

*et al.*<sup>7</sup> now show that postnatal NPCs are heterogeneous and contain a subpopulation destined to preferentially become adult NSCs<sup>7</sup>. It will be of interest to learn whether this NPC subpopulation continues neurogenesis from developmental to adult stages rather than undergoing the neurogenic-to-gliogenic switch characteristic of NPCs in almost all other regions of the CNS during development—and, if so, what mechanism underlies this difference.

Another intriguing discovery of Furutachi *et al.*<sup>7</sup> is that the CDK inhibitor p57 is essential, not just to slow the cell cycle in, but also to generate, the embryonic cells from which adult NSCs originate during development. Thus, deletion of the *p57 (Cdkn1c)* gene in embryonic NPCs reduced the number of adult NSCs, possibly as a result of premature exhaustion of this population. Conversely, overexpression of p57 increased the number of NPCs maintained in the ventricular zone for a longer period, suggesting that the slowing of the cell cycle is causal in establishing this persistent stem cell population<sup>7</sup>. Clarification of the mechanistic link between the slow cell cycle and NSC maintenance may provide further evidence for such a causal role. Given that adult stem cells in some other tissues are also quiescent and express p57 at high levels<sup>10</sup>, it will be interesting to examine whether p57 expression (or a slow cell cycle) has a common function in establishing adult tissue stem cells.

The adult SEZ consists of subdomains that generate distinct neuronal subtypes<sup>1</sup>. Adult NSCs that reside in these SEZ subdomains are thought to originate from the corresponding embryonic subdomains defined by transcriptional codes<sup>1</sup>. Furutachi *et al.*<sup>7</sup> found that adult NSCs located in the lateral and ventral subdomains of the SEZ tend to retain H2B-GFP transiently expressed at E9.5 to a greater extent

than those located in the medial and dorsal subdomains. Although this may be a result of differences in the timing of cell cycle slowing between the subdomains, it is also possible that adult NSCs in medial and dorsal SEZ subdomains may originate from different types of embryonic NPCs. In this regard, lineage tracing has revealed that adult NSCs in the medial and dorsal subdomains, but not those in the lateral and ventral subdomains, are derived from Axin2-expressing NPCs at E12.5 (ref. 11).

Regulation of the cell cycle in NPCs (apical radial glia) also appears to differ between those in the ventral and dorsal telencephalon during development. The cell cycle of basal progenitors is longer than that of apical progenitors in the dorsal telencephalon (neocortex), whereas it is shorter in the ventral telencephalon (ganglionic eminences), with cells of the latter being similar to the adult NSCs in the lateral wall of the ventricles<sup>12</sup>. In the neocortex, manipulation of the length of the cell cycle changes the cellular output of apical and basal progenitors<sup>12</sup>. Furutachi *et al.*<sup>7</sup> add to the concept that the cell cycle does not simply regulate cell numbers, but also determines cell fate<sup>12,13</sup>.

The study by Furutachi *et al.*<sup>7</sup> raises several questions: First, is this newly identified, slowly dividing embryonic NPC subpopulation conserved during evolution? [<sup>3</sup>H]Thymidine pulse-chase labeling analysis has suggested that quiescent NPCs may exist at the midgestation stage in the rhesus monkey<sup>14</sup>, although it is not clear whether they later contribute to adult NSCs. Slowly dividing embryonic NPCs also exist in the zebrafish brain, where they give rise to region-specific adult NSCs. In this case, however, rapidly dividing embryonic NPCs in different domains also contribute to adult NSCs in the corresponding domains of the zebrafish brain<sup>15</sup>. Second, are NSCs in the adult SGZ also derived from a slowly dividing

distinct subpopulation among embryonic NPCs? Third, what mechanism underlies establishment of the adult NSC population, and is it related to the slowing of the cell cycle? Fourth, how is the expression of p57 controlled in the slowly dividing subpopulation of embryonic NPCs? This is key to understanding the mechanism by which the embryonic origin of adult NSCs is established. It is also important because embryonic NPCs disappear in most parts of the CNS after development, with neurogenic NSCs remaining only in restricted niches in the adult brain. Addressing this question may reveal the molecular basis of the niche for adult NSCs and thereby facilitate its manipulation in regenerative medicine approaches to its replenishment in patients with defective neurogenesis.

#### COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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## Strength in more than numbers

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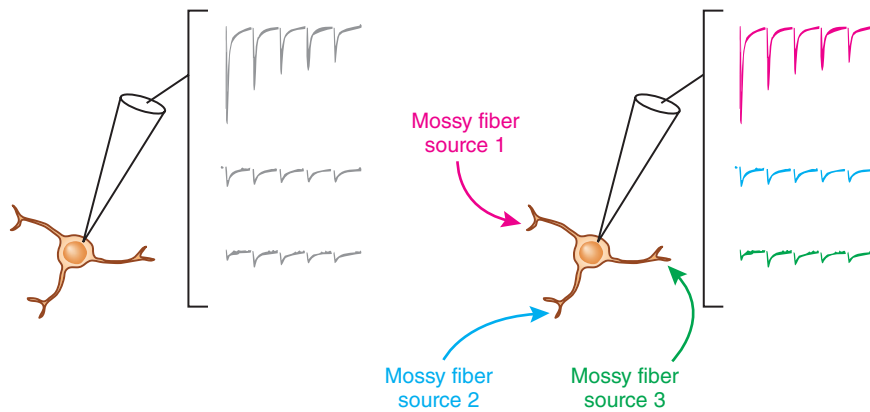
**Theory suggests that cerebellar granule cells combine sensory and motor signals originating from different sources. An unexpected logic governing how granule cells process different input sources may enhance computational power.**

Cerebellar researchers may be closing in on the function of a large population of neurons in the brain: the tiny granule cells at the input stage

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of the cerebellar cortex. These are by far the most numerous vertebrate neurons, estimated to account for more than three-quarters of the 80 billion neurons in the human brain<sup>1</sup>. In the early 1970s, David Marr<sup>2</sup> and James Albus<sup>3</sup> developed compelling theoretical accounts to explain why so many granule cells would be useful. However, because of the technical

difficulties involved in recording from these small, densely packed neurons *in vivo*, experimental tests of these theories have only recently become possible<sup>4,5</sup>. In this issue of *Nature Neuroscience*, Chabrol *et al.*<sup>6</sup> provide evidence for unsuspected order among the diversity of input filtering properties of mossy fiber synapses onto granule cells. Paradoxically,



**Figure 1** Presynaptic origins of diverse granule cell responses. Left, synaptic transmission into granule cells shows a diversity of strengths (note different amplitude of top versus middle and bottom traces) and short-term dynamics, including depression (top, middle traces) and facilitation (bottom trace). Right, by tracing presynaptic mossy fibers to their sources, Chabrol *et al.*<sup>6</sup> found that specific synaptic properties are associated with specific sources: primary vestibular (source 1), secondary vestibular (source 2) and visual (source 3).

this order may act to enhance the random mixing of signals proposed by the theory.

Input to the cerebellum is carried by axons called mossy fibers (so-named by early anatomists because of their distinctive appearance under the light microscope) that arise from many parts of the brain and carry a variety of sensory, motor and even cognitive signals. Before reaching Purkinje cells, the sole output neurons of the cerebellar cortex, the information conveyed by mossy fibers is first recoded in a much larger number of granule cells. This distinctive anatomical arrangement led Marr<sup>2</sup> and Albus<sup>3</sup> to suggest that the granule cell layer functions analogously to so-called hidden layers in neural networks, in which input signals are mixed together before converging through modifiable synapses onto read-out neurons, the role of the Purkinje cells in their model. This mixing creates a richer, higher dimensional representation of the input that makes certain computations, such as learning to discriminate between different input patterns, easier<sup>7</sup>.

Recent studies have provided some evidence for these longstanding ideas. Genetic tagging of anatomically and functionally distinct sets of mossy fiber axons provided direct anatomical evidence for multimodal convergence onto individual granule cells in some regions of mouse cerebellum<sup>8</sup>. An *in vivo* electrophysiological study of granule cells in a cerebellum-like circuit in weakly electric fish showed that granule cells fire action potentials in response to specific combinations of sensory and motor signals conveyed by distinct sets of mossy fibers<sup>9</sup>. Thus, although granule cells receive, on average, only four excitatory inputs, these appear to carry the variety of signals needed to create a mixed high-dimensional representation.

