]fluorodeoxyglucose

[FDG]). SPECT, given its cost-effectiveness and wide availability, is more commonly used. SPECT yields a greater number of cerebral abnormalities than concurrent structural imaging studies (Gray et al., 1992; Newton et al., 1992; Nedd et al., 1993; Kant et al., 1997; Abdel-Dayem et al., 1998). These findings have in turn been related to neuropsychological test performance (Goldenberg et al., 1992; Ichise et al., 1994; Jacobs et al., 1996). In SPECT, however, the radioisotope uptake characteristics cannot be related to absolute regional perfusion; interpretation of perfusion abnormalities is instead made in comparison to an internal standard (such as the cerebellum). Interpretation in the SPECT literature is further

complicated by lack of control over co-morbid conditions (e.g., depression) that are associated with cerebral blood flow changes (Ricker and Zafonte, 2000). FDG PET, which can provide an absolute measure of cerebral glucose metabolism and has higher spatial resolution than SPECT, has been applied in a handful of TBI studies. Like SPECT, FDG PET is sensitive to functional abnormalities not appreciated by structural neuroimaging (Langfitt et al., 1986; Tenjin et al., 1990; Alavi et al., 1997), again with some relationship to neuropsychological test performance (Rao et al., 1984; Ruff et al., 1994; Fontaine et al., 1999).

These functional neuroimaging studies, although providing useful supplementation to structural neuroimaging findings, 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.

Activation Functional Neuroimaging

$H_2^{15}O$ PET and functional MRI reflect task-related changes in regional cerebral blood flow (rCBF). As a result of the explosion of cognitive functional neuroimaging research in the 1990's, the neural circuitry in response to specific tasks in all major domains of human cognition has been studied (Cabeza and Nyberg, 2000). Functional neuroimaging findings in healthy adults provide useful templates against which to interpret functional imaging findings in special populations such as TBI. For example, altered patterns of task-related brain activation have been identified in normal aging (Grady et al., 1994; Cabeza et al., 1997), Alzheimer's disease (AD) (Woodard et al., 1998; Backman et al., 1999), and schizophrenia (Mattay et al., 1997; Spence et al., 2000). In addition to identifying focal metabolic deficits, these techniques have documented regions with metabolism similar to or greater than in healthy comparison subjects, thus indicating preservation in normal task-related systems as well as re-organization in response to neurocognitive deficits. Such functional re-organization is most explicitly seen in activation studies of patients with focal lesions following recovery from specific neuropsychological deficits (Engelien et al., 1995; Weiller et al., 1995; Buckner et al., 1996), who show increased activation relative to non-injured comparison subjects in areas adjacent to the damaged tissue or in contralateral

homologues to damaged regions that would normally mediate task performance.

Methodological Issues

Evaluation of activation functional neuroimaging studies is complicated due to the number of factors contributing to method variance across studies. Most contemporary studies capitalize on the blood oxygen level dependent (BOLD) response as an indirect measure of neuronal activity in functional magnetic resonance imaging (fMRI). Other studies have assessed regional cerebral blood flow with positron emission tomography (PET). While fMRI is the preferred technique due to higher temporal resolution, greater availability, lower costs, and absence of ionizing radiation exposure, it is associated with low signal sensitivity and a variety of image artifacts, such as susceptibility artifact between air and tissue in ventral frontal and temporal regions.

Both PET and early fMRI studies presented and analyzed stimuli grouped across trials in what is known as a blocked design. Later developments in fMRI technology and analysis allowed for event-related design, meaning trials need not be grouped but may rather be interleaved and analyzed individually, as they would be in a standard cognitive experiment. Blocked designs have good signal sensitivity and remain appropriate for processes spanning over trials (e.g., sustained attention), although event-related designs are usually preferred as they are not confounded by task set effects that may accompany sequences of trials, as well as other factors (Zarahn et al., 1999).

Scanning patients with TBI introduces a number of other methodological factors that affect interpretation of results. TBI is a heterogeneous disease with multiple neuropathologies that evolve over time. Imaging findings from moderate or severe TBI likely differ from those produced by patients with mild TBI. Within patients, findings will likely be affected by the time of scanning relative to the time of injury; this effect is reduced with stabilization of recovery. Signal in brain regions encroached by focal lesions will obviously be greatly affected relative to signal from intact tissue. Signal drop-out due to focal lesions may therefore significantly bias results.

