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Invited review

# Myelin and oligodendrocyte lineage cells in white matter pathology and plasticity after traumatic brain injury

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ABSTRACT

Impact to the head or rapid head acceleration–deceleration can cause traumatic brain injury (TBI) with a characteristic pathology of traumatic axonal injury (TAI) and secondary damage in white matter tracts. Myelin and oligodendrocyte lineage cells have significant roles in the progression of white matter pathology after TBI and in the potential for plasticity and subsequent recovery. The myelination pattern of specific brain regions, such as frontal cortex, may also increase susceptibility to neurodegeneration and psychiatric symptoms after TBI. White matter pathology after TBI depends on the extent and distribution of axon damage, microhemorrhages and/or neuroinflammation. TAI occurs in a pattern of damaged axons dispersed among intact axons in white matter tracts. TAI accompanied by bleeding and/or inflammation produces focal regions of overt tissue destruction, resulting in loss of both axons and myelin. White matter regions with TAI may also exhibit demyelination of intact axons. Demyelinated axons that remain viable have the potential for remyelination and recovery of function. Indeed, animal models of TBI have demonstrated demyelination that is associated with evidence of remyelination, including oligodendrocyte progenitor cell proliferation, generation of new oligodendrocytes, and formation of thinner myelin. Changes in neuronal activity that accompany TBI may also involve myelin remodeling, which modifies conduction efficiency along intact myelinated fibers. Thus, effective remyelination and myelin remodeling may be neurobiological substrates of plasticity in neuronal circuits that require long-distance communication. This perspective integrates findings from multiple contexts to propose a model of myelin and oligodendrocyte lineage cell relevance in white matter injury after TBI.

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## 1. Introduction

Traumatic brain injury (TBI) most commonly results from head impact and/or rapidacceleration–deceleration of the head. Within the brain, these forces initiate tissue damage in white matter tracts that is characterized by traumatic axonal injury (TAI) and may be accompanied by microhemorrhages. With TAI, damaged axons are dispersed among intact axons within white matter tracts. The extent and location of axon damage becomes more distributed with increasing injury severity, which has led to clinical classification as grades of diffuse axonal injury (DAI) (Adams et al., 1989; Kim and Gean, 2011). Grade I DAI involves TAI in areas of gray matter-white matter junctions in the corona radiata. Grade II DAI involves TAI in gray matter–white matter junctions and the corpus callosum, with progression from the splenium toward the genu with increasing severity. Grade III DAI involves sites from Grades I and II with the addition of brainstem tracts.

Mitigating this TAI pathology is the focus of studies aiming to improve diagnosis and treatment of patients who experience impact-acceleration head injuries. While TAI is the primary concern in white matter injury after TBI, multiple pathological features that accompany TAI have important roles throughout the post-injury time course. Although blood vessels are considered less vulnerable to damage than axons, the presence of microhemorrhages is an important indicator of white matter injury in TBI (Blumbergs et al., 1995; Kim and Gean, 2011). Additionally, neuroinflammation has gained significant attention as a major contributor to chronic neurodegeneration in white matter tracts after TBI (Johnson et al., 2013). On the other hand, the impact of TBI on myelination has been relatively understudied even though TAI occurs in the white matter environment. A recent review focused on the role of myelin in the susceptibility of axons to TAI and subsequent neurodegeneration (Armstrong et al., 2015). This review will put forth the perspective that oligodendrocytes and myelin play important roles in the progression of white matter pathology and in the potential for plasticity after TBI.

