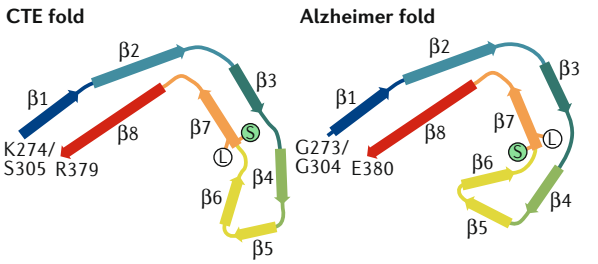


Models of the tau folds in chronic traumatic encephalopathy and Alzheimer disease. Adapted with permission from Falcon, B. et al. *Nature* https://doi.org/10.1038/s41586-019-1026-5 (2019), Springer Nature Limited.

filled with other molecules. We do not yet know what these molecules are, but the channel is too small for proteins."

The researchers say that more studies are needed to determine what causes CTE. They are keen to find out what the molecules inside the CTE tau filaments are, and what their role is in tau aggregation.

Rebecca Kelsey

> "in AD the filaments are C-shaped, whereas the CTE filaments adopt a more open shape"

ORIGINAL ARTICLE Falcon, B. et al. Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. *Nature* https://doi.org/10.1038/s41586-019-1026-5 (2019)
FURTHER READING Smith, D. H. et al. Chronic traumatic encephalopathy — confusion and controversies. *Nat. Rev. Neurol.* **15**, 179–183 (2019)

The team generated iPSCs from two individuals with ASD and loss-of-function mutations in *SHANK2*, alongside control lines from three unaffected parents of these individuals and one unrelated individual. The ASD neurons made more synaptic connections than did control neurons, and they had longer, more branched dendrites. "In a complex, multi-networked and sub-networked system like the brain, increasing connectivity could make some regions and networks perform differently than they would otherwise," points out Salter.

The results raise the possibility of new therapeutic strategies for ASD based on decreasing the observed hyper-connectivity. "Such approaches could be quite different than those one might envisage to increase hypo-connectivity, which has previously been implicated in ASD," notes Salter.

Sarah Lemprière

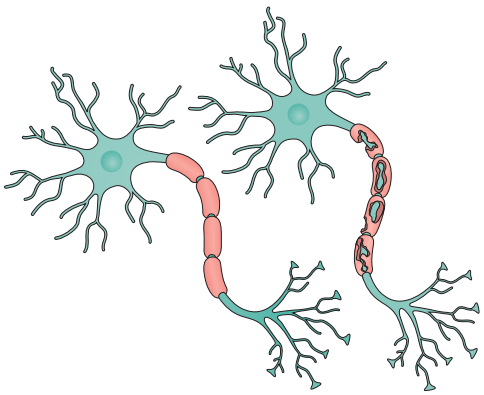
> "ASD neurons made more synaptic connections than did control neurons"

ORIGINAL ARTICLE Zaslavsky, K. et al. *SHANK2* mutations associated with autism spectrum disorder cause hyperconnectivity of human neurons. *Nat. Neurosci.* https://doi.org/10.1038/s41593-019-0365-8 (2019)

MULTIPLE SCLEROSIS

Premature cellular ageing limits remyelination in progressive MS

Chronic demyelination in the CNS is one of the defining characteristics of progressive multiple sclerosis (PMS). A study recently published in PNAS has provided evidence that the decreased remyelination potential in patients with PMS is attributable to premature senescence of neural progenitor cells (NPCs) in the brain.



Credit: Philip Patenall/Springer Nature Limited

"We previously demonstrated that induced pluripotent stem cell (iPSC)-derived NPCs from patients with primary progressive MS (PPMS), unlike cells developed from age-matched controls, did not provide protection against demyelination, nor did they foster oligodendrocyte growth and maturation," comments study leader Stephen Crocker, who is based at the University of Connecticut School of Medicine, USA. In the current study, Crocker and colleagues set out to further explore the molecular and cellular mechanisms underlying these observations.

For their new experiments, the researchers once again used iPSC lines derived from patients with PPMS. After differentiation into NPCs, these cell lines were found to express molecular markers of cellular senescence, including $p16^{Ink4a}$, p53 and senescence-associated β-galactosidase.

In collaboration with Anna Williams at the University of Edinburgh, UK, the investigators also used immunohistochemistry to analyse post-mortem brain samples from patients with PMS. This analysis revealed that $p16^{Ink4a}$ was expressed by progenitor cells that accumulated in demyelinated lesions, thereby providing in vivo evidence of cellular senescence in association with demyelination.

Consistent with the earlier findings from Crocker's group, the iPSC-derived NPCs from patients with PPMS had a reduced capacity to support the growth and maturation of oligodendrocytes — the myelinating cells of the CNS. This capacity was restored by treating the NPCs with rapamycin, a drug that has previously been shown to prevent cellular senescence. In addition, rapamycin reduced the expression of senescence-associated markers by the NPCs.

"These findings support the idea of MS as a disease of ageing, even though the MS patient population is not what we would typically consider an aged population," concludes Crocker. "We are currently using in vitro and in vivo models to explore how additional means of affecting cellular senescence can influence CNS myelination, and to examine whether functional differences in NPCs occur in other clinically defined subtypes of MS."

Heather Wood

ORIGINAL ARTICLE Nicaise, A. M. et al. Cellular senescence in progenitor cells contributes to diminished remyelination potential in progressive multiple sclerosis. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1818348116 (2019)
FURTHER READING Nicaise, A. M. et al. iPS-derived neural progenitor cells from PPMS patients reveal defect in myelin injury response. *Exp. Neurol.* **288**, 114–121 (2017) | Stangel, M. et al. Achievements and obstacles of remyelinating therapies in multiple sclerosis. *Nat. Rev. Neurol.* **13**, 742–754 (2017)