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Role of diffusion tensor imaging as an imaging biomarker and theranostic tool in structural imaging of traumatic brain injury

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ABSTRACT

Neuroimaging technology is at a "newborn" stage in the evaluation of TBI. While additional literature are obviously required to decide whether these modalities and progress in knowledge with noninvasive monitors will allow early and consistent recognition of revocable secondary brain damages, the final query is whether these new modalities will help in treatment plans that will absolutely mark result. DTI is an influential instrument for assessing white matter anatomy and related anomalies. DTI was formerly an investigation tool, but is using clinical practice. Accepting the terms and basic ideas of this method can aid in the clinical implementation and interpretation of this blend of structural and physiologic white matter evaluation. In conclusion, although DTI is as a diagnostic tool for severity of TBI and as an outcome predictor, but severe preclinical and clinical validation of each imaging method should be a top importance.

KEY WORDS: diffusion tensor imaging, biomarker, theranostic tool, traumatic brain injury.

1. INTRODUCTION

Traumatic brain injury (TBI) is a universal public health issue, with a large number of deaths amongst the severest wounds and lasting loss of operation even amongst persons with minor TBI (Whiteneck, 2004). The incidence of TBI is hard to evaluate as not all patients pursue medical care, and complete registrations from primary health care are hard to find (Roozenbeek, 2013). The total of hospital-admitted TBI patients is regarded as a significant index of the influence of local injuries on hospital resources. Numerous international epidemiological investigations have reported changes during the last decade in the trends of TBI hospitalizations, incidence and mortality rate (Kraus and McArthur, 1996). There are about 10 million persons affected yearly by traumatic brain damage (TBI) throughout the world (Feigin, 2013). In the US, TBI is the main reason for mortality and handicap with about 52,000 yearly mortalities and 5.3 million Americans damaged by its consequences. TBI includes over 30% of all related mortalities in the US and is called the silent epidemic of our time (Yue, 2013). European TBI prevalence statistics is not reliably documented by each country but it has been supposed that 1.6 million head-injured patients are hospitalized yearly in Europe with a frequency rate of about 235 per 100,000. There is an average mortality rate of about 15 per 100,000 and a case fatality rate of about 11 per 100. The TBI intensity ratio of hospitalized patients is about 22:1.5:1 for mild vs. moderate vs. severe cases, respectively (Papa, 2012). As reported by the World Health Organization, TBI will exceed numerous diseases as the major cause of mortality and handicap by the year 2020. TBI is the main reason for morbidity and death amongst resident and armed inhabitants. The initial injury sets in motion a number of cellular and molecular challenges ending in the development of secondary processes that profoundly impact the result. One of the principal subordinate pathologies is raised intracranial pressure (ICP). If not preserved under 20 mm Hg, raised ICP can origin deprived cerebral perfusion, brain herniation, and decease. Mostly, ICP increases in a slowly, reaching its peak level between days 3-5 post-TBI. Though, no prophylactic management is presently accessible to stop raised ICP, neurointensivists and neurosurgeons often use tranquillizers, mannitol, hypertonic saline, cerebrospinal liquid drainage, decompressive craniectomy, and/or barbiturate-induced coma to tackle this disorder. In addition to affecting the patient, TBI has a straight influence on their relatives, families, concierges, and public setting. The TBI associated prices are huge, which may result from long lasting hospital admissions and therapy but also because of secondary charges resulting from defective production in formerly well persons as a result of death and handicap. Traumatic brain injury (TBI) has proven one of the most challenging human maladies to classify: while some diseases have entered an era of robust and meaningful molecular classification, TBI is highly categorized by clinical severity or physical mechanism (Grafman and Salazar, 2015). Predictive tools for risk stratification of TBI patients are limited in the initial phases of damage in the emergency setting for all severities of TBI. As opposed to additional physical conditions in which quick diagnosis using biomarkers from blood tests are clinically vital to monitor the diagnosis and management; for

example, for myocardial ischemia or kidney and liver failure, there are no fast, conclusive diagnostic tests for traumatic brain damage (Papa, 2012; Rahmani Tanha, 2016). Furthermore, the reference standard for TBI is also harder to define than for example cardiac ischemia. No golden standard for stratification of patients by severity exist. Now, diagnosis of TBI relies on a diversity of methods containing neurological examination and neuroimaging (Mondello, 2012).