## 2. Effect of axon degeneration on the myelin-oligodendrocyte unit after TBI

Depending on the injury severity, TBI exhibits heterogeneous damage with different implications for the survival of oligodendrocytes and potential for myelin repair. In normal white matter, a single oligodendrocyte maintains myelin sheaths around a cohort of axons (Fig. 1A). In relatively mild TBI with TAI, the dispersed pattern of axon degeneration in the white matter would be expected to involve relatively few of the axons myelinated by a given oligodendrocyte (Fig. 1B). Consistent with this prediction, experimental closed skull impact that produced a low density of TAI in the corpus callosum did not appear to disrupt the myelin-oligodendrocyte unit. In this impact-acceleration model, oligodendrocyte survival was not altered and there was continued synthesis and transport of a reporter protein into myelin membranes (Sullivan et al., 2013; Mierzwa et al., 2015). Therefore, in response to TAI, oligodendrocytes may survive, maintain processes to myelin sheaths, and be left responding to signals from a mixed cohort of degenerating and intact axons (Fig. 1B).

Focal lesions with destruction of white matter tissue can result from microhemorrhages or neuroinflammation associated with TBI (Fig. 1C). Focal lesions result in axon loss along with the death of oligodendrocytes, which is due to caspase-3 mediated apoptosis (Lotocki et al., 2011; Flygt et al., 2013). With this damage to axons and oligodendrocytes, myelin sheaths will collapse and undergo degradation. However, clearance of collapsed sheaths and myelin debris is a protracted process in the CNS (Vargas and Barres, 2007).

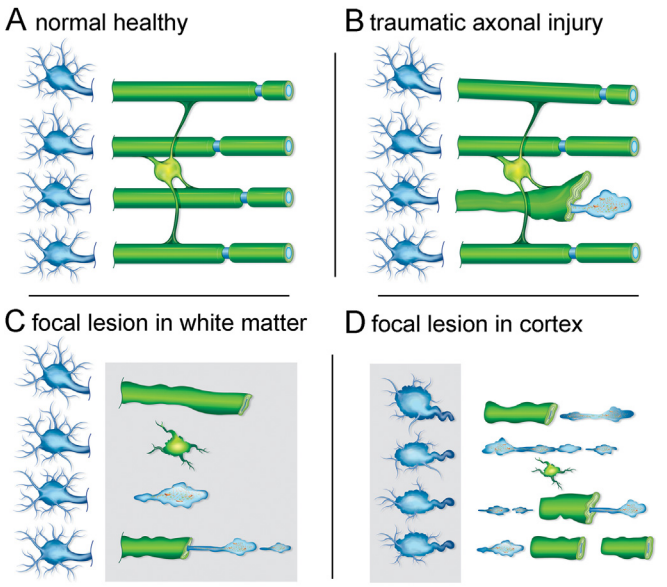


**Fig. 1.** Effect of axon degeneration on the myelin-oligodendrocyte unit in different pathological scenarios following traumatic brain injury. Schematic of a myelin-oligodendrocyte unit in the normal adult brain (A) or after different pathologies associated with traumatic brain injury (B–D). In the healthy condition (A), neurons (blue) in the cerebral cortex (left side of panel) extend axons that project through the white matter (right side of panel). Myelin and oligodendrocytes are shown in green. Each oligodendrocyte forms myelin sheaths around multiple axons. Nodes of Ranvier (blue) are specialized regions of axon between adjacent internodal lengths of myelin. Traumatic axonal injury (B) causes axon degeneration, as illustrated by a single damaged axon among a set of adjacent intact axons. Axon damage from traumatic axonal injury often initiates at nodes of Ranvier. Damaged axons swell, fragment, and form end bulbs with accumulations of organelles and cytoskeletal elements. Double-layered myelin sheaths often extend out from degenerating axons. The length of these myelin figures exceeds that expected from collapse of the myelin sheath around a degenerating axon. Traumatic brain injury can cause focal lesion areas in white matter (C, gray box). Focal lesions, for example from microhemorrhages or neuroinflammation, damage a high proportion of axons, oligodendrocytes, and myelin. The cerebral cortex can undergo similar focal tissue destruction (D, gray box), particularly in cortical regions underlying the site of an impact to the head. Axons become disconnected from damaged cortical neurons. Degeneration of a high proportion of axons in a white matter tract leads to subsequent myelin degradation and oligodendrocyte death. These three scenarios (B–D) focus on damage to the neuron and axon to show the relationship to the myelin-oligodendrocyte unit. Scenarios C and D illustrate loss of myelin as a result of overt tissue damage that includes loss of axons. None of the examples illustrates actual demyelination, i.e. loss of myelin around an intact axon, which can also occur after traumatic brain injury.

