ALZHEIMER'S DISEASE

Lost memories found

Enhancing synaptic connections between neurons in the brain's hippocampus that are normally activated during memory formation rescues memory deficits in a mouse model of early Alzheimer's disease. SEE LETTER P.508

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Some 44 million people worldwide are affected by the neurodegenerative disorder Alzheimer's disease or related dementia[1]. Episodic memory decline in the early stages of disease often precedes biological hallmarks such as the abnormal accumulation of amyloid-β and tau proteins. It is also better correlated than these traits with defects that occur in the synaptic connections between neurons in patients' brains[2]. However, whether this memory impairment reflects a failure to encode new memories or an inability to retrieve stored ones is not known. In a fascinating paper on page 508 of this issue, Roy *et al.*[3] shed light on the matter, rescuing synaptic and memory deficits in a mouse model of early Alzheimer's disease by reactivating an ensemble of neurons that had been previously activated by experience.

Memory is a biological function that allows animals to encode, retain and retrieve information. The brain's hippocampus is a key player in these processes. Hippocampal damage can be assessed in mice using a behavioural model called contextual fear conditioning, in which animals learn to show defensive behaviour in a certain environmental context after it becomes associated with an aversive stimulus — for example, learning to freeze when placed in a box in which they have previously received an electric shock to the foot. Roy and colleagues found that mouse models of the early stages of Alzheimer's disease can encode memories of an aversive experience, but that their recall of the experience when placed in the same environment a day later is severely impaired (Fig. 1a).

Neuronal ensembles that undergo enduring biochemical changes during an experience, and that are reactivated during recall of that experience, are referred to as engram cells[4]. Using mouse models of early-stage Alzheimer's disease, Roy *et al.* modified a previously described protocol[5] so that engram cells in the dentate-gyrus subregion of the hippocampus that are activated by an aversive experience are tagged with a gene that encodes a light-sensitive ion channel. The authors then used blue light to selectively open the channel, activating the engram (the population of engram cells in the dentate gyrus) and so manipulating the memory trace at a later time.

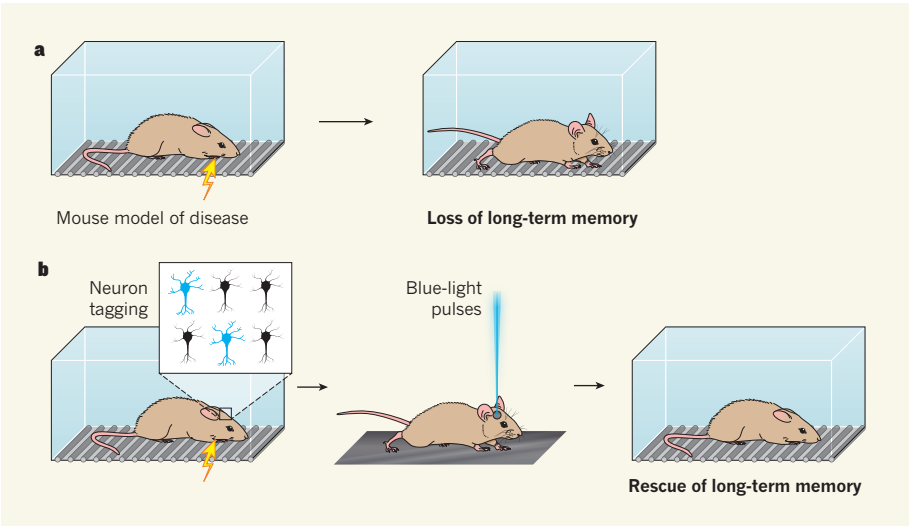

Figure 1 | Light-induced rescue of episodic memory. **a**, During contextual fear conditioning, a mouse is placed in a box where it undergoes an aversive experience, such as a footshock (yellow arrow), which causes it to freeze. Healthy mice recall this experience and freeze when placed back in the same box (not shown), but mice that model Alzheimer's disease do not, indicating that they have long-term memory defects. **b**, Roy *et al.*[3] genetically tagged neurons that were activated during the aversive experience with a light-sensitive ion-channel protein (tagged neurons indicated in blue). They then removed the mice from the fear-conditioning environment and used pulses of blue light to repeatedly reactivate these neurons. In doing so, the authors rescued long-term memory in the model mice.

Light-induced reactivation of the tagged engram cells led to recall of the aversive memory. However, memory rescue did not extend beyond the duration of the light treatment, so it could not reinstate memory recall when, a day later, the animals were returned to the context in which they experienced the footshock (known as a natural cue). This finding suggested that the standard optical reactivation regimen did not strengthen the engram enough for it to have a lasting effect. Indeed, it is known that associative memory traces need to be consolidated — strengthened and stabilized — to facilitate future retrieval in response to natural cues[6].