Pathophysiology of TBI: The pathophysiology of TBI is highly complex and involves multiple pathophysiologic processes. Importantly, TBI should not be seen as an event, but as a progressive disease, in which further damage may occur over hours, days, weeks, months, or even years. Secondary damage is preventable and potentially treatable (Sener, 2016). Detection, quantification, and tracking of such secondary damage is thus of paramount importance. Subordinate injury may contain brain swelling because of vascular engorgement or brain edema, which may be intracellular (cytotoxic) or vasogenic (extracellular). Cerebral ischemia, is one of the most frequent problems in TBI. It may happen regionally (in the penumbra of a contusion) or more widespread and could be worsened by systemic conditions, such as low blood pressure or insufficient blood oxygenation. Traumatic axonal injury, formerly considered a mechanical disturbance of axons, has now been revealed to happen from metabolic breakdown of axonal transport mechanisms (Johnson, 2013). Both hypo- and hyper metabolism may happen at different stages after injury. Disorders of the mitochondrial transition pore are thought to be a main cause of mitochondrial insufficiency after TBI. Inflammatory cascades are activated, some of which may be protective, others—when in excess—detrimental. Much insight into these mechanisms can be gained from MR Imaging (Zasloff, 2002). Diffusion weighted imaging (DWI) and ostensible diffusion coefficient (ADC) mapping can offer information about ischemia and edema, whilst MR spectroscopy can provide insight into metabolic imbalances.

In addition, in TBI, the primary damage is the direct result of foreign forces, including mechanical deformation of the tissue (Morrison, 2003). It causes neuronal depolarization and release of neurotransmitters that stimulate the release of Glutamate and Aspartate which binds to Glutamate and causes calcium influx. Calcium, calcium-dependent phospholipases, proteases and endonucleases that reduces fat, activate proteins and nucleic acids (not shown). Calcium sequestration in the mitochondria, leads to a calcium disorder, lack of energy, formation of free radicals, and starting of apoptosis. Augmented creation of reactive oxygen and nitrogen lipids, oxidize proteins and nucleic acids after TBI. TBI increases many transcription factors, provocative mediators, and declines receptors for the neurotransmitter release mechanism. Increased expression of cytokines, and harmful chemokines may cause brain edema, blood-brain barrier damage, and cell death (Kadhim, 2008). The result of the cascade after TBI complex is the injury and cell death that leads to functional defects. Significant experimental and clinical data accumulated during the past decade suggests that the adult brain is capable of reorganizing the structure and function after injury (Kozorovitskiy and Gould, 2003). This, in turn, may help to improve their own performance.

Prognosis, diagnosis and imaging in TBI: Currently, the development of all-digital medical imaging techniques produces high-quality images and generates a wide range of information contained in these images (Chakraborty, 1996). Simultaneously, the huge growth of computing has enhanced the images used to diagnose and guide the treatment of many diseases. Furthermore, imaging biomarkers are being industrialized as an manifestation of this interaction amid digital images and their computational processing (Adelson, 1984). These ground-breaking growths extract from the medical images quantitative information that cannot be visually spotted or assessed in the source images (Qu, 2002). The use of imaging biomarkers will allow us, radiologists, to change the concept and the process mapping of our work, opening up the traditional medical imaging to other fields such as engineering and physics. Because of their huge potential, imaging biomarkers have emerged as one of the most active research fields, allowing for the visualization and measurement of physiological and biological processes using 3D modeling of a region of interest in a specific patient. An imaging biomarker can be demarcated as a specific presentation taken out from the descriptions of a person that can be empirically dignified and acts as an indicator of a regular biological development, a disease, or a response to a therapeutic intervention (Bonmati, 2012). From simple size or shape dimensions to complex computational models, biomarkers have showed important in providing essential data to the traditional radiological diagnosis to express the presence of a sickness or lesion; measure its biological condition; define its natural history and progression; stratify phenotypic abnormalities and assess the treatment response (Bonmati, 2012). In theory, biomarkers may be obtained from any imaging modality but, among all the available techniques, MRI is unique for its great adaptability in the study of diverse types of tissues and processes. Imaging biomarkers have two major advantages (Bonmati, 2012). First, they represent quantitative variables that characterize and measure different parameters, obtained from medical images that are relevant to a specific disease. Second, parametric images let us to examine the spatial distribution of the biomarker in the sample seen through its visual image (Bonmati, 2012). These pictures are produced to offer a graphical representation of the values of each biomarker or parameter calculated on the basis of initial image post-processing. Imaging has a long history in medicine. Several technologies are used for imaging *in vivo*. X-rays are the oldest form of *in vivo* imaging and form the basis of computer tomography imaging. The current focus in relation to imaging biomarkers is on molecular imaging, which is defined as the

visualization, characterization, and quantity of biological processes at the molecular and cellular levels in individuals and other creatures. The advent of the modern neuroimaging era with the development of the computed tomography (CT) scanner has fundamentally changed the way we think of TBI (Bonmati, 2012).

