Current Biology
Dispatches

Vision: Rules of thalamic mixology

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https://doi.org/10.1016/j.cub.2022.06.029

The retina generates rich feature representations of the visual world that pass through the thalamus on their way to cortex and perception. A new study reveals rules that govern the separation and combination of retinal inputs in the thalamus.

Anyone who has constructed a convoluted metaphor knows the challenge of combining the right pieces of information and avoiding incongruous or distasteful mixtures. Our cortical convolutions concoct elaborate percepts from sensory ingredients served up by thalamic nuclei. The fundamental ingredients for visual perception are the feature representations of retinal ganglion cells[1]. Initially, it was thought that the dorsolateral geniculate nucleus (dLGN) of the thalamus pours the retinal feature representations into visual cortex neat. However, recent work suggests that dLGN, at least in mice, blends some retinal information[2,3]. In this issue of *Current Biology*, Jiang, Litvina *et al.* identify important rules of thalamic mixology[4].

Transcriptomic, morphologic, and functional surveys have identified more than 40 retinal ganglion cell types in mice, which send unique visual feature representations to the brain[5–7]. More than 30 retinal ganglion cell types innervate the dLGN, which contains a single (or at most a few) thalamocortical (TC) projection neuron type(s)[8–10]. How can the rich retinal feature representations be maintained or improved on their way to cortex across such a mismatch in neuronal diversity?

Initially, the answer to this question seemed to lie in the low numeric convergence of retinal ganglion cells onto TC neurons[2,3]. In the extreme, if only one retinal ganglion cell provided input to each TC neuron, the latter would simply inherit and pass on the feature preferences of the former. However, from 2015 to 2017, a series of studies significantly raised estimates of retinal ganglion cell convergence in the mouse dLGN, reigniting interest in the functional organization of retinal information in the thalamus[11–14].

Retinal and thalamic projection patterns divide the dLGN into shell and core regions. Different retinal ganglion cell types preferentially innervate the dLGN shell or core, and TC neurons in the shell and core project to layers 1–3 and 4 of primary visual cortex, respectively, establishing parallel pathways from the retina to the cortex[2,3,15]. To what extent and in what patterns retinal feature representations are separated or combined within these pathways remains unclear. The dLGN shell is densely innervated by ON-OFF direction-selective ganglion cells (ooDSGCs), which respond strongly to bright (ON) and dark (OFF) objects moving in one of four cardinal directions (ventral, dorsal, nasal, and temporal in the retinal image)[1,16]. Jiang, Litvina *et al.* analyze the patterns of functional ooDSGC convergence in the dLGN shell[4].

The authors generate transgenic mice in which either the ventral- or the ventral- and the dorsal-motion-preferring ooDSGCs express channelrhodopsin-2, allowing them to selectively activate the

