Age-related myelin dystrophy impairs signal transmission in a pyramidal neuron model and working memory in a network model of the prefrontal cortex

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Behavioral studies show that aging leads to an impairment in working memory performance. Working memory crucially relies on persistent neuronal activity in several brain areas, in particular in the prefrontal cortex (PFC). Aging also leads to structural and functional changes in cortical pyramidal neurons and in white matter pathways, with particularly significant myelin dystrophy in both grey and white matter. Specifically, electron microscopy studies have shown 1) extensive alterations of myelin sheaths of nerve fibers and 2) remyelination in pyramidal neurons in the rhesus monkey PFC. However, the functional consequences of these alterations in myelination remain unclear. Here, we study this question in single neuron and neural network models. Using a pyramidal neuron model with myelinated axons, we explored alterations in action potentials transmission due to the empirically observed alterations in the myelin sheaths, by modeling demyelination. That is, removing different amounts of wraps in different percentages of the myelinated segments along the axons. To model remyelination, we replaced given percentages of previously demyelinated segments by new, shorter and thinner, myelin sheaths. We investigated how the altered sheaths affected the action potential transmission and we observed a reduction in action potential propagation speeds as wells as failures in the action potential transmission until the distal end of the axons. This velocity reduction and failure increased progressively for a higher percentage of demyelinated segments and with a higher percentage of wraps removed. Moreover, remyelination led to a significant conduction velocity recovery and less transmission failure, and this improvement increased when the remyelinating sheaths were less thin. We then studied the effects of action potential failures in a spiking neural network model of working memory, and we found that demyelination impaired performance similarly to the single neuron model. Remyelination worked as a compensatory mechanism, almost recovering unperturbed performance. In addition, we combined healthy and perturbed axons (demyelinated or remyelinated) in a more realistic way, and we checked the effect on the network performance. We found that the performance improved while increasing the percentage of normal sheaths in these groups of axons and while decreasing the percentage of remyelinated segments. These results support previous electron microscopy findings showing that monkeys with a higher proportion of normal sheaths and a lower proportion of paranodal profiles (remyelination) perform better. Thus, our model allows us to make predictions that can be tested against the empirical data.