of transected cord. Further studies would benefit from ablating the grafted neurons to prove that the motor improvement in monkeys depended directly on the engrafted cells and their vector-specific connections with the host.

SCIs are varied in nature, as are their clinical presentations and prognosis; no two are the same. A patient with incomplete and nontransective injury can improve over time, and this improvement may be as significant as it is unpredictable. But if there is one common theme, it is that patients with frank transections or severe contusions with tissue cavitation are left with permanent injuries with severe impairment and little improvement over time. These patients are thus likely to be the greatest beneficiaries of a neural-progenitor-based treatment strategy and are the first in whom it is likely to be assessed. By convincingly demonstrating that transplant-based reconstruction of neural circuits in the injured spinal cord can be effective and in doing so in nonhuman primates, Tuszynski and colleagues[2] have thus significantly advanced the cause of neuronal replacement therapy for spinal repair and have brought this exciting strategy one step closer to the clinic.

COMPETING INTERESTS
The author declares no competing interests.

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A molecular mechanism governing memory precision

Josue Haubrich and Karim Nader

A key molecular mechanism has been identified that dictates whether memory will maintain or lose its details over time and that is relevant in post-traumatic stress disorder and dementia.

Memories enable people to recollect events from the past to both plan for the future and properly guide their behavior in the present. However, memories change over time, often losing details. Minor loss of memories or details is common and usually not cause for alarm—however, in many cases the erosion of memory details can reach pathological levels that can significantly decrease quality of life. This extreme dysfunction can occur with pathological memory decline during aging and also as a symptom of post-traumatic stress disorder (PTSD) in the form of intrusive flashbacks that occur even in contexts unrelated to trauma[1]. Previous studies in rodents have linked memory imprecision with a gradual reorganization of the brain circuits supporting that memory[2]. In a new study, Sahay and colleagues[3] unveiled a critical mechanism governing both memory reorganization and the maintenance of its details over time.

The hippocampus is critical in forming, maintaining and accessing explicit memories. Over time, memories in the hippocampus may undergo a process called systems consolidation, through which memory becomes gradually independent of the hippocampus and dependent on cortical circuits[4]. It is thought that this consolidation might also play a role in precision of memory recall[2]. In addition, converging evidence suggests that dentate gyrus cell (DGC) connectivity in the hippocampus is also important for memory precision[5–7] and that this connectivity guides memory maturation in cortical networks over time[8]. Improper changes in this circuit may help explain aging-related memory loss[9] and excessive fear associated with PTSD upon unclear memory recall[10]. The DGC sends excitatory projections—called mossy fibers—to pyramidal neurons in the hippocampus CA3 area. Importantly, mossy fibers can also connect to GABAergic interneurons, which in turn inhibit the pyramidal neurons in CA3. This unidirectional circuit, in which a common projection simultaneously activates both inhibitory interneurons and excitatory pyramidal neurons to varying degrees, dictates the CA3 activation pattern and is thought to mediate complex tasks such as pattern separation—the process through which memories are stored as unique representations—and completion—the process through which an experience is recalled when a component of that memory is activated (such as by a specific location)[5,7]. The uniqueness of this DGC–CA3 circuit in regards to its relationship to precise information processing and time-limited engagement in memory recall led the authors to hypothesize that there must be mechanisms linking the DGC–CA3 engagement in memory and the maintenance of details over time.

The authors trained mice to associate a specific context with a foot shock and later tested recall in these mice by placing them back in the original surroundings in which they received the shock or in a new context with distinct features in which they never received a shock (**Fig. 1**). When the authors conducted a test 1 day after training, mice easily discriminated between contexts by showing fear only in the context that they were trained to associate with being shocked; however, 16 days after training, the mouse memory became imprecise, and mice began to show fear in the context not associated with shock. The authors used genetic labeling to identify the DGCs participating in memory and found that, compared to untrained mice, trained mice had DGCs that displayed increased synaptic contacts with both CA3 pyramidal neurons and inhibitory interneurons 1 day after training when memory was precise; however, when memory later became generalized, these contacts returned to the untrained baseline levels. The authors identified a molecule localized in DGC–interneuron synapses called actin-binding LIM protein 3 (ABLIM3), the levels of which decreased when mice were learning to associate context with shock. They found that experimentally reducing levels of ABLIM3 in these synapses resulted in increased DGC–interneuron connectivity and in turn enhanced inhibition onto CA3 neurons. Thus, ABLIM3 is able to promote DCG recruitment of inhibition onto CA3.

