Distinguished Neuropsychologist Award Lecture 1999

The lesion(s) in traumatic brain injury: implications for clinical neuropsychology

Erin D. Bigler*

Departments of Psychology and Neuroscience, Brigham Young University, 1001 SWKT, Provo, UT 84602, USA

Accepted 26 September 2000

Abstract

This paper overviews the current status of neuroimaging in neuropsychological outcome in traumatic brain injury (TBI). The pathophysiology of TBI is reviewed and integrated with expected neuroimaging and neuropsychological findings. The integration of clinical and quantitative magnetic resonance (QMR) imaging is the main topic of review, but these findings are integrated with single photon emission computed tomography (SPECT) and magnetoencephalography (MEG). Various clinical caveats are offered for the clinician. © 2001 National Academy of Neuropsychology. Published by Elsevier Science Ltd.

Keywords: Traumatic brain injury; Neuroimaging; Neuropsychological assessment; Rehabilitation outcome

Fibres as delicate as those of which the organ of mind is composed are liable to break as a result of violence to the head. (Gama, 1835)

Traumatic brain injury (TBI) represents one of the most common disorders seen by clinical neuropsychologists (Ponsford, 1995). For neuropsychologists, the initial consultation typically involves some form of assessment to evaluate neurobehavioral sequelae associated with

* Much of the recent research reprinted in this article has been supported by grants from the Ira Fulton Foundation. The illustrations were prepared by Tracy Abildskov and manuscript preparation was assisted by Allison Neal.

* Tel.: +1-801-378-4287; fax: +1-801-378-7862.

E-mail address: erin_bigler@byu.edu (E.D. Bigler).
the injury (see Bigler & Clement, 1997). While numerous investigations abound concerning the type and nature of cognitive/behavioral and physical deficits following TBI, it is only now that a more complete picture of the neuropathological basis of TBI is being understood. This review focuses on the neuropathological substrates of TBI in relation to neuropsychological outcome. To demonstrate the types of neuroimaging abnormalities associated with TBI, images using computerized tomography (CT), magnetic resonance (MR), single photon

Fig. 1. The vascular system is used to illustrate CNS complexity (A and B). Arterioles are depicted in red with venules in blue from a coronal section through a single gyrus. Recognizing that neural cells are considerably smaller than the vascular system that supplies them helps appreciate their (the neural cells) complex matrix as well. In (B), brain tissue has been removed to aid in visualizing just the vasculature (from Haughton, Daniels, and Hudetz, 1998). The photomicrograph in (C) is from a section of the cerebral cortex from a rat, again depicting this intricate latticework of blood vessels (bar = 100μm; from Mironov, Hritz, La Manna, Hudetz, & Harik, 1994). As with neurons, while blood vessels have some elasticity, there are of a fixed length and tolerate only limited stretch before injury or rupture of the vessel occurs. It takes very little imagination to perceive the damaging effects of high-speed impact injury on this vascular network.

Fig. 11. Lateral 3-D MR-generated lateral surface image of the right hemisphere of the brain from the patient depicted in Figs. 8–10. The focal abnormalities of the injury as visualized in MR imaging are depicted in blue. Note that they represent the smallest areas of damage; whereas both SPECT and MEG findings represent substantially greater abnormalities that exceed the boundaries of visualized focal damage on the MR scan.

Fig. 20. This patient sustained a moderate to severe TBI and actually had frontal and temporal areas of contusion seen on acute neuroimaging, that could not be viewed with follow-up scanning 1 year later. The top views represent 3-D MR surface reconstruction with areas of significant ALFMA superimposed. Although structural nor metabolic imaging do not provide any specific abnormalities, MEG does (adapted from Davis et al., submitted for publication).
emission computed tomography (SPECT), and magnetoencephalography (MEG) will be used. However, this review is written with the assumption that the reader has familiarity with these imaging modalities. If that is not the case, the reader is referred to several texts and reviews that provide excellent coverage of this topic (Bigler, 1996a, 1996b; Kertesz, 1994; Kretschmann & Weinrich, 1998; Orrison, 1995, 2000; Thatcher, Hallet, Zeffiro, John, & Huerta, 1994).

1. Central nervous system (CNS) complexity

Before pathology can be fully understood, normal neuroanatomy must be tacitly understood. Obviously, only an overview can be offered here, with excellent comprehensive reviews presented elsewhere (see Hanaway, Woolsey, Gado, & Roberts, 1998; Kretschmann & Weinrich, 1998). It is estimated that the human brain contains 100 billion neurons and several times that in supporting cells (Purves et al., 1999). In 1 mm$^3$ of cortical tissue, there are billions of synapses (Defilpe, Marco, Busturia, & Merchan-Perez, 1999). One only has to view but a smidgen of human behavior to realize that the neural network that drives behavior is complex (see Koch & Laurent, 1999). Illustrating some of this complexity can be achieved through visual examination of the vascular network of a single slice of a human gyrus as presented in Fig. 1. The arterioles in this single slice develop a complex, intercalated matrix of delicate vessels. What is more astonishing, however, is that each of these vessels feed a multitude of cells (both neurons and glial) that cannot be seen at this magnification. From a trauma standpoint, the reader needs to visualize this delicate tissue in the throws of high velocity impact injury. Any stretch, any twisting, or compression has the potential to alter the physical status of the cell and/or vessel. Moderate to severe physical forces have the potential to sever, rupture, or fracture these delicate structures. It should be recognized that this visualization only emphasizes the physical structure or anatomy, and not metabolic or biochemical functioning, which will be discussed later (see also Alexander, 1995). Complex systems achieve complex functions only with efficient, well-integrated, and fast recruitment of constituent parts, followed by a rapid response. Anything that disrupts this complex system, even subtly, will render the system less efficient and prone to errors in processing and responding.

2. The basic physics of injury

The physics of injury, also, is a complex topic and the reader is referred to detailed treatises elsewhere (see Bandak, Eppinger, & Ommaya, 1996; Narayan, Wilbarger, & Povlishock, 1996; Varney & Roberts, 1999; Ziejewski, in press). For the purposes of this paper, three major motions will be reviewed and are presented in Fig. 2. In each of these illustrations an actual human brain reconstructed from a volume acquisition MR scan will be “morphed” to mimic the pathological action of the physical force. Neuronal injury in each of the pathological scenarios presented in Fig. 2 is dependent on rigid physical tolerance characteristics of neural tissue. Since each neural cell or vessel has a fixed length along with an origin...
and terminus and is held in position along its trajectory by other cells, there is limited elasticity in any cell or vessel. Thus, finite tolerance limits are present when any force or motion is imposed on neural tissue. As presented in Fig. 2, these tolerance limits can be quickly overcome by simple stretching, twisting, rotation, or compression.

As can be seen in viewing Fig. 2, all of these pathological motions simultaneously involve large areas, if not the entire brain. While damage may be seen in a localized area, it should always be kept in mind that these movement forces, as illustrated in Fig. 2, affect the entire brain. When TBI is the product of high velocity impact, such as that observed in a motor vehicle accident (MVA), and the patient is said to have an identifiable "lesion" on some type of imaging study, the use of the term "lesion" can often be misleading. Despite what may be visualized on any contemporary neuroimaging, whether it be an isolated lesion or multiple lesions, damage to the brain is always beyond just the visually identified "lesion" (see Fig. 3). For example, in a high-speed collision with roll-over, within a few seconds the brain goes from some given speed to stationary, with extreme motion, torsion, and tensile effects occurring.

