

its δ subunit. Therefore, although AchRs alone on plasma membranes are not sufficient to form condensed clusters via phase separation, the receptors are likely to promote phase separation of Rapsn upon formation of the AchR/Rapsn complex via augmentation of the valency of the molecular network. Consistent with this hypothesis, AchRs are required for clustering Rapsn in myotubes (Bruneau et al., 2008). The role of the dystrophin-associated protein (DAP) complex, a multiprotein complex assembled on muscle membranes and essential for maintaining muscle strength, in the AchR/Rapsn cluster formation is also a worthy question. The RING domain of Rapsn specifically interacts with the cytoplasmic tail of β -dystroglycan. The DAP complex is a highly condensed molecular network formed by multiple scaffold proteins including dystrophin, syntrophin, utrophin, dystrobrevin, and transmembrane protein β -dystroglycan. It will be interesting to investigate how the AchR/Rapsn condensates and the DAP condensates may interact and regulate each other in NMJs. Furthermore, AchR/Rapsn clusters are concentrated at the shoulder areas of NMJ fold crests and aligned with presynaptic active zones (Figure 1D). Such a nanoscale organization has also

been reported in synapses within the central nervous system, thus representing a conserved mechanism for effective synaptic transmission. Adhesion molecules are believed to play essential roles in *trans*-synaptic alignment and restricting the diffusion of receptors. Whether the DAP complex or other *trans*-synaptic adhesion molecules function to align the active zone condensates and AchR/Rapsn condensates in NMJs needs to be evaluated in future research.

The study by Xing et al. (2021) represents a new starting point for studying NMJs through the lens of phase separation. Clustering of the AchR/Rapsn complex via Rapsn-driven phase separation also provides a new paradigm for elucidating mechanisms of neurological disorders caused by mutations of NMJ proteins.

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Aligning one's sights: The pulvinar provides context for visual information processing

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<https://doi.org/10.1016/j.neuron.2021.05.028>

The pulvinar (lateral posterior [LP]), like other higher-order thalamic nuclei, receives input from—and sends output to—multiple neocortical structures. In this issue of *Neuron*, Blot et al. (2021) demonstrate that LP integrates multimodal inputs to put visual information in context.

Converging data from studies of the visual system have supported a new interpretation of thalamic function. Rather than simply relaying information between sensing structures and the neocortex, thalamic

neurons can transform this information in important ways. For example, neurons in the lateral geniculate nucleus (LGN), once thought to be simple relays between retinal ganglion cells and primary visual cortex

(V1; Figure 1B), have response modulation by attentional state (Schneider, 2011; McAlonan et al., 2008; Dhruv and Carandini, 2014) and past visual experience (Durkin et al., 2017; Huh et al., 2020). These



