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Function and Mechanism of Myelin Regulation in Alcohol Abuse and Alcoholism

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Abstract

Excessive alcohol use has adverse effects on the central nervous system (CNS) and can lead to alcohol use disorders (AUDs). Recent studies have implicated that myelin reductions may directly contribute to CNS dysfunctions associated with AUDs. Myelin consists of compact lipid membranes wrapping around axons to provide electrical insulation and trophic support. Regulation of myelin is considered as a new form of neural plasticity due to its profound impacts on the computation of neural networks. In this review, we first discuss experimental evidence showing how alcohol exposure causes demyelination in different brain regions, often accompanied by deficits in cognition and emotion. Next, we discuss postulated molecular and cellular mechanisms underlying alcohol's impact on myelin. It is clear that more extensive investigations are needed in this important but underexplored research field in order to gain a better understanding of myelin-behavior relationship and to develop new treatment strategies for AUDs.

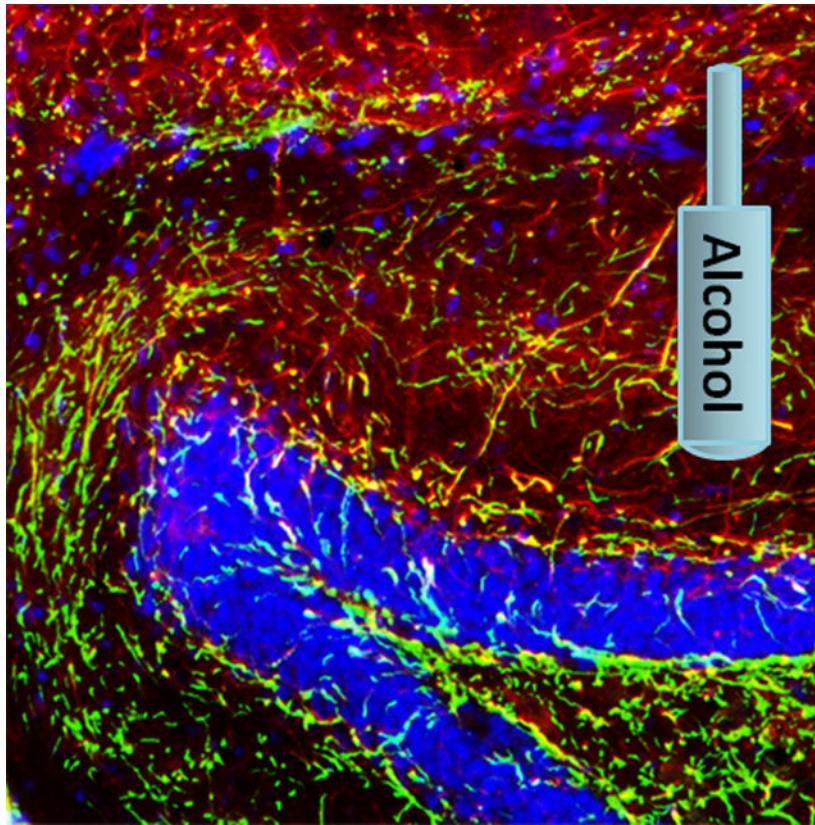
Graphical abstract

Myelin consists of compact lipid membranes wrapping around axons to provide electrical insulation and trophic support, and can be regulated to profoundly alter brain functions. In this review, we discuss recent progress regarding how alcohol exposure causes demyelination in different brain regions, accompanied by deficits in cognition and emotion.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.



Keywords

Alcohol use disorder (AUD); central nervous system (CNS); alcohol addiction and dependence; myelin; oligodendrocyte (OL); oligodendrocyte progenitor cell (OPC); activity-dependent neural plasticity

1. Introduction

Alcohol use disorders (AUDs) represent an enormous social and economic burden. Alcohol, also known by its chemical name ethanol (EtOH), is one of the oldest and most commonly consumed psychoactive substances worldwide. EtOH is typically classified as a depressant of the central nervous system (CNS) that affects multiple neurotransmitter systems, especially the GABAergic system, in various regions throughout the brain. Moreover, EtOH is a known teratogen, and particularly damaging during critical periods of rapid brain development. Consumption of high levels of EtOH is associated with its neurotoxic effects in the CNS, and alcohol addiction or AUDs in humans. AUD is a chronic relapsing disease of the brain characterized by compulsive alcohol use, loss of alcohol intake control, and a negative emotional state when not using ^[1]. EtOH-related problems can manifest themselves after both acute and chronic exposure as not only an impairment in neurophysiological functions, but also behaviorally, including craving, tolerance, physical dependence and withdrawal. Besides indirect effects on the brain through other organs/systems, such as the heart, liver, pancreas and the immune system, EtOH can directly impact brain cells. Chronic

EtOH exposure can cause receptor up/down regulation and structural alterations of neurons and high doses of EtOH can lead to myelin cell death. For instance, EtOH has been shown to interfere with long-term potentiation and long-term depression, two potential mechanisms in the regulation of memory formation and storage [2,3]. These functional changes appear associated with changes in the formation of dendritic spines and the expression of neuronal genes [4,5]. Deficits in white matter and its related functions have also been reported. Recent studies show a strong link between EtOH consumption and the function of CNS myelin [6].

