

Impaired Social Behavior in Mice with Tyrosinemia Type I is Associated with Hypermyelination of the Cerebral Cortex

Marissa E. Moore and Gordon G. MacGregor
Department of Biological Sciences

Overview

Tyrosinemia type I (TT1) is a rare metabolic disorder that causes a deficiency of the enzyme fumarylacetoacetate (FAH). Recently it was reported that children with TT1 show social and behavioral problems (van Ginkel et al., 2016). Here we study social behavior and brain histology in a mouse model of tyrosinemia type I to gain an insight into the mechanism behind these problems.

Results

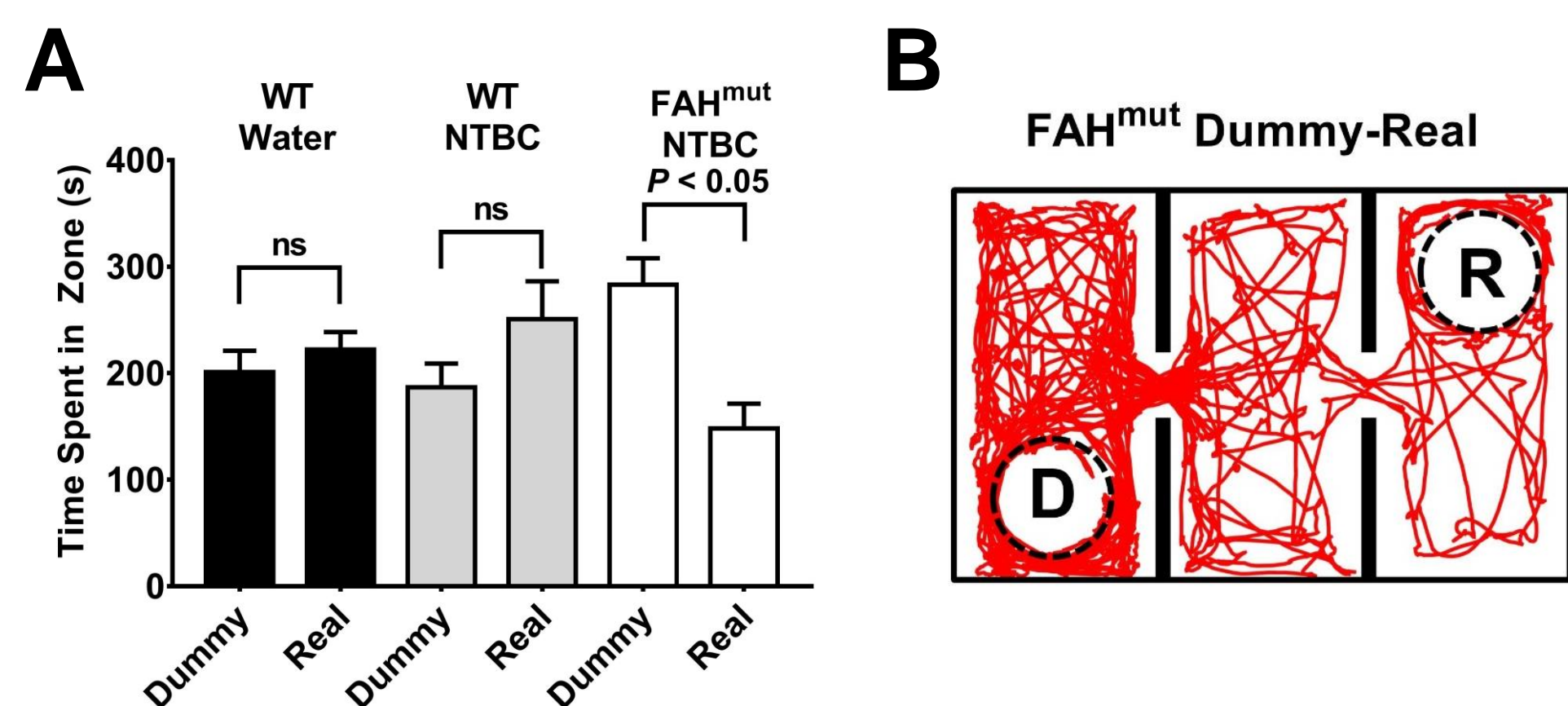


Figure 1. A. FAH^{mut} mice show abnormal social behavior and spend twice the time investigating a dummy compared to a real mouse. **B.** An example of a FAH^{mut} mouse trail showing more time spent investigating a dummy mouse.

