of regulation related to intercellular competition for synaptic inputs. Second, how do relative amounts of NL1 in neighboring neurons regulate synapse density? The authors suggest that neurons may compete for binding to limiting amounts of presynaptic neurexins. Neurons that have more NL1 are better at attracting and/or maintaining contacts with neurexin-expressing presynaptic boutons; this hypothesis, however, remains to be tested. Binding of NL1 to presynaptic neurexins may also displace other neurexin-binding partners, yet the relative functions of the varied neurexin-binding partners remains mostly unexplored. Finally, how many other synaptogenic CAMs regulate synapse density through intercellular competition, and which of them coordinate with NL1? Addressing these questions is fundamental to discovering how neuroligin mutations that cause autism spectrum disorders alter connectivity in the developing brain. The present findings will undoubtedly intensify the competition among neurobiologists to unravel the complexity of CAMs and how they govern synaptogenesis.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.


New neurons retire early
Timothy J Schoenfeld & Elizabeth Gould

Using a new retrovirus-optogenetics technique, researchers have found that new neurons in the adult hippocampus are important for memory, but only at an immature stage, when they show enhanced synaptic plasticity.

Over the past decade, almost 2,000 papers have been published on adult neurogenesis in the hippocampus. Many of these studies have aimed at understanding the function of new neurons in the adult brain. Yet despite this intensive investigation, a unified picture of new neuron function has not emerged. New neurons in the hippocampus have been linked to a wide range of functions, such as formation of spatial and contextual memories, pattern separation, anxiety regulation and feedback of the stress response. These findings have been difficult to evaluate, however, given that the primary experimental approach for assessing new neuron function has been to obliterate adult neurogenesis and then test for behavioral deficits. The use of drugs, X-rays or transgenic animals in this lesion type of approach, although highly informative, has potential confounding effects associated with collateral damage and reorganization.

In this issue of Nature Neuroscience, Gu et al. applied retroviral labeling of new neurons and optogenetics to temporarily activate and inactivate new neurons without destroying them, providing an important confirmation that new neurons function in certain cognitive processes. Gu et al. also find that new neurons participate in such functions only during a specific time window that begins after they are incorporated into hippocampal circuitry and that ends when they pass on to a more mature state (Fig. 1).

To address the question of new neuron function, Gu et al. infected the hippocampus of adult mice with retroviruses expressing one of three optically switchable ion channels: channelrhodopsin 2 (ChR2), a variant of channelrhodopsin (ChIEF) or archaerhodopsin-3 (Arch). Because retroviruses infect only dividing cells and light-induced activation of ChR2 or ChIEF excites cells, whereas light-induced activation of Arch silences cells, the authors were able to use optical fibers to reliably turn on or off new neurons at various stages of maturation. Using this approach, they first examined axonal

Figure 1 New neurons have enhanced synaptic plasticity at 4 weeks of age and are functionally relevant for memories that require the hippocampus. Using retroviral-optogenetic technology, Gu et al. applied blue light to turn on new neurons that were specifically 4 weeks of age and found enhanced synaptic plasticity in CA3 pyramidal neurons. Conversely, applying orange light to silence 4-week-old neurons impaired memory retrieval on a task that requires the hippocampus, spatial navigation in the Morris water maze. EPSP, excitatory postsynaptic potential; LTP, long-term potentiation.

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projections of new neurons in hippocampal slices and confirmed that new granule cells gradually form mature projections onto neu-
rons in the CA3 region of the hippocampus over the course of the first 4 weeks. Optical stimu-
lation of 2-week-old granule neurons evoked excitatory postsynaptic responses in CA3 pyra-
midal neurons that peaked and plateaued at 4 weeks, continuing to full maturation.

The researchers then explored the effects of optically silencing new neurons of differ-
ent ages in living mice to determine their influence on cognitive function. To do this, they examined two different learning tasks that are dependent on the hippocampus: spa-
tial navigation in the Morris water maze and contextual fear conditioning. Silencing new neurons had no effect on memory in ver-
ions of these tasks that do not require the hippocampus, namely navigation to a visible platform in the Morris water maze and cued fear conditioning. By contrast, silencing new neurons had a profound suppressive effect on memory retrieval in both of the hippocampus-de-
dependent versions of these tasks, but only when the silenced cells were of a certain age.