In the CNS, myelin is formed by processes that emanate from mature oligodendrocytes (OLs) that are differentiated from oligodendrocyte progenitor cells (OPCs) throughout the brain. As opposed to the Schwann cells that myelinate axons in the peripheral nervous system, OLs can myelinate multiple segments of multiple nearby axons. Myelin sheaths are made up of compact lipid membranes that wrap around the axon, providing electrical insulation and trophic support [7]. Myelin facilitates the propagation of action potentials along an axon in a saltatory fashion that is faster and more energy efficient compared to unmyelinated axons. Dense bundles of myelinated axons crossing the brain appear white to the naked eye and are thus known as white matter. While most research involving myelin has focused on these white matter tracts, many axons in gray matter are also myelinated. However, the function and mechanism of gray matter myelination remain poorly understood. Recent studies found that a significant proportion of gray matter myelination in the cortex is present on the axons of local inhibitory interneurons in both rodents and humans [8,9]. Besides potentially different intrinsic properties, it is anticipated that gray matter and white matter myelination may be regulated differently in the brain due to the distinct microenvironments.

Although myelin has traditionally been thought of as merely a passive insulator, recent reports highlight the role of OLs and myelination in the function and development of the CNS (for more details see recent review articles [10–12]). Disruption of myelin can lead to the dysregulation of various neural circuits and give rise to disease symptoms associated with not only sensory and motor functions, but also higher brain functions, including those manifested in multiple sclerosis (MS), bipolar disorder, and schizophrenia [13]. Uncovering the regulators of myelination has become increasingly important for diagnosis and treatment of these diseases, perhaps including AUDs as well in the near future.

2. Alcohol-induced myelin damage in human brains

Several recent studies have reported detrimental effects of alcohol on white matter integrity and function in humans. Using magnetic resonance imaging and diffusion tensor imaging techniques, Monnig et al (2015) found a significant association between severity of alcoholism ratings and white matter fractional anisotropy (FA). As AUD ratings increased, FA values, as a measure of white matter integrity, decreased. This relationship persisted even when controlling for the number of years drinking [14]. Similar results were reported in another study that utilized a longitudinal research design in subjects who sought treatment for AUDs and then either abstained from alcohol or relapsed after treatment. Interestingly, FA deficits reported in subjects with AUDs were reduced in those that abstained from alcohol compared to those that relapsed. Although FA values in the abstaining group were

lower than controls, the trend in these individuals over the course of the study was positive and approaching control levels, while the opposite was true for those that relapsed. Furthermore, measures of FA and axial diffusivity in heavy-drinking relapse subjects demonstrate accelerated white matter aging [15]. Although these studies involved individuals from heavy-drinking human populations, even moderate EtOH consumption in adults has been shown to impact white matter microstructure. Structural MRI scans in a cohort of adults that were followed for 30 years found that moderate and heavy drinking subjects were significantly more susceptible to hippocampus atrophy and microstructural damage in the corpus callosum. These structural deficits were correlated with declining lexical fluency [16]. Of note, white matter reduction only suggests potential demyelination, since white matter also contains other cell types, including axons and astrocytes, in addition to mature OLs.

Postmortem studies have confirmed demyelination in humans with a history of AUDs. Multiple studies have reported reduced brain weight in individuals with AUDs, most of the decrease being in white matter (See more details in review articles [17,18]). A recent study showed that human AUDs are associated with substantial reduction of frontal lobe white matter lipid expression with regional variability, using MALDI imaging mass spectrometry to characterize lipid biochemistry for correlation with lifetime exposures and white matter degeneration, altered gene expression, and responses to abstinence or treatment [19]. Altered myelin ultrastructure in human AUDs was detected using transmission electron microscopy (TEM). In white matter from the brain of human alcoholics, there was an increase in the frequency of myelin membranes that were irregularly folded and split, indicating vacuoles between the myelin lamellae (Figure 1A, B), as well as swollen axons with enlarged mitochondria [20]. Other reports have noted changes in gray matter brain regions as well in subjects with AUDs [21]. Autoradiography studies used to detect specific neurotransmitter receptors in individuals with a history of alcohol use found decreased serotonin (5-HT) receptor binding in several brain regions, including the insular cortex, the cingulate cortex, the medial temporal lobe, and the raphe nucleus-the primary locus of 5-HT neurons in the CNS [22]. Significant increases in glutamate receptor (GluR) subtypes GluR2 and GluR3 were found in the hippocampus of alcoholics postmortem, suggesting alterations in glutamate signaling [23]. These brain areas are critical to limbic system function, and are implicated in various behaviors that are known to be affected by alcohol, including social behavior, learning, short- and long-term memory, and addiction. These regions also contain gray matter myelin, but the extent to which gray matter myelin is altered in AUDs remains unknown.

