Imaging of Traumatic Brain Injury

Lyubomir Zagorchev$^{1,2}$ and Thomas McAllister$^3$

$^1$Clinical Sites Research Program, Philips Research North America, Briarcliff Manor, NY
$^2$Thayer School of Engineering, Dartmouth College, Hanover, NH
$^3$Psychiatry & Neurology, Dartmouth Medical School, Lebanon, NH

Abstract

Traumatic brain injury (TBI) represents an enormous public health challenge and is often associated with life long neurobehavioral sequelae in survivors. Several factors including higher percentages of individuals surviving TBI, as well as increasing concern about potential long term sequelae of even relatively mild injuries is changing the role of neuroimaging in the management of this condition. Historically the role has been the detection and acute management of life-threatening complications requiring surgical intervention. However there is an emerging need for neuroimaging biomarkers that would facilitate detection of milder injuries, allow recovery trajectory monitoring, and identify those at risk for poor functional outcome and disability. This paper reviews the current status of different neuroimaging techniques in TBI and outlines some of the challenges involved in moving towards an expanded role in these domains.

Corresponding author:
Lyubomir Zagorchev, Ph.D.
Philips Research North America
345 Scarborough Road
Briarcliff Manor, NY 10510

Lyubomir.Zagorchev@philips.edu
Incidence

Traumatic brain injury (TBI) is a significant public health problem worldwide. Epidemiological studies vary but it is estimated that in Europe there are well over 200 hospitalized cases of TBI each year per 100,000 population and 150 cases per 100,000 population in the United States. Of note is that these figures reflect hospitalized cases only, and do not include injured individuals who do not seek or have access to care. Thus, the actual incidence of injury is probably 3 to 4 fold larger than the quoted numbers. Approximately 3-5 million Americans suffer from some degree of TBI-related disability [1]. TBI-related disability has been of particular concern in the context of the conflicts in Iraq and Afghanistan in which about 20% of those deployed were exposed to a TBI.

Severity, types, and mechanisms of brain injury

Although differing in subtle ways, most current definitions of TBI include the need for an external force acting upon the brain that results in structural injury or disruption in physiological function as manifested by disturbance or loss of consciousness, loss of memory for the event, new neurological deficits, or brain lesions (usually detected with neuroimaging). The initial severity of a TBI is usually assessed by the length of the loss of consciousness, the duration of associated anterograde amnesia (also known as post traumatic amnesia), and Glasgow Coma Scale (GCS)[2]. The latter is a quick clinical screening tool that assesses best verbal, motor, and oculomotor function. Using these parameters, TBI is classified into mild, moderate, or severe. Individuals with loss of consciousness of greater than 24 hours and GCS scores of 4-8 are considered to have severe injuries. Individuals with loss of consciousness and post traumatic amnesia of less than 30 minutes and 24 hours duration respectively, and GCS scores of 13-15, are usually classified as having mild injuries. Moderate TBI are those that fall in between these parameters. Although useful as a rough indicator of injury severity, it is important to recognize the limitations of this method. The GSC is not always available, and the score may be confounded by factors including facial trauma, influence of alcohol, language difference, etc. Some injuries are unwitnessed thus the presence or duration of unconsciousness is not known. Most importantly these parameters assess initial injury severity and do not always accurately predict long term outcome. Although initial injury severity is reasonably good at predicting outcome measures such as mortality, they are less helpful at predicting disability. Patients with severe TBI are typically hospitalized, often have prolonged loss of consciousness or coma, and have high rates of chronic functional and neurobehavioral disabilities[3]. Individuals with severe TBI typically have easily identifiable brain lesions on neuroimaging.

There is much greater variation in outcome associated with mild and moderate TBI. This is of interest because these groups make up the vast majority of injured individuals. Although studies vary, it is estimated that 60-80% of traumatic brain injuries can be considered mild, 10-15% moderate, and the rest fall in the severe category [4]. The overall prognosis for this population is better than that for moderate and severe injury [5-7]. However there remains a good deal of variance in outcome, both short and long-term in this group. Although many factors contribute to this, the presence of structural brain lesions detected with neuroimaging may be a particularly important factor. Individuals with abnormal initial neuroimaging findings (usually CT scans)
may represent a different group (often referred to as complicated mild TBI) whose prognosis is similar to those with moderate TBI [8, 9]. Thus, the combination of clinical signs and symptoms shortly after injury and initial radiological findings may be a better scheme for predicting outcome.

This highlights the potential importance that neuroimaging can play in the evaluation and recovery monitoring of individuals with TBI. However the pathophysiology of TBI is complex and presents a challenge to the development of neuroimaging biomarkers in this field. These factors are briefly reviewed in order to inform the development of neuroimaging strategies.