Fig. 2. These images are based on an actual 3-D MR surface image of the brain taken from a normal adult male. The theoretical impact is a high velocity side impact that is rotating the brain with twisting action as depicted in (A), which represents a dorsal view with frontal lobes pointing right, representing the physical forces involved in angular rotation. (B) Frontal view, depicting similar twisting action but due to linear forces as observed from a frontal pole perspective. (C) Stretching (tensile) action across the lateral surface of the right hemisphere. Such twisting and stretching action disrupts the cytoarchitecture of the neuron and may lead to actual fracture of the axon (see Fig. 6, adapted from Ziejewski, in press).
throughout. While, a solitary “lesion” may be observed on a CT or MR scan, what underlies that lesion and how it was created is far from solitary. Likewise, a patient may have a focal clinical deficit (i.e., hemiplegia), but even a focal deficit in the TBI patient is certainly superimposed on a more general pathology beyond the discrete boundaries producing the focal neurological deficit. The diffuse nature of brain injury is the common theme of this paper.

Typical “lesions,” as well as other abnormalities that occur as a consequence of TBI that can be assessed by contemporary neuroimaging, include focal shear injury, contusion, vascular compromise, edema, excitotoxic reaction, and diffuse axonal injury (DAI), along
with diffuse brain injury (DBI). Each of these mechanisms of injury and the associated lesion(s) or abnormalities will be reviewed under the major topical headings of DAI, shear injury, and contusion. Imaging examples that demonstrate these various conditions will be provided, where appropriate.

2.1. Diffuse axonal injury

Although considerable neuropathological descriptions of brain injury were published in the late 1800s through the 1940s, the first detailed histological and neuropathological characterization of “diffuse degeneration of the cerebral white matter (p. 163)” in head trauma has been attributed to Strich (1956, 1961); also, see review by Gennarelli, Thibault, and Graham (1998). The collaborative work of Adams, Graham, and Gennarelli (1985) and Gennarelli et al. (1982) lead to the term DAI. The term DAI has been widely used, but it is important to review what these authors originally meant when using the DAI acronym. For example, their DAI definition is based on a traumatic injury that “involves a prolonged traumatic coma that is not associated with mass lesions or ischemic damage, and forms a continuous spectrum of increasing severity associated with increased numbers of damaged axons” (Gennarelli et al., 1998, p. 202). For clinical neuropsychologists, the term DBI, may be a more appropriate term to use, which Gennarelli et al. suggest includes DAI, but is more than DAI because it incorporates damage secondary to vascular edema and ischemic injury. As with DAI, DBI also results in a preponderance of white matter damage. It may be that neuropsychology should embrace the DBI term when discussing the underlying pathology associated with TBI than the all too frequent use of DAI (see Fig. 3).

Ultimately, Gennarelli et al. (1998) suggests that brain injury produces a common axonal pathology, but differs in amount, location, and severity. In this perspective, differences in brain injury could be viewed on a continuum, where greater deficits progressively involve more and more axonal damage. Thus, Gennarelli et al. conclude that brain injury can be viewed as a “spectrum of events beginning with concussion syndromes and ending in the most severe type of brain impairment that includes immediate coma associated with decerebrate posturing, prolonged coma, and incomplete recovery (p. 203).” Furthermore, Gennarelli et al. suggest three levels or grades of DAI. In Grade I, widespread nonspecific axonal damage is present, without focal abnormalities. Grade II assumes presence of Grade
I, with the addition of focal abnormalities particularly in the corpus callosum, often associated with small tissue tear hemorrhages (see Figs. 3 and 4). Grade III DAI assumes Levels I and II, with the addition of rostral brainstem injury, often with multiple tissue tears. With regards to severity, less severe DAI has been objectively identified in the postmortem brain of an individual with as little as 60 s of recorded loss of consciousness (Blumbergs et al., 1994).

While the pathological effects of injury are set into motion immediately upon impact (or acceleration/deceleration), the earliest that DAI can be identified using electron microscopy is some time within 1 h following injury. The full spectrum of acute pathological changes take hours to days for full expression at the ultrastructural level. Delayed axotomy is common, with onset being anywhere from 6 to 12 h, and may not reach maximum pathological change for 24–72 h. In regards to the axon, the node of Ranvier appears to be the “weak-link,” and the earliest morphological changes destined to become DAI occur at the node and can be visualized as early as 10 min postinjury (Gennarelli et al., 1998). The cytoarchitecture of the axon changes (Povlishock, 1996; Povlishock & Christman, 1995). In addition to the mechanical stretch and compression effects of the injury, complex biochemical aberrations are set into motion immediately following injury that likewise have deleterious effects on structure and function (see Povlishock, 1996; Povlishock & Christman, 1995). Conti, Raghupathi, Trojanowski, and McIntosh (1998), in a rat fluid percussion brain injury model,

![Fig. 4](image)

Fig. 4. The panel on the far right (no date above the column) is from a non-head-injured, normal control. Note the size and configuration of the corpus callosum in the midsagittal view in the top right panel. In the same subject, the axial view at the body of the lateral ventricle is presented. The three panels to the left show the patient from the DOI on the left followed by similar imaging 5 days later and over 4 years postinjury. The DOI scan was clinically interpreted as “normal,” although in retrospect the signal abnormalities that became evident in subsequent scanning can actually be seen in the genu of the DOI scan. Note how the DOI scan can be used as baseline to assess the subsequent changes that occur in the brain. Note, also, how the entire ventricular system is uniformly dilated. The arrows in the sagittal view on 9/4/94 demonstrate acute signal changes in the white matter subsequent to shearing, with complete fracture of the top of the genu evident in the 11/23/98 scan. Note also the uniform thinning throughout the corpus callosum evident in the 11/23/98 scan.
have shown regional differences in brain injury-induced apoptosis, where delayed cell death occurs in some structures for up to a month. With more severe experimental injury, Pierce, Smith, Trojanowski, and McIntosh (in press) have shown changes of even longer duration. We have shown that total brain volume continues to reduce for up to 3 years postinjury Blatter et al. (1997). Accordingly, although acute injury can be visualized, there are dynamic structural changes that occur after brain injury that take time to be fully expressed. This can be seen in Blatter et al.’s study that shows the gross morphological changes over time since injury (see Fig. 5).

Gennarelli et al. (1998) also reviewed some of the basic biophysics of injury, wherein it has been demonstrated that the brain is most vulnerable if it is moved laterally and least affected with sagittal movement. Movement in the horizontal plane is intermediate to the lateral and sagittal. Experimentally, Gennarelli et al. (1982) demonstrated that the greatest degree of widespread axonal damage occurs with lateral movement, where the strain pattern peaks due to the position of the falx and tentorium. However, rarely will the MVA be something akin to the controlled head injury produced in the laboratory. For example, the case presented in Figs. 3 and 4 of a young female struck in a cross-walk, by a car traveling approximately 40 miles/h. The patient was flung over 70 ft, knocking her shoes off her feet. She landed on the pavement, where her body did not come to rest for some 20+ ft. Dissecting the impact, the body is hit, the head most likely struck on impact, and then the body shot 70 ft, hitting the ground and then coming to rest. This all happens in less than 5s. Once the pavement is hit, the body with significant inertia in addition to whatever fall impact dynamics are at play does not immediately come to rest, but incurs further impact injury. With the first impact, the patient is unconscious so there are no defensive reflexes in place to assist in bracing for the secondary impact. The brain further twists, rotates, and moves within the cranium. Accordingly, within a very brief period, the jostled brain moves in multiple vectors, and not just in a simple linear sagittal, horizontal, or lateral plane. Obviously, these multiple

![Brain volume chart](image)

Fig. 5. Brain volume has been normalized to a scale of 1.0. The dark line represents the change in brain volume over time following TBI. Note that volume first increases, most likely secondary to brain swelling. After that peak increase, there is rapid drop-off in brain volume that does not match the same rate of decline as normal aging until approximately 3 years postinjury. However, brain volume never returns to its preinjury baseline. Because of this, all aging will be superimposed on a damaged brain that has less volume (fewer neurons).
movement vectors, often diametrically opposed, produce significant axonal strain. The mechanical deformation also produces deficits in the cell membrane, which further disrupt cell function.