There are limitations associated with human studies, despite their necessity in understanding AUDs. First of all, most of these studies involve self-report of alcohol consumption. The timing of alcohol exposure and the type of alcohol consumed are highly variable and difficult to control for. In particular, developmental alcohol studies in humans have to rely on self-reports from subjects and families involved in prenatal or adolescent EtOH exposure that tend to be underestimated and unverifiable. Furthermore, it is difficult to carry out mechanistic studies with human subjects. Therefore, it is essential to use animal models to gain a better understanding of the role of myelination in AUDs.

3. EtOH-induced alterations of CNS myelin in animal models

The impact of EtOH on myelin in the brain has been established in various animal models. The extent of EtOH-induced demyelination varies in different brain regions and at different ages. Alcohol exposure during pregnancy can lead to fetal alcohol spectrum disorders (FASDs). Imaging studies revealed white matter abnormalities associated with cognitive impairment in children with FASDs [24,25]. Using a third trimester-equivalent mouse model of FASD, Newville and colleagues found a 58% decrease in the number of mature OLs and a 75% decrease in the number of proliferating OPCs within the corpus callosum of EtOH-exposed mice at postnatal day 16, but not the numbers of these cells derived from the postnatal subventricular zone [26]. Similar to the findings in the corpus callosum, a significant decrease in the number of prenatally derived mature OLs was observed in two other brain regions. These effects, albeit partially recoverable, can lead to long-lasting white matter injury, an observation that is consistent with FASD in humans [26]. In contrast, prenatal exposure of EtOH had no effect on myelination in the developing caudal pyramidal tract (i.e. corticospinal axons) in rats [27]. Progressive white matter atrophy in the corpus callosum with altered lipid profiles is partially reversed by short-term abstinence in a chronic binge model with adult male rats [28].

An important brain region that is affected by EtOH exposure is the medial prefrontal cortex (mPFC), which is critical for higher-order learning and social behavior. The mPFC has been shown to continue to develop well into adulthood, and numerous studies have been carried out to investigate the effects of EtOH exposure during adolescence on related neurobehavioral function [29]. Prolonged abstinence from EtOH leads to increases in myelin basic protein (MBP) expression in the mPFC [30], while acute exposure to EtOH during adolescence results in damaged myelin in the mPFC of rats [31]. This result is similar to the reductions in mPFC have been reported in mice that were socially isolated for up to 8 weeks [32]. It should be noted that re-socialization with their cage mates resulted in the stabilization of myelin-associated protein levels in these mice. Adolescent mice treated intermittently with EtOH for 2 weeks demonstrated ultrastructural alterations of myelin including inter-laminar splitting of myelin sheaths (Figure 1C) [33]. It would be interesting to investigate the extent to which EtOH and other stress (e.g. social isolation) affect myelination through a similar mechanism. Taken together, the studies using animal models showed EtOH-mediated effects on myelination, resembling some aspects of AUDs in humans. Experimental results from animal models lay a foundation for further mechanistic studies.

4. EtOH impacts the development of OLs

EtOH can affect myelination at multiple stages of OL development (Figure 2). Several lines of research have implicated multiple signaling pathways through which EtOH exposure may directly disrupt OPC differentiation and survival in the CNS. Developmental studies show that *in vitro* EtOH disrupted the expression of platelet-derived growth factor receptor alpha (PDGFR α) [34], which is crucial for the differentiation of OPCs into myelinating OLs. More recently, Vangipuram and Lyman [35] used human fetal brain tissue cell cultures to show that EtOH reduced Wnt3a and Wnt5a expression, while Wnt signaling can regulate OL cell fate specification, differentiation and proliferation, besides its role in regulating neurons

[36][37,38]. Given that blocking Wnt signaling is associated with reduced expression of multiple myelin proteins and myelin sheath compaction [39], it appears that Wnt signaling might mediate the regulation of myelin by EtOH exposure.

Signaling pathways involved in early life brain development are also important in relation to the teratogenic effects of EtOH. The signaling pathway of brain derived neurotrophic factor (BDNF) plays a key role in myelination [40–42], and can be altered by EtOH exposure. EtOH exposure and withdrawal were shown to bidirectionally alter BDNF levels in the amygdala via the expression of the immediate-early gene *Arc*. The blockade of *Arc* function on the BDNF pathway in the amygdala lead to increased EtOH consumption and anxiety-like behavior in rats [43]. The cannabinoid (CB) pathway is implicated in myelin function and impacted by EtOH as well. Postmortem studies found a link between alcoholism and CB receptor function. In the PFC, there was an increase in CB receptor 1 binding that coincided with reduced levels of monoacylglycerol lipase, extracellular signal-regulated kinase, and cyclic-AMP response element-binding protein, which are all critically involved in CB signaling [44]. WIN55212.2, a CB receptor agonist, increased OPC proliferation *in vitro*, as well as MBP mRNA and protein expression in mice [45], whereas blocking the metabolism of endogenous CBs decreased OL excitotoxicity and demyelination *in vitro*, and preserved myelin integrity in a demyelinating mouse model [46]. EtOH exposure alters CB ligands in several brain areas related to memory and addiction (e.g. PFC, Amygdala [47]). CB receptors on GABAergic neurons were implicated in modulating the effects of acute EtOH exposure [48] in the amygdala, and systemic blockade or deletion of CB receptors leads to reduced voluntary EtOH consumption and operant responding for EtOH in rodents [49]. Furthermore, using genomic profiling of transcripts in the PFC, a recent study showed that binge ethanol reduced myelin-related gene expression and altered chromatin modifying genes involved in histone demethylation at H3K9 and H3K36. Thus, EtOH may regulate histone methylation as a switch for regulation of myelin [50]. These are the potential pathways that EtOH exposure during critical periods of development can have long-lasting effects on neurobehavioral function and could, in part, explain the deficits noted in FASDs, as well as persistent cognitive and behavioral problems related to adolescent binge alcohol exposure. As an extension of this, it would also be interesting to investigate how changes in CB/myelin function might underlie subsequent EtOH consumption and addiction.