Myelin debris may trigger or exacerbate neuroinflammation since myelin-enriched debris has been shown to stimulate microglial activation (Clarner et al., 2012).

Impact and/or acceleration of the head that results in TAI in the white matter may also involve contusions on opposite poles of the brain, due to movement of the brain relative to the skull (Dawson et al., 1980; Bayly et al., 2005). Contusions can lead to the death of cortical neurons, including those with axons projecting through the same white matter tracts exhibiting TAI (Fig. 1D). A focal cortical region of neuronal cell death will result in degeneration of the associated axons along with myelin collapse. Subsequently, microglia and macrophages will be stimulated to phagocytose the axon and myelin debris. Oligodendrocyte loss is expected to follow due to the lack of axonal interaction and the detrimental effects of the neuroinflammatory environment.

After TBI, abnormal myelin histopathology in white matter tracts can present as loss of stain, myelin globoids, and myelin pallor (Ng et al., 1994; Onaya, 2002; Johnson et al., 2013). Interpretation of these myelin findings depends on the integrity of the axons. White matter injury that involves myelin loss along with

axon loss is distinct from demyelination of intact axons. Electron microscopy is the gold-standard for evaluating demyelination as loss of myelin around intact axons. In an animal model of TAI, studies using electron microscopy have demonstrated that demyelinated axons are a significant component of white matter pathology (Sullivan et al., 2013; Mierzwa et al., 2015). Work in demyelinating diseases has shown that demyelination leaves intact axons more vulnerable to subsequent damage whereas remyelination protects axons and leads to recovery of function (Irvine and Blakemore, 2008; Bruce et al., 2010). Thus, demyelination is a possible factor in the evolution of chronic neurodegeneration in TBI while approaches to promote remyelination could augment neuroprotective strategies.

## 3. Myelination as a factor in vulnerability to neuropsychiatric disorders after TBI

TBI is associated with complex neurobehavioral, cognitive, and motor deficits that vary with injury type, severity, and the specific neuroanatomical location of the tissue damage. Mild TBI, or concussion, can cause prolonged symptoms referred to as postconcussive syndrome (Laborey et al., 2014). Repetitive mild TBI increases the probability of postconcussive syndrome, which has symptoms that overlap with posttraumatic stress disorder (PTSD) and depression; this relationship appears to cross both civilian and military settings for mild TBI exposures (Goldstein et al., 2012; Kontos et al., 2013; Haagsma et al., 2014; Lagarde et al., 2014; Reid et al., 2014). TBI, especially when experienced late in life, can also increase the risk of neurodegenerative diseases including Alzheimer's, Parkinson's, and motor neuron disease (Daneshvar et al., 2015; Gardner et al., 2015; Gardner and Yaffe, 2015). The long term sequelae from repetitive mild TBI, and potentially subconcussive head impacts, contribute to chronic traumatic encephalopathy (CTE), which also exhibits differential symptoms based on age. The neuropsychiatric components of TBI and CTE raise interesting implications for exploring axon vulnerability relative to the delayed myelination of the frontal lobes.

CTE is diagnosed postmortem based on a constellation of pathological features that includes abnormalities of tau, a microtubule binding protein, that result in formation of neurofibrillary tangles. Hyperphosphorylated tau is found in perivascular foci that are typically found around small vessels at the depth of the cortical sulci; the frontal cortex is the most common site of tau neurofibrillary tangles when only a few epicenters are present (CTE Stage I) and the frontal and temporal lobes exhibit the most severe neurofibrillary degeneration when tau pathology is widespread (CTE Stage III) (McKee et al., 2013). Younger adults diagnosed with CTE have have been reported to have mood and behavioral changes, symptoms in common with PTSD and depression, while older patients with CTE have primarily exhibited cognitive deficits similar to Alzheimer's disease and more frequently show amyloid-β deposits (Goldstein et al., 2012; McKee et al., 2013; Sundman et al., 2014).

