Yet many aspects of OPC biology differ fundamentally between mice and humans, so much so that one cannot assume that Wnt-regulated processes yield analogous cellular outcomes in mouse and human OPCs[14]. To address this concern, Fancy *et al.*[11] assessed the differential expression of these Wnt-regulated transcripts in tissue samples from infants with severe hypoxic-ischemic encephalopathy. Perinatal hypoxic ischemia is a major cause of cerebral palsy, and although most presentations of cerebral palsy involve white matter loss, the contribution to its etiology of frank OPC loss, as opposed to dysfunction and maturational arrest, has been controversial[2,15]. Fancy *et al.*[11] found that resident OPCs in the white matter lesions of these children shared remarkable molecular similarities with those derived from APC-null mice: they had no detectable APC and hence manifested derepressed Wnt signaling, with high levels of LEF1 and SP5, as well as other Wnt-driven, APC-deficient colon cancer–associated products that included v-ets avian erythroblastosis virus E26 oncogene homolog 2 (ETS2), dual specificity phosphatase 4 (DUSP4) and ring finger protein 43 (RFP43). Lest these expression patterns be considered transient, the authors describe bipolar RNF43$^+$ OPCs in a 12-year-old child with cerebral palsy, whose perinatal hypoxic-ischemic event had presumably yielded not only a disabling degree of white matter loss, but also a functionally insufficient OPC population whose maturational arrest had in no way diminished with the passage of time.

It is the sustained nature of that maturational arrest that presents the greatest problems for those interested in mobilizing OPCs for therapeutic purposes. Can a transcription factor–based regulatory network sustain such an exquisitely balanced state of maturational arrest by a nominally self-renewing progenitor cell population without additional epigenetic changes to ensure the new status quo? If such changes do occur, will simple antagonism of Wnt-dependent pathways and downstream activators, such as SP5, be sufficient to reinitiate oligodendrocytic differentiation and myelination? Fancy *et al.*[11] do not answer these questions, but they certainly do provide a window into how the virtual suspended animation of arrested, functionally compromised oligodendrocyte progenitors might be reversed. At the same time, the authors provide a model system in which those events involved in homeostatic maintenance may be decoupled from those involved in mitotic expansion, and the latter from oncogenesis and malignant transformation. As such, the worth of this study lies not only in its insights into the pathophysiology of hypoxic-ischemic white matter injury, but also in its identification of processes by which we may now attempt to manipulate the mitotic expansion and myelination by endogenous progenitor cells across the entire spectrum of adult as well as pediatric myelin disorders, and how we might do so without the risk of concurrent oncogenesis. Rare indeed is it that such richness is offered in such a small package.

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Dark matter of the bulb

Sasha Devore & Dmitry Rinberg

A study now shows that granule cells deep in the olfactory bulb exhibit wildly different response dynamics depending on behavioral state, suggesting they could configure network changes across behavioral states.

The olfactory system is under constant assault from an ever-changing mix of volatile molecules that waft through the air, impinging on the nasal mucosae with each new inhalation, yet the brain effortlessly extracts the relevant signals to guide behavior. The nervous system solves this task in part by dynamically tuning the olfactory bulb, the earliest olfactory processing network in the CNS, rendering it dependent on factors such as the wakefulness of the animal, the hedonic value of the incoming odorants and the recent history of odor stimulation (for review, see ref. 1). Flexible sensory information processing is thought to be mediated by extensive feedback projections to the olfactory bulb from cortex and subcortical neuromodulatory nuclei[2–4]. In particular, the granule cells, an extensive network of inhibitory neurons deep within the bulb, integrate inputs from nearly all of these centrifugal projections and are thought to orchestrate bulbar dynamics across behavioral states. Although they have been the subject of many theoretical models of bulbar processing[5,6], relatively little is known empirically about the function of granule cells *in vivo*. A study by Cazakoff *et al.*[7] in this issue of *Nature Neuroscience* opens a window into the deepest layers of the bulb by characterizing, for the first time, the odor- and breathing-related activity of individual granule cells in awake mice.

