persistent NK cells have on the neurogenic niche. Chronic EAE induces an increase in type A and decrease in type B and C NSC proliferation[11], and the authors tested whether infiltrating NK cells influence this phenomenon. Antibody-mediated NK cell depletion increased $BrdU^+$ cells in the SVZ, resulting in a corresponding rescue of type B stem cell numbers in the niche[2].

How could NK cells be affecting stem cell proliferation? Using an *in vitro* co-culture between NK cells and NSCs sorted from EAE mouse brains, the authors showed that NSCs from chronic, but not peak, EAE brains were uniquely susceptible to NK cell killing[2]. This observation narrowed their focus to NK cell cytotoxic mechanisms, typically governed by MHC I–detecting NK receptors. The authors hypothesized that NSCs were downregulating expression of MHC I molecules during late-stage EAE, thereby making them susceptible to NK cell killing. The authors therefore measured expression of several MHC I genes in NSCs sorted from naive, peak and chronic EAE brains. Notably, they observed a dramatic reduction in one MHC I gene, *H2-T23* (encoding Qa1), specifically in type B stem cells[2]. This loss of Qa1 is important, as viral delivery of a constitutively active Qa1 construct to the SVZ prevented NK killing of NSCs, reversed impairments in NSC proliferation and improved EAE outcome[2].

Production of IL-15 by NSCs has been previously described, and it regulates their proliferation *in vivo*[10], but the current study unveils what may be thought of as an off-target function of IL-15 in promoting NK cell survival during neuroinflammation. This interaction certainly seems deleterious[2], although the overall influence of NK cells on EAE, and more importantly MS, warrants further investigation.

Decades ago it was thought that MHC I was not expressed at all by neurons. Then pioneering work by Shatz and colleagues revealed that not only are MHC I molecules expressed in the brain, but many have a vital role in synaptic plasticity[12]. This was an unexpected function for what classically is thought of as a purely immune protein and is a prime example of nature 'recycling' molecules for different purposes.

What are the reasons and causes for downregulation of Qa1 by NSCs in the chronic phase of EAE? Why would a cell downregulate such a specific immune receptor in the context of inflammation, where all it apparently does is increase susceptibility to NK killing? Perhaps MHC I molecules expressed by NPCs have a non-immune function and the downregulation of Qa1 has implications beyond its NK cell interactions. Given the dual purpose of MHC I molecules, it is possible that NSCs downregulate Qa1 for a CNS-specific physiologic function and the introduction of NK cells has the unexpected consequence of killing these cells. This finding could then be an example of the downside of recycling molecules. Giving the same protein different context- or location-dependent functions works well most of the time, but when systems pathologically interact, as the nervous and immune systems do during MS, detrimental consequences may arise. Additional 'immune' molecules, such as TNF[13] or complement[14], have alternate purposes recently described in the nervous system, and studying these in the context of neuroinflammation promises to be a fruitful and important line of future investigation.

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Life goes by: a visual circuit signals perceptual-motor mismatch

Nao Ishiko & Andrew D Huberman

Connections between a specific thalamic structure and the neocortex convey mismatches between internal perceptions and external events. These findings help to define the circuits controlling contextual modulation of visual-motor processing.

Your brain is constantly making predictions about the outside world on the basis of your internal perceptions and your actions. Take, for example, the experience of walking down a crowded sidewalk to catch your evening train. If the people around you walking in the same direction suddenly start to quicken their pace, you are likely to speed up too. As you do this, the people walking toward you will appear to pass by more quickly, but somehow you 'know' that this reflects your change in pace, not theirs, and there is no reason why it should change your behavior.

This simple scenario highlights a basic, but critical, feature of brain function: our capacity to visually compare our internal perceptions and motor behavior with events in the outside world and, from that, perform adaptive predictions, thoughts and behaviors while avoiding irrelevant ones. The remarkable thing is that all the downstream outcomes and implications emerge from essentially one computation: the degree of visual mismatch between self-motion and the motion of objects 'out there' in the world. What are the neural circuits that endow the brain with this capacity to compare internal and external events? These contextual modulations are thought to be the result of computations carried out in the cortex, and cortico-cortical connections in particular.