Consolidation of contextual fear conditioning involves long-lasting strengthening of the synaptic inputs to neurons in the dentate gyrus from neurons in another brain region, the entorhinal cortex[7]. Such strengthening is known as long-term potentiation (LTP). Roy *et al.* reasoned that the memory-retrieval deficit in the model mice came from an inability to strengthen these 'perforant path' synapses. To test this theory, they repeatedly activated the engram with serial high-frequency light pulses[8], optically inducing LTP in the perforant-path inputs.

With this clever strategy, the authors rescued long-term memory deficits in the mice (Fig. 1b). A reduction in the density of tiny neuronal structures called dendritic spines, which receive synaptic inputs, is associated with memory loss in Alzheimer's disease, and optically induced LTP returned spine density to normal. Moreover, this strategy rescued deficits in two other hippocampus-dependent memory tasks: active place avoidance, in which an animal learns to avoid the specific place where it previously received a footshock, and novel object recognition, which tests recognition memory. This indicates that the engram-based technique can be generalized to improve recall for various memory types.

Next, Roy *et al.* found that optically inducing LTP in perforant-path inputs to a broader

range of dentate-gyrus neurons did not rescue long-term memory. This finding is intriguing, because it suggests that simultaneous reactivation of multiple neuronal ensembles in the dentate gyrus cancels out the effects of reactivating a specific engram. Consequently, treatments such as electrical stimulation of deep brain regions, which are used to treat human neurological disorders but cannot discriminate between engram and non-engram cells, may not improve memory in patients.

Notably, a previous study[9] showed that electrical stimulation of the perforant path increases levels of amyloid-β in the interstitial fluid around hippocampal cells. Further work is needed to determine whether Roy and colleagues' engram intervention increases amyloid-β levels, and whether the strategy can ameliorate memory impairments in late-stage Alzheimer's disease if combined with techniques[10] to reduce amyloid-β levels and aggregation of tau.

To both tag and manipulate engrams in mice, Roy *et al.* introduced genetic constructs in two viruses — a strategy that comes with caveats. One construct contained a short, 1-kilobase promoter region, which drives gene expression in active neurons. In its natural state in the genome, the promoter drives *c-Fos* expression, but in the viral construct it promotes expression of an 'activator' gene that, in turn, drives expression of a second construct that encodes the ion channel. However, this promoter naturally acts in concert with enhancer elements that span the 50 kilobases of DNA surrounding it[11]. Excluding these gene-regulatory elements from the viral construct results in an incomplete engram, because some neurons that are activated by the aversive experience less strongly than others will not be tagged. The engram could be labelled with greater specificity by incorporating the activator into the genomic position of *c-Fos*, such that all the gene-regulatory elements can act in concert to tag neuronal ensembles in response to aversive experience.

In addition, regardless of promoter expression, the construct containing the ion channel can be activated only when an antibiotic called doxycycline is removed from the animals' diet. Roy and colleagues tagged engram cells for 24 hours from the start of contextual fear conditioning. This design lacks precision, so some nonspecific neurons are probably included in the tagged ensemble. Engram labelling could be optimized by decreasing the time for which doxycycline is removed from the diet, or by using an alternative engram-tagging strategy that allows a shorter time window for labelling[12].

Nonetheless, the potential to rescue long-term memory in dementia is exciting. In the future, Roy and colleagues' findings might help to guide engram-based strategies that rescue memory deficits in patients with early-stage Alzheimer's disease. ■

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ANIMAL MIGRATION

Dispersion explains declines

Migratory birds are declining globally. A broad study of European migratory birds finds that species that disperse widely during the non-breeding season are less likely to be in decline than are species with more restricted dispersion.

RICHARD A. FULLER

Migratory birds undertake some of the most extraordinary journeys of any animal, but many of these birds are in catastrophic decline[1]. The very mobility of these species makes it extremely difficult to diagnose causes of the declines, and painstaking ecological studies are needed to unpick them on a case-by-case basis[1]. Writing in *Ecology Letters*, Gilroy *et al.*[2] present data hinting at a much-needed general explanation for why some migratory species are more vulnerable than others. In an analysis of 340 migratory bird species, they show that species that disperse widely during the non-breeding season, relative to their breeding distribution, are much less likely to be declining than are species that have relatively more-restricted distributions outside the breeding season.

The distances travelled by some migratory birds are astounding. The blackpoll warbler (*Setophaga striata*), a forest songbird weighing only 12 grams, flies more than 2,500 kilometres

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Figure 1 | Wood warbler (*Phylloscopus sibilatrix*). Although this declining bird species has extensive breeding grounds across Europe, it spends the non-breeding season in a relatively small area in west and central Africa. Gilroy *et al.*[2] find that such low migratory dispersion is associated with population decline.