There are also conceptual issues related to interpretation of functional imaging results from patients, and more generally from any functional neuroimaging data set. Patterns of activation must be interpreted in the context of a control task. Ideally, this task is matched to the experimental task on all factors except those of interest to the experimenter. In functional neuroimaging, it can be very difficult to ensure that this is the case. Some control tasks engage cognitive processing, producing deactivation relative to the experimental task. For example, visual fixa-

tion (i.e., resting with eyes open and fixated) has been often used as a control task, yet visual fixation alone produces a reliable pattern of brain activation likely related to environmental monitoring and to self-related information processing (Gusnard and Raichle, 2001).

In the case where patients have impaired performance and altered patterns of brain activation, it is impossible to know whether differences in brain activation are attributable to brain damage or whether they merely reflect altered performance. In other words, could control subjects mimic the patient's pattern of brain activity if they are made to perform the task as poorly as the patients? If so, attribution of the patients' pattern is ambiguous. Optimally, patients and non-injured comparison subjects would be matched for performance. However, this creates a paradox as tasks where patients are impaired are of the most interest. One solution to this paradox is to scan patients with impaired performance using an event-related design, and only analyze those events where performance was matched to non-injured comparison subjects. Alternatively, patients may be scanned on a performance-preserved variant of an impaired task. For example, Price and colleagues (2001) scanned Broca's aphasia patients with an implicit reading task previously known to engage the language system in an obligatory fashion. The patients could perform this task, yet showed differences from non-injured comparison subjects downstream in the language system.

Interpretation of imaging data is also affected by degeneracy of brain systems. Degeneracy refers to the ability of more than one brain system to yield a similar behavioral output, as in dual routes (lexical or semantic) to reading (Price and Friston, 2002). Healthy subjects may activate two or more degenerate systems at the same time, in which case it is impossible to know which activated regions belong to which system. Alternatively, one system may inhibit the other (as is often the case with contralateral homologues), so that sub-threshold activity in the inhibited system is not detected in a functional neuroimaging study. In this sense, functional neuroimaging data in general is unconstrained; it is unknown whether the pattern of activation is necessary for task performance. Additional data from lesion studies helps to constrain interpretation of functional neuroimaging data.

Armed with tasks with known neuroanatomical correlates as established through previous functional imaging and lesion studies, the researcher is better able to interpret patterns of activation when scanning patients with TBI (assuming performance is comparable to non-injured comparison subjects). Activation in regions overlapping with non-injured comparison subjects suggests that these regions may mediate performance in both groups, increasing the likelihood that these regions are necessary for task perfor-

mance. Regional activation in non-injured comparison subjects but not in patients suggests that these areas are incidental to the task or reflect another degenerate system. Finally, areas of activation may be observed in patients, but not in non-injured comparison subjects. These may indicate a system that was either untrained or inhibited in non-injured comparison subjects (Price and Friston, 2002).

Because of these methodological factors, we emphasize group studies over case studies in the present review. Additionally, this review is restricted to research using contemporary activation functional neuroimaging paradigms with a temporal resolution on the order of seconds (i.e., $H_2^{15}O$ PET and fMRI)

Activation Functional Imaging in Moderate-to-Severe TBI

Functional neuroimaging studies in TBI can be divided between those that have adapted standard neuropsychological tests for use in the scanner versus those that use experimental procedures developed in prior functional neuroimaging studies. Christodoulou and colleagues (2001) studied nine patients with moderate-to-severe chronic-phase TBI and seven non-injured comparison subjects with blocked-design fMRI using a modified version of the paced auditory serial addition task (PASAT) (Gronwall, 1977). The control task consisted of imagining brushing teeth. Structural MRI indicated clear focal lesions in three of the patients. Although patients were able to perform the task, they made significantly more errors than non-injured comparison subjects. Results indicated more right-lateralized and dispersed activation in the patients as compared to the non-injured comparison subjects, possibly reflecting the difficulty of the task for the TBI patients. Using fMRI, Prigatano and colleagues (2004) found greater bilateral frontal activation on the Halstead (1947) finger tapping test versus rest in eight healthy non-injured comparison subjects as compared to seven severe chronic-phase TBI patients, although this finding was only significant for right-handed tapping. Performance was matched across groups. Three of the patients had focal lesions by history. When five patients with chronic-phase severe TBI and no large lesions were compared to 11 non-injured comparison subjects on a modified Stroop task in a blocked-design fMRI study (Soeda et al., 2005), the TBI patients were found to have reduced activation in the cognitive division of the anterior cingulate, previously shown to be activated by healthy non-injured comparison subjects. However, group differences in activation were not statistically evaluated. Although the patients made more errors than non-injured comparison subjects, performance did not differ significantly across the two groups.