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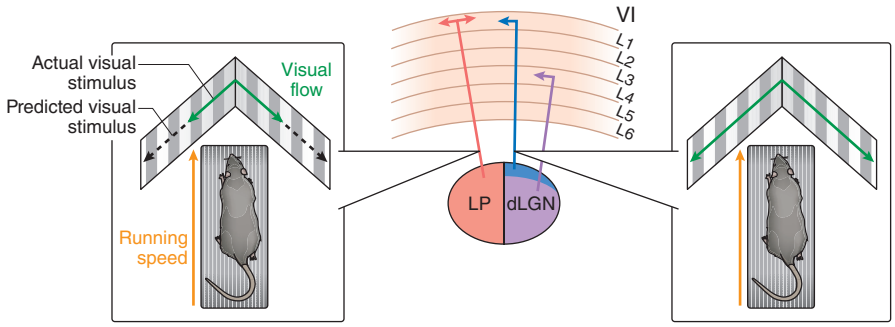

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Figure 1 Separate thalamic structures and pathways for conveying contextual information to visual cortex. Roth *et al.*[1] analyzed the activity patterns of neurons in LP or dLGN of mice at the level of their axon projections to V1. The inputs from dLGN to V1 were active when the running speed of the animal was matched to the predicted and actual visual flow speed of the virtual environment. The inputs from LP to V1 were preferentially activated when there was a mismatch between the mouse's running speed (and thus the predicted visual flow speed) and the actual visual stimulus flow speed in the virtual environment. LP → cortex connections are more widespread and terminate more superficially than dLGN → cortex connections.

In this issue of *Nature Neuroscience*, Roth *et al.*[1] describe a neural circuit that signals visual and motor information from a specific thalamic structure, the latero-posterior nucleus (LP) to the neocortex. Using a diverse and elegant array of technical approaches, Roth *et al.*[1] parse the anatomical and physiological features of LP neurons and their connections with the cortex. They conclude that the LP-cortex thalamo-cortical circuit represents a dedicated brain pathway for signaling mismatches between internal sensory experiences and events in the outside world.

The basic neural pathways for sensing visual information in the outside world have been worked out in detail over the last century. Light enters the eye, where photoreceptors convert that light into electrical signals the rest of the nervous system can understand. The other retinal neurons, the interneurons and retinal ganglion cells, then further process and send that electrical information to the brain, where it diverges into two main pathways related to sight[2]. Some of visual information leaving the eye flows to the dorsal lateral geniculate nucleus (dLGN) and from there to primary visual cortex (V1), whereas other visual information is sent by the retinal ganglion cells directly to the midbrain superior colliculus (SC), and from there to the pulvinar and then up to the cortex[3]. Thus, there are essentially two pathways for visual perception: a direct pathway consisting of two synapses between the eye and V1 (retina → dLGN → cortex) and an indirect pathway involving three synapses (retina → SC → pulvinar → cortex)[3]. Our understanding of how the indirect pathway functions in visual perception has lagged behind that of the direct pathway, but this is quickly changing.

In efforts to better understand this circuit and its contributions to sensory processing, Roth *et al.*[1] studied rodent LP, a thalamic nucleus that sits adjacent to the dLGN and is the likely homolog of primate pulvinar. First, Roth *et al.*[1] wanted to determine the anatomical connections of LP and compare them to the direct route involving dLGN connections with V1. Injections of adeno-associated viruses that label neuronal cell bodies, dendrites and axons revealed that dLGN neurons connect to V1 and synapse mainly in layer 4, but also in the more superficial layers 1–3, consistent with the results of previous studies[4–6]. By contrast, labeling of LP neurons revealed that they connect broadly to V1, extrastriate areas and cingulate cortex and that, in those areas, they preferentially synapse in the superficial-most layers, including layer 1. Retrograde tracing revealed a similar theme: small focal injections of tracers into V1 led to tight clusters of labeled neurons in the dLGN, indicating a high degree of retinotopic precision in the dLGN-to-cortex pathway, whereas injections of equivalent size into V1 led to broad swaths of labeled neurons in LP, indicative of crude retinotopic precision. Thus, the spatial organization of visual signals in the direct (retina → dLGN → V1) versus the indirect (retina → SC → LP → V1) pathways is markedly different, and the projections are therefore likely to carry different qualities of information (**Fig. 1**).

