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LEARNING AND MEMORY

Locating lost memories

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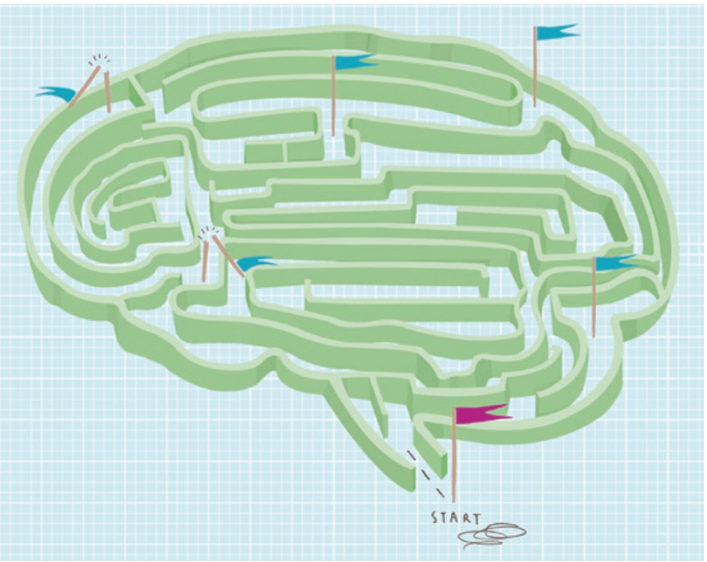
It is well known that Alzheimer's disease (AD) is associated with a loss of spatial memory and brain pathologies including tau-containing neurofibrillary tangles and amyloid-β plaques. The functional relationship between memory decline and the cellular pathology in AD is poorly understood, but a new study by Cheng and Ji shows how the encoding of new spatial memories is disrupted in the degenerating hippocampus.

Place cells are neurons in the hippocampus that reliably fire at particular locations within an environment. As an animal travels through a novel space, sensory input from the environment drives hippocampal place cells to fire in a particular sequence, and this sequence is reactivated each time the animal travels through that space or by later recall.



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rTg4510 mice overexpress a mutant form of human tau and, as in people with AD, these mice exhibit age-dependent neuronal loss (around 50% decrease in the thickness of hippocampal area CA1), neurofibrillary tangles and memory deficits. The authors made electrophysiological recordings from the CA1 region of rTg4510 mice while they performed spatial navigation tasks. First, mice were placed on a familiar rectangular track. The hippocampal place cells of wild-type mice fired in a particular, predictable sequence at specific spatial locations on the track. Place cells of rTg4510 mice, however, fired in robust, predictable sequence orders that were not location-specific. Second, mice were tested in a familiar open-field arena. Wild-type mice showed the usual location-specific place cell firing, but rTg4510 mice did not.

Unexpectedly, and unlike their wild-type counterparts, the robust sequence orders of place cell firing observed in rTg4510 mice on the track were also observed in a familiar open-field environment in which exploration patterns were random. This indicated that these firing sequences observed in rTg4510 mice were not driven by spatial location in the open field but were possibly generated internally.

The authors then investigated the influence of novelty on place cell firing. When exposed to a novel open field or a novel track, place cells in rTg4510 mice again fired in robust sequences but showed little location specificity; similar results were obtained in the open-field test. These findings suggest that, unlike in wild-type mice, in which formation of these firing sequences (a key part of spatial learning) is dependent on experience of the external environment, this influence is much reduced in rTg4510 mice.

Is there a complete disconnect between the environment and place cell activity in rTg4510 mice? Not quite it seems, as the authors found that as familiarity of a space increased, the likelihood of a particular sequence occurring was also increased, indicating a small influence of the environment on place cell firing in rTg4510 mice.

Taken together, these data indicate that in rTg4510 mice, place cell firing sequences are strongly disconnected from environmental influences and that the observed firing sequences originate internally. The authors speculate that these could be old, irrelevant spatial memories that are being recalled. If these internally driven sequences predominate, they might prevent the formation of new spatial memories. These data suggest that a possible reason for the inability of individuals with AD to form new memories is because old memories, retrieved inappropriately, predominate.

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ORIGINAL RESEARCH PAPER Cheng, J. & Ji, D. Rigid firing sequences undermine spatial memory codes in a neurodegenerative mouse model. *eLife* **2**, e00647 (2013)