With regards to strain effects, three stages of axonal injury have been proposed (Gennarelli et al., 1998). In Stage I (biochemical alteration), a rapidly but minimally stretched axon does not tear, but will undergo biochemical aberration that may be transient. It appears that for this injury a minimum of a 5% strain load (i.e., a 5% increase in axon length from its resting length) is needed to produce a transient disruption of the neuronal membrane, which allows influx of Na⁺, Ca²⁺, and Cl⁻, and K⁺ efflux. This transient change blocks the neuron’s ability to propagate an action potential, but neural function may fully return within minutes. However, we do not know in humans what the threshold is for excitotoxic action, which may result in neuronal damage (Obrenovitch & Urenjak, 1997; Palmer et al., 1993). Stage II (cytoskeletal damage) occurs with a minimum of 5–10% strain load and produces local swelling and enlargement of the injured axon, which, in turn, may disrupt axoplasmic transport (Povlishock, 1996; Povlishock & Christman, 1995). The degree of cytoskeletal changes tend to be in proportion to the strain load, with lesser strain leaving the cytoarchitecture more intact. Oppositely, increasing strain load produces greater structural damage to the architecture of the neuron. McCracken, Hunter, Patel, Graham, and Dewar (1999) have shown distinct cytoskeletal damage in the corpus callosum. Stage III axonal injury (secondary axotomy) occurs with strain 15% or greater with both the biochemical and structural abnormalities of Stages I and II occurring, with a greater likelihood of permanent damage. At Stage III, the injury process is not self-reparative. Stage IV (primary axotomy) represents the immediate structural disruption of the axon at the time of injury. Strain load is usually in excess of 20%, and this produces immediate, irreversible damage. In addition to the above effects, various excitotoxic actions also occur at all stages of injury (Shah, Yoon, Xu, & Broder, 1997). These various “strain” effects are hypothetically demonstrated in Fig. 6.

### 2.2. Focal shear injury

Very brief but intense shear, strain, and/or rotational forces may occur at the point of rapid acceleration and/or deceleration that accompanies high-speed impact injuries, such

---

Fig. 6. Neuron schematic. An actual neuron has been recreated from a photomicrograph and digitized so the axon can be morphed. The neuron on the left is at original size. For all subsequent images, the axon has been stretched by the percent factor listed. Note that it is difficult to perceive the degree of stretch, even in the one that was stretched 20%. This illustration facilitates the appreciation that it does not take much to alter the cell to cause damage.
as an MVA or violent shaking of the head (Bonnier, Nassogne, & Evrard, 1995; Gennarelli et al., 1998; see Fig. 7). These lesions occur literally as a rupture across axons most typically at the white–gray matter juncture or Stage IV axonal injury — primary axotomy (compare Fig. 6 with Fig. 7). With axon severed, anterograde, as well as retrograde, degeneration begins and within several days to weeks postinjury a well defined “lesion” develops (see Povlishock, 1996; Povlishock & Christman, 1995); Fig. 4 depicts the evolution of a corpus callosum shear in a patient with severe TBI. These lesions can produce powerful focal effects, if dedicated pathways are disrupted. For example, in the patient presented in Fig. 4, where part of the genu of the corpus callosum ruptured due to shear effects, the patient developed an acute left-hand apraxia to verbal command. As can be visualized in Fig. 7, the shear is most likely to occur at the gray–white boundary, and shear injury may result in a disproportionate reduction in white matter (Levin et al., 2000; Thatcher et al., 1997).

2.3. Contusion

Since bone is solid and relatively inflexible, while brain tissue is soft and fragile, compression impact of the brain with the inner table of the skull often produces contusions as the brain and its vasculature strikes and compresses against the bony surface, and then rebounds (Adams et al., 1985; Gean, 1994). The delicate nature of the cortical vasculature has already been shown in Fig. 1. With such a delicate latticework of vessels, it is easy to see why...
a contusion develops and how disruptive to underlying tissue it can be. There is another factor that creates common sites of contusion, and that is the ridge created by the sphenoid bone as it differentiates the anterior cranial fossa from the middle. In Fig. 8, the primary site is along the boundary of the sphenoid bone, producing contusions in both the frontal (typically inferiorly or posterior-lateral) and temporal (typically inferior-anterior and/or medial) lobes. This factor, the frequency of frontal and temporal lobe contusions, likely plays a role in the nature of “frontotemporal” deficits commonly observed in neuropsychological profiles of TBI patients. For example, it is far more likely to see executive, memory, attention, and emotional deficits in TBI subjects than it is to see more posterior syndromes,

Fig. 8. The CT scan on the left represents the first DOI scan performed after a high-speed T-bone collision, where he was the passenger recipient of the T-bone impact. (A) Inferior lateral hemorrhagic contusion (white area) just anterior to (B) the sphenoid bone. (C) Contusions in the peri-Sylvian area related to impact along the sphenoid. The MRI on the right was obtained 3 years later and demonstrates the chronic status of the previously focal lesions. Note the extensive anterior and mesial signal abnormality involving (D) the temporal pole. The CT scan also depicts effacement of the ventricular system involving the right hemisphere. Some surrounding edema is also observed around the focal hemorrhage sites in (C). (E) The chronic stage of the peri-Sylvian contusions has left that affected region with encephalomalacia. (F) Deep white matter lesions most likely secondary to shearing. These lesions have been depicted in 3-D in Fig. 9.
such as sensory agnosias (Bigler & Clement, 1997; Van der Naalt, Hew, van Zomeren, Sluiter, & Minderhoud, 1999).

2.4. The lasting effects of vascular compromise and edema

Obviously, contusion(s) represents a vascular compromise and was partially discussed above. Cerebral edema refers to a localized inflammatory reaction in the brain that may become widespread (Kimelberg, 2000). Edema and compromised blood flow are often discussed together because serious tissue swelling will be hemodynamically disruptive, and

Fig. 9. These are 3-D reconstructions depicting the ventricular system (images on top), with the deep white matter lesions and peri-Sylvian damage shown below. The ventricular system in 3-D is compared to a normal subject. The areas of focal damage depicted in Fig. 8 are graphically outlined below and show extensive involvement of the posterior right frontal and anterior temporal lobe (from Bigler, 1999).
disruptive blood flow may drop glucose and oxygen delivery below energy demands of the cell. With compromised glucose and oxygen delivery, a whole new set of metabolic problems for cellular function occur. Returning to Fig. 8, acutely significant edema surrounds the contusion site (see C and also the effacement of the lateral ventricle). However, the follow-up MR scan several years postinjury shows a circumscribed area of focal encephalomalacia that does not exactly match the site of contusion and surrounded edema (see Fig. 8) and can be clearly seen on the 3-D image analysis (Fig. 9). However, SPECT imaging (see Fig. 10) demonstrated even greater disruption of tissue integrity in the area around the lesion and MEG even more (see Fig. 11). Thus, the focal lesion viewed may not be representative of the actual localized damage because the physiological disruption may exceed the boundaries of the MR-viewed “lesion.”

As mentioned above, the problem with oxygen delivery to brain tissue is a potential catastrophic consequence in TBI. Gale et al. (1999) have demonstrated an imaging pattern of diffuse damage characterized by reduced brain volume and increased global cerebrospinal fluid (CSF) with ventricular dilation in patients with moderate to severe anoxic brain injury secondary to carbon monoxide poisoning with no head trauma. Similarly, Hopkins, Abildskov, Bigler, and Weaver (1997) and Hopkins et al., 1999 demonstrated in non-head-injured ventilated adult respiratory distress syndrome (ARDS) patients compromised neuropsychological status secondary to hypoxia, even though every attempt was made to ventilate and medically treat these acutely ill patients. Accordingly, oxygen deprivation alone can damage the brain.