Although these studies provide useful information regarding the functional neuroanatomy of the finger tapping, Stroop, and PASAT tests in patients with TBI, these tests were designed for clinical assessment, rather than functional neuroimaging. They therefore do not take full advantage of the experimental design options afforded by functional neuroimaging technologies, such as event-related designs. Furthermore, given the potential confounds specified above, interpretation of functional neuroimaging data can be very difficult in studies that use applications of tasks specifically for a single study rather than paradigms with a reliable neural signature in healthy adults, forming the basis for interpretation of patient data.

Perlstein and colleagues (2004) administered a very well-validated working memory task in an event-related design to seven TBI patients and non-injured comparison subjects that were part of a larger behavioral study. In this *n*-back task, subjects must identify consonants matching the previous item (0-back), the one immediately preceding the previous item (1-back), and so on, up to the 3-back condition, allowing for investigation of the parametric effects of increased working memory load. Compared to non-injured comparison subjects, the TBI patients showed reduced right dorsolateral prefrontal, left inferior frontal, and left parietal activation with increased working memory load. Behavioral results from the larger sample indicated a deficit in strategic or associative processes rather than in speed or in simple maintenance of representations in working memory. Accordingly, the functional neuroimaging data indicated a lack of sustained, load-related increase in activation within Broca's area, thought to mediate active verbal rehearsal and sequencing (Cohen et al., 1997). One drawback of this study was the fact that the TBI patients did not perform at the same level as control subjects. Additionally, focal lesions were not documented.

Reduced self-awareness or insight is a common and disabling TBI-related deficit. Schmitz and colleagues (2005) used a previously validated self-appraisal task presented in a blocked design in which subjects decided whether or not adjectives described their own personal traits and abilities. Activation in response to this task was contrasted to judgment of the affective valence of adjectives. Twenty moderate-to-severe TBI patients and twenty non-injured comparison subjects were scanned. Patients with focal lesions were included. Patients were selected for high self-other disparity scores in the Patient Competency Rating Scale (PCRS) (Prigatano, 1986), indicating self-awareness deficits. Increased activation associated with self-evaluation was reported in the anterior cingulate, right anterior temporal pole, and the precuneus. Additionally, regression of PCRS and Digit Symbol scores on whole-brain data indicated a focus of activa-

tion in the right superior frontal gyrus that was specifically associated with PCRS discrepancy scores.

We used a previously validated cued recall paradigm with $H_2^{15}O$ PET to study the effects of TBI on mnemonic retrieval activations in seven chronic-phase moderate-to-severe TBI patients (Levine et al., 2002a). Both patients and non-injured comparison subjects ($n = 11$) showed topographically similar task-related patterns of activation in response to memory retrieval demands. The patients, however, showed relatively high activation of ventrolateral and dorsolateral frontal and anterior cingulate regions, including recruitment of left frontal regions previously observed in older adults using the same task. They also engaged additional posterior regions involved in lower level perceptual processes, particularly the medial parietal region. The non-injured comparison subjects' pattern was more focused, possibly aided by increased activation of subcortical nuclei. With one exception, patients were free of lesions encroaching on the PET scanning window. One patient with a large left frontal contusion did not show the left frontal activation, providing a mirror case to a previously published case study with a right frontal lesion (Levine et al., 1998). Both cases, however, shared the other features of the TBI activation pattern.

We are currently scanning samples of patients with moderate-to-severe TBI on a series of tasks derived from the cognitive science functional neuroimaging literature. The stop-signal task (Logan, 1994) is among the best studied of response inhibition tasks. In a typical stop-signal experiment, subjects respond to stimuli ("go-signals") presented on a computer screen. On a certain proportion of trials, the go-signal (the letter) is followed by a "stop-signal" (change in the color of the letter) indicating that the response is to be withheld, which requires response inhibition. This task has proven a sensitive measure of response inhibition in a number of populations (Logan, 1994). We reported results from five TBI patients and five non-injured comparison subjects with fMRI while performing the stop-signal task (Easdon et al., 2004); we have since augmented this sample to eight per group (O'Connor et al., in preparation). Patients and non-injured comparison subjects were very tightly matched for response speed and number of correct inhibitions. As this was an event-related study, we were able to separately examine trials involving successful and unsuccessful inhibitions. During successful inhibitions, non-injured comparison subjects showed greater activation than TBI patients in the left dorsolateral prefrontal cortex, previously associated with response inhibition (Liddle et al., 2001), whereas TBI patients showed greater activation than non-injured comparison subjects in the medial parietal region, similar to two above-described reports

(Levine et al., 2002a; Schmitz et al., 2005). During unsuccessful inhibitions, non-injured comparison subjects showed greater right dorsolateral prefrontal activation than TBI patients, consistent with increased response monitoring, whereas TBI patients showed greater activation than non-injured comparison subjects in left dorsal and ventral prefrontal, anterior cingulate, and parietal regions, reflecting an alteration in error-related processing.

