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New Neurons Don't Talk Back

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<http://dx.doi.org/10.1016/j.neuron.2014.12.047>

GABAergic interneurons enforce highly sparse activity patterns in principal neurons of the dentate gyrus. In this issue of *Neuron*, [Temprana et al. \(2015\)](#) show that immature adult-born neurons largely function independently of inhibitory feedback circuits, neither receiving nor generating feedback inhibition.

Two hallmarks of the adult dentate gyrus that distinguish it from most other brain regions are the highly sparse patterns of neural activation and the continual incorporation of new neurons from resident stem cells. Sparse activation refers to the small percentage of principal dentate granule cells (GCs) that spike during behaviorally relevant stimuli on a background of even lower spiking activity ([Aimone et al., 2011](#); [Piatti et al., 2013](#)). Low levels of GC spiking result primarily from GABAergic circuits that generate powerful feedforward and backward inhibition ([Ewell and Jones, 2010](#); [Coulter et al., 2011](#)). Yet within the largely silent granule cell layer, neurogenesis produces a continually renewing small population of putative hyperexcitable immature GCs endowed with higher intrinsic excitability and reduced levels of inhibition compared with their mature neighbors ([Marín-Burgin](#)

[et al., 2012](#); [Dieni et al., 2013](#)). Understanding the relationship between excitable immature neurons and sparse dentate coding is a major challenge in the fields of adult neurogenesis and dentate function.

Mossy fiber axons originating from dentate GCs exhibit two types of functional terminals. Giant mossy fiber boutons provide powerful excitation to a few CA3 pyramidal cells and glutamatergic hilar mossy cells, whereas highly abundant *en passant* boutons innervate a large number of GABAergic interneurons ([Henze et al., 2000](#)). Mossy fiber recruitment of interneurons that project back to the dentate is proposed to provide a competitive form of feedback inhibition necessary for the formation of GC place fields and rate coding ([Rennó-Costa et al., 2010](#)). In the current issue of *Neuron*, [Temprana et al., \(2015\)](#) provide new insight into

the involvement of mature and immature GCs in dentate feedback inhibition.

The authors measure feedback inhibition by selectively expressing channelrhodopsin (ChR2) in three classes of GCs according to their cellular birth date. GCs generated in developing mice represent the majority of mature GCs in the adult. Adult generated GCs examined 4 weeks after cell birth represent immature adult-born neurons in a “critical period” when they have a special role in dentate functions due to their unique intrinsic and synaptic properties ([Aimone et al., 2011](#); [Sahay et al., 2011](#)). Adult-generated GCs examined 7–8 weeks after cell birth represent GCs that have progressed through the critical period and thus presumably possess the intrinsic properties and synaptic connectivity of mature GCs. An important technical consideration is that wide-field light activation in

acute slices can trigger spiking in all ChR2-expressing cells within the field of view. Thus there must be similar numbers of ChR2-expressing cells in each GC class to interpret the consequences of light activation. Since little, if any, death of adult-born neurons occurs between 4 and 8 weeks after cell birth, the authors directly compared functional connectivity of immature and mature GCs by assaying light-evoked synaptic activation in downstream target neurons.

First, the authors target ChR2 expression to GCs born in neonatal mice using an inducible transgenic approach to label a large population of mature GCs in slices prepared from adult mice. Light-induced stimulation of these mature GCs evokes robust EPSCs and IPSCs in downstream CA3 pyramidal cells. Both EPSCs and IPSCs are blocked by the AMPA/NMDA glutamate receptor antagonist kynurenic acid (KYN), demonstrating that IPSCs result from feedforward recruitment of interneurons (Figure 1, left). ChR2 activation also generates KYN-sensitive IPSCs in neighboring mature dentate GCs (that do not express ChR2), illustrating that mature GCs generate robust feedback inhibition to neighboring mature GCs. These results are expected, based on well-known mossy fiber synaptic connectivity. Yet they are important for establishing the feasibility of identifying feedback inhibition in the isolated slice preparation where cut fibers could compromise connectivity. This likely explains the lack of feedback excitation mediated by hilar mossy cells that are also well-known targets of mossy fibers but primarily innervate distant GCs through longitudinal ipsilateral and contralateral projections.

