Neuronal activity in vivo enhances functional myelin repair

Ortiz F.C.

Habermacher C.

Graciarena M.

Houry P.-Y.

Nishiyama A.

Oumesmar B.N.

Angulo M.C.

In demyelinating diseases, such as multiple sclerosis, demyelination of neuronal fibers impairs impulse conduction and causes axon degeneration. Although neuronal activity stimulates oligodendrocyte production and myelination in normal conditions, it remains unclear whether the activity of demyelinated axons restores their loss of function in a harmful environment. To investigate this question, we established a model to induce a moderate optogenetic stimulation of demyelinated axons in the corpus callosum at the level of the motor cortex in which cortical circuit activation and locomotor effects were reduced in adult freely moving mice. We demonstrate that a moderate activation of demyelinated axons enhances the differentiation of oligodendrocyte precursor cells onto mature oligodendrocytes but only under a repeated stimulation paradigm. This activity-dependent increase in the oligodendrocyte pool promotes an extensive remyelination and functional restoration of conduction, as revealed by ultrastructural analyses and compound action potential recordings. Our findings reveal the need for preserving an appropriate neuronal activity in the damaged tissue to promote oligodendrocyte differentiation and remyelination, likely by enhancing axon-oligodendroglia interactions. Our results provide new perspectives for translational research using neuromodulation in demyelinating diseases.