By Ho Ko

David Marr and Tomaso Poggio proposed that in order to figure out information processing in the brain, we must understand its operation at the computational, algorithmic, and implementational levels (1). Computational tasks of the visual system, for example, include extracting properties of the external world, such as recognizing objects, and estimating their locations and movements. Algorithmically, the visual system adopts a hierarchical organization, whereby visual features of increasing complexity are represented and integrated at successive stages of processing. Some retinal ganglion cells respond best to small, round, visual stimuli of high contrast. This information is relayed by the lateral geniculate nucleus of the thalamus to the primary visual cortex (V1), where neurons become sensitive to the orientation and motion direction of visual features (2). Further up the visual processing hierarchy, neuronal representations become increasingly more complex, as neurons become responsive to contours and objects often invariant of their precise location in visual space. What remains unknown is how, at the implementational level, these computations at different stages of the visual system are carried out by the neuronal networks. Similar to many proteins whose structures determined by crystallography provide mechanistic insights into their functions, knowledge of the connectivity-function relationship of neuronal networks may provide a mechanistic understanding of how the brain generates the representation of increasing levels of abstraction. In view of this, my work with Thomas Mrsic-Flogel and Sonja Hofer at University College London has helped to develop an experimental approach that allowed us to relate the connectivity between cortical neurons to their visual response properties (3).

With the technique, we first studied the functional organization of local synaptic connections between excitatory pyramidal neurons in V1. It has been unclear whether pyramidal neurons sample sparse input without bias from their neighbors (4, 5), or if there exist fine-scale subnetworks consisting of neurons sharing similar functional properties (6). To address this question, we carried out two-photon calcium imaging of layer 2/3 (L2/3) neurons in mouse V1 to characterize their visual response properties (figure, (A), upper panels). We then carried out multiple whole-cell recordings in the imaged regions in vitro to assay synaptic connectivity between small motifs of pyramidal neurons and matched the identities of neurons to the images acquired in vivo by affine image registration [figure, (A), lower panels]. By relating the probability of finding connections in vitro to the similarity of visual responses in vivo, we found that pyramidal neurons with more similar visual feature selectivity (e.g., stimulus orientation) are more connected (3) [figure, (B)]. Moreover, connections between neurons with highly similar visual responses were often bidirectional (3). Therefore, we revealed that the connectivity between L2/3 neurons in V1 is highly specific, though nonexclusive, with respect to their feature selectivity. Such a specific connection scheme may serve to amplify the incoming thalamic signal by providing strong excitation that is closely matched to thalamocortical input (7–9).

How does the functionally specific connectivity in V1 emerge during development? One possibility is that feedforward input and recurrent connections are both established by intrinsic factors before the onset of sensory experience (10–12). Alternatively, visual input after eye opening may be needed to drive the refinement of local synaptic connections (13). We thus carried out the experiments at different postnatal ages to investigate the sequence of developmental events in mouse V1. We found that at eye opening, L2/3 pyramidal neurons already exhibit mature receptive fields, suggesting that feedforward input is well established (14). However, at eye opening, visually responsive neurons are connected nonspecifically with respect to similarity in orientation preference or responses to naturalistic stimuli (14) [figure, (C)]. Therefore, an extensive reorganization of local cortical connections occurs after the onset of vision, whereby neurons with more similar response properties are preferentially connected. This developmental sequence of events can be captured in a network model in which feedforward activity drives the reorganization of recurrent connections by spike-timing-dependent plasticity rules (14, 15). Visual experience is only partially required for this maturation process, as some refinement of connections with respect to response properties does occur in the absence of visual input (16).

Sensory processing in local cortical circuits relies not only on the interaction between excitatory neurons but also on diverse inhibitory cell types. In contrast to pyramidal neurons, fast-spiking parv-
albumin-expressing (PV) interneurons are generally reported to have broad orientation tuning (17–21). We next asked, at the network level, what is the connectivity that confers fast-spiking PV interneurons with specificity or lack of specificity in responses? We showed that fast-spiking PV interneurons receive very dense input (close to 90% connection probability) from neighboring excitatory neurons, and the connections are on an order of magnitude stronger than those between excitatory neurons (22). Probability of pyramidal neuron to fast-spiking interneuron connection and connection strength did not exhibit specificity with respect to degree of tuning or similarity of orientation preference [(22), also see (23)] [figure, (B)]. Therefore, these interneurons acquire their tuning from nonspecific, dense, and strong excitatory connections from the local network and in turn provide nonspecific inhibition for controlling the overall network excitation and modulation of tuning in excitatory neurons (24–27).

In conclusion, we have begun identifying the rules that govern how neurons with different intrinsic and functional properties connect to each other. These are the first steps in revealing the functional synaptic organization of cortical circuits and providing a circuit-level mechanism of how individual neurons, and the ensembles they form, represent visual information. The data can be used to inform detailed models of cortical circuits to test existing theories and determine which network parameters give rise to different sensory computations. In the future, we will require a more complete characterization of neuronal function (e.g., detailed receptive field properties of neurons), as well more complete wiring diagrams (connectomes) of the cortex by combining functional imaging and various circuit-mapping methods, including large-scale electron microscopy (23, 28–30), trans-synaptic viral tracing tools (31, 32), mGRASP (33), and chemical clearing methods [e.g., CLARITY and CUBIC (34, 35)]. These will eventually allow us to better understand the physical realization of computations by neuronal networks.

**REFERENCES AND NOTES**


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