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Optogenetic stimulation of the mouse motor cortex incites proliferation of myelin-producing cells and axonal myelination.

# Neuronal Activity Promotes Oligodendrogenesis and Adaptive Myelination in the Mammalian Brain

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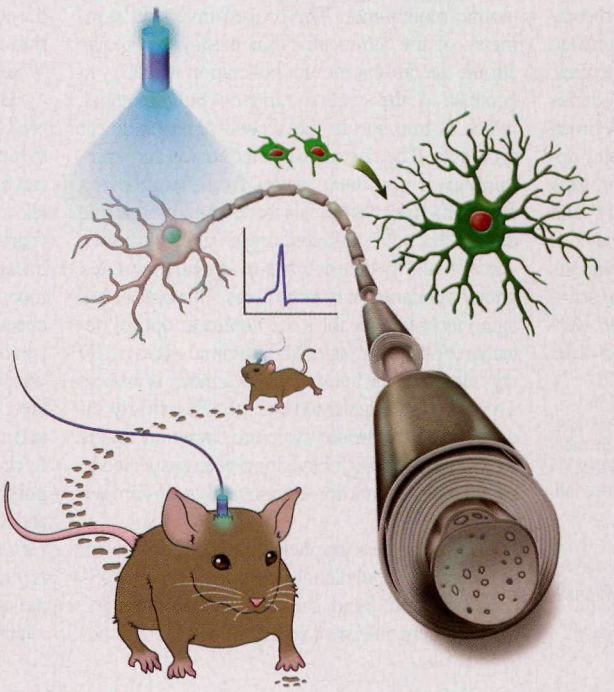
**Introduction:** Myelin is formed by mature oligodendrocytes to facilitate fast propagation of action potentials in axons. Small changes in myelin thickness can confer substantial changes in conduction speed and may thus alter neural circuit function. The idea that active neurons may modulate myelination is supported by in vitro studies and correlations between experience and myelin microstructure, but direct in vivo evidence demonstrating that neuronal activity regulates oligodendrocyte precursor cell (OPC) proliferation, differentiation, or changes in myelin microstructure has been lacking. We use in vivo optogenetic techniques in awake, behaving mice to provide direct evidence that neuronal activity regulates changes in myelin-forming cells within an active circuit.

**Rationale:** Demonstrating the direct effects of behaviorally relevant neuronal activity on oligodendroglial lineage cells in vivo has been a challenge because traditional methods of directly promoting neuronal activity involve placement of an electrode, and the resultant tissue injury and subsequent inflammation affects OPC dynamics. Optogenetic technology allows for in vivo control of neuronal firing with millisecond precision using light delivered at a distance from the target and, thus, avoids extensive electrode-related tissue damage. We used an optogenetic (Thy1::ChR2) mouse model in which 470-nm light delivered near the brain surface stimulates the excitatory opsin channelrhodopsin expressed by cortical layer V projection neurons. Wild-type littermate controls lacking channelrhodopsin were identically manipulated to control for effects of surgery, optical fiber placement, and light exposure. In Thy1::ChR2 mice, light stimulation delivered unilaterally to the premotor cortex elicits complex motor behavior (unidirectional ambulation). The thymidine analog 5-ethynyl-2′-deoxyuridine (EdU) was administered at the time of optogenetic stimulation to mark actively dividing cells. Animals were evaluated at various time points to examine the effects of neuronal activity on myelin-forming cells and myelin microstructure, as well as the functional consequences of neuronal activity–regulated myelin changes.



**Neuronal activity promotes OPC proliferation, oligodendrogenesis, and myelin remodeling.** Optogenetic stimulation of unilateral premotor cortex layer V projection neurons in awake, behaving Thy1::ChR2 mice promotes OPC proliferation (light green cells, red EdU$^+$ nuclei), oligodendrogenesis (newly generated, EdU-marked oligodendrocyte; dark green cell), and an increase in myelin sheath thickness (viewed in cross section, gray). Together with these adaptive myelin changes, motor performance of the correlate limb is improved during normal gait 4 weeks after premotor cortex stimulation.

**Results:** Optogenetic stimulation of cortical layer V projection neurons resulted in robust proliferation of OPCs within the premotor circuit, from the deep layers of the premotor cortex to the subcortical projections through the corpus callosum. Four weeks later, an increase in newly generated oligodendrocytes and increased myelin sheath thickness were found within the stimulated premotor circuit. Behavioral testing revealed increased swing speed of the correlate forelimb. Pharmacological blockade of OPC differentiation prevented activity-regulated oligodendrogenesis and myelin changes, as well as the associated behavioral change.

**Conclusion:** Neuronal activity regulates OPC proliferation, differentiation, and myelin remodeling in the murine brain with accompanying changes in behavioral function. Taken together, these findings suggest that adaptive changes in myelin-forming cells represent a type of behaviorally relevant neural plasticity, raising numerous conceptual and mechanistic questions. Mechanisms regulating myelin plasticity may be important for adaptive neural function and could be leveraged for interventions in diseases of myelin. Conversely, dysregulated myelin plasticity could conceivably contribute to disease.

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