Odor molecules in the air enter the nose by inhalation, and they are first detected by olfactory sensory neurons (OSNs) embedded in the nasal epithelium, each typically expressing a single olfactory receptor gene (selected from ~1,200 in rodent and ~300 in humans). In an impressive display of convergence, the axons from OSNs expressing the same receptor bundle together, forming distinctive glomerular structures in the outermost layers of the olfactory bulb (**Fig. 1**). Mitral and tufted (M/T) cells, the principal output neurons of the bulb, each send a primary dendrite into a single glomerulus. According to this basic wiring diagram, M/T cells are poised to convey information detected by a single receptor type to downstream cortical targets. However, extensive inter- and intraglomerular processing can occur via neurochemically and anatomically diverse networks of inhibitory neurons, which outnumber M/T cells by almost two orders of magnitude[8]. The responses of M/T cells to odors are far from simple: in awake animals,

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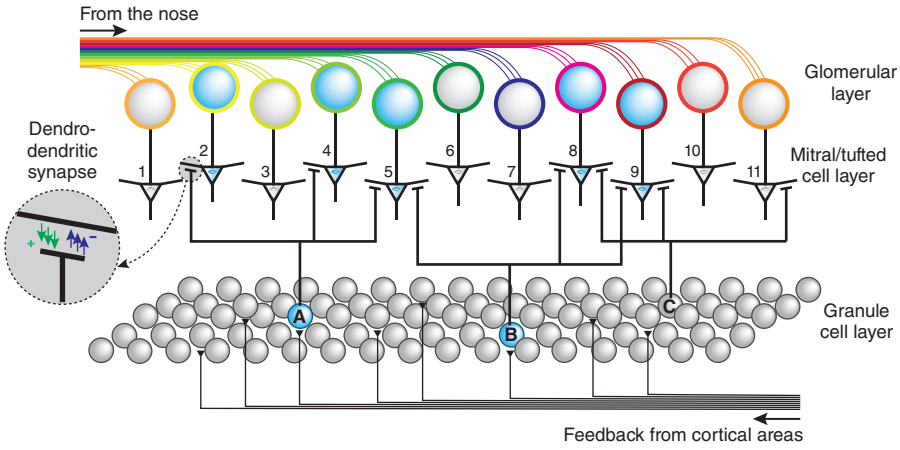

Figure 1 A partial schematic of the olfactory bulb. An odor activates a subset of olfactory sensory neurons (OSNs) in the nose, which send their axons to the olfactory bulb. Axons from OSNs that express the same olfactory receptor (colored lines) converge onto one or two glomeruli (colored circles). M/T cells receive excitatory input from a single glomerulus and send their output to higher brain areas (not shown). Granule cells form reciprocal dendro-dendritic synapses with M/T cells (inset); these cells are also targets of feedback from cortical areas. Light blue fill indicates active cells/glomeruli. Granule cells are considered, on the basis of M/T cell–granule cell connectivity, to be specific-feature detectors[11]. For example, granule cell A is activated (light blue) because M/T cells 2, 4 and 5 are simultaneously active, and similarly for B, whereas cell C does not receive sufficient drive to fire because only two of its three input cells are active. The level of activation of granule cells, and thus the level of M/T cell inhibition or suppression of the specific patterns, may be controlled by feedback from the cortex and modulated by the state of the animal.

individual M/T cells are typically spontaneously active, with some emitting a temporally precise burst of spikes locked to a particular phase of the sniffing cycle that varies depending on odor identity and concentration and others exhibiting odor-driven suppression[9,10]. In stark contrast, odor coding is markedly different in anesthetized animals, with M/T cells exhibiting reduced spontaneous activity, but producing stronger, more sustained responses following odor inhalation[2,4]. It has been hypothesized that these state-dependent changes in odor processing may arise from the action of feedback from cortex and subcortical neuromodulatory nuclei on inhibitory networks in the bulb, particularly through regulation of the granule cell network[1–6].

