insights into these distinct capping mechanisms by the L proteins of NSVs are particularly useful to develop effective and selective antiviral strategies.

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When Visual Circuits Collide: Motion Processing in the Brain

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How is sensory information transformed by each station of a synaptic circuit as it flows progressively deeper into the brain? In this issue of *Cell*, Mauss et al. describe a set of connections in the fly brain that combines opposing directional signals, and they hypothesize that this motif limits global motion noise as the fly moves through space.

To understand "how the brain works" will require a thorough explanation of how neural circuits transmit and elaborate representations of the sensory world from one synapse to the next. A lot is known about the specialized tuning of neurons in the sensory periphery. A lot is also known about neurons that reside deep in the brain and how their activities relate to perception and behavior (e.g., Britten et al., 1992). A major goal of modern neuroscience is to bridge these levels of understanding by deciphering how peripheral signals are kept separate or are combined in specific ways in order to generate more elaborate sensory representations. In this issue of *Cell*, Mauss et al. (2015) provide an elegant example of how neurons several synapses deep into the fly brain encode specific categories of information about the visual world and thereby create behaviorally relevant, coherent motion representations.

The computation of directional motion signals is fundamental to the survival of many animals. In the mammalian retina, direction selectivity arises from a circuit involving asymmetric inhibition of interneurons onto direction-selective retinal ganglion cells (DSGCs) (Briggman et al., 2011). Several theories have been raised about how the mammalian brain uses information extracted from DSGCs to create more sophisticated receptive field properties in downstream neurons, such as ultra-sharp direction tuning or the property of orientation selectivity (Levick et al., 1969; Cruz-Martín et al., 2014). Recent work showed that, in flies, temporal delays in synaptic convergence, not asymmetric inhibition, establish the first set of visual neurons that encode directional motion (Maisak et al., 2013), thereby confirming the classic model first proposed by Hassenstein and Reichardt (1956). Serial electron microscopic (EM) analyses showed that these temporal delays arise in the signals transferred several synapses downstream from the retina, in the medulla (Takemura et al., 2013). Maisak et al. showed that, in turn, direction-selective medullar neurons (T4/5) project to their target, the lobula plate, in the form of a layered map whereby each layer represents a different cardinal direction of motion. This organization raises an exciting mystery: how are the various directional motion signals combined at deeper stations within the brain?

In this issue, Mauss et al. characterized the role of lobula plate local neurons in directional signal computations. First, the authors labeled the neurons

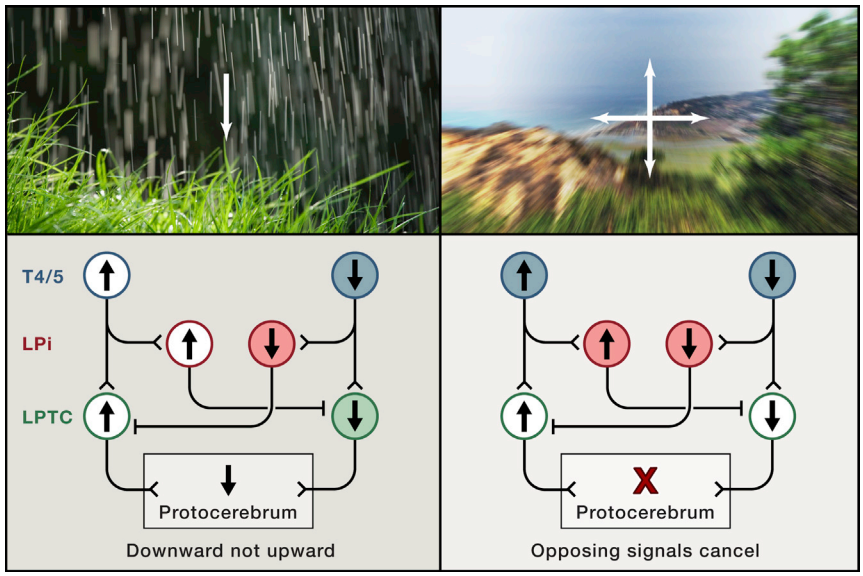

Figure 1. LPTC Neurons Integrate Opponent Direction Signals in the Lobula Plate

Transformation of directional motion signals as they flow from medulla to the lobula plate and into the protocerebrum. Lobula plate tangential cells (LPTC, green) receive excitatory input from direction-selective T4/5 cells (blue) in the preferred direction and inhibitory input from direction-selective LPi (red) in the null direction. Filled circles indicate active neurons, and arrows indicate preferred direction of the cell. (Left) Directed object motion downward results in excitatory T4/5 cell input to LPi and LPTC neurons with the same downward preferred direction. The outcome is a LPTC signal representing "down not up" that is sent to the protocerebrum. (Derek Croucher/Getty Images.) (Right) Global motion in all directions results in both upward and downward excitatory T4/5 cells to provide input to their respective LPi and LPTC targets. LPi neurons reciprocally inhibit the null direction LPTC. In turn, the opposing direction signals cancel, and LPTCs do not pass on a direction motion signal to the protocerebrum.

that innervate opposing directional layers of the lobula plate, called lobula plate intrinsic (LPi) neurons. Second, using two-photon calcium imaging, they demonstrated that LPi neurons are direction selective and robustly tuned to the same preferred direction as their excitatory T4/T5 inputs. Third, the authors recorded the tuning of downstream lobula plate tangential cells (LPTC) while reversibly silencing LPi neurons. This led them to an exciting discovery. They found that, while LPTC neurons receive excitatory inputs from T4/5 for the preferred direction, at the same time they receive inhibitory inputs from LPi neurons for the null direction (Figure 1).