A most important study has recently been published by LaFuente and Cervos-Navarro (1999), where patients who sustained craniocerebral trauma and died were examined at postmortem for presence of microthrombi. They demonstrated significant development of microthrombi not only in regions of contusion, where it might be expected, but also in the

---

Fig. 10. The MR on the left represents the chronic postinjury effects of a severe TBI (see Fig. 8). The SPECT scan was taken the same day and demonstrates diminished frontal perfusion, but of particular interest is the area of focal lesion seen on the MRI (posterior frontal region, just anterior to the Sylvian fissure — the cylindrical dark spot and a corresponding, yet smaller focal area in the anterior tip of the temporal lobe). While these lesions are clearly focal and adjacent tissue has a more normal signal, the perfusion defect extends beyond just the focal lesion areas.
contralateral hemisphere were no contusion was present. They also found that microthrombi may develop over time, even up to 9 days postinjury. Lastly, microthrombi were more prevalent in younger than older patients. Returning to Fig. 1, it is no wonder that vascular lesions may result in secondary complications (either direct shear, edema, or ischemic) of head injury either by direct rupture, disrupted coagulation factor, and spread of thrombi or leakage. Furthermore, Zubkov, Pilkington, Bernanke, Parent, and Zhang (1999) have shown, at postmortem, that nearly 45% of severe TBI patients show evidence of having had vasospasm with residual changes in vessel morphology. Glass, Fabian, Schweitzer, Weinberg, and Proctor (1999) also have shown hemorrhagic contusion at the gray–white matter interface in experimental mild TBI to occur in conjunction with hypotension, another common secondary complication of injury (Shackford, Mackersie, Davis, Wolf, & Hoyt, 1989). The compromised vascular system in head injury has been an overlooked source of pathology as part of the underlying pathology that affects neuropsychological function in the TBI victim.

3. Clinical caveats for the neuropsychologist

3.1. The “lesion” is always larger than can be visualized on MR or CT imaging

A misplaced assumption is that a visually identified “lesion” has definitive boundaries that define the anatomical abnormality. Returning to Figs. 8–11, it is apparent that a large frontotemporal contusion has occurred. The boundaries of that right frontotemporal injury appear pretty straightforward when viewing the MR scan. However, when SPECT is fused with the MR, it is obvious that perfusion defects are much larger than the structural abnormality observed on MR. Furthermore, when a physiological index of pathology is added, the MEG depicts even more extensive pathology (see Fig. 11). Accordingly, observed structural abnormalities on MR may only represent the “tip-of-the-iceberg” phenomena with regards to pathology.

3.2. The so-called mild TBI and “normal” clinical MR imaging

We have rather conclusively shown that mild cases of TBI, including simple concussion, typically do not result in detectable abnormalities on traditional clinical MR scans (Bigler & Snyder, 1995). However, that should not be interpreted as meaning absence of pathology (it may also be the case that new MR imaging technologies will be sensitive to pathology associated with concussion (see McAllister et al., 1999). In animal fluid percussion models, mild injury, while not producing tissue tears, does produce neuronal cytoskeleton abnormalities that have the potential to render the cell dysfunctional. The dysfunctional cell may not “die,” and, therefore, the structure-dependent MR scan appears grossly normal. As recently demonstrated by a series of articles published in the Journal of the American Medical Association, concussion produces mild, but persistent neurocognitive deficits (Collins, Grindel, et al., 1999; Collins, Lovell, & McKeag, 1999; Kelly, 1999; Matser, Kessels, Lezak, Jordan, & Troost, 1999; NIH concensus development panel
on rehabilitation of persons with traumatic brain injury, 1999; Powell & Barber-Foss, 1999; Thurman & Guerrero, 1999). Lewine, Davis, Sloan, Kodituwakku, and Orrison (1999), using MEG, have shown persistence of MEG abnormalities in mild TBI cases where MR imaging is normal. Using fMRI techniques, McAllister et al. (1999) have shown different cerebral activation patterns during working memory tasks in mild TBI subjects when compared to controls. Mild TBI subjects required greater recruitment of cortical areas for performing the same task. This suggests a disruption in the efficiency of neural networks in the mild TBI brain, the type of deficit that would be predicted with white matter injury. Lastly, Friedman, Brooks, Jung, Hart, and Yeo (1998) have demonstrated, with MR spectroscopy (MRS), abnormal changes even in regions where no abnormality can be visualized on the MR scan. In conclusion, the absence of abnormality on standard MR imaging of the TBI patient who has experienced a significant injury may simply be below the threshold of detection (see Assaf, Geit-Yannal, Shohami, Berman, & Cohen, 1997).

Mild head injury and the syndrome of “whiplash” will continue to have its share of controversy (Berry, 2000; Bogduk & Teasell, 2000; Cassidy et al., 2000; Hachinski, 2000). The controversies will likely dissipate, as more definitive measures come to bear on the issue of neurologic sequelae from minor head trauma. Recently, Mosimann, Muri, Felblinger, and Radanov (2000) demonstrated “saccadic” eye movement disturbances in whiplash with persistent complaints. They interpret their findings as best explained by frontal dysfunction. In a compelling video analysis of concussion in sport-related injury, McCrory and Berkovic (2000) demonstrate subtle motor manifestations associated with concussion that they attribute to basal forebrain, limbic, and/or brainstem pathology. These studies of “minor” injury point to a neuropathologic basis. Nonetheless, Mittenberg and Strauman (2000, p. 790) have made the statement that persistent postconcussive syndrome “can be accurately characterized as a psychological rather than neurological disorder in most cases.” I argue that, as greater sophistication develops in neuroimaging and neuroimaging protocols to detect structure–function relationships, this type of position will no longer be tenable. Furthermore, since all “psychological” phenomena are rooted in CNS function (Mesulam, 2000), it is difficult to make the conclusion that someone who has had a significant injury is only suffering the effects of a psychological malady.

3.3. Do not trust the day-of-injury (DOI) scan if that is the only scan performed

While certain abnormalities, such as prominent hemorrhages, edema, or midline shift may be observed in the first CT or MR scan done on admission, as has been already discussed and demonstrated, many neuropathological consequences of TBI take time before the full pathological expression of the injury is observed (see Wilson, Wiedmann, Hadley, Condon, & Teasdale, 1988). In fact, even when significant pathology is observed on the DOI scan, the DOI scan in many cases can still serve as a baseline (see Fig. 8). Even in severe injury, the DOI scan may initially appear “normal.” This is the circumstance in the case presented in Figs. 3 and 4. The DOI MR scan was read as normal and, as can be visualized, no hemorrhages are seen, along with no edema, and there is excellent gray–white matter differentiation. Clinically, the patient was in deep coma (GCS < 5), and
follow-up MR scan was obtained 5 days later. The 10/4/94 scan shows signal change in the
genu and splenium of the corpus callosum and the beginnings of ventricular expansion.
About 4 years later, generalized atrophy with specific callosal atrophy and shearing of the
genu of the corpus callosum are clearly noted. Thus, what is deemed “normal” on the DOI
scan, may become spectacularly abnormal over time. For neuropsychological outcome, do
not trust that the DOI scan will give you all the information necessary to relate brain
pathology to neurobehavioral deficit.