There are two broad categories of forces that result in brain injury: contact (or impact) and inertial (acceleration or deceleration). Contact injuries result from the brain coming into contact with an object (which might include the skull, or some external object). This typically results in damage to scalp, skull, and brain surface (e.g. contusions, lacerations, hematomas) [10]. Because of the configuration of how the brain is situated in the skull and the uneven surfaces of the inner table of the skull, some regions such as the anterior temporal poles, the lateral and inferior temporal cortices, the frontal poles, and the orbital frontal cortices are often the site of structural injury [11].

Inertial injury results from rapid acceleration or deceleration of the brain that produces shear, tensile, and compression forces. These forces have maximum impact on axons and blood vessels, resulting in axonal injury, tissue tears, and intracerebral hematomas. These mechanisms also produce more widespread or diffuse injury (“diffuse axonal injury”) to white matter. Once again some brain regions including the corpus callosum, the rostral brainstem, and subfrontal white matter are at greater risk for damage from these forces [10].

The recent conflicts in Iraq and Afghanistan have called attention to the effects of “blast injury”. Explosions generate a rapidly moving wave of over-heated, over-pressurized air, followed by a low pressure trough. These waves are particularly damaging to air and fluid filled organs and cavities, and can be associated with significant brain injury as well [12-14]. Whether the effects of blast injury on the brain are related to the mechanical effects of the pressurized wave, with distortion of vascular tissue, neural tissue or both, the inertial effects of being buffeted by the alternating high and low pressure events, or some other mechanism has not yet been clearly established.

In addition to structural injury described above, the injury event is accompanied by a massive release of neurotransmitters with subsequent triggering of excitotoxic injury cascades [15]. These excitotoxic cascades and other forms of secondary injury such as hypoxia/ischemia have a disproportionate effect on certain brain regions, such as the hippocampus, even in the context of an otherwise fairly mild injury [16].

Thus, the typical profile of injury involves a combination of primary injury (occurs at time of application of force) and secondary injury (evolves over time subsequent to the primary injury) as well as a combination of focal and diffuse injury. Furthermore a wide array of neuropathological processes can be involved in TBI, including changes in bone (e.g., a skull fracture), tissue density and water content (edema), blood flow, white matter integrity and
pathway connectivity (diffuse axonal injury), and subtle changes in the neuronal and extracellular biochemical milieu. This suggests that it is unlikely that a single imaging technique will be capable of addressing all of these processes [17, 18] and raises the question of whether multi-modal imaging would be more useful and how that might be configured most efficiently. Several imaging modalities have already been shown to be of interest in the diagnosis and recovery monitoring of TBI and these are now briefly reviewed.

**Structural imaging**

CT is the current modality of choice when it comes to standard clinical assessment of acute TBI on the day of injury. It can be done quickly and despite its lower spatial resolution, CT remains superior to structural MR for identifying skull fractures, hemorrhages, contusions, and edemas. Despite its superiority in identification of acute TBI on the day of injury, CT has been shown to be a poor predictor of long term outcome[19]. That is attributable to the fact that it takes weeks to months for the injured brain to recover[20, 21], and for some injury associated changes to evolve. CT has proven useful in tracking the progression of injury over time. The scan acquired on the day of injury can be used as a baseline in an attempt to track brain changes over time, after the brain injury has been identified and established[22].

Due to its high spatial resolution and excellent soft tissue contrast, MR is typically used to track progression of disease/recovery and follow-ups[23]. MR is well suited for tracking structural atrophy and white/gray matter changes. It is superior in detecting cerebral atrophy that typically manifests in ventricular dilation and thinning of the corpus callosum[24], as illustrated in Figure 1.

![Figure 1](image-url)
Figure 1: Cross sections from a T1 weighted structural MR of: (a) and (c) a healthy control patient, and (b) and (d) a patient diagnosed with moderate TBI. The ventricular dilation and thinning of the corpus callosum as indicated by arrows are pronounced in (b) and (d).

Furthermore, MR imaging does not require radiation and is suitable for monitoring volumetric structural changes over time. TBI has been associated with structural atrophy in various studies. Because of its relatively high spatial resolution, MR has been used for quantitative analysis of a number of sub-cortical structures including: amygdala, caudate, hippocampus, corpus callosum, cerebellum, thalamus, and globus pallidus[24]. A connection between the severity of injury and the amount of atrophy has also been established [25]. An important question that remains unanswered is how early in the injury progression quantitative changes could be detected.