As this technology advances and integrates other know-hows such as bioinformatics and neuroimaging, characterization of CNS proteins will happen rapidly and many more probable markers will be validated in a shorter timeframe (Papa, 2012). Another important challenge in validating biomarkers for TBI will be that traditional consequence events used to measure injury severity are, in and of themselves, limited. This is true for all severities of injury, and is particularly germane to the less severe injuries where neuroimaging, such as CT, may not prove any clear pathology (Papa, 2012). Traditionally, TBI has been detached to three very broad groups: mild, moderate and severe. Unfortunately, this cataloguing system is no successful in capturing the spectrum of TBI and the dissimilar types of damages related to it. The trouble in classifying damage extent is one which has made clinical trials in the field of TBI inspiring. Therapeutic clinical trials for TBI have met with negative results at a cost of over $200 million (Papa, 2012). These letdowns have been accredited to a crowd of factors but particularly to the heterogeneity of TBI which makes classification of the dissimilar injury types challenging. This heterogeneity, together with the deficiency of initial decisive procedures of severity unlocks the way for using biomarkers as early prognostic indicators. Hypothetically, biomarkers could deliver early product measure for clinical trial available much more consistently and sparingly than ealier neurological evaluations, thereby knowledgeably plummeting the dangers and prices of human clinical trials (Papa, 2012). Currently, a diagnosis of TBI is based on medical history, findings on neurological examination, clinical assessment scales, and neuroimaging, such as CT of the head and MRI of the brain. While a diagnosis of moderate to severe TBI is often self-evident from patient history and associated signs of injury or abnormalities on neurological examination and neuroimaging, a diagnosis of TBI frequently remains difficult (Crooks, 2007). Multiple classification schemes for mild TBI exist; although there is some overlap, there is also controversy regarding the qualifying diagnostic criteria, such as presence of loss of consciousness and duration of changes in sensorium. It has been generally. New biomarkers of TBI and advanced MRI-based neuroimaging technologies are currently being evaluated. Advances in MRI and other imaging technologies have led to greater understanding of the impact of TBI with the expectations of improved diagnostic certainty in the identification of TBI and in the prediction of clinical outcome (Bettermann and Slocomb, 2012). The pathophysiology of mild TBI may soon be better understood using newer MRI modalities such as MR spectroscopy, which allows researchers to monitor metabolic changes that occur after TBI and during recovery of brain function. Conventional and advanced MRI also may improve insight into structural damage following TBI, such as axonal shear injury, and into processes of brain plasticity that follow the injury. With both hardware and pulse sequence design advances, novel MRI approaches have confirmed the ability to discover and localize with high resolution numerous pathologic and pathophysiologic consequences of TBI. Advances in MRI-based neuroimaging techniques, such as diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and perfusion weighted imaging (PWI), have brought new potential to TBI diagnosis (Ruthotto, 2012; Fatehi, 2016). DTI investigation of TBI patients has fascinated investigators since this imaging modality is particularly sensitive to microscopic white matter (WM) alterations and may be able to spot diffuse axonal injury in TBI. Advanced MR Imaging, and in particular DTI, calls for openings to examine this black box, and to extract data that can be utilized to better illustrate injury, track disease courses, and to launch a more specific prognosis (Sener, 2016). In the acute phase, structural brain damage is best assessed by CT scanning, as this is rapidly available and can be performed quickly. This is important, as rapid detection and—if indicated-prompt elimination of an intracranial hematoma is one of the major values based on that, attention for the TBI patient is founded (Sener, 2016). CT scanning further permits a broad characterization of TBI by the Marshall CT classification. This classification offers a descriptive approach, which is important, as TBI is a very heterogeneous disease encompassing a broad range of pathologies. The Rotterdam CT score was established based on a extrapolative viewpoint and syndicates dissimilar CT features into a sum score. This score has been shown to be more strongly related to outcome than the Marshall CT classification. Likelihood of consequence, though, is better achieved by joining dissimilar variables (clinical, radiological, and laboratory) into a multifaceted model (Sener, 2016). TBI is a dynamic process, and pathology evolves over time. In patients with contusions, new lesions may develop in up to 16 % of cases and existing contusions may increase in size in up to 40 % of cases (Diaz, 1979). This lesion progression mainly occurs within 6–9 h after injury. Follow-up imaging is therefore essential. The disadvantage of CT scanning is that it only captures limited evidence on the full extent of physical injury and does not provide any understanding into function. MRI can provide better insight into the extent and severity of primary and secondary brain injury. Specific MRI sequences, i.e., susceptibility weighted imaging (SWI) and DWI, are more sensitive for detecting structural changes in the brain, particularly smaller lesions, such as micro hemorrhages, diffuse axonal injury (DAI), and traumatic axonal injury (TAI) (Fatehi, 2016; Rostamzadeh, 2014). DTI (DTI) offers excellent extra data on white matter and structural injury, and is consequently mainly tailored to characterize the presence and degree of injury and understand pathophysiological mechanisms in neurotrauma (Huisman, 2004). MR

