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Neural Polyamory: One Cell Forms Meaningful Connections with Hundreds of Partners

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Reconstruction of one thalamic neuron, mapping hundreds of presynaptic inputs and postsynaptic outputs, reveals diverse types of interaction in a neural microcircuit.

A textbook description of a neuron views it as one input-output unit; inputs arrive at the dendritic end and outputs are sent from the axonal end. Although this sort of abstraction is a useful framework for broad-level appreciation of a given network (or neural circuit) in the brain, to truly understand how neurons connect and communicate with each other, one must disabuse oneself from this notion and appreciate the complexity that is the neural connectome. In a heroic study published in the May 6, 2020 issue of *Neuron*, Morgan and Lichtman (2020) shed light on this complexity using serial electron microscopy to create a stunning three-dimensional reconstruction of one neuron and its connections (synapses) in a major visual area of the brain: the dorsal lateral geniculate nucleus (dLGN). They revealed this one cell had over 1,400 input and output synapses and its far-reaching neurites spanned almost half of the visual field represented in the dLGN. Strikingly, almost all of its neurites simultaneously contained both input and output synapses, therefore defying any kind of conventional classification in neuroscience.

An essential function of the brain is to generate accurate visual representations of the world. When light enters the eye, photons are transduced into electrical signals in the retina and transmitted through the axons of retinal ganglion cells (RGCs) to the dLGN before being sent to the visual cortex for higher processing (Figure 1). Functionally, the rodent dLGN can be subdivided into a core and a shell region, each with distinct visual feature representations and downstream projections (Kerschensteiner and Guido, 2017). The cellular landscape of the dLGN is populated by two types of cells that receive direct inputs from the retina: excitatory thalamocortical (TC) neurons and GABAergic local interneurons (LINs), the latter representing roughly 10% of dLGN neurons and whose neurites never exit the dLGN (Kerschensteiner and Guido, 2017) (Figure 1). Despite their sparse population, LINs are thought to be important for sharpening the spatial and temporal features of visual stimuli in TC neurons and their activity might enhance image perception (Hirsch et al., 2015). In biology, structure often informs function. Yet, in neuroscience, mapping the complete connectivity of a neuron has only recently been made possible with the advent of advanced electron microscopy of large volumes of brain tissue and tracing methodologies.

In their work, Morgan and Lichtman (2020) sliced up a large of chunk of the rodent dLGN into 10,000 serial sections and generated a 100 terabyte-sized ultrastructural dataset. They identified an ideal LIN for detailed analysis (termed LIN1), traced its neurites, and found that they spanned the entire depth, and almost half the visual field representation, of the dLGN. Interestingly, the breadth of this arborization crosses multiple functionally distinct zones of the dLGN (Figure 1). For one, it spans both the shell and the core regions. In addition, recent advances in transgenic labeling of individual RGC subtypes has revealed additional functional organization based on the selective axonal arborization of distinct RGCs in specific areas of the dLGN—areas that LIN1's arbors pass through (Monavarfeshani et al., 2017). This invites the hypothesis that a single LIN is involved in processing multiple visual features originating from separate retinal channels.

Yet, the wide expanse of LIN1's arborization alone is not necessarily an indicator of synaptic connectivity, which is the critical question raised here. To address this, Morgan and Lichtman (2020) brought to bear the quantitative power of electron microscopy by characterizing all of LIN1's synapses contained within the dLGN volume, making several remarkable discoveries. They found 775 retinal inputs across the entire neurite arbors, further suggesting that a single LIN can receive input from multiple distinct RGC subtypes. How many individual RGCs can one LIN be innervated by? Several recent studies have asked this question in the context of TC neurons and found that at least a dozen or more RGCs can converge on a single TC neuron (Hammer et al., 2015; Morgan et al., 2016; Rompani et al., 2017). The number of retinogeniculate synapses Morgan and Lichtman (2020) identified on LIN1 suggests even more convergent retinal input onto dLGN LINs, pointing again to a more complicated computational role than previously thought. This is something which can be experimentally interrogated by combining single-cell-initiated monosynaptic rabies tracing and two-photon calcium imaging as previously done in visual cortex (Wertz et al., 2015).

Not all LIN afferents are retinal. Morgan and Lichtman (2020) identified at least 70 inputs to LIN1 from other LINs and 54 inputs which they classified as unknown.