The Sustained Attention to Response Test (SART) (Robertson et al., 1997) is a go/no-go task that assesses endogenously activated attention by requiring subjects to press a key in response to single digit numbers appearing in rapid succession, except for a single nominated digit for which the response must be withheld. This task is sensitive to TBI and related to patients' reports of real-life attentional slips (Robertson et al., 1997). In 10 healthy adults performing the task in a combined event-related and blocked design fMRI study, we showed that the SART activates a thalamic-right prefrontal-right parietal network classically associated with sustained attention (O'Connor et al., 2004). This study also incorporated a version of the SART with random auditory tones designed as an exogenous cue to remind the subjects to pay attention (cf., Manly et al., 2002). Activation in the sustained attention network was diminished in the presence of alerting tones (performance was not affected), consistent with the hypothesis that this network is maximally engaged in situations requiring top-down control of endogenous activation of attention.

We are currently scanning chronic phase moderate-to-severe TBI patients on this same paradigm, with performance matched to the non-injured comparison group. Preliminary results ($n = 5$) indicate that the SART-associated thalamic and right parietal foci are preserved in TBI, but right ventral prefrontal activation was observed instead of right dorsolateral prefrontal activation. The anterior cingulate was additionally activated in patients with TBI (Richard et al., in preparation). This network was not attenuated by the tone manipulation, suggesting that TBI patients did not use the tone in the same manner as non-injured comparison subjects. This finding leads to a specific rehabilitation target: teaching patients to use the tone or other alerting cues to exogenously engage their impaired endogenous alerting systems. Our next study will investigate the effects of an executive functioning and attention rehabilitation intervention (Levine et al., 2000) on SART performance and associated activations with pre-/post-rehabilitation fMRI.

Activation Functional Imaging in Mild TBI

Functional neuroimaging studies of mild TBI differ from those addressing moderate-to-severe TBI in several

respects. Most obviously, they involve a quantitatively different neuropathological process. In the case of moderate-to-severe TBI patients with focal lesions, the neuropathological processes differ both quantitatively and qualitatively. In studies of moderate-to-severe TBI, patients are scanned in the chronic phase, after acute injury effects have resolved. Most studies of patients with mild TBI involve scanning in the acute or sub-acute phase, before symptoms have resolved. A major advantage of scanning patients with mild TBI is their increased availability, allowing for larger sample sizes. Furthermore, patients with mild TBI are neuropathologically homogeneous relative to patients with moderate-to-severe TBI. A more detailed review of functional neuroimaging studies of patients with mild TBI can be found in this special issue (McAllister et al., 2006).

McAllister and colleagues (1999) studied auditory n-back activations with fMRI in 12 patients within 1 month of mild TBI and 11 control subjects. Both groups showed increased frontal and parietal activation corresponding to increasing working memory load, however the control groups showed increases from the 0-back to the 1-back conditions, whereas the TBI patients showed more extensive increases from the 1-back to the 2-back conditions. Performance did not significantly differ across groups, although the TBI group showed higher variability. Moreover, they were drawn from a larger sample where significant group differences were observed (McAllister et al., 2006). The findings were replicated in a follow-up study, where a 3-back condition was added (McAllister et al., 2001). Both patients' and non-injured comparison subjects' performance declined in this condition, but non-injured comparison subjects showed a stepwise increase in activation from the 2-back to the 3-back conditions, whereas the patients showed relatively less increase across these two conditions, particularly in the left frontal and parietal regions. Thus mild TBI appears to affect working memory brain activity such that moderate loads are associated with an excessive increase in activation but low and high loads fail to elicit the same increases as observed in non-injured comparison subjects.

The classification of mild TBI includes concussions that involve a transient alteration in consciousness (1997). Most concussions do not involve loss of consciousness or hospitalization. Although full recovery is expected to occur spontaneously, approximately 15% of patients develop more persistent post-concussive symptoms (Rutherford et al., 1978; McLean et al., 1983). Due to the high prevalence of concussion, there is significant potential for these patients to contribute to our understanding of TBI effects, with the constraint that this potential is maximal during the relatively short time win-

dow during which these patients are symptomatic (i.e., within 1 week in the case of grade 1 or “ding” concussions; Lovell et al., 2004).