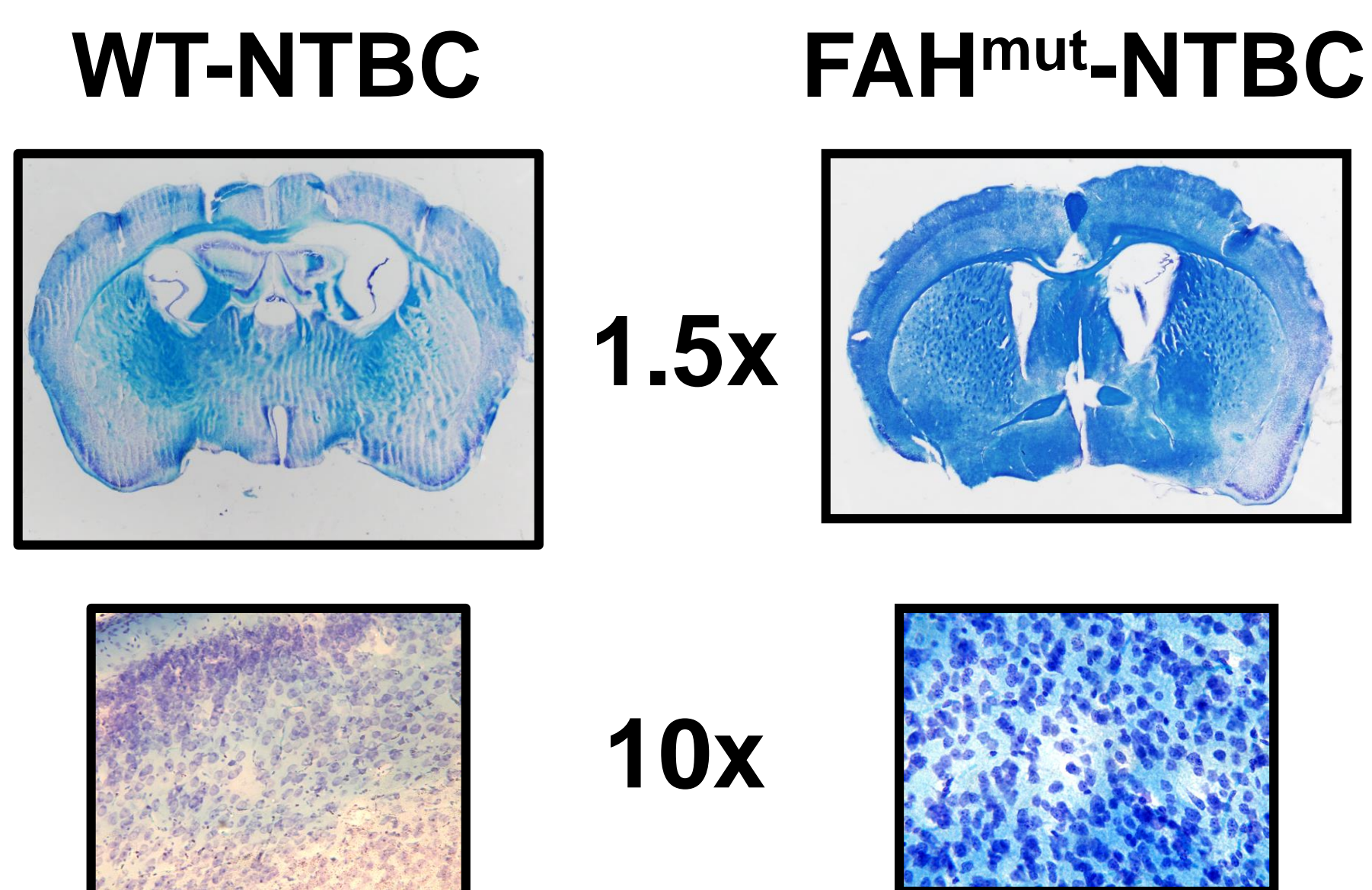


Figure 2. FAH^{mut} mice display increased myelination of the cerebral cortex. Top image shows a 20 μ m coronal brain slice (1.5x) from Bregma -1.0 and bottom image shows cerebral cortex (10x). Myelin is stained blue and the cell nucleus is stained purple (Kluver and Barrera, 1953).