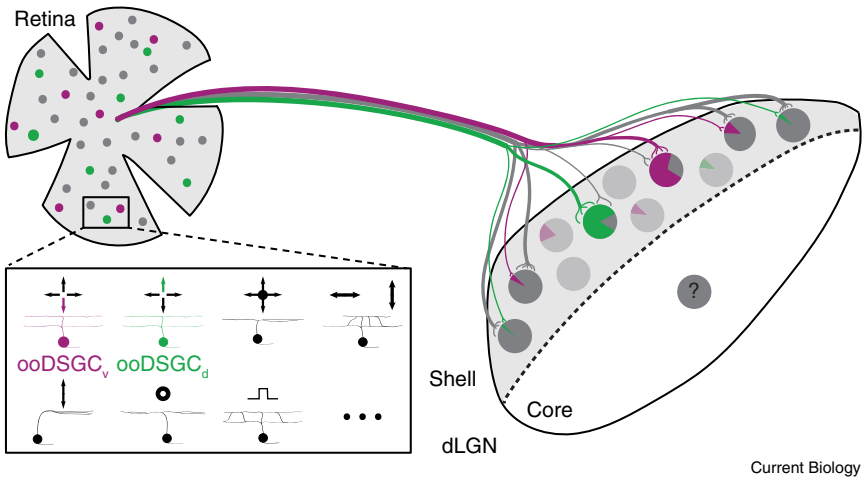

Figure 1. Mixed convergence patterns from the retina to the dLGN shell.
Diverse retinal ganglion cell types, each encoding specific visual features, innervate the dLGN. Consistent with a labeled-lines view of dLGN, Jiang, Litvina *et al.*[4] find that ooDSGCs preferring ventral (purple) or dorsal (green) motion dominate input to a small subset of TC neurons in the dLGN shell. By contrast, most TC neurons in the dLGN shell receive only weak input from ooDSGCs mixed with other yet unknown retinal ganglion cell types (grey). In nearly all cases, ooDSGCs preferring ventral and dorsal motion avoid one another at the level of individual TC neurons. This finding suggests that, despite the abundant mixing of retinal ganglion cell inputs, the dLGN shell maintains the separation of specific information channels to preserve and expand the visual feature representations in precise ways on their way to the cortex and perception.

respective axons directly with light (i.e. optogenetics). Jiang, Litvina *et al.* confirm that axons from both ooDSGC sets innervate the dLGN shell and stimulate them optogenetically while recording excitatory postsynaptic currents from TC neurons in the dLGN shell. They also record the currents elicited in the same TC neurons by electrical stimulation of all retinal ganglion cell axons and compare input distributions to their previous results from optogenetic stimulation of all retinal ganglion cells[14] to estimate the input fractions contributed by ventral- and dorsal-motion-preferring ooDSGCs.

The results from these experiments, backed by clever modeling, support three main conclusions (Figure 1). Firstly, ventral- and dorsal-motion-preferring ooDSGCs dominate the input to a small subset (~10%) of the TC neurons they innervate. Secondly, ventral- and dorsal-motion-preferring ooDSGCs provide weak input to many TC neurons that receive dominant input from other retinal ganglion cells. And, thirdly, ventral- and dorsal-motion-preferring ooDSGCs do not (or rarely) converge in dLGN.

The observation that a small fraction of TC neurons receives most of its input from ventral- or dorsal-motion-preferring ooDSGCs is consistent with the traditional view of dLGN as a labeled-line relay. It suggests a subset of dLGN pathways send retinal feature representations to visual cortex unadulterated[2,3]. However, most ooDSGC inputs to TC neurons are weak and mixed with non-ooDSGC inputs. What retinal ganglion cell types converge with the weak ooDSGC inputs, and to what end?

Recent functional imaging experiments of retinal ganglion cell axons in the dLGN shell revealed that direction-selective boutons (i.e. presumptive sites of transmitter release) cluster with boutons that prefer motion along the same axis and boutons with diverse contrast preferences irrespective of motion directions[17]. Thus, the set of retinal ganglion cell types converging with ooDSGCs could be quite broad within the confines of axon stratification in the dLGN shell and core.

To what end may ooDSGCs and other retinal ganglion cell types converge in dLGN? First, convergence could function as an AND gate that restricts TC neuron responses to the intersection of the retinal ganglion cells' responses. An ooDSGC converging with an OFF-selective retinal ganglion cell could result in a TC neuron that responds only to dark objects moving in a particular direction (i.e. feature complication). Second, convergent inputs could cancel orthogonal preferences to isolate a specific feature. Thus, a TC neuron receiving input from ooDSGCs, which prefer fast over slow motion, and retinal ganglion cells preferring slow-moving stimuli could encode motion direction independent of stimulus speed (i.e. feature isolation, also known as invariance)[17]. Third, convergence could function as an OR gate and expand TC neuron responses to the union of the retinal ganglion cells' responses (i.e. feature expansion). Indirect evidence for feature expansion comes from a study showing that TC neuron responses to full-field stimuli of varying contrast amplitude and temporal frequency can be recreated by linear combinations of two to five retinal ganglion cell types' response patterns[10]. Finally, weaker ooDSGC inputs to TC neurons may be functionally insignificant and reflect the error tolerance of retinogeniculate wiring. Recent results suggest that this may be the case for binocular convergence in the dLGN core[18]. It will be critical, therefore, in the future to test the contributions of ooDSGCs to TC responses across a range of input strengths.

