> endothelial nitric oxide is critical to maintain the homeostasis of tau

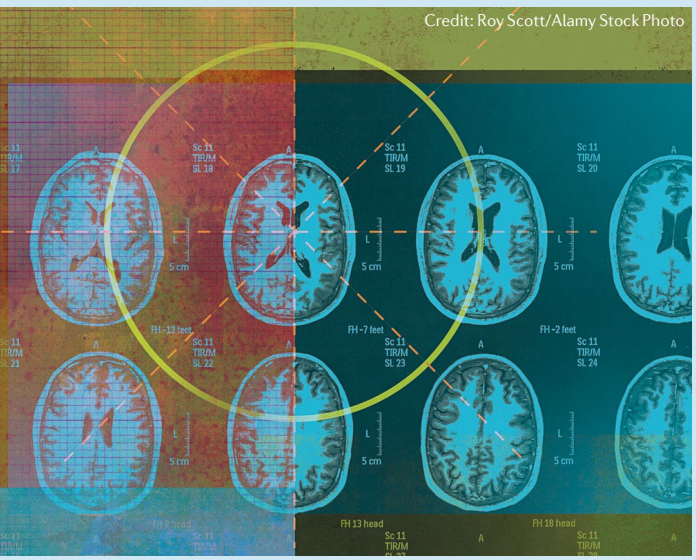
observed leads to de-nitrosylation and activation of calpain, which activates cyclin-dependent kinase 5, an enzyme that phosphorylates tau. Furthermore, mice that were deficient in tau or treated with anti-tau antibodies did not develop cognitive impairment, despite a reduction in cerebral blood flow, demonstrating that the effect was mediated by tau.

"Our findings provide a previously unrecognized link between vascular risk factors and Alzheimer pathology," points out Iadecola. "In addition, we found that endothelial nitric oxide is critical to maintain the homeostasis of tau."

The researchers conclude that excess dietary salt should be avoided to prevent tau pathology, but also that the mechanisms present new opportunities for prevention of cognitive impairment caused by cerebrovascular dysfunction.

Ian Fyfe

ORIGINAL ARTICLE Faraco, G. et al. Dietary salt promotes cognitive impairment through tau phosphorylation. *Nature* **574**, 686–690 (2019)



Credit: Roy Scott/Alamy Stock Photo

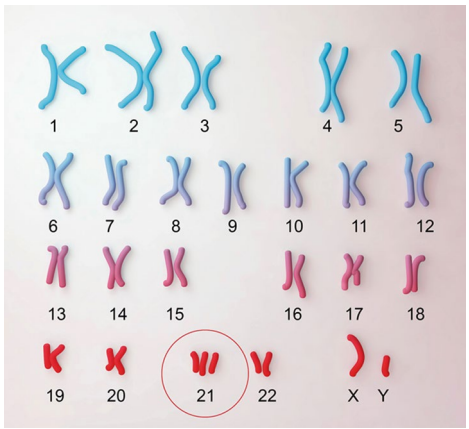
be desirable for intervention studies as a more valid surrogate than single MRI findings," the authors conclude in the paper.

Ian Fyfe

ORIGINAL ARTICLE Jokinen, H. et al. Global burden of small vessel disease-related brain changes on MRI predicts cognitive and functional decline. *Stroke* https://doi.org/10.1161/STROKEAHA.119.026170 (2019)

NEURODEVELOPMENTAL DISORDERS

Integrated stress response mediates cognitive decline in Down syndrome



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Down syndrome (DS), a neurodevelopmental disorder that results from the presence of an extra copy of chromosome 21, is a common cause of intellectual disability in the general population, but little is known about the molecular mechanisms that underlie the cognitive deficits. In a new study published in *Science*, Mauro Costa-Mattioli, Peter Walter and colleagues provide evidence that a signalling network known as the integrated stress response (ISR) mediates cognitive decline in DS.

"We hypothesized that loss of proteostasis — the process by which the cell's proteins are monitored and maintained at homeostasis — could explain the memory deficits associated with DS," comments Costa-Mattioli. "Protein synthesis is known to be required for long-term memory formation, and loss of proteostasis is associated with a wide range of cognitive and neurodegenerative disorders."

The ISR is an evolutionarily conserved pathway, the normal role of which is to regulate protein synthesis under conditions of cellular stress. To investigate the relationship between the ISR and cognitive impairment in DS, Costa-Mattioli and colleagues used the Ts65Dn mouse model, which recapitulates the types of cognitive deficit that are observed in humans with this condition.

Activation of the ISR, as indicated by phosphorylation of eukaryotic translation initiation factor 2 (eIF2), was detected in the hippocampus in the Ts65Dn mice and also in post-mortem brain tissue samples from people with DS. ISR activation led to reductions in protein synthesis in the brains of Ts65Dn mice and in induced pluripotent stem cells derived from individuals with DS.

Genetic or pharmacological inhibition of the ISR was found to restore protein synthesis and improve long-term memory in Ts65Dn mice. "We have previously identified that the ISR serves as a long-term memory switch, and in this study we found that the switch is off in DS," explains Costa-Mattioli. "We showed that turning the switch back on by inhibiting the ISR reverses the cognitive decline associated with DS."

The new findings raise the possibility that pharmacological manipulation of the ISR could help to alleviate cognitive impairments in individuals with DS. The investigators plan to further explore the mechanisms that lead to ISR activation in DS and to determine whether ISR inhibition can reverse cognitive deficits in other neurological conditions in which proteostasis is dysregulated.

Heather Wood

ORIGINAL ARTICLE Zhu, P. J. et al. Activation of the ISR mediates the behavioral and neurophysiological abnormalities in Down syndrome. *Science* **366**, 843–849 (2019)
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