Recently, the endogenous opioid system was implicated in remyelination, or the active generation of new myelin sheaths around previously demyelinated axons. Opioid function has a long-established link to the rewarding effects of EtOH and other drugs of abuse [51–53], but recent evidence suggests that opioid function is related to remyelination. Specifically, antagonism of kappa opioid receptors led to increased differentiation of OPCs in both rodent and human cell culture, and also led to increased remyelination after focal demyelination *in vivo* [54]. Furthermore, the deletion of kappa opioid receptors in knockout mice lead to even greater myelin damage after induction of experimental autoimmune encephalitis, a mouse model of MS [55].

EtOH effects during development are particularly important, as OPCs that have yet to differentiate into OLs are more vulnerable to excitotoxic damage than mature OLs. Specifically, there are several factors that contribute to this increased sensitivity of OPCs to

apoptosis, including higher AMPA/kainite GluR expression [56], elevated metabotropic GluR expression, and an increase in the expression of calcium-sensitive GluR subunits in OPCs. Consistent with this observation, a recent study in human brain tissue found elevated levels of NMDA GluR subunits in both gray matter and white matter regions of the brain. These NMDA subunits include one highly permeable to calcium influx, and the other insensitive to magnesium. These factors indicate that OPCs, as well as neurons, in the developing brain are particularly sensitive to Glu activation and thus more likely to suffer excitotoxicity and apoptosis [57]. In order to link this developmental sensitivity to excitotoxicity with EtOH exposure, Creeley et al [58] used non-human primates to examine the effects of prenatal EtOH exposure on OL apoptosis. Results showed that OL lineage cells were far more likely to be damaged/dying compared to other glial cells, and that this was directly related to EtOH exposure during the 3rd trimester period of development. These OLs appear to be specifically vulnerable to the teratogenic effects of EtOH when they are just beginning to express MBP prior to myelinating nearby axons. It is important to note that above-mentioned signaling pathways have also been shown to regulate neurons in addition to their impact on myelin cells. Further research is needed to identify myelin-specific regulatory pathways affected by EtOH.

5. EtOH impacts mature OLs

EtOH can affect mature myelinating OLs or myelin. Several studies have focused on the proteins that make up the actual myelin sheath, including MBP, proteolipid protein (PLP), myelin associated glycoprotein (MAG), and myelin oligodendrocyte glycoprotein (MOG). Brain tissue taken from the fetuses of pregnant BALB/C mice that were exposed to a liquid EtOH diet from gestational day 4–17 had reduced MBP expression compared to controls. There was no difference in the expression of neural cell adhesion molecule, suggesting that EtOH effects were specific to the myelin protein [59]. Similarly, Zoeller and coworkers [60] found that cerebellar MBP and MAG levels were not altered by prenatal alcohol exposure in rats at postnatal day 15. However, when rat pups were exposed to EtOH postnatally from days 4–10, a developmental period that is equivalent to the third-trimester of development *in utero* for humans, deficits in MBP and MAG expression were found that persisted into adulthood. This third-trimester equivalent exposure to EtOH occurs during a period of rapid development in the cerebellum [61], suggesting that myelin defects after EtOH exposure might be regionally and developmental-period dependent. Work utilizing primary glial cell cultures from Sprague-Dawley rats exposed to EtOH during the last two weeks of gestation found delayed MBP and transferrin expression that persisted for up to three weeks, without affecting other glial markers [62].

To evaluate the relationship between myelin and EtOH, one strategy is to investigate how overexpression of myelin-associated proteins impact EtOH consumption in rodents. A recent paper utilized this approach by virally overexpressing the zinc finger protein Myelin Transcription Factor (MyT1) in the dentate gyrus of rats. After recovery, MyT1 rats and sham controls were tested on a variety of behavioral tasks to assess anxiety-like behavior and EtOH consumption. MyT1 overexpression was associated with a decrease in anxious behavior on the elevated plus maze, and decreased voluntary EtOH consumption [63]. This result suggests that increasing myelination in the dentate gyrus may have an anxiolytic effect

on behavior, while reducing EtOH consumption. This result is consistent with the human literature showing a negative correlation between white matter integrity and responsiveness to alcohol cues in individuals with AUDs [14,64].