Myelination changes may amplify the psychiatric component of TBI or contribute to susceptibility to prolonged symptoms. Frontal brain regions that are involved in major affective disorders are also regions frequently injured in TBI. Frontal lobe regions experience a high probability of axon damage from TBI based on force estimates, neuroimaging analysis, neurocognitive assessments and neuropathological evidence (Wallesch et al., 2001; McAllister et al., 2012; McKee et al., 2013; Eierud et al., 2014; Carman et al., 2015). Importantly, myelination continues into adulthood in white matter tracts of association areas such as frontal cortex, which undergoes extensive myelination after 20 years of age (Yakovlev and Lecours, 1967; Bartzokis et al., 2001; Baumann and Pham-Dinh, 2001; Lebel et al., 2012). Late myelination may increase the vulnerability of axons to primary and secondary damage from TBI, similar to the high vulnerability of unmyelinated axons to TBI (Reeves et al., 2005, 2012). Myelin and oligodendrocytes protect axons by reducing energy demand and providing metabolic and trophic support (Hirrlinger and Nave, 2014; Nave and Werner, 2014; Simons et al., 2014). In this context, it is intriguing that Braak and Braak noted that the neuroanatomical pattern of neurofibrillary pathology in the progression of Alzheimer's disease recapitulates the inverse sequence of cortical myelination (Braak and Braak, 1996). Furthermore, abnormal myelin fatty acid composition in the frontopolar cortex has been correlated with major depressive disorder (Tatebayashi et al., 2012).

Correlations between myelination and specific neuropsychiatric symptoms after TBI are challenging based on current clinical evidence. Animal studies provide examples that support oligodendrocyte and/or myelination roles in behavioral symptoms related to TBI. Myelination changes in prefrontal cortex result from social isolation during critical periods in mouse development; these myelination deficits are not reversed by reintroduction to a social environment (Makinodan et al., 2012). Similarly, in adult mice, social isolation results in epigenetic changes in oligodendrocytes that impair myelination in prefrontal white matter (Liu et al., 2012). Mice with a myelin gene deletion provide a proof-of-principle example of a potential causative relationship. Mice with only one allele of the gene for CNP (2′,3′-cyclic nucleotide 3′-phosphodiesterase) have low grade neuroinflammation in white matter tracts that is exacerbated with aging and correlated with development of catatonia and depression-like symptoms (Hagemeyer et al., 2012). This phenotype in CNP haploinsufficient mice is similar to reports of patients with the AA allele of CNP, which causes a lower level of CNP expression in frontal cortex (Hagemeyer et al., 2012). Experimental TBI in CNP haploinsufficient mice exacerbated neuroinflammation and neurodegeneration that corresponded with deterioration of working memory (Wieser et al., 2013). Further studies of neuropsychiatric sequelae in TBI will be required to determine the extent to which myelination and oligodendrocytes may play direct roles or may set the stage for vulnerability to further damage and dysfunction, as has been implicated in other disorders (Edgar and Sibille, 2012; Haroutunian et al., 2014; Nave and Ehrenreich, 2014).

## 4. Myelination as a factor in plasticity after TBI

Reduced white matter integrity in TBI correlates with functional deficits in cortical circuits (Hulkower et al., 2013; Eierud et al., 2014; Perez et al., 2014). Slowed or reduced action potential conduction results from loss of myelin internodes, disruption of paranodes, and/or abnormal widening of nodes of Ranvier (Arancibia-Carcamo and Attwell, 2014). Therefore, demyelination or changes in myelin structure can contribute to desynchronized neural circuits or impaired information processing speed, which is a prominent symptom in patients with mild TBI (Waxman, 2006; Dams-O'Connor et al., 2013; Donders and Strong, 2014; Pajevic et al., 2014). The resolution of symptoms may then indicate effective remyelination. Within 2–4 weeks after traumatic injury, myelin sheaths can form with reconstruction of the node of Ranvier to support restoration of impulse conduction (Sasaki et al., 2006; Powers et al., 2013).