3.4. Emotional sequela in TBI

Psychiatric disorder is commonplace after TBI (Deb, Lyons, Koutzoukis, Ali, &
McCarthy, 1999). Examining patients with demonstrable damage on MRI following TBI,
Russo et al. (1996) demonstrated that patients with mild TBI actually had greater emotional
dysfunction than those with more severe head injury (see Fig. 12). When comparing the
mild to severe TBI groups with quantitative magnetic resonance (QMR) imaging, as
expected the severe TBI group had significantly more diffuse damage and greater cognitive
deficits, yet the moderate and severe brain-damaged groups actually endorsed fewer
symptoms of emotional distress than did those with mild injury. So why, as a group, do
TBI patients with more mild injury exhibit greater endorsement of psychological distress?
One interpretation of these findings centers on the development of anosognosia associated

Fig. 12. The left four histograms categorize patients by their injury severity based on GCS. The four histograms to
the right are based on actual VBR findings, where TBI subjects are categorized by severity of structural brain
damage, regardless of injury severity. Regardless of whether the injury is categorized by severity of structural
damage or severity of injury, the subjects with severe injury or the greatest amount of structural brain damage, 
endorsed the least degree of symptoms based on these three MMPI scales. Four histograms to the left based on
severity of injury: severe: GCS = 3–6, n = 5; moderate/severe: GCS = 7–9, n = 8; moderate: GCS = 10–12, n = 11;
mild: GCS = 13–15, n = 24. Four histograms to the right based on degree of trauma-induced brain atrophy as
measured by VBR: VBR WNL = VBR within 0.5 S.D. from normative, non-brain-injured control sample, n = 9;
VBR mild: <1.0 S.D. from control but >0.5 S.D., n = 9; VBR moderate: >1.0. S.D. but <2.0 S.D., n = 7; VBR
severe: >2.0 S.D. from control, n = 8 (from Russo et al., 1996).
with diffuse injury in the severe TBI subjects (Prigatano & Schacter, 1991). More serious injury probably disrupts the ability to process self-awareness. Combined with a lack of awareness, the memory deficits in more severely injured TBI patients probably also leads to rapid forgetting of any emotional stressor. Also, TBI-induced emotional lability may lead to a rapid cycling of emotion. In contrast, the mild TBI patient may have a more keen sense of awareness of differences between before and after injury (i.e., loss of cognitive ability, speed of processing, etc.) and an inability to regulate emotion (Fann, Katon, Uomoto, & Esselman, 1995). Panic-like symptoms may mediate cognitive deficits in the TBI patient as well (Scheutzow & Wiercisesiewski, 1999). Colantonio, Dawson, and McLellan (1998, p. 557) have reported similar findings, where they observed TBI patients with “mild injury reported more symptoms than persons with more serious injury.” Since mesial temporal lobe is frequently injured, and as already discussed, the hippocampus in particular is vulnerable to injury, a double deficit can be accounted for by limbic system injury — damaged mesial temporal lobe structures are involved in both memory and emotion. Additionally, emotional changes in TBI, probably, are also associated with the likelihood that frontal and temporal lobe regions often sustain a disproportionate level of injury (see Berryhill et al., 1995). Lastly, non-TBI patients with recurrent depression have memory deficits relative to matched first episode depression and control subjects (Basso & Bornstein, 1999). Furthermore, depression has been associated with changes in the limbic system (Nemeroff, 1998), specifically hippocampal atrophy (Sheline, Shanghavi, Mintun, & Gado, 1999). Thus, potentially the affective state itself sets a domain less compatible with memory performance. In TBI, we do not know the relative effect of the affective state alone vs. the underlying emotional neural systems at play in producing the deficit (LeDoux, 1996). However, studies with patients who have multiple sclerosis (MS) have some bearing on this issue. For example, Arnett et al. (1999) demonstrated that limited working memory capacity in MS is probably a reflection of deficits of the central executive component of the working memory system. Since the underlying pathology of MS is a white matter disease, it seems intuitive that a similar disruption of white matter affecting the central executive component of the working memory system may be responsible for impaired working memory in TBI, and it may also be this system at play in affecting emotional awareness and responsivity.

Since in TBI the frontal and temporal lobes are more likely to be damaged, in addition to just or interconnected with, the organic emotional changes are often deficits in social and moral behavior (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999). These types of deficits may be independent of any cognitive or emotional change that accompanies the injury.

Kim, Manes, Kosier, Baruah, and Robinson (1999) examined irritability following TBI in 66 patients admitted to a shock trauma center. One-third of these patients met clinical criteria indicating significant irritability. Acute onset irritability was associated with a higher frequency of left cortical lesions. Delayed onset irritability (3–12 months postinjury) was associated with presence of cortical damage but without lateralization or localization. Delayed onset irritability was associated with greater impairment in social functioning and activities of daily living. The greatest problems with irritability were most likely to occur in the more mildly injured patients.
3.5. Substance abuse exacerbates brain damage

Substance abuse is a factor in TBI (Kolakowsky-Hayner et al., 1999; Tate, Freed, Bombardier, Harter, & Brinkman, 1999). We have published three papers on this topic (Barker et al., 1999; Bigler, Blatter, et al., 1996; Wilde, Bigler, Gandhi, Lowry, & Bartholomew, submitted for publication), with more to come. Substance abuse at the time of injury probably exacerbates structural damage to the brain. This is illustrated in Fig. 13 for patients intoxicated with alcohol at the time of injury. Distinctly, in the TBI subjects intoxicated at the time of injury, the VBR is almost twice the size of nonintoxicated age, injury severity, and head size-matched controls when imaging is performed more than 6 months postinjury. The neuropsychological implications of these findings are not fully understood at this time, but typically, those who are intoxicated at the time of injury have greater neuropsychological deficits as well. It is now well known that alcohol and drugs of abuse may directly lead to biochemical, physiological, and/or structural CNS changes (McCann, Lowe, & Ricaurte, 1997) and significant neuropsychological sequelae even in adolescents (Tapert & Brown, 1999). Accordingly, it is speculated that the interaction of injury with already existing deleterious effects of substance use/abuse effects exacerbates the excitotoxic effects of CNS injury. However, the issue is quite complicated because at certain levels of alcohol intoxication alcohol may actually be protective (Kelly et al., 2000).

3.6. Stress, TBI, and substance abuse

Ursano et al. (1999) found that 1 month after an MVA, 34.4% of the MVA victims met criteria for PTSD (vs. 2.4% in comparison subjects who had been involved in, non-MVAs). PTSD symptoms in these MVA victims continued at high rates even 3 (25.2%) and 6 (18.2%) months later. With regards to psychiatric morbidity, PTSD is the most common disorder.
following MVA (Blanchard, Hickling, Taylor, & Loos, 1995). In a non-TBI model using Vietnam combat veterans with PTSD, Bremner et al. (1995) found that symptoms of PTSD began soon after exposure (although there may be a postexposure period, where the patient functions somewhat “normally”), that hyperarousal symptoms where first to occur and that polysubstance abuse problems paralleled the course of PTSD. In earlier studies, Bremner et al. (1993) demonstrated hippocampal atrophy to be associated with PTSD. Sapolsky (1992) reviews the mechanisms for stress-mediated hippocampal damage (see also Conrad, Magarinos, LeDoux, & McEwen, 1999). At this point, it is difficult to fully understand complex relationships between stress and brain injury, but it appears that either physical and/or psychological stress issues are at play in the TBI victim (see also Bryant, Marosszeky, Crooks, & Gurks, 2000; Harvey & Bryant, 2000). It may be that the combination of injury, stress, and the patient’s psychological adaptation play a role in postinjury damage. Also, it needs mention that premorbid factors may also influence postinjury symptoms (Cicerone & Kalmar, 1997).