imaging can picture irregularities, in line with axonal damage in up to 30–50 % of patients, in whom CT showed no ostensible structural injury. It is significant to distinguish such injuries since TAI is a major source of cognitive damage and disability after TBI and thus a determining factor for result. For example, in mild TBI patients with impaired executive function, reduced FA values were seen in the dorsolateral prefrontal cortex. Based on diffusion of tissue water molecules and by exploiting the anisotropic nature of diffusion it is possible to gain information about the microstructural organization and integrity of WM fiber tracts that interconnect various brain regions. The most commonly used DTI-derived measures are the fractional anisotropy (FA) that reflects diffusion anisotropy and mean diffusivity (MD) that represents average diffusivity and axial diffusivity (AD), and radial diffusivity (RD) (Acosta-Cabronero, 2010). Together, these DTI measures could serve as markers of tissue integrity. Previous DTI reports on TBI have produced somewhat inconsistent results. Reduced FA and elevated MD in various WM regions in the acute and chronic phase of TBI were reported. Increased FA and MD were also reported both in acute and subacute phases. Brain atrophy is generally thought to represent neurodegeneration (Narayana, 2015). MRI is an excellent modality for estimating global and regional atrophies in TBI and for following their longitudinal evolution. There are only a few studies that investigated atrophy in TBI. These advanced MR technologies include SWI for hemorrhage detection, MRS for metabolite measurement, DWI and DTI for edema quantification15 and axonal injury detection, PWI and arterial spin labeling (ASL) to measure blood flow to brain tissue, and functional MRI (fMRI), which measures changes in blood oxygen level locally in response to neuronal activity (Table 1). Having many of imaging biomarkers, which are attained in a single scanning session (or multiple for longitudinal study) and are sensitive to different consequences of traumatic injury gives great benefits: 1) enhanced sensitivity; 2) ability to study interrelationships among these biomarkers and between the biomarkers and clinical/ neurocognitive deficits; 3) enhanced clinical care resulting from more accurate characterization of damages; and 4) enhanced power of clinical interventional studies. Furthermore, the information comes ‘‘cheaply’’ since MRI is non-invasive and is widely available (Kou and Haacke, 2014).

Role of imaging biomarkers of Advanced MRI techniques in TBI:

Diffusion tensor imaging: DWI relies on proton diffusion as a contrast-determining parameter in MRI (Bammer, 2009). *In vivo* quantification of diffusion of water molecules using MRI was first described in 1986. Diffusion can be described as random thermic motion, or Brownian motion. The technique utilizes the fact that in tissue diffusion is not necessarily random due to barriers that limit diffusion in one or more directions. Unhindered diffusion of water molecules is referred to as isotropic diffusion. Restriction of movement along only one axis is called anisotropic diffusion (Nicolay, 2001). Among others, the measured diffusion procedure relies on the practical magnetics gradients and the axis of myelinated white matter tracts. In DWI, a spin-echo sequence with a pair of strong diffusion-weighted gradients is used, known as the Stejskal-Tanner pulse sequence. The diffusion weighting applied is dependent on multiple factors represented by the diffusion attenuation factor or b-value. A conventional DWI sequence evaluates diffusion in all directions (Koh and Collins, 2007). In contradistinction, DTI (DTI) assesses diffusion in multiple different directions (represented by vectors with magnitude and direction) to examine the three-dimensional micro anatomical body of brain parenchyma. Each point of the imaged tissue is mathematically signified as a multidimensional diffusion vector that is recognized as a diffusion tensor. Generally, DTI in which diffusion data are acquired in 6 or more directions is used to describe diffusion in an anisotropic system. DTI allows visualization of the location, orientation, and anisotropy of the brain’s white matter tracts. In pure water or cerebrospinal fluid, the diffusion of protons is unrestricted in all directions, and therefore isotropic, often represented as a spherical tensor. Diffusion imaging sequences are sensitive to traumatic axonal injury (TAI) secondary to stretch and shear forces (Zappala, 2012). DTI measures the bulk motion of water molecular diffusion in biological tissues. It is most valuable when tissues are anisotropic, i.e. when diffusion is not equivalent in all directions, such as in skeletal muscle or axons in white matter of the central nervous system. Histological correlates have validated DTI’s sensitivity to brain injury for both focal33 and diffuse axonal injury models. The apparent diffusion coefficient (ADC) and fractional anisotropy (FA) are two parameters derived from DTI that have been extensively studied in TBI. ADC is an estimate of the average magnitude of water movement in a voxel (regardless of direction), while FA is an index of the directional non-uniformity, or anisotropy, of water diffusion within a voxel. FA has been used to detect alterations in directional diffusion resulting from tissue damage. FA in white matter is highest when fibers are long (relative to voxel dimension) and oriented uniformly (collinear) within a voxel and lowest when fibers are not collinear (e.g. crossing fibers) or have been damaged. When axons are injured, as in acceleration/deceleration injuries, diffusion anisotropy typically decreases. Loss of diffusion anisotropy is the result of a number of axonal changes after injury including: 1) increased permeability of the axonal membrane; 2) swelling of axons; 3) reduced diffusion in the axial (long axis) direction; 4) deterioration and loss of axons in the chronic stage (Benson, 2007). In general, any pathological alteration of white matter fibers will result in FA decrease, since one or more of these axonal changes occurs in disorders of white matter. Not astonishingly, most clinical investigations of moderate and severe TBI have shown FA to be more sensitive than ADC to traumatic injury. Instead, ADC, FA, and directionally

