also performed poorly in a novel object-recognition test (NORT; which evaluates attention and short-term memory function), which the authors postulate may be due to the disruption of activity-dependent myelination in these mice (although they acknowledge that alternative mechanisms might be at play).

Finally, in mice exposed to MTX and then treated with a small-molecule TrkB agonist (LM22A-4), myelin sheath thickness was restored to control levels and NORT performance was rescued. This cognitive behavioural rescue depended on OPC expression of TrkB.

Together, these findings indicate that aberrant activity-dependent myelination has an important role in CRCI, and suggests that TrkB agonism might be investigated as a potential mechanism to ameliorate cognitive impairment following MTX chemotherapy.

Isobel Leake

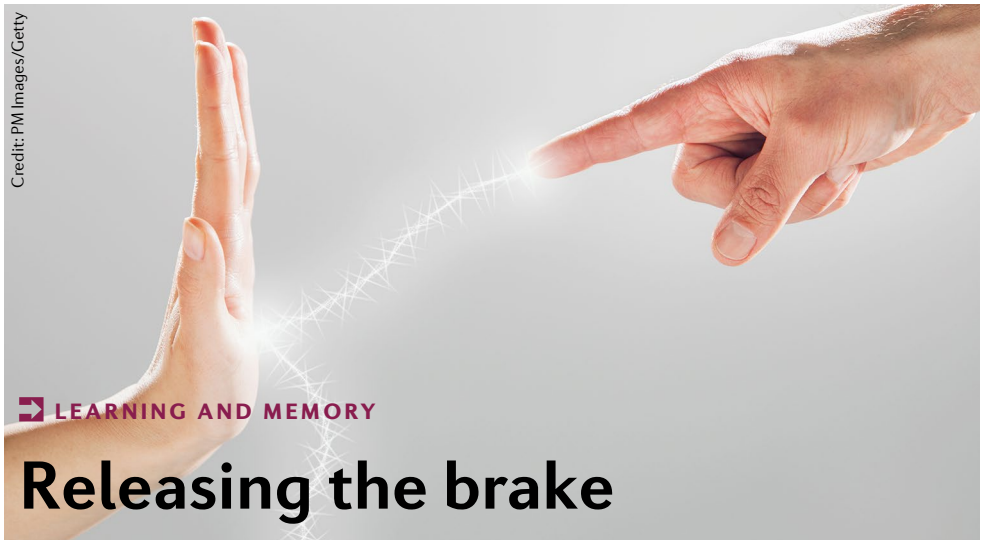
ORIGINAL ARTICLE Geraghty, A. C. et al. Loss of adaptive myelination contributes to methotrexate chemotherapy-related cognitive impairment. *Neuron* https://doi.org/10.1016/j.neuron.2019.04.032 (2019)

Credit: Jennie Vallis/Springer Nature Limited

a crucial role in homeostatic body temperature regulation. Identification of *Ptgds* as a genetic marker for temperature-sensitive neurons could facilitate future research in thermoregulation.

Isobel Leake

ORIGINAL ARTICLE Wang, T. A. et al. Thermoregulation via temperature-dependent PGD_2 production in mouse preoptic area. *Neuron* https://doi.org/10.1016/j.neuron.2019.04.035 (2019)



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LEARNING AND MEMORY

Releasing the brake

The formation of fear memories in mice involves integration of contextual information about the environment with sensory information about the aversive stimulus by CA1 pyramidal cells of the dorsal hippocampus. During the integration process, certain pyramidal cells are activated, whereas the activation of others is prevented through somatostatin-expressing (SOM) interneuron-mediated dendritic inhibition. This results in the selective strengthening of specific synapses and the formation of a memory trace or 'engram'. Which neurons are included and which are excluded was thought to be stochastic, but here, Szőnyi and colleagues show that GABAergic projections from the nucleus incertus (NI) in the brainstem inhibit SOM cells, thus determining which specific cells are included in the engram.

The authors reasoned that if recruitment of CA1 pyramidal cells to a memory trace was an active process, SOM interneurons would be subject to precise, temporally controlled inhibition that would be regulated by incoming subcortical information: this would enable changes in synaptic strength at specific CA1 synapses, specificity in a memory trace and the formation of a precise episodic memory.

The authors hypothesized that GABAergic cells of the NI, which project to the hippocampal CA1 region in which SOM interneuron dendritic arbours are located, might regulate SOM cell activity during memory formation. To investigate this possibility, the authors used Cre-dependent viral tracing methods and found that GABAergic NI neurons project to, and form synapses with, SOM interneurons in the hippocampus. In addition, these NI neurons send axon collaterals to the medial septum where they form synapses with the glutamatergic and cholinergic neurons that activate hippocampal SOM interneurons. These findings suggest that NI input can reduce the activity in SOM interneurons both directly and indirectly.

Next, the authors investigated NI neuron activity by two-photon calcium imaging of NI boutons in the dorsal CA1 when mice were exposed to salient stimuli. Fluorescence increased when water-restricted mice encountered a water reward and when mice were exposed to different sensory stimuli, such as an aversive air puff or light flashes, with the number of activated boutons and the strength of response increasing with increased valence of the stimulus. Moreover, retrograde rabies virus tracing of upstream inputs to NI GABAergic neurons revealed projections from various areas that play key roles in processing aversive and rewarding stimuli and memory encoding, including prefrontal cortex, lateral habenula and median raphe. These findings suggest that NI GABAergic neurons receive and transmit information about salient environmental stimuli.

To test the role of the NI in fear memory formation in mice, the authors paired footshock in a particular environment with optical stimulation of GABAergic neurons in the NI or their terminals in the dorsal CA1; 24 h later, the mice were placed in the same environment and their behaviour monitored. Control mice showed robust freezing behaviour, but mice who had received the optical stimulation in either NI or CA1 showed very little freezing, suggesting an inhibition of contextual memory formation. By contrast, compared with controls, inhibition of NI GABAergic neurons during fear conditioning produced substantially stronger freezing when the mice were tested in the environment associated with the aversive stimulus.

Together, these data suggest that NI GABAergic neurons receive information about salient environmental sensory stimuli and transmit this, both directly and indirectly, to SOM interneurons, thus regulating the selection of pyramidal cells during contextual memory formation.

Sian Lewis

ORIGINAL ARTICLE Szőnyi, A. et al. Brainstem nucleus incertus controls contextual memory formation. *Science* https://doi.org/10.1126/science.aaw0445 (2019)