3.7. Pain, tinnitus, and the TBI patient

Frequently, the TBI patient experiences a chronic pain syndrome associated with related injuries from the accident (Mamelak, 2000). In a most interesting fMRI study, Ploghaus et al. (1999) have demonstrated involvement of medial frontal, insular cortical, and cerebellar activation with the anticipation of pain. Frontotemporal and cerebellar areas associated with the anticipation of pain may be factors in producing diminished cognitive performance in TBI patients with chronic pain. Tinnitus is not an uncommon sequela of head injury, and has particular effects on emotional and neurocognitive functioning. In a study by Vernon (1994) of 89 head injury patients with postinjury tinnitus, 90% found it difficult to concentrate, 86% endorsed sleep disturbance, and 92% endorsed symptoms of irritability and/or nervousness.

4. The argument in support of generalized “brain damage” in moderate to severe injury

4.1. The ventricular system in TBI: generalized dilation following moderate to severe head injury

Examining changes in CSF-filled spaces, including the ventricular system, provides a context or window to examine changes in brain morphology (Symonds, Archibald, Grant, Zisook, & Jernigan, 1999). Since brain tissue is soft, it would fold in or collapse on its self if it did not have some internal force that exerted an outward pressure gradient. This is exactly the role played by naturally pressurized CSF within the normal ventricular system. The normal ventricular system with its neural tube origin is merely a cavity surrounded by ependymal tissue, which is surrounded by brain parenchyma. However, since the size of the ventricle is held in check by brain volume, a dynamic, proportional relationship exists between normal brain size and normal ventricular volume. If there is a loss of brain volume, there will be a proportional but passive increase in ventricular volume. This is called hydrocephalus ex vacuo and is typically readily distinguishable from other types of hydrocephalus where there may be
an over production of CSF, an obstruction of flow or disruption in absorption (Greenberg, 1999; Osborn, 1994). The same principle applies to cortical CSF. With cellular death, a volume loss occurs in the cortical mantle, resulting in loss of gyral volume, which widens sulcal space, thereby producing a passive increase in cortical CSF. This is readily visualized in the two brain injury cases discussed above (see Figs. 3, 4, 8, and 9).

Although clinically reported since the days of pneumoencephalography (Haug, 1962), Levin was the first to provide CT quantitative measures demonstrating ventricular increase in TBI subjects. Subsequently this has been repeatedly demonstrated in numerous studies (Bigler et al., 1984; Blatter et al., 1997; Cullum & Bigler, 1986; Gale, Johnson, Bigler, & Blatter, 1995). In possibly the most comprehensive study of TBI-associated hydrocephalus ex vacuo to date, Blatter et al. demonstrated approximately a 65% increase in ventricular volume, that corresponded to approximately a 50-cc reduction in brain volume. For demonstrative purposes only, Fig. 14 shows a cube with the dimensions of 3.75 cm on each side — a 50-cc cube. In this study, which had subjects from mild-moderate to severe head injury, this was the average total amount of brain tissue lost.

In the Ryser, Bigler, and Blatter (1996) study with moderate to severe subjects, the average brain volume loss was over 100 cc. Again, for illustrative purposes only, if the average brain is between 1300 and 1400 cc, and there are 100 billion neurons, that means a prototype cubic centimeter of brain tissue would contain approximately 750 million neurons. Thus, in this hypothetical 50-cc loss of brain parenchyma, over 3.75 billion neurons would be affected. Of course, this example is overly simplistic, but it is daunting to consider the number of brain cells lost, damaged, or rendered dysfunctional in a significant head injury.

Using the ventricular expansion as a model of diffuse tissue loss, Fig. 15 graphically depicts the changes that occur overtime in a case of severe head injury. Note that on the DOI, the temporal horns are absent, likely related to complete effacement secondary to localized edema. Also, note that while the lateral ventricle is displaced across midline, there is no

---

**Fig. 14.** This cube represents 50 cc. This is the collective amount of brain tissue volume loss following moderate to severe TBI. This is given only as a visual aid. The bottom horizontal line is the one that measures 3.75 cm.
overall dilation. Thus, even though considerable acute pathology is present in the DOI scan, and the ventricular system is significantly distorted, it still can be used as a baseline. Using the DOI scan as baseline, now compare the scan 9 days and several months later. Note the general dilation of the ventricular system, and that the dilation is uniformly distributed throughout the ventricle. The patient does not have primary hydrocephalus. The expansion is a direct consequence of brain parenchymal loss, or hydrocephalus ex vacuo.

Fig. 15. 3-D dorsal view of ventricular system based on CT imaging in a patient with severe TBI. (Left) DOI scan showing multiple hemorrhages in the left temporal lobe, effacement of the left lateral ventricle and a solitary, deep, right frontal hemorrhagic lesion. Nine days later, the ventricular system has expanded considerably and that expansion continues for months as depicted in the scan several months postinjury (right). Note that in DOI scan the temporal lobes are noticeably absent and cannot be visualized on the scan. This is an indication of diffuse bilateral edema, a typical complication of moderate to severe TBI.
Another way to demonstrate the point of nonspecific changes in the brain in response to injury is to examine brain and ventricular volume changes over time. This is depicted in Fig. 16. The decrease is clearly a whole brain reduction in volume with compensatory increase in ventricular space.

4.2. Aging, brain atrophy, and TBI: does dementia come earlier?

Delayed neurobehavioral sequela of TBI have been studied for some time (Gualtieri & Cox, 1991). Previously, we (Bigler, Johnson, et al., 1996; Bigler et al., 2000; Blatter et al., 1995), as well as others (Bertoni, Sclavi, & Sauer, 1998), have shown that brain volume inexorably decreases with age, which probably accelerates in older age (>75). While still a somewhat controversial area, several studies recently have demonstrated a relationship between head injury and dementia (Mortimer et al., 1991; O’Meara et al., 1997; Salib & Hillier, 1997; Schofield et al., 1997); however, also see Mehta et al. (1999). Recently, in the most comprehensive analysis to date, Guo et al. (2000) clearly demonstrated that head injury was a risk factor for AD. Severity of injury appeared to be an issue as well. This seems to be a very intuitive relationship since the brain atrophies with age, and if an injury further reduces brain volume, that brain volume loss is probably accelerated when it interacts with the aging process and the inexorable occurrence of atrophy. The issue of neurogenesis in the adult primate brain has recently been demonstrated (Gould, Reeves, Graziano, & Gross, 1999), which obviously needs to be addressed in the context of aging, injury, and atrophy, but no data are available as of this writing. Likewise, cerebral reorganization after CNS injury needs to be more fully understood as well (Green, Sora, Bialy, Ricamato, & Thatcher, 1999).

One interesting link between aging, dementia, and TBI is the deposition of β-amyloid protein following head injury (Roberts et al., 1994; Smith et al., 1999) and the role that β-amyloid protein plays in AD and its relationship to the 04 allele apolipoprotein E (APOE) (Gomez-Isla et al., 1996; Povlishock, 1996; Schmechel et al., 1993; Warzok et al., 1998).
Mayeux et al. (1995) found the associated risk of AD and head injury to be mediated by 04. Naslund et al. (2000), in aging and degenerative disease, correlated β-amyloid with cognitive decline. The role that β-amyloid plays in neurocognitive deficits following trauma is not known at this time.