When Gu et al.9 investigated the effect of silencing new neurons that were either 2 or 8 weeks of age, they found no effect on spatial or context memory retrieval. However, silenc-
ing new neurons that were 4 weeks of age had a robust effect on spatial and context mem-
ory retrieval. The authors point out that, as their virus labels only a subset of proliferat-
ing cells, these results do not indicate that once new neurons are mature (by 8 weeks) they completely lose any influence on these hipppocampus-dependent tasks. However, given the robust effect on behavior that the authors observed with 4-week-old immature neurons, it seems likely that, if 2- or 8-week-old cells have any such influence, it is much less.

To explore potential mechanisms behind the time-dependent effect of silencing new neurons, the authors examined some of the differences among new neurons at different ages. Previous studies have shown that immu-
ture neurons in the adult dentate gyrus exhibit enhanced synaptic plasticity, which declines with maturation10–12. Gu et al.9 used their retroviral-optogenetic approach to confirm that new neurons pass through different stages of synaptic plasticity as they age. Optically induced stimulation of new neurons at a theta frequency produced long-term potentiation in CA3, with optical stimulation of immature neurons at 3 and 4 weeks of age producing greater synaptic plasticity of CA3 neurons than stimulation of mature neurons at 8 weeks of age. These data suggest that the time period at which synaptic plasticity is maximal coincides with the age at which new cells have a strong influence on memory retrieval.

Because T-type Ca2+ channels have been implicated in the enhanced synaptic plasticity of immature new neurons12, Gu et al.9 tested the effect on CA3 neurons of manipulating these channels. As expected, blocking T-type Ca2+ channels eliminated enhanced synaptic plasticity of new neurons at 4 weeks of age, but had no effect on the basal synaptic plasticity of new neurons at 8 weeks of age. Blocking T-type Ca2+ channels also mimicked the effect of optically silencing 4-week-old neurons during memory retrieval of spatial learning. T-type Ca2+ channel blockade, however, did not have an additive effect when used in con-
junction with optical silencing. These data suggest that enhanced synaptic plasticity of immature neurons is causally linked to their function in spatial memory retrieval.

These findings provide an important con-
firmation of some of the literature using neurogenesis ablation methods to assess the influence of new neurons on cognitive func-
tion and they demonstrate that new neu-
rons are functionally relevant only during a specific time window in their maturation process. Some studies have reported deficits in memory retrieval in rodents lacking new neurons1–4 and others have found that new neurons exhibit enhanced synaptic plasticity in a time-limited manner10–12, but Gu et al.’s results clearly demonstrate that new neuron activation, and not just new neuron presence, in the hippocampus is critical for memory retrieval and enhanced synaptic plasticity.

This study opens the door for the use of optogenetic techniques to confirm the influ-
ence of new neurons of different ages on other proposed functions, such as pattern separa-
tion4, anxiety regulation5,6 and feedback of the stress response. One possibility that can be addressed using Gu et al.’s method is whether new neurons serve different func-
tions during their lifetimes, perhaps pass-
ing from one function to another as they pass through different maturational stages. Another question that is now answerable with this approach is whether different populations of new neurons, such as those located in the dorsal versus the ventral hippocampus13, serve different functions.

Many studies have found that environmental factors can influence new neuron growth and differentiation in positive or negative ways. An enriched environment, physical exercise and sexual experience all foster the growth of new neurons, whereas stress and deprivation have the opposite effect14,15. Using this combined retroviral-optogenetics approach, it would be interesting to see how experiences that hasten or slow neuronal growth affect the action of new granule neurons in hippocampal func-
tion. Gu et al.9 used this approach with high temporal resolution to confirm several impor-
tant findings about the function of new neu-
rons in the adult hippocampus. Like all good studies, this one raises many new questions. With the addition of this method to the adult neurogenesis toolbox, many of these questions are now answerable.

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