discriminating diffusivities (principal, intermediate, and minor components of diffusion) can help to better characterize brain injury pathologies (Benson, 2007). Trace and mean diffusivity are two other measurements similar to ADC and vary similarly. Changes in FA in association with ADC changes can differentiate the type of edema. For instance, in the severe stage, reduced FA in link with augmented ADC proposes vasogenic edema, while increased FA in association with reduced ADC suggests cytotoxic edema. Reduced FA in connection with reduced ADC and decreased longitudinal (parallel to the long axis of the axons) water diffusivity suggests axonal transport letdown as happens in progressive neurological conditions for example in ALS (HAACKE). Regarding the location of brain lesions detected by DTI, Niogi. Summarized that the frontal association pathways, including anterior corona radiata, uncinate fasciculus, superior longitudinal fasciculus, and genu of corpus callosum (CC), were the mostly frequently injured WM structures in this cohort of TBI patients.

Three major approaches are used to examine microstructure damage from DTI data: (1) whole-brain voxel-based analysis, (2) region-of-interest analysis, and (3) *in vivo* tractography (Mechelli, 2005). Briefly, whole-brain voxel-based DTI examination is an operator-independent method that lets the analysis of entire brain volume. Additional approach contains finding a region of attention to recognize between-group differences and correlations in a specific brain region. DTI also delivers chance to achieve *in vivo* tractography, or virtual dissections, of major white matter pathways. Furthermore, DTI of white matter fiber tract integrity were measured in varsity-level college athletes who had sports-related damages devoid of loss of consciousness and experienced symptoms for at least 1 month after injury. Notable abnormalities in structural integrity were present in subjects after they sustained concussion (Tremblay, 2014). The structures most contacted were the left temporal lobe, the retro lenticular part of the internal capsule, and the posterior thalamic radiation, which contains fibers that connect the frontal and occipital lobes as well as the temporal and occipital lobes. Affected patients were found to have amplified mean diffusivity and reduced FA in comparison with control groups.

DTI irregularities of the corpus callosum have been steadily related to reduction in cognitive function in TBI. Potholes were similarly witnessed in patients who experienced TBI in civilian settings and were examined within 90 days after the trauma. White matter ruts may establish a subtle biomarker of axonal injury that can be recognized in TBI at acute and chronic phases of its clinical sequence. DTI holds promise as a method by which to objectively assess abnormal cerebral connectivity underlying cognitive deficits in TBI. Single subject results were not reported but it can be assumed that significant inter-individual inconsistency for location and extent of WM wound exists due to varying injury mechanisms (and forces) and biological (neural and non-neural) differences across patients (Kou and Haacke, 2014).

MRS: Cellular changes to neurons and glia following TBI are complex and dynamic. Proton (1H) MRS has the benefit of assessing brain metabolism *in vivo*, and is able to sense various biochemical processes of brain injury such as the loss (or dysfunction) of neuronal cells. MRS measures brain metabolites that reflect local neuronal integrity and cell membrane turnover (Sailasuta, 2012). Application of MRS to TBI was recently reviewed. Because TBI makes a cascade of alterations in brain metabolites, containing neuronal and axonal loss, MRS has the potential to improve our understanding of the underlying metabolic disturbances in TBI. The major peaks observed in proton MRS of brain include N-acetyl aspartate (NAA) + N-acetyl aspartyl glutamate (NAAG) (it is generally hard to resolve these resonances and NAA + NAAG is referred to as NAA), creatine (Cr), choline (Cho), and myoinisotol (mI) (Castellano, 2012). NAA is believed to be a specific neuronal marker. Creatine resonance has contributions from creatine and phosphocreatine and raised Cr levels may signify gliosis. Choline resonance has contributions from multiple molecules that contain phosphoryl choline, glycerol phosphoryl choline, and choline plasmalogen, and a minor contribution from acetylcholine and choline. Choline top imitates cell membrane metabolism and raised Cho concentration represents discriminating cell membrane turnover as seen in demyelination, remyelination, inflammation, and gliosis (Appenzeller, 2008). Myoinisotol is thought to be glial specific and is also a precursor of phospholipid membrane constituents and its concentration is affected by the formation and breakdown of myelin. TBI is known to induce changes in Nacetylaspartate (NAA) (a neuronal marker), choline (Cho) (a marker for membrane disruption, synthesis, or repair), and lactate (Lac) (a measure of anaerobic glycolysis). Many studies of metabolic changes after TBI have proven MRS to be a sensitive tool to predict neurologic, cognitive, and functional outcome. Significant decreases of NAA and increases of Cho have been observed in ‘‘normal appearing ’’WM or GM following moderate to severe TBI. Elevated Cho may be detected in WM as a breakdown product after shearing of myelin84 and the presence of lactate in the brain suggests hypoxic/ischemic injury. Recently, some researchers found that increased frontal white matter (FWM) Cho/creatine and decreased FWM NAA/Cho at acute stage are useful for predicting functional outcome in patients with moderate to severe TBI (Holshouser, 2006). In addition, they also found that elevated Glx and Cho in the acute stage are sensitive indicators of injury and predictors of poor outcome in normal appearing brain of severe TBI patients. They also found that the decrease of NAA at subacute stage is more predictive of patient outcome in TBI studies, there are relatively less data reported in comparison with moderate to severe TBI studies. For a chronic TBI study, scanned 20 TBI patients and 17 age- and gender-matched