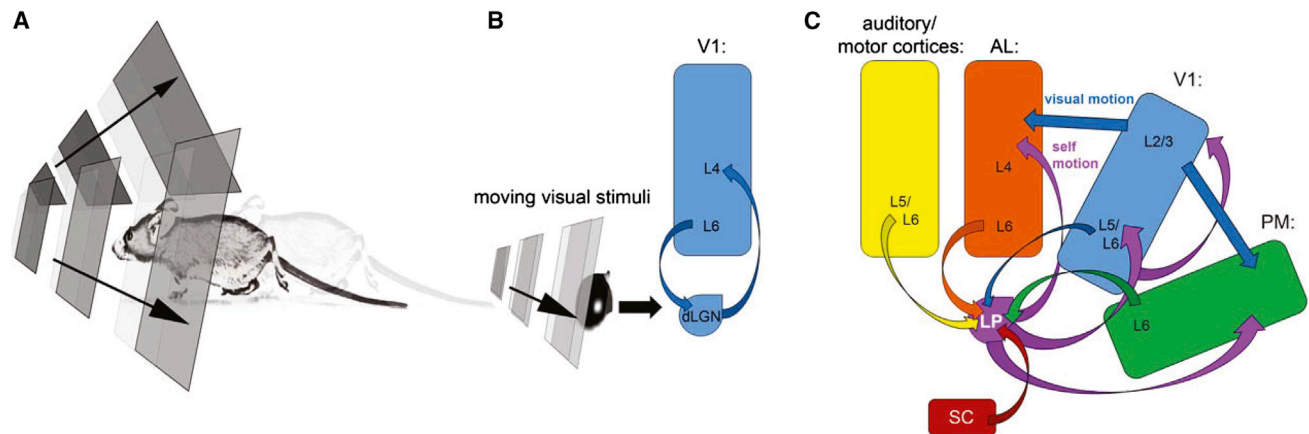


Figure 1. Transthalamic visual pathways provide contextual information for interpreting what is seen

(A) During locomotion, both proprioceptive cues and visual cues (such as optic flow [arrows]) provide information about the changing spatial relationship between one's self and the environment.

(B) Visual movement information (e.g., optic flow) is relayed to the brain via the early visual system—retina, LGN, and V1.

(C) Motion in the visual field during locomotion can be integrated with information from other sensory modalities via the pulvinar (LP; violet). LP receives diverse neocortical inputs from V1 layers 5 and 6 (blue), higher-order visual areas AL and PM (orange and green, respectively), and auditory and motor areas (yellow) and subcortical input from other thalamic nuclei and SC (red). Areas AL and PM receive corticocortical visual input from separate populations of V1 neurons (blue) and transthalamic input from distinct populations of LP thalamocortical neurons (violet). V1 and LP inputs provide different information (about optic flow and self-motion, respectively) to AL.

types of modulation likely emerge from non-retinal inputs to LGN neurons, e.g., corticothalamic feedback from V1 (Figure 1B), and inhibition from the reticular thalamic (RT) nuclei. The pulvinar (lateral posterior [LP])—a higher-order visual thalamic nucleus—receives input from these same structures, other visual cortical regions, and subcortical structures such as the superior colliculus (SC; Figure 1C). In turn, LP sends output to multiple visual cortical areas. This “transthalamic” pathway for visual information processing thus seems capable of functioning in parallel with corticocortical sensory processing. In rare instances, the pulvinar can also compensate for the bilateral absence of V1 to mediate “blindsight” (Warner et al., 2015). However, the nature of and mechanisms for interactions between the transthalamic and corticocortical visual processing streams are largely unknown.

In this issue of *Neuron*, Blot, Roth et al. (Blot et al., 2021) characterize two major, divergent output pathways of LP—to the anterolateral (AL) and posteromedial (PM) visual cortical areas. Neurons in these two cortical structures also receive direct corticocortical input from V1 (although from distinct populations of V1 neurons [Kim et al., 2018]). Both AL and PM have been classified as functioning analogous to the primate “dorsal stream” or “where pathway” (i.e., their neurons

encode more information about the spatial location and movement of an object than its identity or detailed features). However, neurons in the two areas have distinctly different response properties (reviewed in Niell [2011]), and recent data suggest that PM neurons have significantly larger receptive fields than AL neurons, other neurons in the dorsal stream (Murgas et al., 2020).

Using dual-site retrograde labeling from AL and PM, the authors here show that largely separate LP neuron populations send thalamocortical projections to the two areas. The authors also use rabies virus to map presynaptic inputs to the LP neuron populations projecting to each area. They find that both populations receive input from neurons in the SC, the RT and other thalamic structures, layers 5 and 6 of V1, other visual cortical structures (including AL and PM themselves), and also from non-visual (e.g., auditory and motor) cortical areas (Figure 1C).

To understand how this convergence of inputs to LP neurons affects the role of LP in visual processing, the authors record calcium signals from LP terminals in either AL or PM. They quantify terminal responses during presentation of visual stimuli while optogenetically activating parvalbumin-expressing interneurons in V1, AL, or PM to shut down corticothalamic input from these structures to LP.

The inhibition of either feedforward input from V1 or corticothalamic feedback from AL led to suppression of visually driven activity in LP terminals in AL. Suppression of PM corticothalamic input had a more modest effect on visually driven activity in LP terminals within PM, although a small subset of terminals showed significant suppression.