The authors next targeted adult-born GCs using a retrovirus expressing ChR2-EGFP, allowing either 4 weeks or 7 weeks following viral injection to activate immature or mature GCs, respectively. Recordings from CA3 pyramidal cells reveal that monosynaptic excitatory connectivity is established by 4 weeks with little change by 7 weeks, consistent with the timing of new excitatory synapse formation shown by prior studies (Gu et al., 2012). Despite

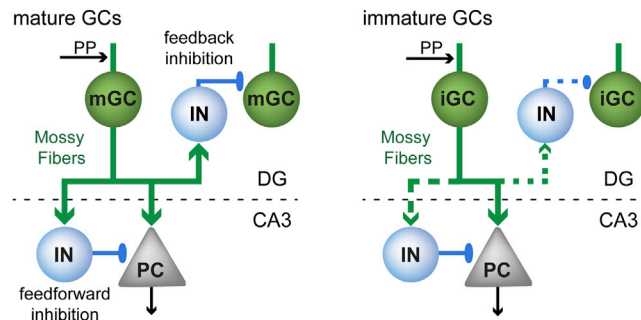


Figure 1. Granule Cell Feedforward and Feedback Inhibitory Circuits Mature granule cells (mGCs, left) recruit interneurons (INs) that generate feedforward inhibition to CA3 and feedback inhibition to neighboring mGCs. Due to weak synaptic connections (dotted lines), immature GCs (iGCs, right) generate little feedforward and feedback inhibition.

the similarity of EPSCs generated by immature and mature GCs, there was a modest increase in the number of pyramidal cells exhibiting feedforward IPSCs evoked by mature GCs as well as an increase in IPSC amplitude (although no difference in total charge). Thus excitatory drive from adult-born GCs to pyramidal cells may be fully developed by 4 weeks, whereas feedforward inhibition continues to increase over time (Figure 1, right). Comparing the magnitude of EPSCs and IPSCs, however, highlights that both immature and mature GCs recruit relatively robust inhibition during low-frequency stimulation (Torborg et al., 2010).

Adult-born GCs undergo a protracted period of maturation during which they develop the intrinsic properties and synaptic inputs characteristic of mature GCs (Dieni et al., 2013), so it is not surprising that downstream circuit connectivity likewise develops in a gradual manner. Yet compared to the modest difference in feedforward inhibition recruited by mature and immature GCs, Temprana et al. (2015) show that immature GCs are particularly ineffective at generating feedback inhibition to the granule cell layer (Figure 1, right). Using recordings from unlabeled mature GCs to assay light-evoked feedback IPSCs, the authors demonstrate that 7-week-old GCs recruit approximately 4-fold larger IPSCs than light activation of 4-week-old GCs. The authors go on to demonstrate that smaller IPSCs translate to reduced functional inhibition by comparing the ability of ChR2-induced inhibition to suppress perforant-path (PP)-evoked population spikes. Whereas feedback inhibition

evoked by mature GCs suppresses PP-evoked population spikes, inhibition evoked by immature GCs has no effect. These results provide a clear demonstration that synchronous activation of a few mature GCs is sufficient to restrict GC activity via feedback inhibition, and also show that immature GCs couple poorly to such feedback loops.

Using a clever combination of transgenic and retroviral labeling, Temprana et al. (2015) also address whether imma-

ture GCs are recipients of feedback inhibition. Immature GCs have low IPSC-to-EPSC ratios in response to stimulation in the entorhinal cortex, suggesting there is delayed innervation by interneurons that mediate PP feedforward inhibition (Dieni et al., 2013). Similarly, Temprana et al. (2015) show that feedback inhibition to immature GCs is weak regardless of whether it is evoked by mature or immature GCs. Together these results converge on the idea that immature GCs function independently from the strong inhibitory circuits that maintain sparse population coding within the mature circuit. Not only are immature GCs less constrained by inhibition, immature GCs also generate less inhibition, particularly feedback inhibition.