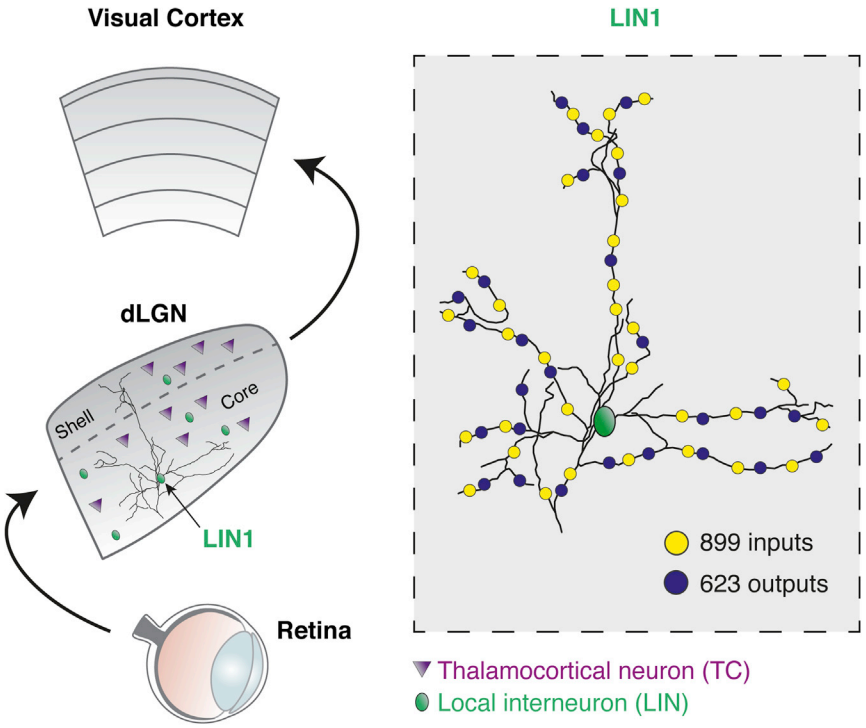

Figure 1. An Individual Thalamic Neuron within the Rodent Visual System
Light-derived information flows from the retina to the visual cortex through the dorsal lateral geniculate nucleus (dLGN) of the visual thalamus. The two functionally distinct domains of the dLGN (shell and core) are separated by a dotted line. Green circles represent inhibitory local interneurons (LIN) and purple triangles represent excitatory thalamocortical relay cells (TC). On the right, the morphology of one interneuron (LIN1) is shown with the numerous input and output connections present on its many neurites. Structures are not drawn to scale.

Roughly half of the LIN1's connections with other LINs were reciprocal, and four were synapses which LIN1 formed with itself. Interestingly, of the unidentified input sources, the most common source was structurally consistent with cholinergic brain stem axons, which can excite TC neurons and inhibit LINs (Guido, 2018). Given their origin, one could speculate afferent brainstem input onto LINs make them sensitive to the ongoing brain state (e.g., arousal, wakefulness, etc.). Such brain state-dependent modulation would establish LINs as a central player for regulating the gain of TC visual information transfer by acting on TC neurons in a context-dependent fashion.

The authors also mapped the output synapses of LIN1 (Figure 1) and identified 492 synapses it made onto TC neurons and 124 synapses it made onto other LINs (including the few onto itself). Importantly, when Morgan and Lichtman (2020) identified the cell body location of TC neurons innervated by LIN1, they found that they were distributed widely throughout the dLGN and, based on the retinal input they receive, encoding different visual features. This raises several pressing questions: what is such a broadly connected LIN doing in this circuit? Does it establish tuning of TC neurons? Does it shape already-established tuning (perhaps by modulating the gain)? Morgan and Lichtman (2020) offer some clues to this by analyzing the kinds (or motifs) of synaptic connections in these cells. They found a diverse array of motifs generated by LIN1 with different synaptic partners. One classical motif found in the dLGN is the triad, wherein a single retinal terminal synapses with the dendrite of a TC neuron and the neurite of a LIN, while the same LIN neurite also synapses with the same TC neuron dendrite. The authors not only described such a triad but also multiple other triadic relationships the same LIN was engaged in, including with other LINs and brainstem afferents.

The myriad LIN1-input and -output connections beg the question, are these *all* meaningful relationships? The answer appears to be *not quite*. These various connections also varied in their terminal sizes, neurite thickness, and/or distance from cell body, so it is not fully clear whether they are *all* functionally relevant synapses that contribute to the visual computations performed by LIN1. It is worth noting here that the age of the tissue used in this study comes at a period of significant plasticity in the rodent retino-geniculo-cortical neural pathway (Hooks and Chen, 2020). This raises the possibility that at least some of these connections are still vestiges of the exuberant connectivity seen in the postnatal visual system and have yet to be eliminated.

At a macroscopic level, the promiscuity of LIN1's connections in the dLGN, and the diversity of the synaptic relationships it is involved in, make it challenging to assign it a single computational role in this circuit. Rather than serving as the end-all definition of a cell's identity or function, mapping the connectome serves as a foundational wealth of new information that can guide future experiments aimed at unraveling the function of neurons embedded within neural circuits. The work by Morgan and Lichtman (2020) offers the community a first look at what we can learn if we held a microscope over each and every one of a LIN's synaptic relationships and relate them to the microcircuit environment in which they reside. Indeed, what these findings suggest is that perhaps the functional unit in this system is not the neuron but the neurite (or an even a smaller compartment).

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