How does EtOH carry out its toxic effect on OLs and myelin? Although EtOH itself has been shown to be neurotoxic, acetaldehyde, the primary metabolite of EtOH, might also contribute to OL excitotoxicity. In fact, a recent experiment in mouse primary OL cultures exposed to various concentrations of EtOH and acetaldehyde for 7 days found that OLs were far more sensitive to acetaldehyde than to EtOH. Significant cell death did not occur with EtOH until doses above 120 mM, while similar levels of OL toxicity were achieved at 50 μ M in acetaldehyde [65]. Therefore, it is important to distinguish the effects between EtOH and acetaldehyde on myelination in future studies.

6. EtOH can indirectly impact myelin through its microenvironment

EtOH can affect microglia in the brain to indirectly alter myelination. Activation of glial toll-like receptor 4 (TLR4) can activate microglia to cause OL cell death and demyelination. In particular, chronic EtOH exposure was shown to activate TLR4 and the downregulation of PLP, MBP, MOG, and MAG protein expression, whereas knockout mice lacking TLR4 receptors did not [66]. To further investigate the relationship between EtOH and TLR4 function, Bajo et al [67] injected mice that were EtOH dependent with the TLR4 antagonist T5342126 for two weeks while measuring their voluntary consumption of EtOH in a 2-bottle choice paradigm. Results showed that blocking TLR4 reduced EtOH consumption while reducing the density of microglia in the central amygdala but not the dentate gyrus. It is important to note, however, that this reduction in EtOH consumption was accompanied by reduced locomotor activity, body temperature, and saccharine consumption. The issue of microglial activation in response to EtOH (and other brain insults) is complex, with both pro- and anti-inflammatory effects reported [68,69]. EtOH appears to promote microglial activation, such that a single binge exposure may be inconsequential, but subsequent EtOH exposure results in even greater activation of microglia [69]. Although a single exposure to EtOH may not have a dramatic effect on microglial activation, it may induce microglial priming, where the microglia are more susceptible to inflammatory insult [70]. Withdrawal from EtOH might be important for this partial activation of microglia, as Walter and Crews [71] report initial decreases in microglial gene expression, followed by increases during withdrawal. Similarly, EtOH exposure during key periods of development can have a long-lasting impact on the immune and inflammatory response on the brain [72,73]. With specific emphasis on myelin and OPCs/OLs, it was previously noted that EtOH activates TLR receptors, leading to an inflammatory response in microglia [66]. When TLR4 receptors are blocked by T5342126, this effect is blunted, and voluntary EtOH consumption is reduced as well [67]. Recent studies suggested that maternal binge-like alcohol consumption induces neuroinflammation (upregulation of TLR4 and NF- κ B) and myelin damage in the brains of offspring and that such effects may underlie the persistent cognitive and behavioral impairments observed in FASDs [74,75]. It was further shown that nalmefene, an opioid antagonist, prevents neuroinflammation and brain damage by blocking the TLR4 response and support the role of central pro-inflammatory immune signaling in the modulation of alcohol addiction [76]. Although these studies highlight the complex nature of microglia

activation (i.e. different subtypes of microglia mediating pro- or anti-inflammatory responses [77]), it is clear that EtOH can damage OL lineage cells and myelin indirectly via microglia activation. TLR4 activity appears to be related to a wide range of functions in the brain, limiting the attractiveness of TLR4 as a therapeutic target for AUDs. Nonetheless, TLR4 signaling in reward circuits continues to be an important focus in relation to EtOH consumption and the progression of addiction in the CNS [78,79].

EtOH can impact the third major class of glial cells in the brain, astrocytes, while astrocytes can also regulate myelination and OL damage. The earliest systematic studies of the effect of EtOH on the development of the human CNS revealed impairments in the proliferation and migration of glial cells [80], and more recent studies suggest that, in addition to altering the brain inflammatory response, EtOH can also negatively impact astrocytes via oxidative stress (see more details in the review article [81]). The blood brain barrier (BBB) is an important brain structure that is dependent on astrocyte function that could also be impacted by EtOH exposure. Haorah et al [82] used human brain microvascular endothelial cells (that make up the BBB) *in vitro* to study the effects of EtOH and acetaldehyde on BBB integrity. EtOH and acetaldehyde exposure reduced barrier tightness, altered barrier permeability, and disrupted monocyte migration across the BBB by activation of protein tyrosine kinase. Such an effect could lead to increased susceptibility to neurotoxic insult or stroke in the brain, providing another indirect pathway by which EtOH could damage OLs and myelin function in the brain.