Next, the authors assessed ABLIM3's role in memory. Optogenetic activation of DGCs involved in memory promoted precise memory recall in the mice when conducted at 2 days, but not 10 days, after learning, showing that DGC engagement in memory fades over time. However, experimentally reducing levels of ABLIM3 prolonged DGC engagement, promoting recall even 10 days after learning. To assess the effect of prolonged engagement of DGCs, as induced by downregulation of

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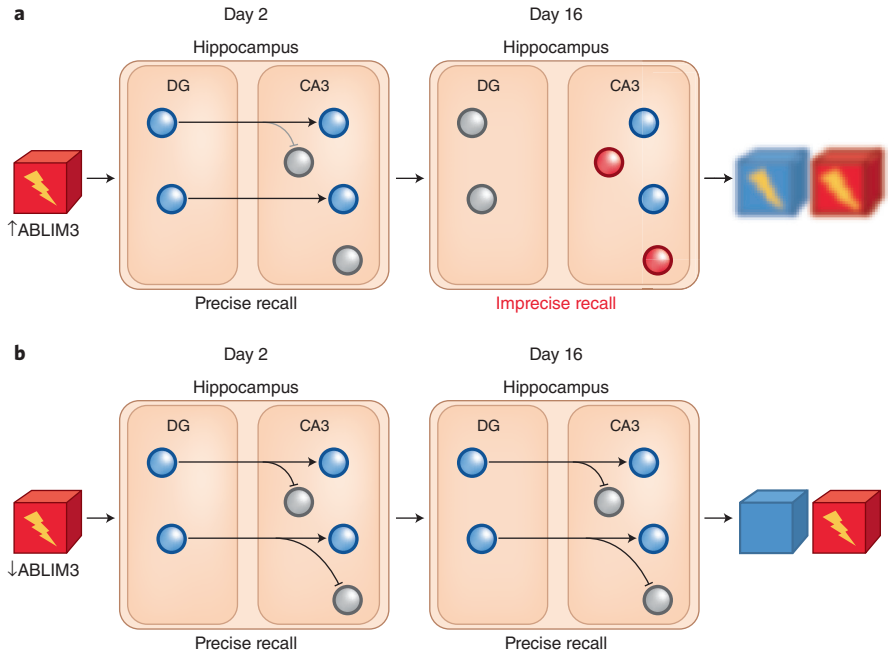

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Figure 1 ABLIM3 is a molecule involved in memory precision. (**a**) Sahay and colleagues[3] trained mice to associate receiving a foot shock with the context of red light. After 2 days, the mice maintained the memory of the correct shock-associated context in the dentate gyrus (DG) through promoting inhibition of CA3 neurons. By day 16, memory was no longer encoded in the DG, and inhibition onto CA3 was lost. This caused the mice to imprecisely remember the shock context. (**b**) Sahay and colleagues[3] found that ABLIM3 downregulation increased inhibition of CA3 and maintained DGC engagement in memory recall over time. As imprecise memory recall is involved in PTSD and dementia, ABLIM3 may have relevance to these diseases.

ABLIM3, on quality of learning, the authors labeled the neurons involved in memory in mice, and either 1 or 16 days after learning, these mice were exposed to the shocked context or to a new, distinct context. At the remote time point (16 days), control mice failed to discriminate between contexts and showed generalized fear (**Fig. 1a**). Also, brain activity patterns induced by recall were the same in both contexts. Mice with downregulated ABLIM3 were able to discriminate between contexts better than mice with normal levels of ABLIM3, and the activation of circuits representing the memory occurred only in the context that they had learned to associate with receiving a shock (**Fig. 1b**). This demonstrated that ABLIM3 downregulation in DGC–interneuron circuits maintains DGC engagement in memory recall and memory precision over time. Also, it strongly suggests that increased ABLIM3 expression underlies memory fear generalization over time. Finally, the authors addressed the important topic of memory deficits in aging. The downregulation of ABLIM3 in aged mice reversed deficits in learning and plasticity through improving contextual discrimination and restoring DGC inhibition onto CA3. Together, these results reveal critical mechanisms that dictate memory precision and hippocampal engagement over time.

This study provides insights into the biology of memory impairment in aging and overgeneralization of fear responses in PTSD. Although humans also express ABLIM3, prospects for translation to therapy for human conditions are far down the pipeline. The authors' results are constrained by the limitations of mouse models, but without question, they provide an alluring new target for future research. Also, these data support using ABLIM3 as a biomarker of cognitive impairment, and as such, it could be a target for interventions aiming to tackle memory decline. With further investigation, new technologies may make use of this important molecule to improve memory for countless individuals afflicted by devastating impairments.

COMPETING INTERESTS

The authors declare no competing interests.

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