The cell bodies of granule cells lie in the deepest layers of the bulb (**Fig. 1**) and are more numerous than any other cell type in the bulb[8], although the reason it needs such vast quantities is elusive. Granule cell dendrites project radially toward the external plexiform layer (EPL) of the bulb, where they form reciprocal dendro-dendritic synapses along mitral cell lateral dendrites. By mediating lateral inhibition between restricted sets of M/T cells, granule cells are theoretically poised to function as higher order feature detectors, capable of detecting and learning specific combinatorial patterns of M/T activation (**Fig. 1**) and reciprocally enforcing restrictions on M/T spatial and temporal activation patterns[5,11]. As granule cells are the targets of a diverse set of centrifugal cortical and neuromodulatory inputs to the bulb[4], the state-dependent modulation of spatiotemporal M/T activity could be achieved by regulating the granule cell network. However, the lack of recordings from granule cells *in vivo* has kept these hypotheses in the realm of theory.

Because of their small size, granule cells have proved extremely difficult to record from *in vivo*, as conventional metal microelectrodes and silicon probes do not reliably record high-fidelity signals from them. To circumvent this problem, Cazakoff *et al.*[7] advanced a glass patch pipette through the deep layers of the bulb and blindly formed loose seals onto single cells, yielding recordings with high signal-to-noise ratios. By recording from only a single cell per penetration and juxtacellularly labeling it with dye, the authors were able to reconstruct and visualize individual cell morphologies and definitively identify recordings from granule cells.

Armed with a technique that allowed stable, high-quality recording from granule cells *in vivo*, the authors proceeded to address two fundamental, but related, questions regarding granule cell activity in the mouse olfactory bulb. First, they systematically characterized odor-related activity in individual granule cells across the breathing cycle. Second, they examined the state dependence of this activity. Their observations paint the granule cell network as disparate as night and day, contingent on the wake state of the animal.

In anesthetized mice, granule cells were relatively quiet, firing on average approximately 2, but not more than 8, spontaneous spikes per s; moreover, odor-driven responses were weak and infrequent. Activity in individual granule cells was tightly coupled to the breathing cycle, and most granule cells in the population were active at a coincident phase of the respiration cycle. As a result, the activity in granule cells carried odor-related information in a time-limited manner. When animals transitioned from anesthetized to awake states, the granule cell network itself awoke and became both more spontaneously active and odor responsive. On average, the spontaneous activity in granule cells nearly quadrupled in awake animals. Notably, granule cells in awake animals exhibited much stronger and more broadly tuned odor responses, with substantial increases in firing rate observed for many of the odors that were tested. Somewhat surprisingly, the increased firing rates of granule cells arose, in part, because of a smearing of activity across the sniff cycle, resulting in relatively weak coupling to respiration phase. Furthermore, the preferred phase of individual granule cells was variable, resulting in an overall desynchronization of the granule cell network at the population level. Thus, under anesthesia, the granule cell network is weakly active, but coherent, whereas the opposite occurs in the waking state, with the granule cell network exhibiting stronger, but less synchronized, responses.

By developing a technique for recording from granule cells in awake animals, Cazakoff *et al.*[7] have taken a critical step forward toward an understanding of inhibition in the olfactory bulb network. However, their results leave open many questions as to precisely how granule cells influence M/T cell output from the bulb, as well as their functions in different behavioral tasks[12]. For example, given the strong, but weakly respiration phase–coupled, granule cell activity, to what extent are granule cells capable of sculpting the temporally precise, strongly respiration phase–coupled output from M/T cells[9]? It will be critical for future studies to more directly examine the influence that granule cell activity exerts on M/T cell output. An important question will be to distinguish the function of the granule cell network from that of other inhibitory interneuron networks that also interact with M/T cells in the EPL. For example, recent studies suggest that the parvalbumin-positive interneuron network in the EPL regulates overall levels of bulbar output by broadly inhibiting M/T cells[13,14]. The broad odor-tuning of granule cells observed by Cazakoff *et al.*[7] may actually be relatively selective in comparison to that of the parvalbumin-positive cells[13,14],

leaving open the possibility that granule cells sculpt M/T responses to specific odors (**Fig. 1**). In addition, higher frequency olfactory bulb oscillations, which reflect underlying network activity and are linked to olfactory discrimination learning, have been localized to the EPL[15]. To what extent these oscillations, and the activity of the underlying cell assemblies, are coordinated by granule cell activity versus that of other interneuron networks remains to be addressed. Perhaps the tighter control of behavioral state might reveal unexpected results in future studies, such as stronger respiratory phase coupling during particular phases of behavioral tasks, that may reveal more about how granule cells influence M/T cell output.