Recent studies in mice indicate direct and dynamic roles of myelination in neuronal function that have significant implications for designing rehabilitative approaches in TBI. Surprisingly, the longitudinal distribution of myelin sheaths along an axon varied with the neuronal position among the cortical layers so that the myelination profile could modulate long-distance communication

properties of different neocortical cell types (Tomassy et al., 2014). Further studies demonstrated that the generation of oligodendrocytes and myelin can be specifically modified with changes in neuronal activity. Sensory deprivation from whisker clipping during postnatal myelination resulted in apoptosis of oligodendrocytes in somatosensory cortex, but not motor cortex (Hill et al., 2014). Conversely, neuronal activity in motor cortex promoted oligodendrocyte production with adaptive myelination in motor pathways that was sufficient to alter gait of the corresponding limb (Gibson et al., 2014). Furthermore, motor skill learning was dependent on active myelination (McKenzie et al., 2014). Mastering the skill of running on a wheel with variably placed rungs stimulated oligodendrocyte production in the corpus callosum and was impaired by inducing a deficit in oligodendrocyte production in adult mice. Together, these findings demonstrate a specific and active role of myelin in the function of sensory and motor cortical circuits involving white matter pathways. In theory, effective myelin remodeling in TBI patients may be a neurobiological substrate of neuroplasticity.

In TBI conditions that cause demyelination of intact axons, remyelination also presents an opportunity for plasticity and recovery of function. In an animal model of TAI, electron microscopy of the corpus callosum revealed thinner myelin and higher g-ratio values, which are characteristic of remyelination (Sullivan et al., 2013; Mierzwa et al., 2015). Cellular changes also indicated active remyelination following TBI based on increased proliferation of oligodendrocyte progenitor cells, generation of new oligodendrocytes, and higher levels of myelin gene transcription. However, the source of new cells for remyelination after TBI is not yet clear. In demyelinating disease models, both neural precursor cells from the subventricular zone and oligodendrocyte progenitors in the white matter are sources of remyelinating oligodendrocytes (Xing et al., 2014). Analysis of the subventricular zone response in TBI has focused mainly on models with significant cortical neuron loss (Chen et al., 2003a, 2003b; Ramaswamy et al., 2005; Radomski et al., 2013; Saha et al., 2013). As noted above and illustrated in Fig. 1D, a focal cortical region of neuron cell death will result in degeneration of the associated axons, which precludes analysis of remyelination. The overall proliferation of subventricular zone cells was not altered in response to TAI in the corpus callosum (Sullivan et al., 2013). Direct comparison of TBI models with cortical neuron damage versus corpus callosum TAI revealed distinct responses among subventricular zone cells based on activation of the Sonic hedgehog signaling pathway, an important regulator of neural stem cells in adult CNS (Mierzwa et al., 2014). These studies indicate that analysis of the cellular and molecular mechanisms of regenerative responses to TBI must consider the specific tissue damage in need of potential cell replacement and repair.