Some of the interesting potential links between TBI and dementia may be the vulnerability of the hippocampus in the backdrop of disseminated brain volume loss following injury. We have shown that the hippocampus and fornix are particularly vulnerable to injury secondary to MVA-associated TBI (see Fig. 17, Bigler et al., 1997; Bigler, Johnson, et al., 1996; Gale et al., 1999; Tate & Bigler, 2000). If the hippocampus is vulnerable to injury, it is a straightforward proposition to assume that, following injury, there is a depletion of hippocampal cells (see Albensi et al., 2000; Harding, Halliday, & Kril, 1998; Pike et al., 2000; Shah et al., 1997). Likewise, other experimental models have clearly shown the vulnerability of the hippocampus to injury as well (Conti et al., 1998). If aging results in cellular drop-out, but the injured hippocampus already has suffered neuronal loss, it will likely be more susceptible to the adverse influences of the aging process. Additionally, since hippocampal output is dependent on the integrity of the fornix, trauma-induced fornix atrophy is another potential source where pathology of trauma may interrelate with aging to enhance aging effects. Lastly, Di Patre et al. (1999), in a postmortem study, demonstrated that the progression of neurobehavioral impairment in Alzheimer’s disease was accompanied by a significant increase in senile plaque and neurofibrillary tangles in frontal cortex. White matter changes in this study were associated with cerebral amyloid angiopathy. Since TBI induces disseminated injury throughout frontotemporal regions and white matter, these areas are going to be significantly affected in any TBI patient. Thus, injury may increase the risk for development of dementia.

As previously discussed, Fig. 5, from Blatter et al. (1997), graphically shows that following brain injury, total brain volume drops significantly with in the first 180 days of

![GCS and Hippocampal Volume and Fornix Area](image)

Fig. 17. Hippocampal volume (left y-axis) and a cross-sectional fornix area (right y-axis) by GCS rating (mild: GCS = 13–15, n = 13; moderate: GCS = 9–12, n = 8; severe: GCS = 6–8, n = 18; very severe: GCS = 3–5, n = 11; controls n = 77) in TBI subjects compared to controls. While both the hippocampus and fornix show significant reductions in size, the fornix appears to be particularly sensitive at all injury severity levels.
injury but does not stabilize until approximately 3 years postinjury. It is assumed that this volume loss is related to underlying neuronal death and reduced white matter integrity (see also Fig. 16). However, note that the volume of the injured brain will always be below the volume of the normal cohort. It never returns to its baseline volume following injury. Thus, all aging effects will be superimposed on a damaged brain that has fewer cells, than would have been present had the brain injury not occurred.

Simply stated, if there is cell loss associated with aging and the brain is injured, aging will continue to result in programmed cell loss secondary to aging. In the damaged brain, there will be fewer cells, and with fewer cells the proportional drop-off of cells will accelerate the decline. This is illustrated in Fig. 18. Patients with TBI will cross the threshold earlier in their life span due to the influence of aging and injury. As of this writing, we do not know the relationship of head injury interacting with APOE genotype as it relates to the aging process. Conjecture would argue that TBI subjects with e4 allele would be at greatest risk for the earliest onset of dementia (see discussion below).

4.3. Genetics of head injury and TBI

Two very important studies have demonstrated the role of APOE in TBI (Friedman et al., 1999; Jordan, Relkin, & Ravdin, 1997). APOE is probably involved in some form of neuronal health and maintenance (Poirier, 1994). We have shown that possessing the allele that confers increased risk for AD, the e4 allele, is associated with smaller hippocampal volumes in cognitively normal individuals and those within the earliest stage of Alzheimer’s disease (Bigler et al., 2000; Plassman et al., 1997). Accordingly, there may well be a genetic predisposition factor that needs to be taken in to account in regards to outcome following injury and neuropsychological sequelae. TBI patients with the e4 allele may be destined for

---

Fig. 18. The top curve represents reduced brain volume overtime taken from the Bigler et al. (2000) and Blatter et al. (1995) studies of “normal” aging. The dotted horizontal line represents the average brain volume of AD victims in the Bigler et al. study, as a hypothetical “marker” for the threshold or cross-over point from normal to dementia. Each line represents a theoretical TBI patient with successive 25-cc volume loss of brain tissue, so that the bottom line represents the theoretical TBI patient that starts off with a 100-cc loss. As can be seen after an initial drop in the first decade, some stability during the middle age years occurs, and then the slope accelerates again. The theoretical distribution takes into consideration this acceleration, which is accentuated because with each successive year, fewer neurons are present, which means the proportional loss will be more substantial as time increases.
greater deficits. Additionally, APOE genotype may influence the risk for hemorrhage (O’Donnell et al., 2000).

4.4. Why models of structural damage account for only limited relationships to neuropsychological outcome

We have attempted a number of innovative ways to quantify and classify structural damage to the brain (Bigler, 1994; Turkheimer, Yeo, & Bigler, 1990; Turkheimer, Yeo, Jones, & Bigler, 1990; Yeo, Turkheimer, & Bigler, 1990), but none has been very predictive of neuropsychological outcome. Part of our research was motivated in earlier times when we thought more about lesion-localization. Gould (1997), as well as many others (see Koch & Laurent, 1999), have written about the complexity of the nervous system. For example, Gould (p. 161) has indicated that “nature is infinitely diverse and constantly surprising.” With a structure as complex as the human brain, it should come as no surprise that for most brain areas there is not a linear relationship between the size and location of a particular “lesion” and neuropsychological deficit (also, see Bigler, 2001).

4.5. Tracking recovery of function

Neuropsychology has a long tradition of tracking recovery of function. However, our techniques are influenced by practice effect and test–retest reliability problems. Neuroimaging methods including fMRI and SPECT may aid in monitoring recovery of function (Laatsch, Pavel, Jobe, Lin, & Quintana, 1999; Musso et al., 1999) and may provide, with the development of new technology, more precise ways to predict outcome and direct treatment efforts. This area of neuroimaging techniques in rehabilitation has far-reaching potential to alter neuropsychological practice.

4.6. The TBI “lesion” and neuropsychology

While focal lesions are commonplaces in TBI, and can be vividly identified with contemporary neuroimaging, the prototype mild-moderate to severe TBI “lesion” is probably generalized, nonspecific damage spread throughout the brain, but with greater involvement of the frontal and temporal lobe regions. Viewing Figs. 3 and 4, note that it is the entire brain that exhibits an atrophic response to injury. When compared to a normal brain, essentially all sulci have enlarged and all gyri shrunk. The ventricular system has uniformly increased in size.

This notion of the prototype TBI “lesion” being nonspecific (i.e., DBI) has very important implications for neuropsychology. The use of TBI subjects to study the lateralized effects of a visually identified focal lesion is ill founded. If focal lesions are to be investigated in TBI subjects, they should only be done in the backdrop of nonspecific changes that accompany the injury. What may appear to be a focal effect, may be no more than the focal lesion interacting with the diffuse lesion. Likewise, for the same reasons, TBI subjects are certainly not subjects to use for examination of hemispheric lateralization. Pathways traversing the...
corpus callosum are probably universally injured in any moderate to severe TBI. The delayed reaction time and processing speed in TBI is probably influenced by callosal damage, although the relationship is complex (see Johnson, Bigler, Burr, & Blatter, 1994). Collosal damage further disrupts hemispheric integration and likely creates a circumstance that further compounds any inferences that can be made about hemispheric specialization in TBI patients. When localized pathology occurs, it is more likely to be in the frontotemporal regions of the brain and this may be one factor why memory and executive deficits predominate the clinical picture (Fontaine, Azouvi, Remy, Bussel, & Samson, 1999; Van der Naalt et al., 1999). Lastly, TBI patients with moderate to severe injury have increased likelihood of seizures that persists for at least 30 years postinjury (Annegers, Hauser, Coan, & Rocca, 1998).

While there is clearly a relationship between having a moderate to severe TBI and the evolution of structural damage to the brain, the relationship is far from linear. This can be readily observed simply by examining the different illustrations in this article. The cases discussed in this article all had serious injury, yet the morphological changes are different in each one. This undoubtedly is partly responsible for only modest relationships between GCS, neuroimaging, and neuropsychological outcome. Further studies are needed to better understand how to best utilize information from various neuroimaging methods combined with injury characteristics (GCS and other measures of acute injury) and multiple measures of outcome and neuropsychological performance, to best assess the course of treatment and outcome from TBI. One study by Lowry (1996) demonstrated that the most meaningful neuroimaging relationships with a neuropsychological measure (Trail-Making Test) could be best understood when examined interactively. This is shown in Fig. 19.