By showing that granule cells are strongly influenced by waking state, the authors have confirmed this network of inhibitory interneurons as a viable source of dynamic information processing in the bulb. The door is finally opened to empirically addressing granule cell function *in vivo*.

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Useful dynamic regimes emerge in recurrent networks

Vishwa Goudar & Dean V Buonomano

The internal dynamics of recurrent cortical circuits is crucial to brain function. We now learn that simply increasing the strengths of recurrent connections shifts neural dynamics to a potentially powerful computational regime.

As a pianist plays, spatiotemporal patterns of action potentials in the brain are transformed into changing patterns in the musculoskeletal system. The resulting sounds in turn produce spatiotemporal patterns of neural activity in the auditory cortex of the listener. Similarly, a sequence of words on a page is the product of spatiotemporal patterns of neural activity in a writer's brain, and those words in turn generate patterns of activity in the brains of readers. Ultimately, time-varying patterns of neural activity underlie just about everything we do. It is generally accepted that these spatiotemporal patterns of activity arise in part from the internal dynamics of recurrent cortical circuits. For this reason, considerable efforts have been devoted to understanding how patterns of activity emerge from recurrent neural networks. Although this work has generated many insights, it has also proved humbling. But in this issue of *Nature Neuroscience*, Ostojic[1] takes an important step—in what will undoubtedly be a long walk—toward better understanding neural dynamics in computational models of recurrent neural networks. His work demonstrates that increasing the synaptic strengths between recurrently connected units induces a transition from a regime with little computational potential to one with high potential.

Ostojic[1] based his simulations on a previous model of recurrent neural networks[2] composed of simple spiking units called integrate-and-fire neurons. A typical simulation is composed of 10,000 units, 80% excitatory and 20% inhibitory. All units are randomly connected with a connection probability of 0.1, reflecting the experimental observation that the connection probability between nearby cortical pyramidal neurons is 0.1 to 0.2. Each unit also receives a large tonic input, resulting in spontaneous firing in the absence of any recurrent connections.

One of the most important parameters in this class of models is the connection strength between the units. This value, often denoted by J, determines the strength of both the excitatory and inhibitory weights in the networks (we are making the simplifying assumption that all weights are the same). But the inhibitory weights are further governed by a factor of g. Thus, the total input to a neuron would be proportional to $N_{Ex}J - N_{Inh}gJ$, where J represents the strength of an excitatory synapse, gJ represents the strength of an inhibitory synapse, and N_{Ex} and N_{Inh} represent the number of excitatory and inhibitory synapses, respectively. When $g = 4$, the net input will on average be 0 because there are four times more excitatory than inhibitory neurons; this would represent a perfectly balanced case. Ostojic focused on $g = 5$, meaning that the recurrent connections are dominated by inhibition, but the network is nevertheless said to be 'balanced' because the ratio of excitation and inhibition is constant across a range of activity levels.

Previous studies have demonstrated that balanced excitatory-inhibitory networks exhibit a dynamic regime in which neurons fire irregularly in a manner that resembles the activity of cortical neurons during stationary conditions[2–6]. This type of pattern is referred to as an irregular asynchronous, or a homogenous asynchronous, regime (**Fig. 1a**). The irregular activity arises because excitation and inhibition mostly cancel each other out, but spikes are generated from time to time because of voltage fluctuations.

Ostojic[1] used simulations and an analytical approach to extend these previous results. He found that, as synaptic strength parameter J is increased, there is a transition from a homogeneous to a heterogeneous regime (**Fig. 1b**). In this state, the firing rates vary substantially in time because the units become bursty. This burstiness resembles experimentally observed responses while animals

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