To test whether they indeed do so, Chabrol *et al.*<sup>6</sup> used a combination of *in vitro* and *in vivo* electrophysiology, genetic tagging of mossy fibers and computational modeling to provide an in-depth examination of how granule cells in the vestibulocerebellum, a region known to coordinate balance and eye movements, integrate different mossy fiber inputs. They first found that the striking functional diversity of mossy fiber synapses onto granule cells, which has been noted in previous slice studies<sup>10</sup>, is not random variation, but instead represents a physiological signature of anatomically and functionally distinct classes of mossy fibers (**Fig. 1**). The authors demonstrated this by expressing fluorescent proteins in one or the other of three distinct groups of mossy fibers, those conveying primary vestibular, secondary vestibular or visual (eye movement-related) input. Selective electrical stimulation of these different pathways evoked synaptic responses in granule cells that differed strikingly in their amplitudes and short-term plasticity. Furthermore, genetic tagging of two different mossy fiber pathways, when combined with granule cell recording, revealed that convergence of distinct mossy fiber pathways (for example, visual and vestibular) onto the same granule cell is common in the vestibulocerebellum.

Convergence of different input types is not sufficient to assure effective mixing; this also requires that no single input dominate over the others in controlling the firing of a granule cell. Mossy fibers carrying different forms of information often exhibit different firing patterns; for example, some mossy fibers convey graded information by modulating firing above and below a high mean rate, whereas others signal events by firing in brief bursts, but are otherwise silent.

Tailoring presynaptic properties, including short-term plasticity, to the statistics of presynaptic spike trains could help to balance the input to a granule cell from different sources, giving each an equal opportunity to control its firing. Chabrol *et al.*<sup>6</sup> indeed found that primary vestibular afferents form strong synapses that depress at the high mean firing rates typical of these inputs, whereas synapses from visual inputs are weaker and show facilitation, matching the lower mean rate and burst-like character of their firing. Adjusting synaptic properties to assure equal mixing has been termed synaptic or dendritic democracy in other systems<sup>11</sup>. The small number of inputs onto cerebellar granule cells make them an excellent model system for exploring this interesting topic.

Chabrol *et al.*<sup>6</sup> went on to use a combination of *in vitro* recordings and computational modeling to explore how integration of multiple mossy fiber inputs with distinct synaptic properties shapes the spike output of granule cells. The authors crafted their stimulation protocols to mimic the firing patterns of vestibular and visual mossy fibers observed *in vivo*. Granule cell spikes evoked by combined stimulation of two or three different classes of mossy fibers differed systematically in their latency relative to the onset of stimulation. Chabrol *et al.*<sup>6</sup> used a modeling approach to show that the different delays conferred by input-specific synaptic properties improve the capacity of a read-out neuron (the model analog of a Purkinje cell) to discriminate among mossy fiber input patterns. It remains to be seen whether granule cell spike latency differences help to discriminate naturally occurring input patterns and, if so, how these differences are read out by Purkinje cells. An alternative possibility suggested by studies of weakly electric fish<sup>12</sup> and eyelid conditioning<sup>13</sup> is that diversity in the timing of granule cell firing forms a basis for generating temporal patterns.

An important overarching question concerning granule cell representations is whether the combinations of different mossy fiber inputs are random, as envisaged by Marr<sup>2</sup> and Albus<sup>3</sup>, or whether they have a yet-to-be-determined order produced by either genetic or activity-dependent mechanisms. The alignment of synaptic properties found by Chabrol *et al.*<sup>6</sup> shows a relationship between input identity and synaptic type, but it does not reveal structure in the choice of the inputs that a particular granule cell receives. Instead, it appears to assure that mixed inputs have equal access to the granule cells that they contact. Modeling and electrophysiology in the fish electrosensory lobe<sup>12</sup> and anatomical studies of the mushroom body in *Drosophila*<sup>14</sup> support random input assignments to granule

cells or their analogs in these cerebellum-like structures. Further testing is needed to determine the relevance of input-specific mossy fiber synaptic properties in particular and expansive recoding by granule cells more generally in the cerebellum proper. Emerging genetic tools, including specific manipulations of granule cells<sup>15</sup>, may make it possible to perform such tests. Although much work remains, the elegant study by Chabrol *et al.*<sup>6</sup> provides hope that long-sought links between the heterogeneous features of cerebellar input

and the crystalline structure of its output, including the function of the brain's most numerous neurons, are within reach.

#### COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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## Divide and conquer: strategic decision areas

Nils Kolling & Laurence T Hunt

**Strategic decisions can prove difficult to study. The board game shogi is used to investigate the functional neuroanatomy of strategic decisions, revealing different brain areas from those engaged by other forms of choice.**

Historians debate what moved Napoleon to attack the English at Waterloo or the Duke of Wellington to decide to hold and defend his position. By contrast, readers of this article may ponder their repeated tendency to choose chocolate cake over fruit for their teatime snack. These decisions sound very different from one another because one has the power to shape history whereas the other can only shape one's waistline. But what remains less clear is whether they are also different in terms of the brain regions that they engage. This is because research into the neurobiology of value-based decision-making has so far primarily focused on the latter, 'economic' form of decision over the former, 'strategic' decision. This reflects not an unwillingness among military generals to volunteer for neuroimaging studies, but a more fundamental problem: how might one ask subjects to make strategic decisions inside the scanner while estimating the factors that motivate their choices.

In this month's issue of *Nature Neuroscience*, Wan *et al.*<sup>1</sup> take advantage of a Japanese chess-like strategy game called shogi to investigate the neural basis of strategic reasoning. Shogi not only has many millions of human players who have trained themselves to make rapid

strategic decisions, but it also has computer algorithms that can calculate the precise value of different offensive and defensive moves. The authors scanned amateur shogi players using functional magnetic resonance imaging as they were presented with different board positions and asked to rapidly select whether an offensive or defensive approach was required. A computer algorithm was used to calculate value estimates for different possible strategies, approximating the degree to which subjects might be motivated to attack versus defend in each decision. These estimates were then regressed against neural activity as the subjects made their choice. Crucially, in contrast with moves in many other strategic games, shogi moves can be easily characterized as being part of a defensive or offensive strategy. As such, a clear dissociation could be drawn between neural activity related to the value of either form of strategy or to the comparison of strategies. This approach complements the now widespread use of mathematical models to describe neural activity in the context of many different forms of decision-making, such as economic<sup>2,3</sup>, social<sup>4,5</sup> and foraging<sup>6,7</sup> (Fig. 1).

The two kinds of intuitive strategies participants could choose, defense or attack, were found to relate to activity in three key neural structures. First, posterior cingulate cortex (PCC) reflected the subjective value of offensive strategies. PCC has often been seen to activate in value-based decision tasks, but rarely (with notable exceptions<sup>8</sup>) has it been explicitly discussed as a decision area. Second, rostral anterior cingulate cortex (rACC) activated as a function of the subjective value

of the defensive strategy. Intriguingly, it has recently been shown that neurons in a nearby brain region in macaque monkeys preferentially encode negative information about air puffs<sup>9</sup>, which elicit a defensive response. In humans, rACC does not always appear in decision-making experiments, as it does not seem to directly encode subjective economic values, but it is sometimes differentially active in participants depending on their subjective bias<sup>6</sup>. This is consistent with it signaling the overall approach or strategy they are likely to adopt in the task, varying among people. Lastly, Wan *et al.*<sup>1</sup> focused on how the values of those different strategies could be compared, looking for areas encoding the relative difference between chosen and unchosen strategy values. This highlighted dorsolateral prefrontal cortex (DLPFC), which has frequently been implicated in rule- or model-based decisions<sup>10</sup>, as well as cognitive control<sup>11</sup>. Using functional connectivity between these three regions, it was possible to show that DLPFC connected more strongly to PCC when subjects chose to attack, whereas DLPFC connected more strongly to rACC when subjects chose to defend.

It is notable that the decision signals were distributed across three separate brain areas, and that the comparator region lay outside of regions more traditionally associated with other forms of value-based decision-making (Fig. 1). This result speaks to the idea that decisions may be realized via a distributed consensus<sup>12,13</sup>, a viewpoint that argues that no single brain area is critical to decision-making, but that decisions instead emerge via competitions occurring in many brain regions.

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