Consistent with this model, different fragments of RIM independently rescue its exocytotic functions via Munc13 or its scaffolding role for $Ca^{2+}$ channels (Kaeser et al., 2011). This dichotomy establishes that RIM has separable functions, and these functions could be localized to distinct protein nano-assemblies within an active zone, at least in some cases. Recent technological advances for the high-resolution assessment of the composition and structure of protein complexes *in situ* will likely allow dissecting how individual protein assemblies within an active zone vary in composition, and how these exocytotic machines are aligned with postsynaptic receptor domains.

Ultimately, the ability of synapses to employ different topographical motifs of key molecular players offers neurons new ways to tune their release properties. It is likely that these assemblies do not only differ across synapse types, but also over time and as a function of past activity of a synapse. Future research should build on the striking findings by Rebola et al. (2019) to assess how the computational power of the brain is controlled and modulated by the molecular nano-assemblies that mediate synaptic transmission.

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# Decreasing Influence of Retinal Inputs on the Developing Visual Cortex

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**Before vision matures, spontaneous retinal activity drives downstream visual targets. In this issue of *Neuron*, Gribizis et al. (2019) image activity simultaneously in connected mouse visual areas and demonstrate distinct developmental patterns of signal transformation in thalamocortical versus retinocollicular pathways.**

During development, immature sensory circuits generate spontaneous neural activity, which propagates across nascent synaptic connections and plays important roles in setting up precise wiring patterns of adult circuits. A well-documented example is the spontaneous activity in the mammalian retina, termed "retinal waves." Retinal waves are generated by distinct mechanisms in three developmental stages prior to the onset of vision (reviewed by Arroyo and Feller, 2016). In rodents, the initial retinal waves before birth (stage 1) are mediated by gap junctions. After birth, retinal waves subsequently rely on cholinergic signaling (stage 2) until around postnatal day 10 (P10). Between P10 and the onset of light response at around P12, cholinergic influence diminishes, and retinal waves are mediated by glutamate released from bipolar cells (stage 3). Stage 2 waves propagate to higher visual targets including the thalamocortical pathway and the superior colliculus (SC) (Ackman et al., 2012). Based on extensive studies that monitor and manipulate stage 2 retinal waves

*in vitro* and *in vivo*, it is now well established that the spatiotemporal pattern of stage 2 waves provides instructive cues for proper eye-specific segregation of retinal inputs in the dorsal lateral geniculate nucleus (dLGN), and for the refinement of visual topographic maps in the primary visual cortex (V1) and SC (e.g., Torborg et al., 2005; Cang et al., 2005; Mrsic-Flogel et al., 2005; Burbridge et al., 2014).

As visual circuits undergo the developmental transition from immature connectivity to adult wiring diagrams, spontaneous activity patterns along the visual pathways are altered accordingly as a result of both local and long-range circuit developments (e.g., Siegel et al., 2012; Murata and Colonnese, 2016). Dissecting the effects of local versus long-range circuit maturation on neuronal signaling requires a direct comparison between the input pattern and the corresponding postsynaptic activity pattern of the target area. In this issue of *Neuron*, Gribizis et al. (2019) tackle this technically challenging requirement by simultaneous *in vivo* wide-field calcium imaging of synaptically connected visual areas using two spectrally separated calcium indicators. GCaMP6f and a red-shifted calcium indicator jRCaMP1b were selectively expressed in distinct visual nuclei using local viral delivery or Cre-dependent transgenic mouse lines. By alternating presentation of excitation wavelengths of the two indicators and spectrally separating their emission wavelengths, Gribizis et al. (2019) were able to extract calcium signals from the two indicators even when they were expressed in the pre- and postsynaptic neural populations in the same field of view. This powerful method enables a more direct assessment of signal transformation from the retina to higher visual areas in different developmental stages.

The first knowledge gap filled by Gribizis et al. (2019) is the spatiotemporal pattern of stage 3 retinal waves *in vivo*. By imaging the retinal axon terminal activity in the SC, Gribizis et al. (2019) found that stage 3 retinal waves are distinct from stage 2 waves in multiple parameters. Stage 3 waves travel at faster speeds; have frequent, multiple, but smaller wavefronts; and have shorter duration. Their trajectories exhibit a more pronounced directional bias in the rostral-to-causal direction. Consistent with *in vitro* studies, stage 2 and stage 3 waves are differentially blocked by cholinergic and glutamatergic antagonists, respectively. Furthermore, pharmacological blockade of inhibitory transmission in the retina during stage 3 retinal waves reduces wave frequency and results in stage 2-like wave patterns with single, infrequent wavefronts. These results, together with earlier work on the *in vivo* pattern of stage 2 retinal waves from the same laboratory (Ackman et al., 2012; Burbridge et al., 2014), provide a comprehensive description of postnatal *in vivo* retinal wave patterns in mice before the onset of vision.