controls and reported that the TBI group had more variations in NAA, Cre, and Cho than the control group. Investigation of 20 patients with TBI from 9 days to years after injury and found that whole brain NAA decreased by 12% along with significant global and grey matter atrophy, in comparison with 19 controls. This further demonstrates NAA as a biomarker of neuronal injury or cellular loss. Regarding the investigations of TBI in the subacute or semi acute stages, a few studies reported an NAA/Cr decrease, which is suggestive of neuronal loss. A recent study on 10 patients with TBI in the semi-acute stage showed creatine increases in white matter and Glx (glutamate and glutamine) decreases in grey matter (Wilde, 2014). The creatine (Cre) increases in white matter were correlated with patient's executive function. The same research group also studied a relatively larger group of patients with longitudinal follow-up. In their study of 30 TBI patients at the first visit within 3 weeks after injury, they reported Cre and Glx increases in WM and Glx decreases in GM. Among the patients, 17 returned for follow-up at the chronic stage; their GM Glx demonstrated normalization and their WM Cre and Glx demonstrated a trend of normalization (Mayer, 2015). Of particular note is that, at the first visit, the TBI group did not have any difference from the controls in neuropsychological assessment except for more somatic, cognitive, and emotional symptoms. This demonstrates that MRS may be sensitive to subtle changes of the brain, which may not yet be manifesting significant neural cognitive deficits. As with other MRI techniques, MR spectroscopy has also undergone tremendous advancements in the past two decades, evolving from single voxel MR spectroscopy to 2D spectroscopy imaging and 3D whole brain spectroscopy imaging. Single voxel spectroscopy (SVS) allows gaining of a solitary spectrum from one volume portion (voxel) typically 8 cm3 or more, whereas 2D or 3D MRS, also called chemical shift imaging (CSI), allows for the concurrent gaining of multiple spectra from smaller adjacent voxels through multiple sections of the brain (HAACKE). MRS has an inherent advantage over SVS because it is better able to evaluate regional distributions of neurochemical alterations. Instead of hypothesizing a certain region or certain slice of the brain to have abnormal metabolite signals; 3D MRS allows investigators to search the whole brain to identify any area that might have abnormal metabolites. This could be useful in TBI due to the fact that choosing an arbitrary region to study would be like searching for a needle in a haystack. Used a 3D-MRS sequence to scan 20 mild and 9 moderate TBI patients and found a extensive reduction of NAA and NAA/Cre, and surges of Cho and Cho/NAA, inside all lobes of the TBI subject group, and with the principal alterations seen in WM. Examination of the association between all of the metabolite measures and the neuropsychological test scores found the strongest negative correlations to occur in the frontal lobe and for Cho/NAA. One caveat of the previous MRS work on TBI is that Cre has been used as an internal reference with the assumption that Cre levels will remain constant after injury. However, this might not be true in an injured brain, which could have Cre disturbance after TBI. The Cre increase in TBI patients at the semi-acute stage might give a false impression of decreased NAA/Cre level. It is therefore important to quantitate metabolite concentrations carefully, particularly after TBI, to determine possible small changes in all metabolites. Comparing metabolite ratios may mask important metabolite changes. However, the results for MRS in TBI are not always consistent, but studies suggest that quantification of neurochemicals with MRS could offer a noninvasive and safe approach to assessing brain cellular injury and response.

