after removing this suppression, either allowed the network to recover or immediately suppressed activity in the motor thalamus. Mice could perform the reach task when the motor cortex suppression was released if there was no thalamic suppression, but reaching was blocked during thalamic suppression after motor cortex suppression. Therefore, continued external inputs are crucial for movement.

To determine whether the temporal pattern of the external input is important for proper movement, the authors optogenetically activated terminals of motor thalamic neurons in the motor cortex using pulses of light at three different frequencies: 4 Hz, 10 Hz and 40 Hz. The three frequencies did not substantially affect overall firing rates in the motor cortex, but they had different effects on the reaching behaviour. When mice were stimulated at 4 Hz, they could still reach the pellet, although their forelimb trajectory showed transient perturbations when the light pulses occurred. With 10 Hz stimulation, the mice could start moving their forelimb, but they typically failed to reach the pellet. By contrast, 40 Hz stimulation severely impaired initiation and execution of the reach task. Thus, the temporal patterning of external inputs is important for motor control.

Electrode recordings revealed that the activity of motor thalamic and motor cortical neurons was modulated when the animal made a movement. The authors used regression analyses to establish whether external inputs or local dynamics in the motor cortex made a greater contribution to cortical population activity. This approach revealed that both external inputs and local dynamics predicted cortical population activity, with the 'dominant' influence varying according to the individual mouse.

Overall, this study demonstrates that temporally patterned external inputs to the motor cortex are crucial for proper motor control throughout forelimb movement.

Natasha Bray

ORIGINAL ARTICLE Sauerbrei, B. A. et al. Cortical pattern generation during dexterous movement is input-driven. *Nature* **577**, 386–391 (2020)

inhibition of *Rspo2*$^+$ neurons during fear extinction training enhanced learning, whereas activation of these neurons impaired extinction memory learning. By contrast, the activation of *Ppp1r1b*$^+$ neurons enhanced fear extinction learning, whereas their inhibition reduced such learning. This suggested that *Ppp1r1b*$^+$ neurons might be a crucial site of fear extinction memory formation and storage.

To determine whether *Ppp1r1b*$^+$ neurons are indeed responsible for the storage and retrieval of fear extinction memory, the authors carried out a two-step 'engram cell identification' procedure. The *Ppp1r1b*$^+$ neurons that were activated during the retrieval stage of the putative contextual fear extinction memory were first labelled. Subsequent optogenetic activation of the labelled neurons during a second round of fear extinction training accelerated fear extinction learning and maintained the fear extinction state during the memory retrieval tests, confirming that these cells are fear extinction memory engram cells.

Next, the authors examined the relationship between the fear extinction engram cells and the population of BLA neurons that respond in a valence-specific manner to rewarding stimuli. They found that a high proportion of *Ppp1r1b*$^+$ neurons that were responsive to a rewarding stimulus (for instance, delivery of water after water deprivation) were also activated by fear extinction training. Furthermore, optogenetic activation of *Ppp1r1b*$^+$ fear engram neurons drove appetitive behaviours, whereas activation of water-responsive neurons accelerated fear extinction learning.

This study reveals a link between the neural circuits that encode reward and drive appetitive behaviours and those involved in the extinction of aversive memories. The findings may provide insight into conditions, such as post-traumatic stress disorder or anxiety disorders, that are thought to involve impairments in fear extinction.

Katherine Whalley

ORIGINAL ARTICLE Zhang, X., Kim, J. & Tonegawa, S. Amygdala reward neurons form and store fear extinction memory. *Neuron* https://doi.org/10.1016/j.neuron.2019.12.025 (2019)

GLIA

Withdrawn support

The accumulation of misfolded proteins in neurons is a cell stressor that triggers the unfolded protein response (UPR), which restores protein homeostasis and is dysregulated in neurodegenerative disease. One branch of the UPR involving protein-kinase R-like endoplasmic reticulum (ER) kinase (PERK)-mediated phosphorylation of the α-subunit of eukaryotic initiation factor 2 (eIF2α) halts protein synthesis and can lead to neuronal loss. Little is known about UPR dysregulation in astrocytes, which provide crucial trophic support to neurons. Astrocytes in an activated, 'reactive' state are often observed in neurodegenerative disorders, and here, Smith et al. show that dysregulated PERK–eIF2α signalling in reactive astrocytes alters their secretome and induces synaptic loss and behavioural deficits in a mouse model of prion disease.

First, the authors investigated the effects of UPR activation in primary cultures of mouse hippocampal astrocytes. Exposure to the ER stressor thapsigargin (Thaps) resulted in PERK–eIF2α activation within 2 h, and increased expression of several markers of a reactive, neurotoxic state. These markers were substantially reduced by PERK inhibition, suggesting that PERK signalling is a key driver of this distinct 'UPR-reactivity' profile.

Next, the authors tested astrocyte-conditioned medium (ACM) from UPR-reactive astrocytes on primary hippocampal neuron cultures. Whereas ACM from control astrocytes increased synaptic density, ACM from UPR-reactive astrocytes had no effect, but the synaptogenic effect was restored in the presence of a PERK inhibitor. Further analysis revealed that control ACM contained various synaptogenic factors such as collagen, fibronectin and glypican 4 that were reduced in ACM from Thaps-treated astrocytes. Notably, Thaps–ACM contained increases in chaperone proteins, indicating that the secretome alterations reflect a specific state rather than a general downregulation of protein synthesis.

Last, the authors investigated UPR-reactive astrocytes in the *tg37*$^{+/-}$ mouse model of prion disease. In this model, increasing levels of prion protein induce PERK–eIF2α signalling, which leads to neuronal loss in the hippocampus, followed by more widespread neurodegeneration and behavioural symptoms. As in the Thaps-treated astrocytes, astrocytes of *tg37*$^{+/-}$ mice exhibited concurrent elevations in PERK–eIF2α signalling and expression of UPR-reactive state markers. Disruption of PERK–eIF2α signalling selectively in astrocytes of *tg37*$^{+/-}$ mice reduced the expression of UPR-reactive state markers. Moreover, inhibition of PERK–eIF2α signalling in *tg37*$^{+/-}$ mice reduced spongiform degeneration substantially, prevented hippocampal neurodegeneration, reduced astrocyte density and reactive astrocyte morphology, and increased survival. Together, these findings suggest that PERK–eIF2α signalling in reactive astrocytes contributes to neurodegeneration by disrupting trophic support.

Sian Lewis

ORIGINAL ARTICLE Smith, H. L. et al. Astrocyte unfolded protein response induces a specific reactivity state that causes non-cell-autonomous neuronal degeneration. *Neuron* https://doi.org/10.1016/j.neuron.2019.12.014 (2020)