Different MR image sequences are sensitive to different pathological changes and should be acquired simultaneously to increase the reliability of lesion detection[26, 27]. Standard T1 imaging is useful for detection of focal injuries or structural atrophy. Cerebrospinal fluid changes can be monitored reliably in both T1 and T2 sequences. The standard gradient echo sequence is helpful in detecting hemosiderin, an iron-storage complex found within cells such as macrophages, which tend to accumulate in the area of injury. FLAIR, proton density (PD), and diffusion weighted (DW) imaging have been used for white/gray matter related trauma. Diffusion weighted imaging and diffusion tensor imaging (DTI) capitalize on the ability to detect the diffusion behavior of water molecules in the brain. Regions where there are no constraints to water diffusion are described as being isotropic, that is diffusion is equally likely to occur in all directions. Regions constrained in some way, such as along the long axis of an axon, or along a fiber bundle, show greater diffusion along the long axis and thus are said to show anisotropic diffusion behavior. The degree and direction of such anisotropy, can be used to characterize neural tissue and changes in these parameters are thought to reflect changes in tissue, particularly white matter integrity [28, 29].

Diffusion tensor imaging (DTI) has recently been explored as a sensitive method to detect subtle white matter changes hypothesized to be the neuropathology associated with mild TBI. However, although abnormal DTI parameters have been reported in mild TBI patients, the
indices and brain regions involved have varied [30-34], suggesting that further work on diffusion weighted techniques is needed. For example several studies have reported reduced fractional anisotropy (FA) values in mild TBI [31, 35-38] whereas others have reported increased FA [30, 33, 34, 39]. There are probably several reasons for these discrepant findings. First, different studies have used different injury to imaging intervals, and the underlying white matter pathology evolves over time. For example studies that have shown increased FA [30, 33, 34, 39] have been in the peri-injury period (typically days-2 weeks) although not all such semi-acute studies found this [31, 35, 36].

Functional imaging

Although recent advances in CT and MR imaging technology have opened new and exciting opportunities for structural studies, functional imaging modalities provide complimentary information and unique opportunities for analyzing brain activity within specific target regions associated with TBI. Examples of functional imaging modalities sometimes used in clinical practice include Positron Emission Tomography (PET) and single photon emission computed tomography (SPECT). Nonionizing radiation techniques widely used for clinical research include functional MR (fMRI) and magnetic resonance spectroscopy (MRS).

Both PET and SPECT require the use of tracers, radioactively labeled compounds which when administered into the circulation accumulate in specific targeted area. The imaging hardware provides a 3-D image volume representing the spatial and temporal distribution of the trace localized at the target. The main advantage of these molecular imaging techniques over structural imaging modalities is their sensitivity. Very low concentration of a radioisotope is sufficient to delineate a lesion based on its pathophysiological characteristics. Because of limited background radiation, they inherently provide a relatively high signal to noise ratio. Furthermore, due to the small size of the tracer, it is readily available in the capillary network.

The most commonly used PET tracer is [18F]-fluorodeoxyglucose, a glucose analog also known as FDG. Similar to glucose, FDG is transported into the cell by a glucose carrier protein and is rapidly converted into FDG-6-phosphate. However, as FDG lacks a hydroxyl group, it cannot undergo further phosphorylation and stays trapped in the cell until the radioactivity decays at which point it is metabolized as regular glucose. Therefore, PET scans using FDG represent glucose metabolism.

The commonly used clinical SPECT tracer is 99mTc-HMPAO, a radioactive agent used in the evaluation of regional cerebral blood flow. In contrast with PET, SPECT tracers are less expensive and readily available but at the expense of lower resolution of the imaging hardware. Kinetic modeling is often used with both PET and SPECT to describe the dynamics involved in the utilization of the radioisotopes. Simplified kinetic models represented by tissue compartments and transfer rates attempt to capture the spatial and temporal distributions of isotopes that result from complex pathophysiological events at cellular level. In a recent FDG-PET study of TBI patients in the acute stage, kinetic modeling has shown reduced hexokinase activity in the cerebral cortex, corresponding to reduced glucose metabolism [40].
fMRI utilizes the fact that oxygenated and deoxygenated hemoglobin have different magnetic properties[41, 42] and result in different MR signal intensity values. Tasks which increase regional brain activity and ultimately regional blood flow can be administered in the scanner. The subsequent changes in the ratio of oxygenated to deoxygenated blood can be used to generate images of task-related metabolic activity. This technique has been used to study cognitive function in individuals with TBI. Such studies suggest TBI patients have alterations in their ability to match cognitive processing activity and resources to cognitive demand [23, 24, 43]. Some of the advantages of fMRI include a better resolution comparing to PET and SPECT, and nonionizing radiation. The considerable technical expertise that is required for reliable fMRI acquisition coupled with the interpretive nature of the scans, however, has prevented its extensive clinical use.