What about the patient with significant brain injury, but “normal” CT, MR, or SPECT scan findings? Obviously, the absence of positive imaging findings is not to be equated with the absence of brain pathology. With current clinical imaging methods, slice thickness can get down to 1 mm. Remember the introduction — the brain has a 100 billion neurons and several times that in supporting cells! From vertex to the foramen magnum, the brain will span between 15 and 20 cm. Even a millimeter-thick slice of brain tissue will contain hundreds of millions of neural cells. The excitotoxic effects are generalized and persistent (Gong, Philips, & Lyeth, 1999). This does not take into account any physiology, synaptic count of functional organization of the brain, nor any neurochemical or synaptic action. Not surprisingly, contemporary structural imaging simply cannot detect all pathology at the microscopic level (see Felderhoff-Mueser et al., 1999). Nonetheless, advances are being made in the detection of physiologically and neurochemically relevant brain abnormalities in individuals who ostensibly have normal structural imaging. For example, Lewine et al. (1999) have shown MEG abnormalities in TBI patients with mild head injury, even when nothing is revealed in standard clinical MR imaging. Davis, Bigler, Valdivia, Chong, and Lewine (submitted for publication) have shown striking MEG abnormalities in a TBI patient, who acutely had documented moderate-to-severe injury, with MR scans clinically read as “normal” (see Fig. 20). Further studies integrating MEG with more traditional MR and SPECT imaging, along with neuropsychological outcome will undoubtedly further our understanding of the residual effects of TBI.
MRS also appears to hold great promise in the assessment of the TBI patient. Friedman et al. (1998) demonstrated reduced N-acetylaspartate (NAA) in white matter and elevated choline in gray matter. NAA is a biochemical marker of neuronal integrity and falls in the presence of neuronal damage. These authors interpret their findings as direct evidence of neuronal injury. What is important from the neuroimaging standpoint is that the MR scan where the voxel was taken for MRS quantification appears grossly normal. Furthermore, the degree of NAA reduction was correlated with the degree of neuropsychological impairment. MRS is another noninvasive neuroimaging tool that holds great promise in evaluating the TBI patient.

Early in the days of clinical neuropsychology, we characterized test results as either indicating organicity or not (Bigler & Ehrfurth, 1981; Bigler & Steinman, 1981). We also engaged in attempts to establish profiles or patterns of neuropsychological test performance based on severity of injury, time postinjury, or location of damage in TBI (Bigler et al., 1984). However, in light of contemporary neuroimaging findings, as reviewed in this paper, and an updated understanding of the neuropathology associated with head injury, there is likely no set neuropsychological pattern to TBI based on these variables. Each case will yield different structural and behavioral pathology dependent on the nature of the injury and physical forces.

Fig. 19. This 3-D depiction of the interaction of injury severity, brain region and neuropsychological performance. The z-axis represents a combined severity rating based on GCS and performance based on the Trail-Making Test, Part B. A designation of “1,1” represents TBI patients with the best performance on TM-B and the highest GCS. Oppositely, “3,3” represents TBI patients with the most impaired performance on TM-B and lowest GCS. The x-axis defines the different brain structures quantified and the y-axis is a z-score transformation of the QMR findings. Note that with less injury and better performance on TM-B, QMR findings are relatively stable, but dramatically change in the direction of atrophy with increasing severity of injury and impaired TM-B performance. This illustration emphasizes the need for integration of information in determining the interplay between severity of injury, neuropsychological outcome, and structural damage to the brain.
of impact along with the age, sex, genetic endowment, and experience of the individual injured at the time of injury. Thus, what should guide the clinician is a comprehensive battery of neurobehavioral tests that broadly assesses all domains of function, clearly and concisely integrated by the neuropsychologists.

5. Conclusions for the clinical neuropsychologist

Because individual brains are unique compositions of genetic endowment and environmental interaction, brain–behavior relationships will, in large part, be unique for each individual, with the exception of some dedicated motor and sensory pathways. Although current MR neuroimaging provides magnificent views of gross anatomy, anatomy is only one aspect of function. However, even our best contemporary functional neuroimaging tools — MEG, SPECT, PET, fMRI, etc. — at this time are limited in their ability to assess neurobehavioral correlates. Furthermore, the regional boundaries of “damage” differ depending on the neuroimaging technique employed. Nonetheless, neuropathological and neuroimaging studies demonstrate diffuse damage as a consequence of at least mild-moderate to severe TBI, regardless of whether focal damage exists or not. Thus, neuropsychological assessment of the TBI patient needs to be broad-based. Even though lesion–localization relationships do occur in trauma, the neuropsychologist should not have expectations of finding a particular lateralized or focal brain–behavior relationship, just because a lesion is identified in a scan. In TBI, a focal lesion will always be superimposed on the back-drop of a more global, diffuse injury. Additionally, the effects of diaschisis and focal injury may further obscure any specific brain–behavior “focal” relationship of the damage. Neuropsychologically, TBI can result in just about any type of behavioral deficit. However, the likelihood that frontal–temporal injury predominates pathology suggests that memory, executive, certain perceptual–motor abilities (especially those requiring speed of processing), and problems related to personality–temperament changes would predominate the clinical picture. Lastly, the absence of an imaging abnormality is not equivalent to absence of an abnormality. In cases where no neuroimaging findings are positive yet, the patients history is significant (i.e., documented LOC with 12 h PTA), trust that a brain injury, with all its microstructure abnormalities as described above, has occurred. Since significant structural damage can occur in individuals with GCS >12, clinical correlation is always needed between history, scan data, and neuropsychological performance. If valid neuropsychological evaluation and testing supports residual deficits, trust that those deficits are organically based and that the neuropsychological technique remains sensitive in the detection of neurobehavioral consequences of TBI, even if no neuroimaging abnormality is detected.

Finally, a major challenge to traditional neuropsychological assessment is rapidly emerging. I speculated on these changes in the clinical landscape of neuropsychology a decade ago (Bigler, Yeo, & Turkheimer, 1989). What was once speculation is now reality, and as neuropsychologists we must address these assessment issues quickly. Using functional neuroimaging techniques, neurobehavioral probes (with appropriate psychometric properties) are being developed wherein function and anatomy can be simultaneous assessed in the individual patient. The fMRI techniques are rapidly permitting “noninvasive” visualization
of fundamental processing modules in the human brain (Vanzetta & Grinvald, 1999). These techniques hold great promise for further refining methods of integrating neurobehavioral assessment and imaging, particularly in the assessment of TBI (see McAllister et al., 1999). Success in the areas of functional brain imaging will undoubtedly change the face of neuropsychological assessment. Accordingly, I believe that dramatic changes are in store for the practicing clinical neuropsychologist. In fact, as technology drives further refinement in neuroimaging techniques interfaced with sophisticated neurobehavioral probes, simultaneous neurobehavioral assessment with imaging will occur. I envision no difficulties in ultimately developing well-standardized and psychometrically sound clinical neurobehavioral probes that address the traditional areas of neuropsychological function (language, memory, executive, sensory–perceptual, perceptual–motor, and emotional). The successful implementation of neurobehavioral probes on line with neuroimaging will likely replace many of the current methods of neuropsychological assessment.

References


Davis, J. T., Bigler, E. D., Valdivia, S., Chong, B. W., & Lewine, J. D. Multimodal imaging in the evaluation of traumatic brain injury (submitted for publication).