Although Jiang, Litvina *et al.* did not determine which retinal ganglion cell types converge with ooDSGCs and to what end, they convincingly show that ventral- and dorsal-motion-preferring ooDGGCs converge rarely, if at all. This demonstrates specificity beyond axonal stratification in the retinogeniculate wiring. The finding is surprising given the clustering of retinal ganglion cell boutons preferring motion in opposite directions[17] and the abundance of orientation-selective TC neurons in the dLGN shell, which had been suggested to arise from the convergence of opposite ooDSGCs (i.e. feature expansion)[19]. This highlights the importance of testing functional connectivity directly and suggests that most orientation-selective responses in dLGN are inherited from orientation-selective retinal ganglion cell inputs[20].

The study of Jiang, Litvina *et al.* significantly advances our understanding of the (re-) organization of cell-type-specific retinal information in the dLGN. It also raises intriguing questions for future investigations, including what retinal ganglion cell types converge with ooDSGCs in dLGN, how weak ooDSGC inputs contribute to the feature representations in dLGN and beyond, and whether rules that govern convergence in the dLGN shell are upheld in the core. We predict that this elegant work will shake a few preconceived notions and stir the field into action to address the questions it raises.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Anesthesia: Synaptic power failure

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https://doi.org/10.1016/j.cub.2022.06.043

One of the greatest unresolved mysteries in medicine relates to the molecular and neuronal mechanisms through which general anesthetics abolish perception. A new study in mice with mutations affecting mitochondrial complex 1 suggests that anesthetic-disruption of cellular energetics impairs endocytosis to alter synaptic function.

Since the first successful public demonstration of general anesthesia in October 1846, it has become widely recognized that ether and its modern-day halogenated anesthetic derivatives are capable of perturbing function not only across eukaryotes, but prokaryotes as well[1]. The incredible ability of inhaled anesthetics to affect organisms that diverged hundreds of millions of years ago either implies an ongoing preservation of molecular targets that arose in one of life's most ancient species or else multiple instances of independent target evolution across distinct lineages. Most perplexing is the question of why evolution wouldn't have altered the targets of anesthetics given the absence of any obvious selection pressure to preserve the binding sites that allow inhaled anesthetics to render organisms insensate. Work by Jung and colleagues reported in this issue of *Current Biology*[2] provides new insights into how anesthetic-induced inhibition of cellular respiration in eukaryotes via Complex 1 may wreak havoc on fundamental energy-dependent processes at the synapse.

Early theories on inhaled anesthetics focused on their lipophilicity, leading to the suggestion that drug interactions with lipid membranes directly impaired brain function. Since the seminal discovery that anesthetics could modulate protein function in the absence of lipids, more recent theories of anesthesia have focused on postsynaptic signalling. General anesthetics potentiate inhibitory postsynaptic signalling, for example through $GABA_A$ receptors as well as other receptors and ion channels (reviewed in Hemmings *et al.*[3]). At the systems level, recent attention shifted to the neural circuits regulating arousal where anesthetic drugs are known to co-opt sleep-promoting systems while inhibiting wake-sustaining ones[4–7], thereby suggesting one explanation for the sedative and hypnotic components of general anesthesia: loss of consciousness under general anesthesia is perhaps like falling into a deep sleep. However, remaining unresponsive during surgery would never occur during natural sleep. Rather, in this regard general anesthesia shares more similarities with comatose states[8]. When exposed to a continuous 'surgical' dose of volatile agents such as isoflurane or sevoflurane, patients are unable to wake up until the drug is removed; hence, additional mechanisms must be at play. What and where might these alternative targets be?

There has been an increased interest in moving the focus of anesthesia research to the other side of the synapse, namely the presynapse. Several studies have shown that clinically relevant concentrations of volatile as well as intravenous agents