What is the purpose of LPTC neurons receiving two opposing directional signals, one excitatory and one inhibitory? The authors speculate that this modulates LPTC tuning by (1) maintaining the direction-selective (DS) tuning preference of the T4/5 cell (e.g., to prefer "up") and (2) using the inhibition of the LPi neuron to prevent responses to the opposing direction (e.g., to *not* prefer "down"). In terms of the functional significance of this computation, Mauss et al. put forth the idea that combining these excitatory and inhibitory motion signals serves to reduce overall levels of noise in the circuit. To test this, Mauss et al. recorded from LPTC neurons while presenting the flies with global motion stimuli, such as dots moving in many different directions or while presenting expanding stimuli. Under normal conditions, LPTC neurons did not respond to global motion. Remarkably, when the direction-selective inhibitory input from LPi to LPTC was blocked, the LPTC neuron responded robustly to global motion. In other words, when LPi was inactive, its target—the LPTC—still responded best to one direction of motion (the one delivered by T4/5), but in addition, it now responded to other motion signals as well. In this way, the precise delivery of directional excitation and inhibition from the medulla to the lobula plate serves to limit responses to global motion signals.

What general themes can we conclude from this work? Nearly a half-century ago, Levick et al. (1969) proposed a model to explain their observation that DS neurons in the brain are more sharply tuned than are the DSGCs that project to them. To explain this, they hypothesized that the retina transfers a preferred direction signal to target cells in the brain in the form of direct excitatory input—for example, from a leftward-preferring DSGC—but also that the retina transfers a non-preferred direction signal to the same target cell/s. The key aspect of their model is that the transfer of the non-preferred direction signal arrives indirectly via an inhibitory interneuron. This arrangement ensures that, from the perspective of the target cell, there is an excitatory "prefer left" signal and an inhibitory "don't prefer right" signal, and in turn, the DS response of the recipient cell in the brain is sharper than the DSGC input it receives. The results of Mauss et al. resemble the Levick model in the sense that the LPTC cell receives both an excitatory preferred direction input and an inhibitory null direction input. Contrary to the Levick model, however, the findings of Mauss et al. do not support sharpening of DS signals because T4/T5 cells are already sharply tuned to one of the four cardinal directions. Therefore, Mauss et al. provide support for the generalizability of the Levick model but also raise a new idea about the functional relevance of this circuit motif: motion opponency. The LPTC cells thus cancel opponent motion signals to respond specifically to signals in one direction but not the other, such as "downward not upward" (Figure 1). Moreover, the functional outcome is greater than the sum of its parts, with LPTCs differentially responding to directed object motion as opposed to widespread global motion. One wonders whether motion opponency is also solved this way in the mammalian visual system and, if so, at which synaptic station along the eye-to-brain pathway.

These results make the next milestone in the field of fly motion processing very clear: to figure out the organizational logic of the downstream connections in the target of the LPTC neurons, the protocerebrum (fly analog to the

mammalian visual cortex) (Sanes and Zipursky 2010). The field needs to know whether there are other cells that encode global motion in the protocerebrum and if so, how they accomplish that task. Also, the behavioral impact of the motion-opponent circuit discovered by Mauss et al. still needs fleshing out. In theory, investigating visually guided behaviors in flies (Maisak et al., 2013) could be used to implicate this circuit in separating self-motion versus object motion as the fly moves through space.

The implications of the findings in Mauss et al. extend beyond the parallels to the mammalian direction-selective circuit because they also raise several new ideas about how the brain can use conflicting signals to disambiguate sensory scenes. Not only can this idea be applied to other types of visual signals, but it may also provide insight into the general purpose of having conflicting sensory inputs converge in the same targets. Across multiple sensory modalities, such convergent computations may result in the refinement of percepts of the external world, depending on the specificity with which they are organized (Sosulski et al., 2011). In the meantime, the new results of Mauss et al. indicate that the brain is highly selective in how it organizes the flow and transformation of directional visual information, and they imply that such stringency may be essential for accurate decoding of feature-rich visual scenes.

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Optical Control of Microtubule Dynamics in Time and Space

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Small molecule inhibitors of microtubule dynamics are widely used as cell biology research tools and clinically as cancer chemotherapeutics. By slight modification to the chemical structure of a known microtubule inhibitor, combretastatin A-4, Borowiak et al. develop a photoswitchable derivative that can be turned "on" and "off" with low-intensity light to spatially and temporally control microtubule dynamics.

Microtubules are abundant, dynamic intracellular polymers that perform key functions in important processes such as mitosis, intracellular transport, and migration. Microtubule-directed small molecules, which inhibit microtubule dynamics, are widely used and valuable tools in cell biology as well as successful chemotherapeutics clinically, most likely a result of their ability to perturb mitosis (Dumontet and Jordan, 2010). However, due to the abundance of tubulin and the importance of microtubules not only during mitosis but also in interphase, treatment with microtubule-directed drugs often leads to systemic side-effects, such as peripheral neuropathies (Carlson and Ocean, 2011). The ability to spatially and temporally control the activity of such drugs could provide a significant advancement in the tolerability, increasing their overall clinical value. In this issue of *Cell*, Borowiak et al. develop a group of photoswitchable microtubule inhibitors, referred to as Photostatins (PSTs), which can be turned "on" and "off" with UV or visible light, respectively (Borowiak et al., 2015). Thus, their work establishes a novel tool for optically controlling microtubule dynamics in space and time.

Borowiak et al. designed PSTs as analogs of combretastatin A-4, part of a group of small molecules that bind to the colchicine-binding domain at the inter-dimer interface between α- and β-tubulin, which have been developed particularly for their vascular-disrupting properties at the tumor tissue level (Dumontet and Jordan, 2010). Critically, different combretastatin A-4 isomers have variable