How does transthalamic input from LP versus corticocortical input from V1 shape visual responses in AL and PM? To test this, the authors again used calcium imaging to compare response properties of either LP thalamocortical terminals in the two structures, V1 corticocortical terminals in the structures, or neuronal cell bodies within AL and PM themselves. Presenting moving grating stimuli of different grating widths (spatial frequencies) and drift speeds, they identified which visual stimuli were most effective in generating maximal responses in these neuron populations. LP inputs to AL were most responsive to stimuli with lower spatial frequency (i.e., larger) and higher temporal frequency (faster-moving) gratings, while V1 inputs to AL responded to a broader range of stimuli. In contrast, LP inputs to PM were responsive to a broad range of stimuli, while V1 inputs to PM preferred stimuli that were higher spatial frequency (i.e., finer detail) and lower temporal frequency

(slower-moving). The differences seen in V1 inputs to the two structures are consistent with previous reports demonstrating that V1 inputs to PM tend to have poorer overall encoding of movement and more precise spatial tuning than V1 inputs to AL (Kim et al., 2018).

Critically, the response patterns of AL neurons themselves generally reflected response patterns of LP inputs, rather than V1 inputs. In contrast, response patterns in PM neurons did not strongly resemble those of either V1 or LP. One possible explanation is that PM neurons' visual responses may be further refined by input from other brain regions. Another is that PM neurons simply integrate large numbers of inputs from V1 and LP such that their receptive field properties appear substantially different than those of either input structure (Murgas et al., 2020).

What are the functional consequences of higher-order thalamocortical (LP) versus feedforward corticocortical (V1) inputs to higher visual structures? Based on the response profiles of pre- and postsynaptic neurons in AL, LP thalamocortical input may play an important role in perception of movement. To explore this idea, the authors again recorded calcium signals from V1 or LP terminals or AL neurons as mice ran on a wheel in a "virtual corridor," where visual stimuli drifted past them on monitors to either side of them. In the experiment, the optic flow of visual stimuli through the virtual corridor (i.e., a visual indicator of self-motion) was independent of the instantaneous running speed. This was done by presenting experimental mice with moving stimuli through the corridor that matched the wheel running pattern of a different mouse, which had previously run through it. The result was that proprioceptive cues of self-motion were independent of the speed at which visual stimuli appeared to move past the experimental mice. The correlation of calcium signals in the three populations with either speed of optic flow itself or

moment-to-moment running speed was then compared.

V1 inputs to AL had activity patterns that tended to correlate with optic flow but had no relationship to running speed. These relationships were positive—i.e., faster-moving stimuli evoked greater V1 input activity. This result is consistent with V1 neurons being driven primarily by visual rather than proprioceptive cues. In contrast, activity patterns of LP inputs to AL (and strikingly, AL neurons' activity) were nearly equally correlated with mice's running speed and optic flow. Intriguingly, relationships between running speed and activity of these populations tended to be negative, where greater running speed tended to suppress rather than enhance activation.

The major finding from Blot, Roth et al.—that transthalamic and corticocortical inputs to higher-order visual cortex convey different information—has important implications for our understanding of how visual information is contextualized. The differences in how LP versus V1 inputs to AL respond to proprioceptive and visual movement cues could, in theory, play an important functional role in perceiving the relative motion of one's self versus one's environment (Figure 1A). For example, discordant information about optic flow and self-movement—i.e., where there is visual movement but no proprioceptive cues for self-movement—would indicate the relative movement of objects through one's environment. On the other hand, concordant information—i.e., where there is both optic flow and a sense of self-movement with similar speeds—would indicate that surrounding objects are stationary. Future studies will be needed to determine whether modification of transthalamic versus corticocortical input to AL (or PM) affects aspects of behavior that would be sensitive to this sort of computation. For example, it would be interesting to determine how these inputs facilitate navigation through novel environments using a com-

bination of proprioceptive and visual cues. What is clear from the present study is that higher-order thalamic input to neocortex has the capacity to be both integrative (providing polymodal context for what one sees) and informative (permitting context-based computations within target structures).

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