References

van Ginkel WG, Jahja R, Huijbregts SC, Daly A, MacDonald A, De Laet C, Cassiman D, Eyskens F, Körver-Keularts IM, Goyens PJ, McKiernan PJ, van Spronsen FJ. (2016). Neurocognitive outcome in tyrosinemia type 1 patients compared to healthy controls. *Orphan J. Rare Dis.* 11: 87.
Kluver H, Barrera E. (1953). A method for the combined staining of cells and fibers in the nervous system. *J. Neuropath. Exp. Neurol.* 12:400-403.

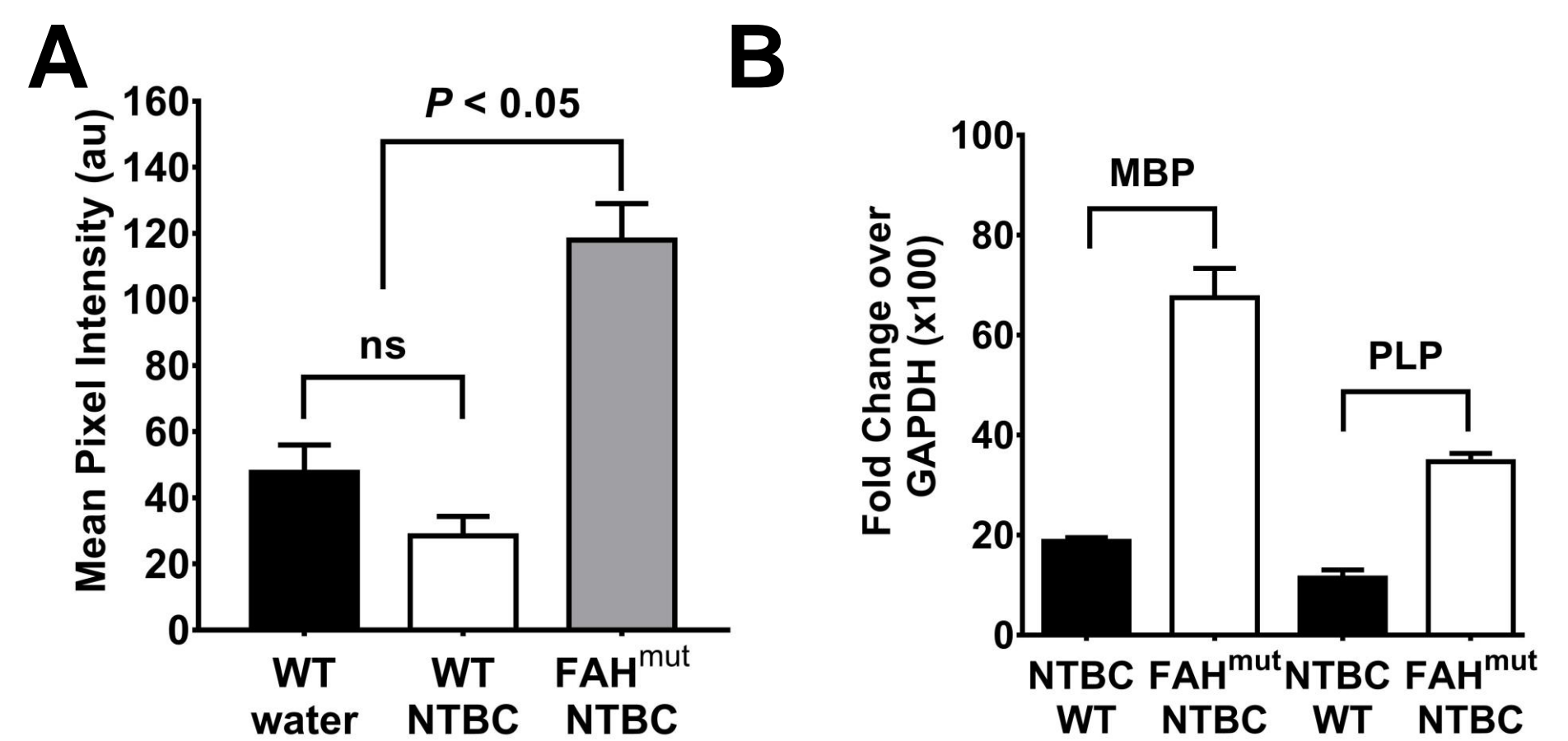


Figure 3. A. Image quantification using ImageJ showed that FAH^{mut} mice had 3-4 more myelin than WT mice. **B.** RT-PCR from cerebral cortex showed 3-4 fold more expression of the myelin associated genes MBP and PLP.

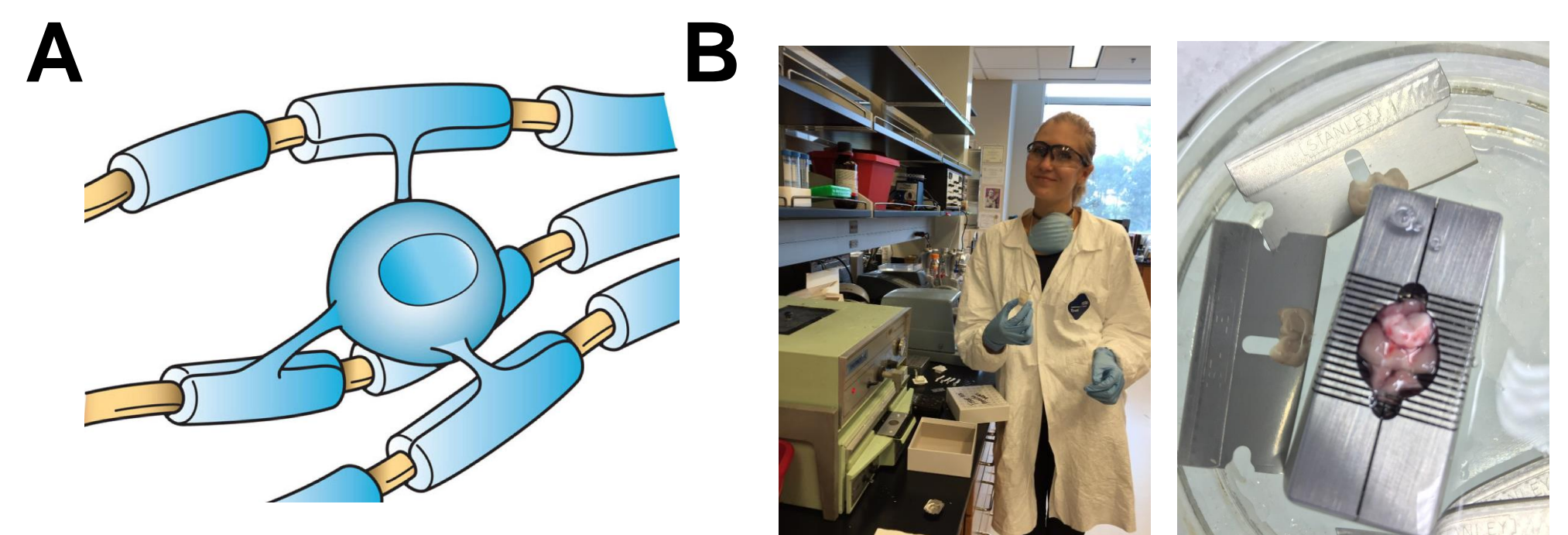


Figure 4. A. Oligodendrocytes synthesize internodal myelin sheaths on axons. **B.** Mice brains were sliced, fixed and stained for myelin visualization.

