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Dynamic regulation of myelination in health and disease

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Since its initial discovery in the 1800s until recently, myelin was considered a simple insulator for axons, and its formation was believed to be regulated by predetermined biochemical and cellular processes. Moreover, both oligodendrocytes and the myelin they generate were considered to be static components of the nervous system. However, recent studies have revealed that oligodendrocyte development and myelination are highly dynamic processes that continue throughout adult life, are influenced by experience and neuronal activity, and contribute to cognitive function and behavior. This represents a dramatic change in the way we think about the development and function of myelin. This paradigm shift is also relevant to the understanding of neuropsychiatric disorders, such as schizophrenia, depression, and bipolar disorder, as myelin defects have been observed in brains of these patients and myelin genes have been linked to these conditions.[1] Furthermore, psychiatric disorders frequently begin in adolescence or young adulthood, a time when myelination in several brain regions, such as the temporal lobes and prefrontal frontal cortex (PFC), is still ongoing. Here we discuss the current thinking on how experience influences myelin and its implications for mental health and disease.

Human imaging studies have documented changes in myelin that correlate with various types of experience. For example, it has been reported that people with piano training exhibit white matter alterations in brain regions involved in sensory-motor processing which correlate with years of practice.[2] Conversely, reduced white matter in auditory centers of the brain has been observed in congenitally deaf adults.[3] The quality of early life experience may also influence the course of myelin development, e.g. reductions in corpus callosum area have been found in children subjected to abuse or neglect.[4] It is therefore apparent that different forms of experience may both increase and decrease white matter size or structure, which in turn are likely to significantly affect brain function. While these human imaging studies provide strong evidence for white matter plasticity, animal-base studies have provided insight into cellular, molecular and physiological mechanisms underlying the interplay between myelin and experience and how these processes relate to psychiatric illness.

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A key question has been how might adverse experience affect myelin in early life and adulthood. To pursue this issue, a recent study by our lab explored the role of social experience on myelin development and function in the PFC, an area of the brain implicated in multiple psychiatric disorders. We discovered that mice subjected to social isolation during the juvenile period develop PFC hypomyelination and display cognitive and social impairments indicative of PFC dysfunction.[5] Importantly, these effects are induced by a brief period of isolation (the 4th and 5th week of life), but not by a longer period (four weeks) if isolation begins at the 6th week of life, indicative of a critical or sensitive period. In addition to myelin defects, social isolation reduces expression of type III NRG1, a neuronal ligand for ErbB receptors that is involved in numerous aspects of brain development.[6] Remarkably, oligodendrocyte-specific ErbB3 knockout produces the same myelin and behavioral deficits induced by social isolation. Together, these findings indicate that juvenile social experience influences PFC myelination via NRG1/ErbB3 receptor signaling between neurons and oligodendrocytes, and that deficits in PFC myelin contribute to the behavioral and cognitive impairments induced by social isolation. A subsequent study reported that longer periods of isolation starting in adulthood also lead to PFC hypomyelination, suggesting that social experience is needed to sustain PFC myelin throughout life. However, whereas deficits in myelin induced by isolation during juvenile development could not be rescued by later social re-integration, the damaging effects of isolation in adulthood are reversed by subsequent social exposure.[7] Thus, it appears that social experience plays a pivotal role in the health of PFC myelination and that isolation-induced myelin abnormalities cause impairments in cognition and social functioning.

What are the mechanisms linking experience to myelin plasticity? One possibility is that alterations in neuronal activity regulate signals produced by neurons, such as cell surface ligands, e.g. type III NRG1, or the axonal release of neurotransmitters, which in turn influence myelin. For instance, it has been reported that glutamate released during neuronal activity induces myelin formation by signaling through NMDA and metabotropic glutamate receptors on cells of the oligodendrocyte lineage.[8] As an alternative to neuronal activity, certain forms of experience, particularly those that activate the hypothalamic pituitary axis, may influence the circulation of stress hormones, which in turn affect myelin. For example, immobilization stress and glucocorticoid administration both promote oligodendrocyte differentiation in the rodent hippocampus.[9] There is also evidence that experience induces epigenetic changes in oligodendrocytes. Specifically, oligodendrocytes in the PFC of juvenile and adult mice subjected to social isolation have less tightly packed chromatin, a feature normally observed in immature oligodendrocytes.[7] If these or other mechanisms drive changes in myelin during experience, it will need to be determined if they preferentially modify myelin in response to distinct forms of experience and in different brain regions.

What is the source of new myelin produced in response to experiential stimuli? There are at least three different cellular populations that might underlie changes in myelin. First, experience may modulate myelin synthesis in pre-existing oligodendrocytes, which would permit changes to myelin thickness along already myelinated axons without the necessity of oligodendrocyte turnover. Second, the brain harbors an abundant supply of oligodendrocyte progenitor cells (OPCs) distributed broadly throughout both grey and white matter.

Although OPCs were once thought only to serve as a source of oligodendrocytes during early development, cell-tracing studies revealed that these cells continue to differentiate into oligodendrocytes well into adulthood and may help remodel myelin along previously myelinated axons.[10] It was also recently discovered that OPCs display robust homeostatic control over cell density in the adult cortex[11], which could enable OPCs to generate oligodendrocytes locally without the need for migration from remote areas of the brain. Finally, adult neural stem cells reside in select niches in the brain, such as the dentate gyrus and subventricular zone, and were recently found to give rise to oligodendrocytes in the rodent hippocampus under conditions of stress.[9]

How might myelin plasticity contribute to psychiatric illness? Experience-driven myelination could allow for increases in conduction velocity along axon pathways thus enhancing synaptic efficacy and the timing of information flow in neuronal circuits. Accordingly, forms of experience that result in thinner myelin could hinder neuronal communication leading to cognitive impairments such as those seen in various psychiatric disorders. However, not all experiences that promote myelination are necessarily favorable to mental health as increases in myelination in certain brain regions may reinforce neural pathways involved in maladaptive, cognitive, emotional, or behavioral patterns. Additionally, changes in myelin may disrupt neurotransmission and profoundly affect brain function. For instance, hypomyelination induced by loss of ErbB in oligodendrocytes alters dopaminergic signaling, a neurotransmitter system that has been implicated in schizophrenia and other disorders.[12] It is also possible that adverse experiences that alter myelin during early life and in adulthood disturb aspects of brain function that are not presently appreciated.

Despite recent advances, many key questions remain about the impact of experience on myelin and how an understanding of this interaction can be used to treat psychiatric illness. For instance, in addition to the role of juvenile social experience and NRG1/ErbB signaling in PFC myelination, what other forms of experience influence myelin development and maturation in the brain? Are all experience-dependent effects on myelination limited by critical periods? Do they share common molecular mechanisms? And very importantly, how stable are experience-induced changes in myelin, and can abnormalities in myelin development be reversed or mitigated by behavioral and cognitive based therapies? Now that it is becoming evident that myelin is plastic, and myelination might continue throughout life, it will be important to further investigate how alterations in myelination contribute to psychiatric disorders and if drugs that target myelin plasticity could be used to treat these conditions.

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