It is well established that EtOH alters neuronal function in a number of brain regions at both the system and molecular levels (See more details in a recent review article [83]). Given the recent interest in how neuronal function can influence myelination in both gray matter and white matter regions (See more details in recent review articles [11,12,84]), it is important to consider how EtOH might influence experience-dependent myelination via disrupted neuronal signaling. It is clear that functional activity can lead to preferential myelination of active axons [85,86], and the cellular processes involved have been the focus of recent research. Interestingly, glial cells, including OPCs/OLs, form unique non-synaptic connections with neurons, and these junctions are important for myelin formation related to neuronal function [85,87]. Operant responding for EtOH [88] and acute EtOH exposure *in vitro* [89] modulate gap junction function, providing an intriguing mechanism for EtOH to impact myelination. Acetylcholine signaling has long been studied with regard to myelin function [90] and is also implicated in the self-administration of EtOH [91,92]. It is clear from these studies that EtOH impacts on neuronal function can lead to alterations in OLs and myelin function in an indirect manner.

7. Conclusions and outlook

OLs and myelin have been implicated in the establishment of addictive behavior and alcoholism [88,93,94]. However, the causal relationship between EtOH-induced myelin alteration and behavioral change remains poorly understood. Regulation of myelin causes long-lasting changes in neural networks. Recent reports have associated myelin changes in the brain with behaviors like skill learning [95–98] and social isolation/defeat [32,99,100], shedding light on designing effective research strategies to address EtOH related questions.

Several signaling pathways have been implicated in EtOH-induced alterations of myelin. However, the specificities of the cell type, brain region and mechanism involved often remain unclear. Of note, recent studies showed that besides highly bundled myelinated axons in white matter, there are extensive myelin networks in gray matter of the brain (Figure 3). These myelinated axons in gray matter are from both excitatory projection neurons and inhibitory GABAergic interneurons, especially the parvalbumin-positive fast-spiking GABAergic interneurons in both mice and humans [8,9]. Currently, little is known regarding the potential role of gray matter myelin in AUDs.

The ultimate goal of understanding EtOH and myelin interactions is to improve the lives of individuals who suffer from AUDs. Promoting myelination may be developed into a new treatment strategy. For instance, choline treatment reversed the behavioral and neurobiological deficits of third-trimester equivalent prenatal EtOH exposure [61,101]. Given that choline is abundant in myelin, it is possible that this restorative effect may involve myelination. Antihistamines were shown to blunt deficits of prenatal EtOH on hippocampal function [102], and enhance myelin formation after social isolation [99], providing another attractive therapeutic approach. Taken together, this is an important but still underexplored research field. The findings from future research will not only contribute to a better understanding of myelin-behavior interactions but also the development of new treatment strategies for AUDs.

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The List of Abbreviations

5-HT	serotonin
AUD	alcohol use disorder
BBB	blood-brain barrier
BDNF	brain derived neurotrophic factor
CB	cannabinoid
CNS	central nervous system
EtOH	ethanol
FA	fractional anisotropy
FASD	fetal alcohol spectrum disorder
GluR	glutamate receptor
MAG	myelin associated glycoprotein
MBP	myelin basic protein

MOG	myelin oligodendrocyte glycoprotein
mPFC	medial prefrontal cortex
MS	multiple sclerosis
MyT1	myelin transcription factor
OL	oligodendrocyte
OPC	oligodendrocyte progenitor cell
PDGFRα	platelet-derived growth factor receptor alpha
PFC	prefrontal cortex
PLP	proteolipid protein
TEM	transmission electron microscopy
TLR4	glial toll-like receptor 4

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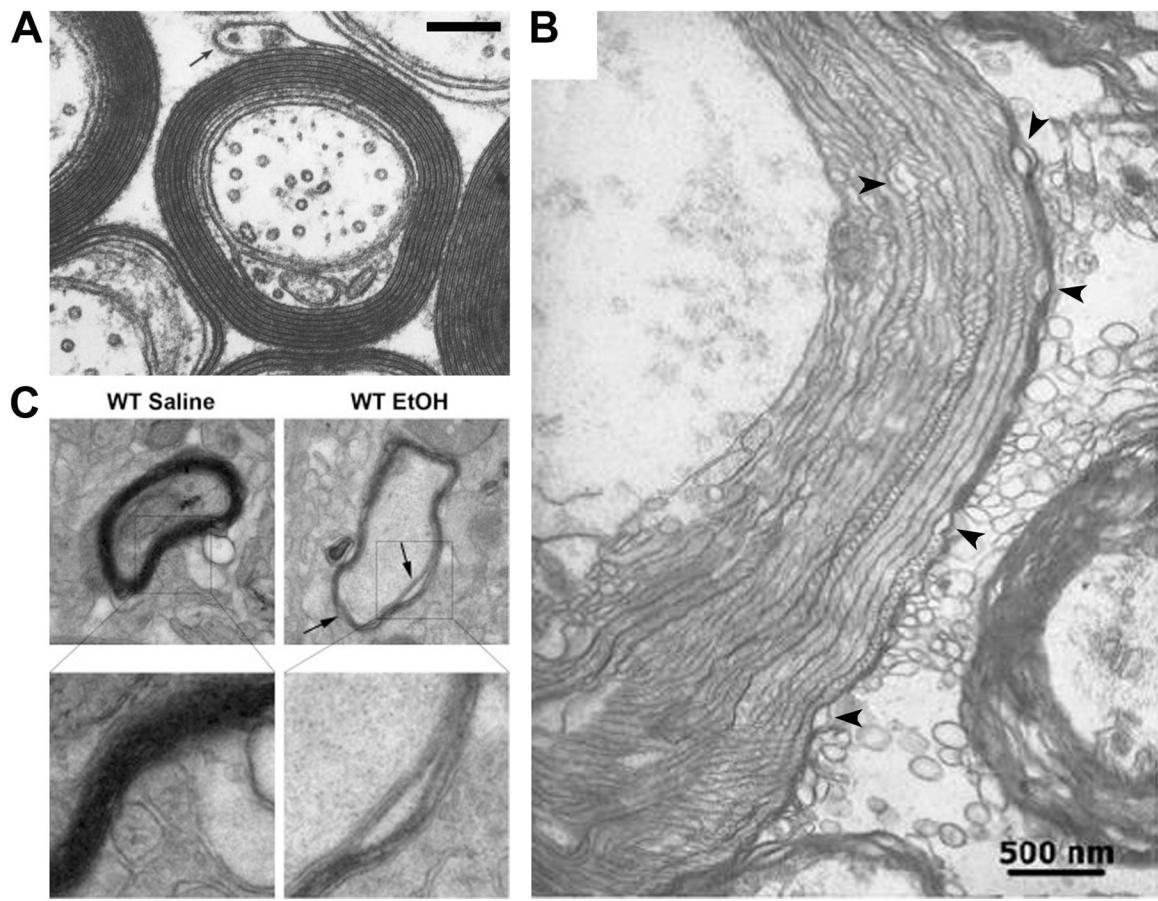