MRS is an imaging modality that provides information on intracellular function and neurochemical composition. It shows promise as an imaging technique sensitive to detecting effects of TBI including changes in neural integrity (reduced NAA levels - an amino acid synthesized in mitochondria, that decreases with neuronal and axonal loss or dysfunction), brain energy metabolism (creatine), and membrane integrity/synthesis/repair (choline - primarily consisting of phosphoryl and glycerophosphoryl choline)[44]. To date much of the study of 1H MRS in TBI has been in adolescents [44, 45], and in more severe injury populations [46, 47]. There have been fewer investigations of 1H MRS in populations with mild and moderate TBI (MTBI) and the results have been less clear cut, in part related to the different methodologies and
different injury to assessment intervals used [48-50]. However, Vagnozzi et al. [51] recently reported reduced NAA/Creatine ratio in 13 individuals studied within 3 days of a sports concussion. The authors conclude that NAA is a sensitive index of the metabolic status of the injured brain, able to discern persistent abnormalities even when patients' early symptoms have resolved, and therefore able to detect a still-vulnerable brain state during which second insults should be avoided. However, the study involved very few patients, and only one with a pre-injury examination.

**The need for multi-modal imaging approach**

Functional changes precede structural atrophy and appear earlier in the course of injury. A multi-modal imaging approach combining the superior visualization of structural imaging modalities with functional information could help significantly with the interpretation of imaging studies. A fairly large study of mild, moderate, and severe TBI patients imaged over a period of 3 years post injury, indicates that functional imaging modalities may be useful in cases where there is no evidence of injury on a structural scan and vice versa [52]. It has been shown that abnormalities of TBI patients seen on SPECT are not always visible on MRI or CT [53]. Furthermore, structural information could be brought into the functional space for better localization and more accurate quantification of underlined activities and interactions. That could help with better localization of activated regions in fMRI, or in the investigation of neurochemical changes with MRS.

**Summary and discussion**

Traumatic brain injury is a significant public health problem worldwide. As trauma care has improved, the number of individuals who survive TBI is increasing. Many of these individuals are injured in the second or third decade of life and will live for many years saddled with an array of complex neuropsychiatric sequelae. An increasing evidence base suggests that some survivors will be at increased risk to develop Alzheimer’s disease and other neurodegenerative conditions [54, 55]. The above review highlights several important issues relevant to the changing role of neuroimaging in the diagnosis and treatment of TBI. Thus the role of neuroimaging in TBI is changing. Most of the emphasis to date has been on the use of imaging in the diagnosis of acute surgical emergencies associated with TBI. Thus for these purposes, CT scanning has been adequate in that it is relatively available, has short image acquisition times, and is quite good at picking up subdural and epidural hematomas, skull fractures, cerebral edema and other potential clinical emergencies. However there is an emerging appreciation for the potential long-term sequelae of milder injuries and here CT scanning is less adept at picking up subtle structural abnormalities, changes in white matter integrity, or functional alterations associated with cognitive tasks.

MR based techniques are more sensitive in this area, but are rarely used acutely due to length of image acquisition, reduced availability, and higher cost. Even when employed, conventional structural MR techniques may be used later in the course of recovery and thus may miss acute injury changes. In order to provide adequate risk assessment for long term sequelae it is helpful to establish that an injury actually occurred. Thus there is a need for highly sensitive
neuroimaging biomarkers to assist in the diagnosis of mild injury. Beyond that, there is a need for recovery monitoring in order to identify those at risk for poor outcomes. Almost half of those hospitalized for TBI will have chronic neurobehavioral sequelae [3], but our ability to establish which half is not good. Preliminary evidence suggests that abnormal neuroimaging findings alters the prognosis in the mild TBI group, could prognostic neuroimaging biomarkers be developed that would allow us to target those at risk for poor outcomes with early or different treatment interventions? For example the ability to have real time assessment of volume and shape of key brain structures known to be affected by TBI such as the thalamus, the corpus callosum, and hippocampus among others might allow tracking of these measures over time and correlation of these measures with key functional measures such as standardized cognitive testing.

The multi-faceted nature of the pathophysiology of TBI suggests that reliance on a single imaging technique is likely to be disappointing. Rather it would be helpful to move towards a user friendly suite of imaging techniques that allow clinicians and researchers to probe and monitor structure, volume, function, and metabolic status and change over time. At this time, each technique is time consuming and increases subject burden, thus such a multi-modal or hybrid approach will have to prioritize speed of information acquisition in order to minimize patient discomfort and burden.

The current focus on the medical and societal significance of TBI provides a unique opportunity to advance and apply emerging and novel neuroimaging techniques in the service of an important public health problem.

References