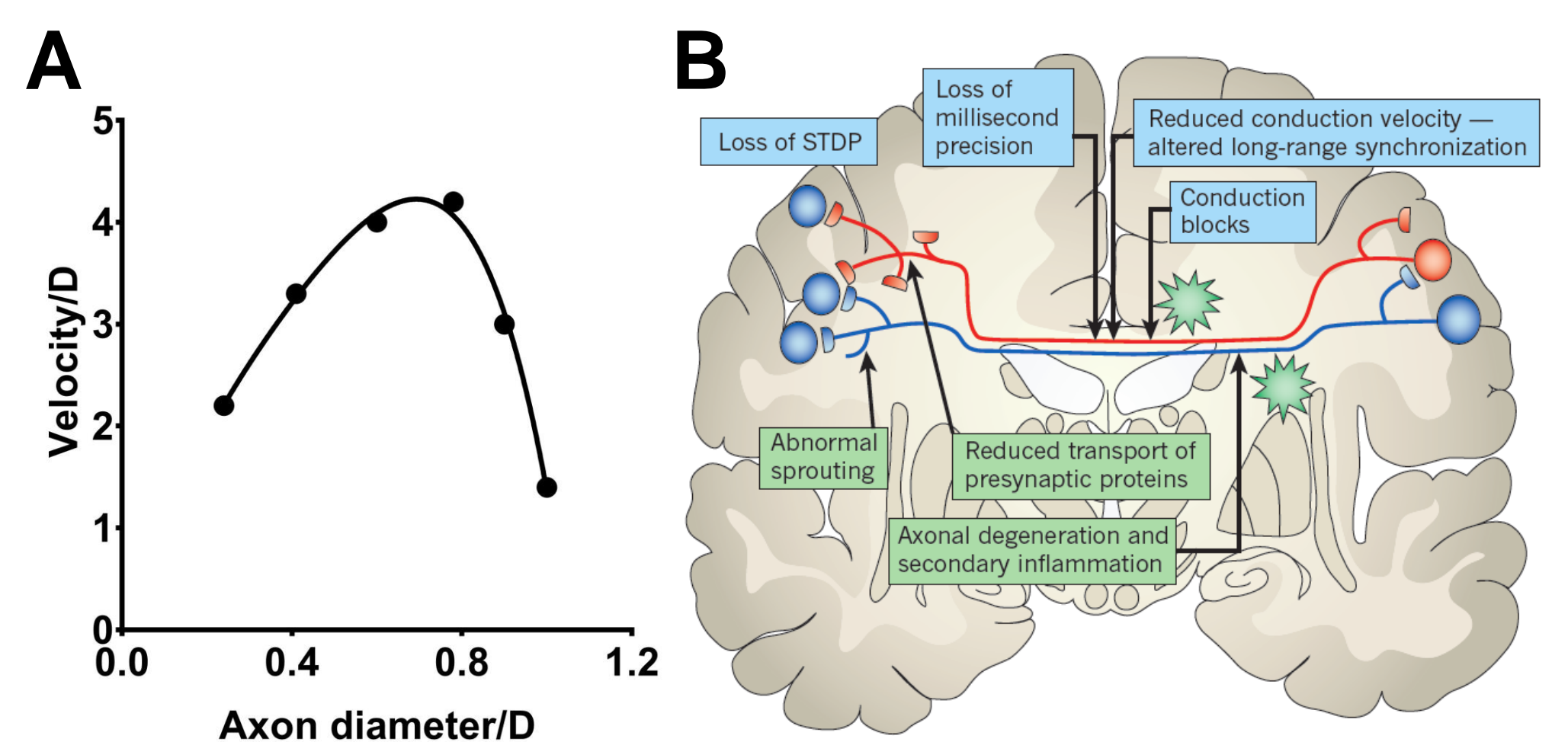


Figure 5. A. Increasing or decreasing myelination on a neuron from an optimum ratio of $g = 0.6$ decreases action potential velocity (Smith and Koles, 1970). **B.** Model of hypermyelination on brain function (Nave 2010).

Conclusions

Mice with TT1 show hypermyelination of cerebral cortex neurons. This increased myelin may paradoxically slow neuronal conduction resulting in abnormal messages that alter social behavior brain circuits.

Nave KA. (2010). Myelination and support of axonal integrity by glia. *Nature.* 468: 244-252.
Smith RS, Koles ZJ. (1970). Myelinated nerve fibers: computed effect of myelin thickness on conduction velocity. *Am J Physiol.* 219:1256-1258.