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Advanced neuroimaging to quantify myelin \textit{in vivo}: Application to mild TBI

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Abstract

Background: Difficulty providing accurate diagnosis and prognosis, especially after mild forms of traumatic brain injury (TBI), has increased efforts to detect changes in white matter microstructure using advanced neuroimaging techniques. Although methods such as diffusion tensor imaging (DTI) have greatly increased knowledge of white matter changes resulting from TBI, several shortcomings limit the utility of these techniques particularly when applied to populations with mild TBI (mTBI) history. \textit{In vivo} imaging of myelin may be particularly well suited to detect changes in white matter microstructure resulting from mTBI.

Review: This manuscript will briefly review the animal and histological data supporting the importance of myelin following TBI, contributions and shortcomings of the use of diffusion tensor imaging (DTI) in mild TBI and the utility of multi-component relaxometry (MCR) techniques as a method for improved visualizing of white matter microstructural integrity in myelin.

Conclusion: The use of MCR-based techniques has potential as a clinical and research tool to assess and track changes in myelin as well as the common behavioural changes such as slowed processing speed following TBI.

Introduction

A traumatic brain injury (TBI) is brain tissue damage resultant from an external force that results in loss or alteration of consciousness and immediate, if only transient, neurological symptoms [1]. TBI severity occurs on a continuum from mild-to-severe, based on length of loss of consciousness, length of post-traumatic amnesia, Glasgow Coma Scale [2] or similar rating and presence/absence of standard imaging findings [3]. White matter tracts are selectively vulnerable to the impact-acceleration forces that occur during TBI. White matter integrity (WMI) is significantly associated with injury characteristics and post-concussive symptoms after even mild forms of TBI (mTBI), with more severe injury and post-concussive symptoms observed in those with greater white matter damage [4–8]. WMI can also predict neurobehavioural outcome if measured acutely after injury [9–11].

Although myelin comprises a large component of white matter, it has been under-studied in TBI [12]. Data from animal studies suggests that myelin loss occurs in mTBI [13–15] and that myelin loss may persist chronically [16], especially after multiple mTBIs [17]. Furthermore, myelin damage likely causes reciprocal damage to the underlying axon it encases [18,19] and has been implicated as an emerging treatment target after TBI [20]. From a behavioural standpoint, loss of myelin may underlie the slowed processing that is commonly observed in those with a history of mTBI [21,22]. By definition, there are no structural imaging findings in mTBI [3], despite the persistence of behavioural symptoms in ~15% of those who sustain a mTBI, although this estimate is highly contested and dependent on the evaluation context [23]. Thus, the attribution of post-concussive symptoms to mTBI is largely reliant on patients’ self-report of their symptoms and cognitive test performance which are non-specific to mTBI and overlap with psychiatric disorders such as depression and post-traumatic stress disorder (PTSD). This has been particularly problematic given increased rates of psychiatric disorders after TBI both in civilians [24] and Veterans [25]. A sensitive biological marker of axonal and, more specifically, myelin damage at the microstructural level would greatly aid in the diagnosis of mTBI, allow for tracking of brain changes over the recovery period and serve as a marker in treatment efficacy studies.

Computed tomography (CT) and structural magnetic resonance imaging (MRI) are commonly used techniques to identify the extent of damage following moderate-to-severe TBI [26]. Although more recently developed neuroimaging techniques such as diffusion imaging have provided foundational...
knowledge about changes in white matter following TBI, they may fall short in capturing the true nature of damage following mTBI, particularly changes in myelin microstructure. More sensitive methods such as multi-component relaxometry (MCR) have recently emerged to quantify myelin content and may aid in understanding of myelin damage and recovery in mTBI.

This manuscript will review the animal and histological evidence for interrogating myelin specifically after mTBI. Next, it will briefly review diffusion tensor imaging (DTI) as it has been widely studied in mTBI in recent years [27], has demonstrated white matter microstructural changes in normal appearing white matter as seen on conventional T1- and T2-weighted MRI [5] and produces a metric that may specifically measure myelin content [28]. Finally, this review will examine the utility of MCR techniques as a method for visualizing white matter microstructural integrity in myelin in individuals with a history of mTBI.

