

# News & views

## Neuroscience

# Closing the window on memory linking

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An immune molecule has an unexpected role in memory formation – specifically, in limiting the window of time in which newly forming memories can be contextually linked.

Memories acquired close together in time often become linked, such that recalling one memory leads to recall of another. For instance, one of us (P.R.) recently visited the Metropolitan Museum of Art in New York City and remembered that the last time she'd been there, she had walked through Central Park just afterwards and spotted a rare and beautiful snowy owl. The museum and snowy owls had become forever linked in her memory. In 2009, two groups<sup>1,2</sup> observed that neurons in the brain can participate in multiple memory networks that are laid down closely in time, thus enabling memory linking. The activity of a transcription-factor protein called CREB promotes this neural co-allocation, but what limits it? Writing in *Nature*, Shen *et al.*<sup>3</sup> make the unexpected discovery that the answer lies in an immune molecule that segregates memories by limiting the time available for linking to occur.

How does the brain know that two events are occurring closely in time? Addressing this question requires an understanding of how time is encoded in memory – a major unknown in memory research. Time can be encoded in an absolute or relative manner and encompasses varied scales. For example, some models suggest a moment-to-moment perception of time through a centralized internal clock<sup>4</sup>. Others suggest a more distributed representation, in which time is an emergent property of the activity of neurons<sup>5–7</sup> and neural populations<sup>8,9</sup> that have an intrinsic capacity to encode relative time of varying durations. Still other models focus on longer-scale circadian time, which might segment behaviour and memories into regular 24-hour blocks<sup>10</sup>.

But little is understood about the brain mechanisms that support each of these varied timescales, and even less about how they work

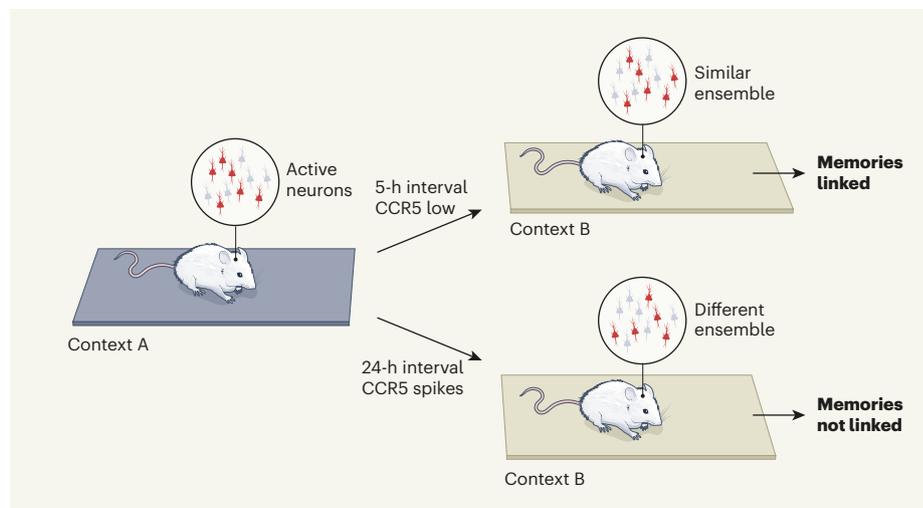
together to create fluid memory representations. Shen *et al.* provide traction on this problem by studying how relative time, in the order of hours, might be coded into memory through the process of memory linking and delinking at the time of learning.

The authors began their study by establishing a behavioural assay for memory linking. The group placed mice in one context (context A), and then five hours later placed them in another (context B). Two days later, they placed the animals back into context B, where the mice

received an electric shock. Finally, after two more days, the mice were placed back into context A. The animals exhibited a fear response (freezing on the spot) in context A, despite never having been shocked in that context, demonstrating memory linking. By contrast, when the initial placing of animals into contexts A and B was separated by 24 hours or more, memory linking did not occur (Fig. 1).

Shen *et al.* noticed changes in the expression of an immune receptor protein, CCR5, in neurons recently allocated to the memory network. CCR5 expression increased in the 12 hours after initial memory encoding, dropping back to baseline levels by 24 hours after encoding. This change parallels the time course of memory linking. Together, these observations suggest a possible role for CCR5 in closing the memory-linking window.

To test this role, Shen and colleagues manipulated the expression and activity of CCR5 in the hippocampus region of the animals' brains in the five hours between the exposures to context A and context B, when memory linking would presumably have occurred. The authors increased the activity of CCR5 in one of two ways: by optically activating a version of the protein that had been genetically engineered to respond to light; or by injecting animals with a CCL5 protein, which binds to and activates



**Figure 1 | The immune receptor protein CCR5 regulates memory linking.** Shen *et al.*<sup>3</sup> designed a memory-linking task in mice to study the window of time in which memories of two environments (contexts A and B) can become linked. First, they placed a mouse in context A, and analysed the most active neurons (red) in the brain's hippocampus – these cells were recruited to memory networks that enabled the animal to recall context A. Either 5 or at least 24 hours later, the authors placed the animal in context B. In the five-hour window, the activity of CCR5 (which reduces neuronal activity) remained low, meaning a similar ensemble of excitable neurons was recruited to memory networks in context B. Memories of contexts A and B were therefore linked. By contrast, in a 24-hour gap, CCR5 activity increased (thereby reducing the activity of context-A neurons) before returning to baseline levels. This CCR5 spike meant that a different neuronal ensemble was recruited to the memory network for context B, and the memories were not linked.

CCR5. Both manipulations impaired memory linking. By contrast, when the authors tested mice that had been genetically engineered to lack CCR5, they found that memories could be linked even when they were encoded up to seven days apart. These results provide key evidence for the role of CCR5 in controlling the duration of memory linking.

But how does CCR5 exert this role? To answer this question, Shen *et al.* recorded neural activity in the animals' hippocampi. They observed that many of the same neurons were active in contexts A and B when mice were placed in the two contexts five hours apart. The overlap between the neuronal populations activated in each context steadily declined as the separation between contexts was increased to one or two days. Mice lacking CCR5 exhibited greater overlap of the two neural ensembles if the events were separated by five hours, and the overlap was sustained even up to seven days' separation. These results support a model in which CCR5 reduces neural excitability and ensemble overlap, and thus memory linking.

The authors made the interesting observation that middle-aged mice have a higher expression of CCR5 than do their younger counterparts. They hypothesized that suppressing CCR5 could reduce the age-related

deficits in memory linking that occur in these middle-aged animals. To test this, they infused a pharmacological inhibitor of CCR5, maraviroc, into the hippocampi of middle-aged mice. This indeed improved the animals' ability to link memories formed five hours apart. Because memory deficits in ageing and in Alzheimer's disease might be dominated by deficits in retrieval (and thus memory linking) rather than memory storage<sup>11</sup>, which involves separate brain circuits<sup>12</sup>, these results could have clinical implications.

The discovery of an unexpected role for CCR5 advances our basic understanding of the brain mechanisms that shape memory linking. More generally, it underscores an increasing awareness of the role of immune molecules in cognitive functions, and hints at exciting therapeutic possibilities.

To return to the question of time in memory, it will be important to determine how memory linking at the time of learning informs the relative time-stamping of these memories during long-term storage and retrieval. It will also be interesting to determine whether other regulators of neural excitability, such as ion-channel proteins and neuromodulatory molecules that act across diverse timescales, collectively support CREB and CCR5 in sculpting a flexible, context-dependent linking duration. More

broadly, the exploration of brain activity during similar behaviours but on more-granular or -continuous timescales will lead to a better understanding of how memories are organized into sequences, episodes and, ultimately, a chronology.

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