Roth *et al.*[1] next explored the basic receptive field properties of visual information delivered to V1 by LP neurons by infecting them with an adenovirus carrying the genetically encoded calcium sensor GCaMP6 and then using two-photon microscopy *in vivo* to image activity fluctuations in their axonal boutons located in superficial V1. They also carried out the same experiment in mice that received injections of GCaMP6 into the dLGN, enabling them to compare and contrast the type of information delivered to V1 from LP versus dLGN neurons. Both dLGN and LP axonal boutons in V1 showed a range of basic receptive field properties, including orientation selectivity, direction selectivity or more concentric 'untuned' spatial properties. The presence of these varied types of thalamic inputs to V1 is supported by other recent observations[5,7]. Roth *et al.*[1] also discovered, however, that LP receptive fields tend to be larger, overlapping and more elongated than dLGN receptive fields, again supporting the notion of less retinotopic precision in this pathway than in the direct pathway involving dLGN. Moreover, Roth *et al.*[1] showed that the receptive fields of neurons in V1 itself are, on average, more sharply tuned for orientation or direction than LP or dLGN neurons. Together, these findings indicate that LP signals similar, but non-redundant, visual information to V1 in the form of retinotopically coarse projections. In this way, LP neurons could be optimally tuned and positioned to signal information about the broad content of visual scenes, but not spatially restricted information about objects located in those scenes.

An intriguing feature of LP neurons is their direct input from the SC and other motor-related centers. This inspired Roth *et al.*[1] to explore whether LP neurons are active during eye movements, particularly saccades. They placed head-fixed mice on treadmills to allow them to run while the mice observed a virtual reality environment involving a hallway with striped walls and a textured floor (**Fig. 1**). The movement of the treadmill was tethered to the flow speed of the stripes on the walls of the virtual hallway, essentially making the mouse think it was controlling the passage of the visual scene. At the same time, the authors carried out Ca^{2+} imaging of LP bouton responses and monitored the mouse's eye movements by infrared video. Some LP boutons were responsive to saccade eye movements, even when the animal was in the dark, indicating that LP carries both pure motor signals as well as crudely spatially organized visual information regarding the orientation, direction and shape of visual features.

Is there a fundamental difference in the type of visual information delivered to cortex by dLGN versus LP and pulvinar neurons? Up until now, it appeared that the lack of retinotopic precision was the only major difference in these two channels for visual information flow. In an extremely clever set of experiments, Roth *et al.*[1] teased out the fundamental distinction between these two pathways and, in doing so, revealed a key role for LP and pulvinar in sensory processing.

While still imaging mice with GCamp6 in either dLGN or LP boutons, the authors compared the condition in which the animal's running speed accurately predicted the animal's speed of passage down the virtual corridor, signaled to the mouse by the rate at which the images of the striped walls and textured floor moved, to an 'open loop' condition in which the animal's running speed did not correlate with its speed of passage down the corridor. In other words, they tested how dLGN versus LP neurons responded to matched or mismatched sensory-motor-perceptual events.