The role of myelin in TBI

Despite accounting for a major component of white matter, the role of myelin pathology is understudied in TBI [12,29]. Myelin is the fatty covering of axons in the brain that allows rapid transmission of information by saltatory conduction [30] and damage and/or loss of myelin can negatively influence axonal integrity. In an adult human brain, myelin comprises ~35% of the dry weight [31] and structurally is composed of a lipid layer surrounded by two layers of protein that border the axon [30]. Oligodendrocytes are responsible for forming myelin [32], which provides maintenance of the cytoskeleton of nerve cells and can protect axons from degeneration [33–35]. Death or dysfunction of oligodendrocytes can also result in impaired brain function [36]. Damage to myelin may occur due to an overt loss of axon and myelin tissue [37,38] or as a result of secondary chemical cascades such as demyelination that occur both acutely and chronically after TBI [39].

Animal studies suggest that TBI induces widespread myelin loss. Several studies have demonstrated myelin loss and oligodendrocyte damage as a result of axonal damage in rat models up to days to weeks after TBI [37,38]. This loss of myelin likely compromises the integrity of the axon, which may in turn affect neuronal signalling and cognitive function [40,41]. Even stretch injuries that cause minor damage to the axon can cause disruptions in myelin sheath as demonstrated in optic nerve studies with guinea pigs [13,14]. Furthermore, a loss of myelin staining in the corpus callosum of the rat brain was observed in association with progressive white matter atrophy up to 1 year post-injury [16].

Accumulating evidence suggests that demyelination of intact axons is a separate process than axon degeneration observed after focal axon loss, a relatively rare occurrence after TBI [12,39,42]. Secondary processes such as Wallerian degeneration and those mediated by oligodendrocyte vulnerability such as oxidative stress, loss of energy, excitotoxicity and pro-inflammatory cytokines may cause myelin injury after TBI [38]. Studies of mild and moderate TBI induced in the rat brain have demonstrated apoptotic oligodendrocyte loss in various white matter regions including the internal and external capsules, corpus callosum and fimbria, possibly due to loss of trophic support [37,43,44]. Another study using a rat model of TBI demonstrated proteolysis of an important myelin structural protein. The authors speculated that this degradation was due to structural damage of the myelin membrane or excitotoxicity of oligodendrocytes, ultimately leading to instability of the myelin sheath and demyelination [45]. Demyelination can promote axonal vulnerability [39,46] and inflammatory processes such as microglial activation, even after mTBI [47].

Furthermore, a study that induced demyelination in rats found impairments on a place avoidance task that was developed to detect cognitive deficits after TBI in rodents [20]. Also in rodents, blast-induced mTBI was associated with changes to both axonal and myelin integrity [15]. Finally, animal studies that have attempted to induce ecologically valid models, such as repetitive mTBI, have demonstrated continued myelin damage 1–2 months after TBI [15,17].

Fewer studies have examined myelin neuropathology in humans with a history of TBI, however there is growing awareness of its role in disorders that affect cognition [48]. A study in patients with head injuries that survived 5 hours to 10 days revealed apoptotic oligodendroglia in white matter using staining techniques to characterize lesions and their time course [49]. Histochemical analysis of diffuse axonal injury (DAI) in humans has revealed both acute myelin globoids [50] as well as damage to long white matter tracts [51].

Myelin is also emerging as a target for treatment after TBI. Remyelination allows for recovery of function in damaged axons and prevents them from further damage [33,52]. Several studies have demonstrated evidence of spontaneous increase of oligodendrocyte progenitor cells days to weeks after myelin loss in TBI rat models [12,38]. Furthermore, this spontaneous remyelination corresponds to the regaining of cognitive functioning that was previously impaired in TBI-induced rats [20]. It is still unknown, however, whether increases in myelin after TBI is indicative of myelin biogenesis and neural plasticity [12,53].