Figure 1. EtOH-induced alterations in myelin ultrastructure.

A, Transmission electron microscopy (TEM) image of myelinated axons in the normal CNS (modified from Basic Neurochemistry: Molecular, Cellular and Medical Aspects, 6th edition. Siegel GJ, Agranoff BW, Albers RW, et al., editors. Philadelphia: Lippincott-Raven; 1999). **B**, TEM image of altered ultrastructure of myelin in substantia nigra of a human alcoholic brain (modified from [20]). Black arrowheads, vacuoles between the myelin lamellae. **C**, The representative TEM images from the PFC of adult (3 weeks after the last treatment administration) WT mice received intermittent ethanol or saline treatment in adolescence. Arrows indicate inter-laminar splitting of myelin sheaths (modified from [33]). Scale bars, 500 nm.

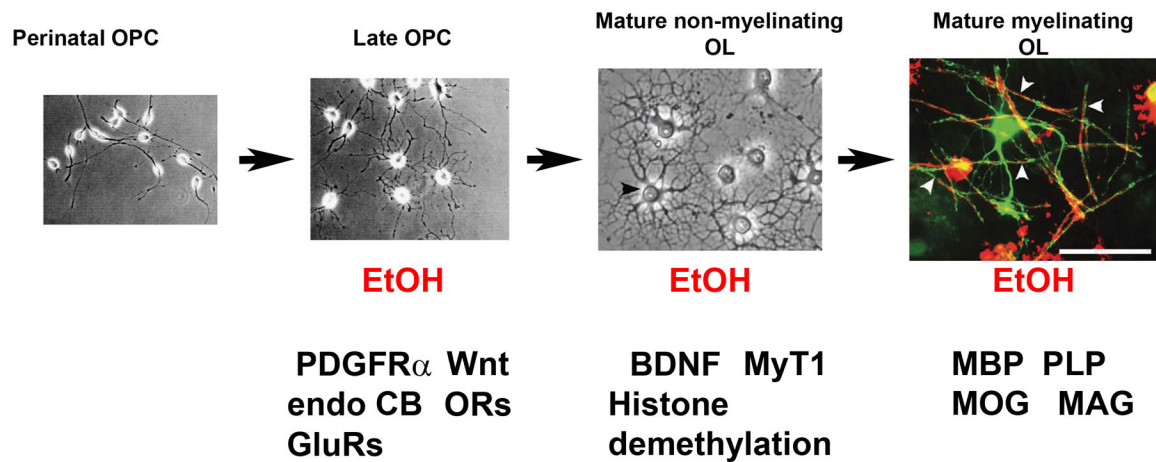


Figure 2. EtOH can affect OLs at different developmental stages through different potential pathways.

Perinatal OPC and Late OPC were from purified OPC culture from rats (modified from [103]). Mature non-myelinating OL (shown by a black arrowhead) and Mature myelinating OL were from hippocampal myelin coculture (modified from [104]). In Mature myelinating OL, myelin coculture was infected with AAV9-GFP at 16 days *in vitro* (DIV), 2 d after OPCs were seeded. The coculture was fixed and stained after 28 DIV. Some mature OLs expressed GFP. One example of GFP-positive and mature OL (green) that developed multiple myelin basic protein (MBP)-positive (red) myelin segments [104]. White arrowheads, GFP- and MBP-positive myelin segments. Red arrows, potential impacts of EtOH on myelin have been implicated at different developmental stages. Scale bar, 100 μ m. PDGFR α , platelet-derived growth factor receptor alpha. Wnt, Wingless/Integrated. Endo CB, endocannabinoid. GluRs, glutamate receptors. MyT1, the zinc finger protein Myelin Transcription Factor. ORs, opioid receptors. BDNF, brain-derived neurotrophic factor. PLP, proteolipid protein. MOG, myelin oligodendrocyte glycoprotein. MAG, myelin-associated glycoprotein.