Neurons in both the dLGN and in the LP responded to and sent information about movement to V1. Indeed, units in LP were sometimes tuned for changes in speed, either increases or decreases, as the animal adjusted its running speed on the motorized treadmill. However, there was a fascinating divergence between dLGN and LP signaling of the animal's running speed and visual flow. The dLGN → V1 pathway was best activated when running speed and visual flow were positively correlated. By contrast, LP neurons signaled the cortex when running speed and visual flow were mismatched. This means that the indirect pathway involving LP specifically carries information about the discrepancy between self-generated and external visual motion, thereby setting the context for processing of visual scenes.

Several new and exciting models emerge from these findings. First, the detailed anatomical tracing experiments confirm that rodent LP appears to have many of the same features as primate pulvinar, and these are therefore very likely to be homologs. Second, LP neurons connect in crude retinotopic order to the neocortex, especially layer 1. Layer 1 harbors many axons (and some neurons) for long-range cortico-cortico connections, and given that layer 5 neurons extend their apical tufts into layer 1 (refs. 6,8), layer 5 neurons may be preferentially modulated by LP inputs. This is of interest because layer 5 cortical pyramidal cells are the neurons that provide feedback to sensorimotor subcortical structures such as the SC. Third, LP itself is a combined visual-motor center and conveys information to V1 about an animal's actions, such as saccades, in addition to conveying information about features of the visual scene, such as directional flow (albeit over broad regions of visual space), and, most importantly, rates of visual change and the degree of match or mismatch between an animal's own motion and that of the outside environment.

So does this mean that, when you are walking to your evening train, the sight of the people and buildings around you is carried by retina → dLGN → V1 circuits, whereas your understanding of how your own motion relates to your perception of the scene is carried by your retina → SC → pulvinar → V1 pathway? The results of Roth *et al.*[1] suggest that this is indeed the case. Along those lines, it is interesting to note that direct and indirect pathways to cortex are hallmarks of all sensory modalities, not just vision, and LP/pulvinar is one major hub through which that sensory information flows[3]. Thus, separate pathways for fast, spatially precise sensory analysis versus slightly slower, spatially diffuse sensory analysis may represent a basic feature of brain organization and processing.

There are several things that must be squared away, however, before one can conclude that LP/pulvinar is the structure that signals and allows the cortex to make sense of the discrepancy between internal percepts and external motion. Foremost, we need inactivation studies as well as gain-of-function studies to test, in a causal way, whether LP is necessary and/or sufficient for this purpose or whether it is simply an indirect readout of a different brain network or area. In addition, pulvinar has been implicated in critical neural functions other than those described here, such as attention[3,9]. Thus, it remains unclear exactly whether LP or pulvinar signals sensori-motor mismatches in a dedicated or secondary way.

Finally, LP, and especially the primate pulvinar, is huge. It may not even be one structure: it has numerous subcompartments that each connect with different regions of the subcortical and cortical brain[3,10]. Detailed parsing of LP and pulvinar connections to cortex will be essential for figuring out the function of this thalamic station and the circuits in which it participates. In the meantime, the results of Roth *et al.*[1] bring to the fore the extent to which secondary pathways to cortex signal key information involved in everyday experiences. They also highlight the importance of exploring neural circuits in a manner that captures the dynamic nature of internal and externally driven sensory experience.

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Seq-ing the cortex one neuron at a time

Hsu-Hsin Chen & Paola Arlotta

The most complete single-neuron transcriptome database of the mouse visual cortex was performed using a large collection of reporter mouse lines. Results highlight the unmatched neuronal diversity of the cerebral cortex.

The immense diversity of neurons and glia that populate the cerebral cortex is central to the execution of vital functions ranging from sensory processing and motor control to language and cognition. Yet, despite its importance, the classification of cortical cell types remains undeniably incomplete. Cortical neurons have been largely classified on the basis of their axonal connectivity, morphology, laminar localization and electrophysiological properties. Transcriptomic studies of distinct populations of neurons have also begun to unravel the molecular basis of cortical neuron subtypes and, notably, to highlight the existence of additional diversity within classically defined populations.

Until fairly recently, the heterogeneity within these populations (and across all cells) could not be further defined at the molecular level, largely because of limitations in available

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