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The Young and the Promiscuous

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It is now well accepted that new neurons continue to be generated in the adult hippocampus. By visualizing and manipulating new neurons in behaving mice, Danielson et al. (2016) begin to define how new neurons contribute to hippocampal function.

In the 1960s a young neurobiologist from MIT discovered a subpopulation of proliferative cells in the dentate gyrus (DG) that appeared to generate new neurons well into adulthood (Altman, 1963). Although Joseph Altman's claims were initially met with skepticism (Altman, 2011), the introduction of more definitive methods for labeling and phenotyping newborn neurons in the 1990s led to broad acceptance of this phenomenon.

With acceptance, attention swiftly shifted away from whether hippocampal neurogenesis persists in the adult brain to how the continued addition of new neurons contributes to hippocampal function. Given the role of the hippocampus in memory, initial studies focused largely on how adult-born granule cells (abGCs) impact hippocampal memory function: finding, for example, that global suppression of neurogenesis impairs encoding of some hippocampus-dependent memories (Shors et al., 2001). More recently, however, the focus has narrowed. Motivated by the idea that the DG is important for pattern separation (Leutgeb et al., 2007; Treves and Rolls, 1994)—the process of transforming overlapping input representations into less overlapping or distinct output representations—current studies have asked how hippocampal neurogenesis regulates this process (Sahay et al., 2011b). These studies report that increasing or decreasing hippocampal neurogenesis, respectively, improves or worsens rodents' ability to encode fine spatial discriminations—a behavioral analog of pattern separation (Niibori et al., 2012; Sahay et al., 2011a). However, these types of studies are not without limitations. First, the interventions chronically alter levels of hippocampal neurogenesis, allowing for the possibility of compensatory circuit-level changes that may muddy the interpretation. Second, while brain slice preparations have identified unique physiological features of abGCs (Marín-Burgin et al., 2012), it is challenging to know how these properties relate to alterations in behavior following global alteration of hippocampal neurogenesis. In the current issue of *Neuron*, a study by Danielson and colleagues begins to bridge this divide. Combining sophisticated transgenic and imaging strategies, Danielson et al. (2016) simultaneously monitor the activity of abGC and mature granule cell (mGC) populations in the DG as mice explore virtual contexts and test whether abGCs are necessary for context discrimination. Accordingly, the authors directly compare abGC and mGC activity in vivo and, in so doing, begin to reveal how abGCs uniquely contribute to behavioral pattern separation.

Danielson et al. (2016) used two-photon calcium imaging in awake, behaving mice to record the activity of DG granule cells expressing the genetically encoded calcium indicator, GCaMP6f. By using transgenic mice in which abGCs were indelibly

labeled with a red fluorophore (tdTomato), they directly compared calcium signals emitted from abGCs and mGCs. As these head-fixed mice traversed virtual linear environments (composed of different visual, auditory, and olfactory stimuli), the authors observed that abGCs were more active than their more mature counterparts: Calcium transients (a proxy for neuronal firing) were detected at higher rates in abGCs, and proportionately fewer abGCs were silent. Previous in vitro studies established that abGCs are more excitable than their mature neighbors (Marín-Burgin et al., 2012). The current study shows that the same holds true in vivo. Moreover, it suggests that abGCs—by virtue of their heightened excitability—more readily respond to stimuli during encoding.

How might this promiscuous activity influence how abGCs encode and represent information? The major subdivisions of the hippocampus (including CA1, CA3, and DG) contain spatially modulated neurons, or place cells, that preferentially fire in one or more spatial locations in a given environment. Although it is clear that spatial information is carried by DG population activity, it is unclear whether immature and mGCs differentially contribute to this signal. To answer this question, Danielson et al. (2016) first examined to what extent GC activity was modulated by location in the virtual environments. While the activity of both abGCs and mGCs was spatially modulated, this modulation tended to be less precise in abGCs. New neurons were less spatially tuned.

Might poorer spatial tuning reduce the ability of abGCs to discriminate similar environments? Danielson and colleagues next monitored GC activity as they altered the virtual environments. While mGCs "remapped" when environments were altered, this remapping appeared to be less efficient for abGCs (although this depended to some extent on how spatial tuning was assessed). Interestingly, though, the authors noted a subpopulation of abGCs that were as discerning as their mature counterparts, showing no difficulty discriminating efficiently between contexts. A more detailed analysis of this subpopulation is necessary to determine what particular properties support their superior discrimination ability. Nevertheless, these findings emphasize the utility of the imaging techniques employed by Danielson et al. (2016) in monitoring subpopulation-specific activity in the DG. The current findings that mGCs more efficiently discriminate contexts than abGCs extends previous research by allowing researchers to classify neuronal activity by cell age (Leutgeb et al., 2007).

Although the present study finds that abGCs are relatively poor discriminators, paradoxically, elimination of this population of cells results in impaired behavioral pattern separation (Niibori et al., 2012; Sahay et al., 2011a). In these studies, neurogenesis levels were typically manipulated prior to training, making it impossible to dissect the role of abGCs in distinct memory processes (e.g., encoding, consolidation, retrieval). Using a transgenic strategy to "tag" abGCs with the inhibitory opsin Arch, Danielson et al. (2016) gained temporal control over when abGCs could be inhibited during different stages of a contextual fear discrimination task. In this kind of task, mice are repeatedly exposed to a fearful (shock-paired) context and similar neutral context over the course of several days and start to show more fearful behavior (e.g., freezing) in the aversive context. Optogenetically silencing abGCs during initial exposures to the neutral, but not the aversive, context impaired this behavioral discrimination. However, silencing abGCs after context discrimination was already acquired, or during exposure to a neutral but dissimilar context, did not impair pattern separation.