Animal studies and emerging data in humans, indicate that TBI induces widespread myelin loss and, from a behavioural standpoint, myelin damage may underlie the slowed processing that is commonly observed in those with a history of TBI [54,55]. Therefore, targeting in vivo imaging of myelin holds promise as a specific metric of these changes. Further exploration of myelin damage in TBI would likely inform diagnosis, prognosis and intervention targets [29], especially given the link between myelin loss and progressive neurodegeneration after TBI as in chronic traumatic encephalopathy [53,56]. Identification of a mTBI event from a thorough medical history is generally clear, but identification of who will experience a protracted recovery or, in post-acute cases, whether non-specific symptoms such as mood, behaviour and cognitive changes are related to a remote TBI event, are not clear; myelin-specific imaging methods could improve diagnosis of mTBI, advance understanding of the pathophysiology of mTBI in humans and enhance prognosis in mTBI.

DTI: assessment of axonal and myelin integrity in mTBI

Advanced neuroimaging techniques like DTI have shown great promise in detecting subtle changes in white matter
and have improved understanding of the pathophysiology of mTBI over and above what could be obtained via conventional techniques (e.g. T1- and T2-weighted structural MRI or CT). White matter tracts such as the cingulum bundle, anterior corona radiata, uncinate fasciculus and superior longitudinal fasciculus are among the most consistently implicated structures in DTI studies of mTBI [57–61], but not all studies have found differences in white matter integrity between mTBI and controls [62]. Fractional anisotropy (FA) is a common metric produced with DTI that describes the degree to which diffusion of water is restricted. Values can range from zero (diffusion is isotropic or unrestricted) to one (diffusion is restricted and occurs only along one axis) and generally reflect white matter integrity. One limitation of DTI is that findings are non-specific; reduced FA in the corpus callosum is also found in those with major depression and PTSD [63,64]. However, reduced FA or other white-matter findings from DTI imaging are not consistently found in mood disorders either [65]. Although DTI has identified subtle white matter changes that standard structural imaging has missed, DTI lacks specificity and is unable to identify whether damage has occurred to the axonal membranes, myelin sheath or other components of the microstructure and microarchitecture [10]. Because DTI metrics reflect fibre coherence, factors such as inflammation, gliosis and axonal loss can also confound interpretation [66].

Radial diffusivity (RD), the diffusion perpendicular to the predominant orientation of axonal fibres, may be the most specific measure of myelin from DTI [67,68]. Increased RD has been demonstrated in adults with a history of mild and moderate-to-severe TBI across the whole brain and specific white matter regions [61]. Furthermore, RD has been found to correlate with cognitive measures in mild and moderate TBI [69]. However, decreased RD has also been identified in those with a history of TBI [70] and can be significantly influenced by inflammation and axonal properties [71,72]. Finally, critics of RD have noted its susceptibility to ‘fictitious change’, especially in the presence of crossing fibres and have highlighted the need for measurement of corresponding eigenvalues underlying tissue structure. However, these measurement methods are complex and typically not available to clinical researchers, thus the use of RD in clinical populations has been discouraged [73]. Damage and recovery after mTBI is complex, thus there is a need for measures that are specific to myelin damage and correlate highly with histopathological studies.

Application of multi-component relaxometry MR techniques to mTBI in vivo

Various MCR-based techniques have been utilized to elucidate tissue microstructure based on the unique relaxation characteristics of distinct tissue compartments. MCR is a robust technique to quantitatively estimate myelin content [74] that has been shown to be more sensitive and specific to myelin growth and degeneration than standard DTI in healthy adults [75]. It also corresponds highly with gold standard histological measurements and has good longitudinal and across-site/platform repeatability in post-mortem multiple sclerosis (MS) and rat models of inflammation and injury [76–78]. A novel MCR-based imaging technique called multi-component-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT) [79,80] has recently been developed to calculate myelin volume in vivo. mcDESPOT decomposes the magnetic resonance (MR) signal into three water compartments: free water (intra- and extra-axonal space), trapped water (between bilayers of the myelin sheath) and the CSF or free water pool and the T1 and T2 of that pool. Each compartment contributes a unique MR signal and results in MWF, a surrogate marker of myelin volume, whereas DTI acquisition only provides information on the directional preference of water diffusion. Emerging studies using mcDESPOT in vivo have found decreased myelin integrity in patients with MS, a disorder that primarily affects myelin, compared to healthy controls. Furthermore, MWF in MS patients was negatively and significantly correlated with worse performance on a timed test of motor dexterity and worse scores on a clinical rating scale of MS disability severity [81,82]. More recently, MWF was shown to correspond to language abilities and processing speed in healthy infants and toddlers [83,84], a stage of exponential development of myelin, and decreased MWF was found in infants at genetic risk for Alzheimer’s disease [85]. Interest in applying this technique to other disorders that affect myelin during development [66] and later in life [86] has also emerged.