Double-layered myelin sheaths are also a prominent finding in TBI models with a relatively low density of TAI (Shitaka et al., 2011; Sullivan et al., 2013; Bennett and Brody, 2014; Mierzwa et al., 2015). Several processes can generate myelin that folds back onto itself rather than tightly wrapping around an axon. Double-layered myelin sheaths can form as myelin collapses around degenerating axons. However, double-layered myelin sheaths that are much longer than predicted from axoplasmic collapse are present in white matter regions with TAI (Mierzwa et al., 2015). Therefore, additional processes may be involved in generating excessively long double-layered myelin figures after TBI. During synthesis of new myelin sheaths, the myelin folds out from the axon and back onto itself to generate excess membrane prior to extending to the full internodal length and tightly enwrapping the axon (Snaidero et al., 2014). These double-layered myelin sheaths folding out from intact axons have been referred to as redundant myelin (Rosenbluth, 1966). Redundant myelin figures are also found in the normal adult CNS, particularly in older animals (Sturrock, 1976; Peters, 2002; Mierzwa et al., 2015). In TBI, the frequency of excessively long double-layered myelin figures strongly correlates with the frequency of degenerating axons (Sullivan et al., 2013; Mierzwa et al., 2015). It is not yet clear whether the excessively long myelin figures observed after TBI are generated during the synthesis of new myelin. One possible scenario is that excessive myelin figures may be generated when an oligodendrocyte is ensheathing a degenerating axon among a cohort of intact axons, as shown in Fig. 1B. Further studies will be required to understand the generation of these long double-layered myelin sheaths and their relationship to myelin synthesis or degeneration in the progression of white matter injury involving TAI.

Beyond the production of oligodendrocytes for remyelination and myelin remodeling, oligodendrocyte progenitor cells have additional roles, particularly in response to trauma. Oligodendrocyte progenitors, often identified by expression of NG2 chondroitin sulfate proteoglycan, are a dynamic population of cells found throughout the brain and spinal cord in both white matter tracts and gray matter structures (Bergles et al., 2010; Trotter et al., 2010). NG2 cells were originally characterized based on their reactive changes after brain injury (Levine, 1994). In response to trauma from experimental stab wound, cortical damage, or spinal cord injury, NG2 cells proliferate and contribute to glial scar formation (Levine, 1994; Hughes et al., 2013; Filous et al., 2014; Susarla et al., 2014). NG2 associated with the glial scar stabilizes dystrophic axons to potently inhibit regeneration (Filous et al., 2014). Traumatic injuries that do not cause overt tissue damage with glial scar formation may still involve NG2 cells through the other roles this progenitor population plays in CNS functions. In the normal adult mouse cerebral cortex, NG2 cells elaborate non-overlapping processes in a grid-like fashion (Hughes et al., 2013). These cortical NG2 cells have GABAergic and glutamatergic synaptic interactions that enable experience dependent proliferation and redistribution, which may regulate information processing at neuronal synapses (Mangin et al., 2012; Sakry et al., 2014) (Velez-Fort et al., 2010). NG2 cell interactions with demyelinated axons may also be modulated by glutamatergic synapses that guide remyelination. In a model of experimental demyelination, corpus callosum axons made transient glutamatergic synapses with NG2 cells prior to differentiation into oligodendrocytes (Etxeberria et al., 2010). These synaptic interactions may be relevant in milder TBI models since NG2 cell density is increased in both the cortex and corpus callosum in closed head TBI that does not cause a glial scar (Sullivan et al., 2013; Mierzwa et al., 2014). The functional implications of these roles of NG2 cells in response to the different forms of tissue damage from TBI will be important to explore given the implications for axon regeneration, neuroplasticity, and remyelination.

## 5. Conclusion

The information reviewed can be integrated into a speculative model that emphasizes the relevance of white matter injury in TBI. Myelination patterns in the brain may influence the vulnerability of neural circuits to initial injury or secondary damage in TBI. Furthermore, TBI that alters neural activity may modify myelination along axons, even in adults. This myelin remodeling can modulate neural circuits to impact diverse functions including social interaction, learning, and movement. NG2 progenitor responses to injury may also modify neural circuit functions. In addition, demyelination may be a significant component of white matter injury in TBI. Demyelination can cause slowing or desynchronization of neural circuits, contributing to diverse symptoms but particularly impaired information processing speed. Importantly, conduction along denuded axons can be restored by

remyelination, which may contribute to a high incidence of symptom resolution in mild TBI patients. However, white matter injury with extensive axon degeneration or conditions that favor neuroinflammation will increase susceptibility to chronic neurodegeneration with prolonged symptoms.

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