Chen and colleagues (2004) studied 16 concussed athletes 1–14 months post injury, in comparison to eight control subjects. All but one of the athletes had post-concussive symptoms at the time of scanning with fMRI. Using very well-validated verbal and abstract design working memory tasks, they found that the concussed athletes had reduced activation in right mid-dorsolateral prefrontal cortex (previously shown to mediate performance on these tasks) relative to non-injured comparison subjects, but they also had numerous additional foci of activation in posterior frontal and non-frontal regions. Performance did not significantly differ across patients and non-injured comparison subjects (owing to training on the task prior to scanning), although the patients were more variable. This variability was not associated with changes in brain activation patterns.

Concussion is one of few neurological conditions with sufficient prevalence to allow for studies of pre-/post-injury function in which patients serve as their own control. This has been accomplished through screening of athletes at risk for concussion, followed by post-injury testing. This research design has significant potential for advancing knowledge of TBI effects by controlling confounds such as inter-individual variability, cohort effects, and repeat scanning effects. Jantzen and colleagues (2004) scanned four football players with fMRI within 1 week following concussion; three of these had pre-season baseline scanning (baseline for the remaining concussed participant was taken at 7 months post-injury). These were compared to four players who did not have a concussion scanned at pre- and post-season with the same measures. The groups were matched for performance on finger sequencing, digit span, and serial calculation tasks. The concussed group showed larger increases in extent and amplitude of activation in association with the sequencing task than did the non-injured comparison subjects (in their second scanning session). The importance of controlling for repeated scanning was illustrated by the fact that the non-injured comparison players also showed activation increases on repeat scanning, although not to the same extent as the concussed players.

Summary. Activation functional neuroimaging, where acquisition of functional neuroanatomical data is time-locked to behavior, offers a powerful adjunct to the lesion- or deficit-focused approach to understanding brain-behavior relationships in TBI. Interpretation of functional neuroimaging data, however, is not always transparent due to variability in the selection of task paradigms, the

comparison task, and degeneracy in brain-behavior relationships. Interpretation is further confounded in studies of patients, who may be highly variable in terms of neuropathology and performance.

Whereas studies of TBI patients’ brain function at rest have emphasized reductions in activation relative to non-injured comparison subjects, activation functional neuroimaging paradigms have revealed both hypo- and hyperactivation. These findings are likely attributable to excitatory or inhibitory deafferentation, neuroplastic responses to injury, or other diffuse injury effects. Although this research is at an early stage, there is converging evidence that TBI produces a more broadly dispersed, weaker signal in the prefrontal cortex relative to non-injured comparison subjects. There is also evidence for increased medial parietal activation in TBI patients across divergent tasks. Confirmation of these findings, however, must await additional studies using more neuropathologically homogeneous subjects (i.e., without focal lesions), well-validated paradigms, and event-related designs controlling for performance differences. Studies of patients with mild TBI are potentially very illuminating as these patients are more homogeneous and may be scanned at both pre- and post-injury. Studies of these patients also show TBI-related changes in prefrontal and posterior function, and often increases in the extent or dispersion of activation.

CONCLUSION

The mechanisms governing brain damage effects—including their trajectory over the recovery process, their rehabilitation, and their high variability across TBI patients—are not yet well understood. In the next decade, research with novel imaging technologies is likely to significantly improve this state of affairs. Research to date is beginning to reveal the widespread nature of human TBI neuropathology at the systems level, not only in terms of the devastating consequences that occur in some cases but also in relation to the potential for neuroplastic reorganization that may support recovery. Continued research along these lines will be critical to refining approaches to targeted rehabilitation that seek to engage these naturalistic recovery processes.

TBI neuropathology is extraordinarily complex. Certain structural and functional neuroimaging measures can be related to behavioral and cognitive outcomes, yet many of these relationships lack psychological and anatomic specificity. Although this is likely a consequence of the non-specific nature of TBI, it is also the case that interpretation of much of the research summarized in this article is confounded by heterogeneity of imaging and behavioral methods as well as neuropathol-

ogy. Further progress in neuroimaging of TBI will require greater attention to this heterogeneity.

ACKNOWLEDGMENTS

Ann Campbell, Catherine Hynes, Sabitha Kanagasabai, Irina Nica, Colleen O'Toole, Karen Philp, Joel Ramirez, Philip Sharkey, Jovanka Skocic, and Gary Turner are thanked for technical assistance. We gratefully thank the TBI patients and non-injured volunteers for participating in this research. This research was supported by the Canadian Institutes of Health Research (grant nos. MT-14744, MOP-37535, and MOP-108540) and the NIH-NICHD (grant no. HD42385-01) to B.L.

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