Recently, MCR has been used with a 32 echo T2 scan sequence in concussed athletes to derive MWF [87]. Reduced MWF was found at 2 weeks post-injury relative to pre-injury scans in several regions including the corpus callosum, posterior thalamic radiation, corona radiata, superior longitudinal fasciculus and internal capsule, but MWF values were recovered to pre-TBI values at 2-month follow-up. Unpublished case study pilot data from the research group shows 6–11% reductions in MWF across whole brain and corpus callosum measurements in a combat exposed Operation Enduring Freedom/Operation Iraqi (OEF/OIF) Veteran with a history of mTBI as compared to a combat Veteran with no mTBI history. These nascent results highlight both the feasibility of acquisition and processing of this data, as well as the potential for its sensitivity to mTBI. However, the samples are small, examine individuals with a single concussive event and did not evaluate relationships between MWF and demographic, injury or neurocognitive variables. Additionally, the Wright et al. [12] study is somewhat contradictory to animal models showing myelin changes in mild closed-skull impacts in mice up to 6-weeks post-injury. Thus, future studies are warranted employing MCR techniques in those exposed to a varying number of mTBIs and the inclusion of other relevant variables (e.g. neurocognitive) to expand understanding of the role of myelin in this population.

Given that histological, animal and one human study suggest individuals with a history of mTBI have more myelin breakdown than those without a history of mTBI, taken together with the limitations of conventional DTI metrics, MCR techniques may be a particularly useful technique to study myelin content in TBI. Further, the mcDESPOT sequence may be particularly well-suited due to its spoiled and fully refocused steady state imaging, which gives it the potential for improved signal-to-noise ratio, shorter acquisition times and greater volumetric coverage compared to other
MCR approaches [88]. MWF is insensitive to confounds, such as oedema, inflammation and crossing fibres, that are often present with other white matter imaging techniques [67,73]. Because myelin integrity is directly related to its conduction velocity, MCR may offer a brain biomarker for the slowed cognitive and motor processing speed that for many individuals persist after the expected recovery period following a mTBI. This is further supported by the significant relationship between slowed motor processing speed and lower MWF in individuals with MS and young children. Despite these factors, there is only a single published report to date that applied MCR to mTBI in humans; therefore, it still needs to be optimized and investigated with this population to determine if it adds greater precision over DTI and whether it is sensitive and specific to mTBI and corresponds to post-concussive behavioural manifestations or symptom complaints.

Conclusion

Although compelling evidence exists validating mcDESPOT results with histology and computer modelling of the human brain in demyelinating diseases and early development, efforts to apply MCR in other conditions that affect white matter, but are not classically demyelinating conditions, are more nascent. There is currently only a single published study using MCR following sports concussion, although emerging pilot data suggest potential utility to also detect lower myelin content in a combat-exposed Veteran with a history of mTBI. Future work will be needed to validate the usefulness of this novel myelin-specific imaging with TBI in larger samples and by examining correspondence between mcDESPOT and neuropathological studies in TBI. Additional work is also needed on how mcDESPOT can be integrated into multimodal imaging protocols, to augment other white matter imaging such as DTI as well as to determine its relationship to measures of resting state functional connectivity. Just as DTI represented significant advance over standard structural imaging in improving understanding of microstructural changes to white matter following TBI, MCR holds great promise to further advance understanding of the contribution of myelin changes following TBI.

Declaration of interest

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