In principle, inefficiency of feedback inhibition could result either from a failure of immature GCs to recruit spiking in GABAergic interneurons, or from recruitment of interneurons that inefficiently innervate mature GCs. To address these possibilities, the authors used designer receptors exclusively activated by designer drugs (DREADDs) to selectively activate adult-born GCs in vivo and assay GABAergic interneuron recruitment using the activity-dependent marker cFos. Chemical activation of mature GCs enhanced cFos expression in parvalbumin (PV)-expressing interneurons, whereas chemical activation of immature GCs failed to alter PV⁺ cell activity. Thus, failure of interneuron recruitment likely underlies the low feedback generated by immature GCs. Although the authors focused on PV⁺ interneurons that are known to exert powerful control over

GC spiking, maturation-induced induction of feedback inhibition might not solely depend on one type of interneuron. A detailed understanding of the interneuron subtypes that mediate dentate feedback inhibition is an important future direction.

The elegant approach described by [Temprana et al. \(2015\)](#) will be useful for addressing this and other questions about feedback inhibition in the dentate gyrus. One outstanding issue is whether inhibition generated by adult-born mature GCs differs from inhibition generated by postnatal-born GCs. Due to differences in the number of ChR2-expressing GCs achieved by postnatal versus adult labeling, the authors could not address this point. A second issue relates to a deeper understanding of the frequency dependence of feedback inhibition, since mossy fibers display prominent cell-type- and activity-dependent facilitation that is important for recruiting downstream targets ([Torborg et al., 2010](#)). This kind of detailed functional mapping using optogenetics, whole-cell recording, and pharmacology is challenging in a more intact system.

What is the significance of [Temprana et al. \(2015\)](#) for elucidating the function of adult-born immature neurons in dentate function? The authors propose a scenario wherein feedback inhibition differentiates the roles of young and mature GCs in novel input discrimination. In their model, familiar input space is encoded by mature GCs that have small and highly specialized input fields due to feedback inhibition. Immature GCs that lack inhibition have large and overlapping input fields that enable them to respond not only to familiar but also to novel input space. Over time, Hebbian learning and a gradual development of feedback inhibition progressively transform broad and overlapping input fields into the small and nonoverlapping fields exhibited by mature GCs. The gradual shift from low to high inhibition is necessary for the transformation, since it does not occur in the model under conditions of constant high or low inhibition. These results highlight the potential role of delayed feed-

back inhibition in the development of a population-based mechanism for input discrimination, in which cortical representations are mapped to specific subsets of GCs. However, there is considerable debate regarding the mechanisms of dentate pattern separation, including the role of population versus rate coding and the involvement of mature and immature GC populations ([Aimone et al., 2011](#); [Sahay et al., 2011](#); [Neunuebel and Knierim, 2012](#); [Piatti et al., 2013](#)).

Despite the current lack of mechanistic understanding of what the dentate does and how it does it, there is widespread agreement that sparse GC activity is an essential component. This brings back the simpler question of how immature adult-born GCs might contribute to neural activity in this quiet brain region. In vitro studies showing that immature GCs have higher intrinsic excitability and less synaptic inhibition than mature GCs predict that immature GCs represent the most active population of dentate GCs in vivo ([Marín-Burgin et al., 2012](#); [Neunuebel and Knierim, 2012](#)). However, preferential activation of immature GCs is not detectable using immunohistochemical approaches that allow confirmation of GC age ([Stone et al., 2011](#)), possibly because high intrinsic excitability and low inhibition are tempered by low excitatory drive ([Dieni et al., 2013](#)). In theory, highly excitable cells that are broadly responsive to afferent activity also degrade rather than improve measures of input discrimination ([Aimone et al., 2011](#)). Thus an appealing and non-mutually exclusive alternative is that immature GCs modify the activity of the larger population of mature GCs, in effect “dictating the tone rather than carrying the message” ([Piatti et al., 2013](#)). In this view, immature GCs could promote rather than degrade sparse neural activity by recruiting inhibition. This idea is supported by the recent report that selective enhancement of neurogenesis reduces the spread of afferent-evoked depolarization in acute dentate slices ([Ikrar et al., 2013](#)). The current results of [Temprana et al. \(2015\)](#) can therefore be viewed in the context of testing a specific mecha-

nism by which immature GCs control the activity of mature GCs. Somewhat unexpectedly, these results strongly argue against the hypothesis that immature GCs sparsify neural coding via feedback inhibition.

So the question remains, if new neurons don’t talk back to their elders, who do they talk to? Further work is required to understand who is listening to what new neurons have to say.

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