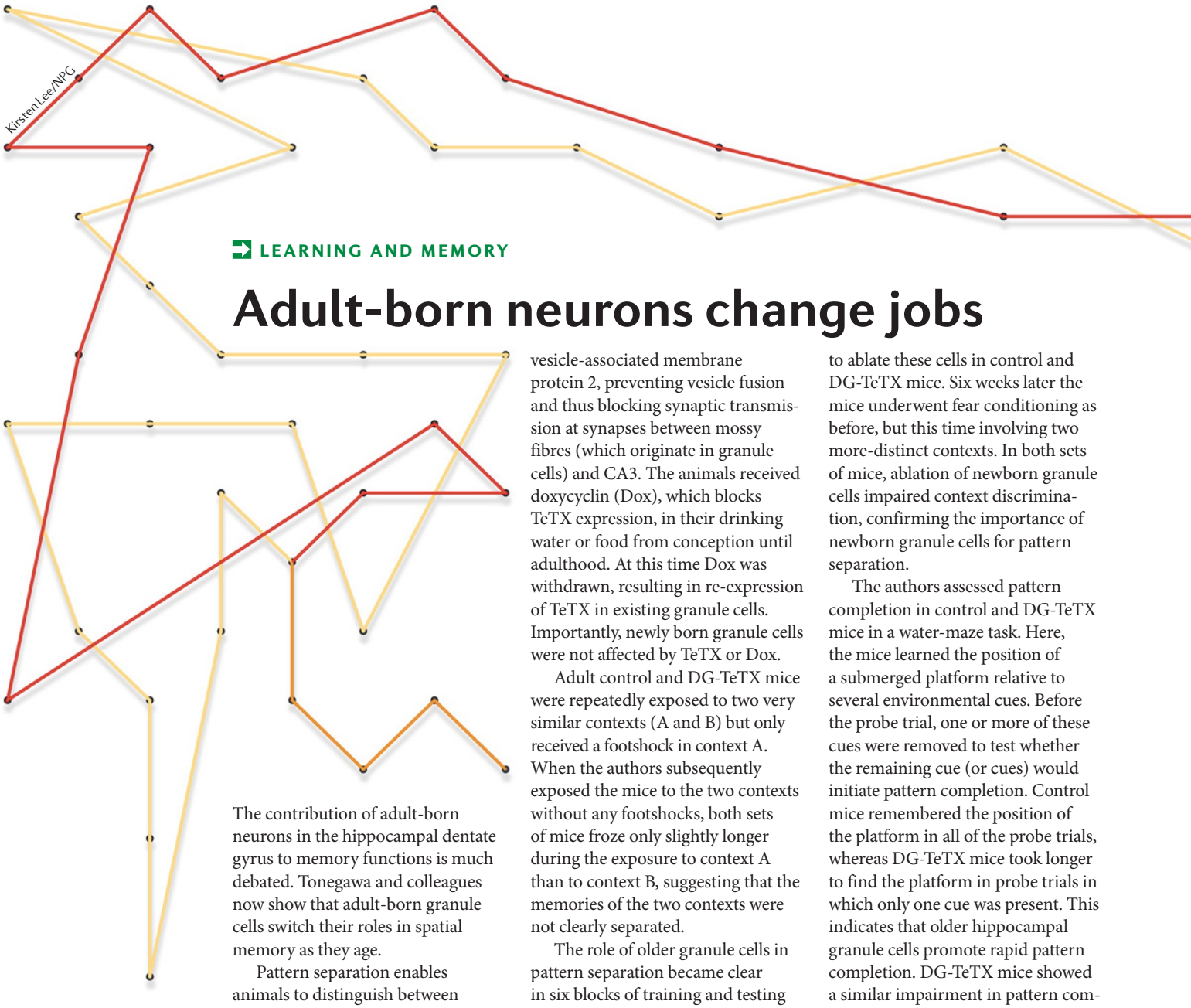

LEARNING AND MEMORY

Adult-born neurons change jobs

The contribution of adult-born neurons in the hippocampal dentate gyrus to memory functions is much debated. Tonegawa and colleagues now show that adult-born granule cells switch their roles in spatial memory as they age.

Pattern separation enables animals to distinguish between similar experiences, whereas pattern completion allows animals to recall a full memory from a subset of cues that were present during the original experience. Adult-born granule cells are thought to have a role in pattern separation, but little is known about the relative contribution to this process of newborn cells versus older adult-born cells and cells born during development. Even less is known about whether granule cells are involved in pattern completion.

To tackle these issues, the authors created triple transgenic mice in which tetanus toxin (TeTX) was expressed specifically in dentate gyrus (DG) granule cells (DG-TeTX mice). TeTX cleaves vesicle-associated membrane protein 2, preventing vesicle fusion and thus blocking synaptic transmission at synapses between mossy fibres (which originate in granule cells) and CA3. The animals received doxycyclin (Dox), which blocks TeTX expression, in their drinking water or food from conception until adulthood. At this time Dox was withdrawn, resulting in re-expression of TeTX in existing granule cells. Importantly, newly born granule cells were not affected by TeTX or Dox.

Adult control and DG-TeTX mice were repeatedly exposed to two very similar contexts (A and B) but only received a footshock in context A. When the authors subsequently exposed the mice to the two contexts without any footshocks, both sets of mice froze only slightly longer during the exposure to context A than to context B, suggesting that the memories of the two contexts were not clearly separated.

The role of older granule cells in pattern separation became clear in six blocks of training and testing sessions that took place over the following 12 days. Here, mice were again exposed to both contexts and received footshocks in context A. DG-TeTX mice immediately showed more freezing in context A than in context B, whereas control mice only did so in the final two training blocks. Thus, the loss of synaptic transmission at mossy fibre–CA3 synapses in older granule cells enhanced pattern separation in highly similar contexts, suggesting that output from older granule cells might actually impair pattern separation.

To assess the contribution of newborn granule cells to pattern separation, the authors used X-irradiation to ablate these cells in control and DG-TeTX mice. Six weeks later the mice underwent fear conditioning as before, but this time involving two more-distinct contexts. In both sets of mice, ablation of newborn granule cells impaired context discrimination, confirming the importance of newborn granule cells for pattern separation.

The authors assessed pattern completion in control and DG-TeTX mice in a water-maze task. Here, the mice learned the position of a submerged platform relative to several environmental cues. Before the probe trial, one or more of these cues were removed to test whether the remaining cue (or cues) would initiate pattern completion. Control mice remembered the position of the platform in all of the probe trials, whereas DG-TeTX mice took longer to find the platform in probe trials in which only one cue was present. This indicates that older hippocampal granule cells promote rapid pattern completion. DG-TeTX mice showed a similar impairment in pattern completion in a pre-exposure-dependent contextual fear conditioning task.

These findings suggest that newborn granule cells are crucial for the formation of distinct new memories and that older cells have a role in spatial and contextual memory recall. Future research may show whether conditions associated with impaired survival of newborn neurons, such as stress, lead to specific impairments in pattern separation or pattern completion.

Leonie Welberg

> “the loss of synaptic transmission at mossy fibre–CA3 synapses in older granule cells enhanced pattern separation in highly similar contexts”

ORIGINAL RESEARCH PAPER Nakashiba, T. *et al.* Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell* 23 Feb 2012 (doi:10.1016/j.cell.2012.01.046)