PWI: PWI was performed arterial spin labeling is a method that utilized an endogenous contrast instrument in which blood cells flowing into the brain are highlighted by the MR signal without need for administration of an external contrast agent, making this method completely noninvasive and repeatable (Mechtler, 2014). Regional flow distributions can be assessed independently. After the primary brain damage occurs, even more devastating secondary brain injuries can occur. This usually includes, but is not limited to, ischemic and hypoxic damage, cerebral swelling, and rise of intracranial pressure, hydrocephalus, and infection in moderate to severe TBI patients at the acute stage. The injury to the brain can result in disturbance of cerebral blood flow (CBF), which correlates with poor brain tissue oxygenation, and unfavorable neurological outcome, which is implicated in rendering the brain vulnerable to secondary damage (HAACKE). It has been recognized that the failure of brain perfusion is the most common type of hypoxic-ischemic brain damage, but is difficult to identify even in histological studies. Cerebral ischemia is present in approximately 90% of patients who die with head injury (Unterberg, 1997). Furthermore, after TBI, the uncoupling between CBF and brain metabolic demand occurs, whereby local cerebral glucose demand increases and local CBF is disturbed due to damage to the vascular muscle tone and arterioles. The early hyper-glycolysis is thought to be due to the cellular efforts to reestablish ionic gradients. Different aspects of ischemia and/or edema after injury can be quantified using perfusion imaging, including PWI and arterial spin labeling (ASL), DWI, and DTI. Kim (2010), used ASL to measure the resting state CBF in 28 moderate to severe TBI at chronic stage and found a) a global decrease of CBF in TBI patients than that in controls, and b) projecting local hypo perfusion in the posterior cingulate cortices, the thalami, and multiple locations in the frontal cortices. Though, in the population of TBI, how cerebral perfusion is being affected in patients and their association with patients' neurocognitive status is still less understood (Kim, 2010). Given the milder severity in TBI patients, PWI at the acute stage could be meaningful both for clinical decision making and patients' outcome prediction. ASL to study 21 TBI patients at the chronic stage and demonstrated decreased CBF in both edges of the thalamus, which is correlated with

the patients' speed of information processing, memory, verbal, and executive function (Legge, 1985). In summary, our knowledge is very limited in the understanding of cerebral blood flow and its impact to TBI patients. PWI of TBI, particularly at the acute stage, might shed new light in our understanding of this disease. Finally, PWI within 1 to 3 hours after injury displays harder and extensive perfusion shortfalls compared with imaging studies that are undertaken 24 hours after head damage.

Table 1. Main imaging modalities include conventional, specific and advanced in prognosis, diagnosis, treatment and management of the TBI.

Characteristics / Modalities	Strengths	Limitations	Potential prospective in theranostic and management
Noncontrast CT	Readily available in emergency department	Insensitive to axonal injury and early infarction	Acute surgical decision making and automated lesion volume measurements for prognostic evaluation
CT with contrast, including CT angiography	Detect most immediately life-threatening traumatic lesions	Poor visualization of brainstem and axonal injury	Relative sensitive in evolution of intracranial lesion and hydrocephalus, and good method for vascular injury assessment
Conventional MRI techniques including T1-weighted, T2-weighted, and FLAIR MRI	Good gray-white tissue contrast, good visualization of brainstem, and sensitive to edema	Insensitive to early infarction and axonal injury	Anatomical visualization of brainstem, especially cisternal effacement, visualization of arterial dissection. Also, Automated volumetric analysis of regional and global atrophy for prognostic and pharmaco dynamic evaluations
Diffusion-weighted imaging (DWI)	Sensitive to early infarction	Anatomical distortions	Assessment of micro hemorrhages for medicolegal purposes and early infarction
Susceptibility-weighted imaging (SWI)	More sensitive to microhemorrhage	Slower to acquire	Assessment of micro hemorrhages for medicolegal purposes. Also, prognostic planning, especially in children
Magnetic resonance Spectroscopy (MRS)	Sensitive to selected aspects of brain chemistry	Slow to acquire, poor spatial resolution, and extensive analysis required	Assessment of injured large white matter tracts for prognostic and pharmaco dynamics evaluations
DTI (DTI)	Sensitive to axonal injury, especially at crossing fibers and close to gray-white junction.	Research only	Assessment of large and moderate sized injured white matter for prognostic and pharmaco dynamic evaluations. Also, potential use in tractography.

Vision of Imaging in TBI and the biomarkers role in their diagnosis, treatment and management: Overcoming the shortage of drugs with proven clinical efficacy in TBI is a major challenge for neuroscience research and the pharmaceutical industry committee (Zitnay, 2008). Pathophysiological heterogeneity of patients with TB, lack of adequate pharmacokinetics analysis to determine the optimal dose, combining data outside the therapeutic window and insensitive measure may therefore limit clinical efficacy. International efforts to develop a diagnostic-therapeutic system based on imaging biomarker for the management and treatment of patients with TBI may facilitate comparison to choose a set of homogeneous group of patient's in future clinical trials (Sharp, 2011).