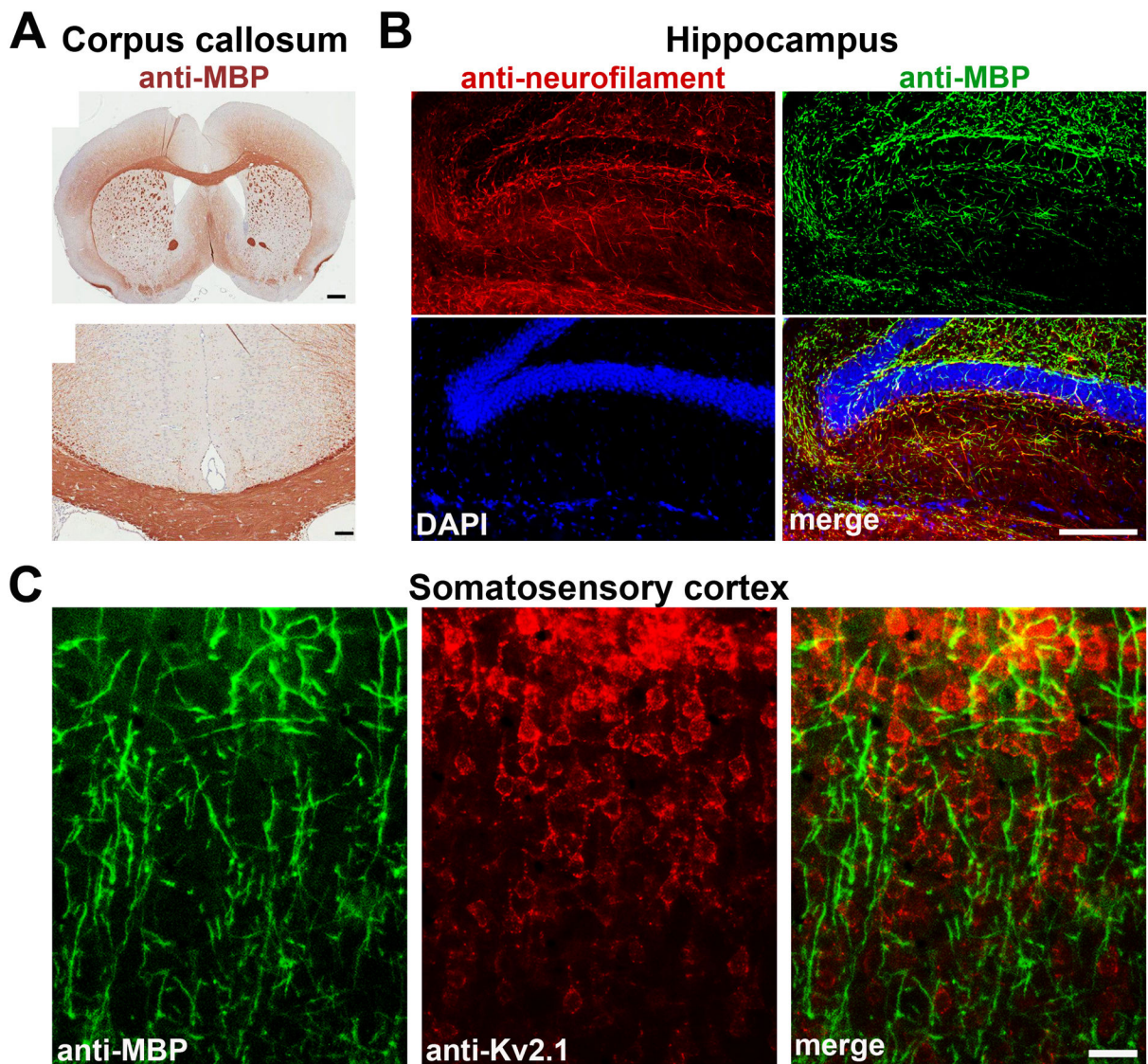


Figure 3. White matter and gray matter myelin in different regions of the mouse brain.

A, White matter bundles revealed by anti-MBP staining in the anterior cingulate cortex of the WT B6 mouse (top). Its corpus callosum is shown in an enlarged image at the bottom (modified from ^[105]). Scale bars, 500 μm (top) and 100 μm (bottom). **B**, Gray matter myelin segments in the mouse hippocampus that was stained for neurofilament (red), MBP (green) and DAPI nuclear dye (blue). **C**, Gray matter myelin segments in the mouse somatosensory cortex that was stained for MBP (green) and Kv2.1 (red). Kv2.1, a Shab voltage-gated potassium channel mainly expressed in the somatodendritic region of cortical pyramidal neurons (Image courtesy of Farida Eid). Scale bars, 200 μm in **B** and 100 μm in **C**.