These data extend previous studies and suggest that abGC activity is necessary during the initial encoding of conflicting contextual stimuli to support pattern separation. But how might this happen? One possibility is that similar contexts are sparsely encoded by non-overlapping ensembles of abGCs, and this might help to reduce interference during memory retrieval. However, in light of the present study's finding that abGCs more ambiguously represent context information (Danielson et al., 2016), this interpretation seems unlikely. Instead, abGCs may act as "pattern integrators." By virtue of their increased excitability, information from distinct experiences might be co-allocated to ensembles of abGCs that partially overlap in their spatial distributions. This idea is supported by computational modeling that predicts that distinct events may be encoded by largely overlapping ensembles of highly excitable abGCs but non-overlapping ensembles of mGCs (Aimone et al., 2009) and would explain why in the current study neuronal activity in new neuron population less efficiently disambiguated context experiences. The small percentage of abGCs that could discriminate contexts may represent a cohort of neurons on the cusp of maturity and therefore display the mGC phenotype, but more temporally precise labeling of immature granule cells is needed to test this possibility. Such experiments will determine whether a specific cohort of abGCs in the heterogeneous immature neuron population can support pattern separation.

Why would the elimination of a population of "pattern integrators" lead to deficits in context discrimination? One idea is that abGCs help "sparsify" the DG code. Immature granule cells form connections with hilar and CA3 interneurons which exert inhibitory drive on mGC and CA3 pyramidal neuron populations to effectively constrain principal cell activation during encoding (Drew et al., 2015; Ikrar et al., 2013; Restivo et al., 2015). Consistent with this idea, increased levels of neurogenesis are associated with reduced DG activation both in vitro (Ikrar et al., 2013) and in vivo (Drew et al., 2015). Conversely, reduced levels of neurogenesis are associated with elevated DG activation both in vitro (Ikrar et al., 2013) and in vivo (Drew et al., 2015). Therefore, pattern separation deficits stemming from optogenetic inhibition of abGCs (Danielson et al., 2016) could be attributed to unrestrained mGC activity during encoding of similar environments and poor separation of memory traces in CA3 (see also Niibori et al., 2012).

What new neurons do in the adult hippocampus has been the subject of much conjecture and debate (Cameron and Glover, 2015). However, just as improved techniques allowed the field to move on from questioning whether neurogenesis persists in the adult hippocampus to acceptance of this phenomenon, improved techniques for imaging new neurons in behaving animals—in essence allowing researchers to watch thought in real time at a cellular level of resolution—will accelerate progress toward defining their function.

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Optogenetics Advances in Primate Visual Pathway

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In this issue of *Neuron*, Klein et al. (2016) used cell-type-specific optogenetics and electrical microstimulation to characterize the koniocellular geniculocortical projections in nonhuman primates. Their work offers a powerful platform for refining our understanding of the mechanisms of visual information processing in the lateral geniculate nucleus and primary visual cortex.

Optogenetics has revolutionized neuroscience research in transgenic animal models and is slowly becoming more sophisticated in nontransgenic models. In nonhuman primates (NHPs), the application of optogenetics has advanced from the initial proof of principle (Diester et al., 2011; Han et al., 2009) to perturbing behavior (Cavanaugh et al., 2012; Gerits et al., 2012), evoking percepts (Jazayeri et al., 2012), and, most recently, projection-specific targeting in the oculomotor system (Inoue et al., 2015). Cell-type-specific targeting, however, has remained a challenge (but see Lerchner et al., 2014). In this issue of *Neuron*, Klein et al. (2016) use optogenetics and electrical microstimulation to target the koniocellular cells of the lateral geniculate nucleus (LGN) in NHPs.

The macaque visual system is among the most thoroughly characterized model systems for thalamocortical processing. Thalamocortical projections to the primary visual cortex (V1) originate from distinct and alternating bands of magno, parvo, and koniocellular cells in the LGN. Decades of research have shown that the magno- and parvocellular projections terminate in the granule layer of V1, whereas koniocellular cells (K-cells) project to the supragranular layers. In addition to their distinct anatomical projections, K-cells are the only cells in the LGN that express the calcium binding protein CamKIIα (Hendry and Reid, 2000). The authors took advantage of this biochemical property and used a viral vector (rAAV5) with an effective CamKII promoter to target the expression of Channelrhodopsin-2 (ChR2) to K-cells. The vector transduced many K-cells with reasonable (but imperfect) specificity and reliability, and reporter gene expression was found throughout the membrane of transduced cells. In addition to K-cells and nearby CamKII-positive cells, the vector was also able to transduce distant layer 6 pyramidal cells of V1 and retinal ganglion cells, presumably through retrograde transport mechanisms.

K-cells have heterogeneous visual response properties and are thus difficult to identify and characterize with visual stimuli. Klein et al. (2016) used optogenetics as an assay to identify K-cells based on their responsiveness to optogenetic stimulation. Optogenetic stimulation can activate both cells of interest that express ChR2 and interconnected cells that do not express ChR2. Klein et al. (2016), therefore, focused their analysis on cells with short-latency responses to optogenetic stimulation that are more likely to have been K-cells with ChR2 expression. They characterized K-cells'