From skull X-rays, to CT, to conventional MRI, to newer MRI methods such as DTI and GRE and SWI, each new models of imaging methods proves more irregularities following traumatic brain damage than the previous one (Haacke, 2012). There is no reason to believe that this progression has reached an asymptote. Even our most sensitive approaches may still misjudge the degree and severity of brain damage following brain trauma. Several characteristics and advantages of imaging biomarkers set them apart from other biomarkers including:

- Imaging has been in routine use for diagnosis and disease management for several decades, and the ability to identify a wide spectrum of pathophysiology using imaging methods is well established.
- Imaging biomarkers are going be much more strictly related with the expressed phenotype of conditions, thus allowing direct associations between therapy and effect.
- Functional imaging provides a dynamic picture of the disease.
- Imaging offers tremendous versatility for providing continuous, structural, and functional assessments of therapy, offering snapshots of the bioactivity of drug compounds overtime.

- Imaging provides therapy assessments in animals and humans similarly and is then a significant tool for advancing translational investigation.
- Imaging has now arrived in the molecular era with molecular imaging and nanoparticles as contrast media (Pien, 2005).

In contrast DTI have some limitations including based on an oversimplified model, not specific to a particular microstructural feature (e.g., myelin content, axon density etc.), unreliable in voxels with >1 dominant, fiber direction: "crossing-fibers" (i.e., most of the brain white matter), dependent on data quality, limited spatial resolution, dependent on data acquisition parameters, quantitative measures influenced by many non-biological factors, changes in quantitative measures are difficult to interpret, results are user and parameter dependent, different scanners have different acquisition settings confounding reproducibility and standardization, cannot differentiate the directionality of axons: afferent vs. efferent, anterograde vs. retrograde pathways, inhibitory vs. excitatory connections, direct vs. indirect routes. Furthermore, the multiple assumptions that underpin the algorithms used in post-processing of DTI data are not always applicable. Practical challenges associated with conducting DTI studies in TBI populations include transportation, logistic issues concerning scanning, timing of DTI scanning, and standardization of data acquisition and analysis protocols (Sener, 2016). Neuroimaging techniques can provide additional clinical information, but the diagnostic capabilities of these techniques are limited by their sensitivities, accessibility, high capital costs, and service requirements. CT is the most rapid and widely available neuroimaging technique, yet its usefulness in detecting diffuse brain damage from axonal shear injury is limited. In critically ill patients and in those with contraindications to undergo MRI, brain MRI frequently cannot be obtained. Furthermore, limited availability, high cost, and the time to acquire and to analyze images limit the use of advanced MRI techniques and capable of detecting regional changes in blood flow but cannot necessarily detect structural damage Ultimately, postmortem pathologic analysis remains the "gold standard" for the extent and severity of injury. Based on this brief description one may conclude that each of the MRI modalities is sensitive to different aspects of tissue pathology. It is possible to improve the pathologic specificity in TBI by using multimodal MRI, but DTI is a potentially validate and prognostic tool in prognosis, diagnosis and surgical evaluation of TBI for neurologists and neurosurgeons. Clearly, brain imaging plays a major role in the diagnosis and management of traumatic brain injury (Gualtieri, 1995). This role is evolving rapidly as new imaging methods are developed and the focus turns towards the less severe injuries which make up the vast majority of cases. Beyond these methodological considerations, and from a neuroscientific point of view, the anatomy of the major white matter association pathways recently has been reanalyzed by associating specimen dissection with *in vivo* DTI. This combination resulted in new findings about CNS anatomy. DTI also is an excellent educational tool, especially because of the development of the atlas of human white matter tracts. Such a 3-dimensional representation of the pathways and their relationships can be very helpful for training young neurosurgeons, neurologists, neuroradiologists, neuroanatomists, neurophysiologists, and neuroscientists. However, it is worth noting that physicians (particularly neurosurgeons) should not mix general information given by DTI as a didactic tool outside the operating theater with individual data provided by DTI during CNS surgery (for example, incorporated in a neuronavigational system). First, as mentioned, DTI is not yet reliable enough to be used routinely at the individual level. It is thus crucial to avoid making any amalgam between statistics underlying DTI and personalized management depending on the functional anatomy of each patient. In addition, DTI will never compensate for the lack of knowledge of CNS anatomy by the physician, who should use this tool to learn anatomical basics before caring for patients. In conclusion, it is too early to speak about the impact of DTI in clinics. This methodology currently has many drawbacks and should be validated before being included in decision making for individual patients, as currently recommended by the experts in this field (Dayhoff and DeLeo, 2001). Today, DTI should be considered a research and educational tool, in order to make us aware that CNS anatomy is not well enough understood in humans.

2. CONCLUSION

DTI is a powerful tool for evaluating white matter anatomy and associated abnormalities. DTI was previously a research tool, but is entering clinical practice. Understanding the terminology and basic concepts of this technique can aid in the clinical implementation and interpretation of this blend of structural and physiologic white matter evaluation.

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