How are retinal waves integrated and transformed along the thalamocortical and retinocollicular pathways in the developing visual system? Gribizis et al. (2019) address this question by performing pairwise comparisons of activity patterns between retina and its downstream target SC, dLGN, or V1, and between dLGN and V1. They found that although stage 2 and stage 3 retinal waves (examined at P5–P8 and P10–P12, respectively) are both relatively faithfully transferred to the SC and dLGN, the activity of the dLGN is more effective in driving V1 activity during stage 2 retinal waves than doing so during stage 3 retinal waves. This decrease in the contribution of dLGN inputs to cortical network activity during stage 3 retinal waves (P10–P12) implies that this is an important time window for the maturation of local cortical circuitry and/or other sources of cortical inputs other than first-order thalamic drive. Furthermore, in contrast to the high and stable transfer fidelity of retinal signals to dLGN and SC throughout stage 2 and 3 waves, decreased signal transfer from dLGN to V1 between stage 2 and stage 3 highlights the emergence of a mode of visual signal encoding by the cortical neurons that is different from that of geniculate and collicular neurons that remain strongly driven by retinal inputs throughout development. It is conceivable that the dual channel calcium imaging method developed in this study will serve as a valuable tool to probe system-level signal transforms in diverse brain circuits of developing and adult animals.

A question naturally arising from the above results of Gribizis et al. (2019) is the underlying neural mechanism of the decreased signal transfer from the retina to V1 before eye opening. While the answer awaits future studies, it is probably not solely due to hardwired connectivity changes, because acutely converting stage 3 retinal waves to stage 2-like wave patterns by pharmacologically blocking inhibitory signaling in the retina significantly increases the full-field correlation between retinal and V1 activities (Gribizis et al., 2019). This raises the interesting possibility that the input-output relationship between retina and V1 at P10–P12 is not static and might be fine-tuned by the pattern of ascending inputs to V1. Indeed, spontaneous synaptic plasticity is prominently featured in the visual cortex in this developmental time window, during which the synaptic strength of the visual cortical neuron is dynamically shaped by the level of correlated activation or clustering of local synaptic inputs on the timescale that matches that of retinal wave dynamics (Winnubst et al., 2015). In light of the concurrent network activity changes and activity-dependent synaptic signaling, it is tempting to speculate that the departure from retinal activity pattern in V1 shortly before the onset of sensory-evoked inputs results from synergistic actions of circuit and synaptic plasticity mechanisms. Future examinations of pre- and postsynaptic activities across multiple spatial scales will yield deeper mechanistic insights into the maturation of the computational algorithm of cortical circuitry for sensory processing.

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# Cortex-wide Computations in Complex Decision Making in Mice

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**Seemingly, a paradox exists between reports of wide-scale task-dependent cortical activity and the causal requirement for only a restricted number of motor and sensory cortical areas in some behavioral studies. In this issue of *Neuron*, Pinto et al. (2019) indicate that scenarios where mice must accumulate evidence and hold it during a delay period are causally linked to wide regions of cortex.**

A cornerstone of neuroscience is the association of unique cortical areas with specific functions. While this is clear for unimodal sensory processing, work extending back to Lashley's doctrine of neuronal mass action (Lashley, 1931) posits that complex tasks are widely distributed. Lower cognitive loads can be more localized, while complex tasks are orchestrated across larger regions of brain and cortex. Recently, through the development of mouse lines expressing channelrhodopsin-2 in all GABAergic neurons (VGAT-ChR2) (Zhao et al., 2011) and the use of transcranial brain windows, reversible optical inactivation of candidate cortical regions has shed causal light on their involvement in increasingly complex behaviors. In this issue of *Neuron*, Pinto et al. (2019) contrast the role of several cortical areas during an elegant virtual reality (VR) decision-making task. They show that a complex accumulation of evidence task involves more spatially distributed cortical computations than simpler actions in mice. Previous cortical inactivation studies have found relatively localized effects on performance, even though wider areas of cortex are potentially activated by the tasks. In seminal work employing multisite cortical VGAT inactivation, Guo et al. (2014) and Chen et al. (2017) have selectively implicated the anterior lateral motor (ALM) cortex and medial motor cortex (MM) in decision/motor preparation, as well as the sensory phase of the task, by unilateral as well as bilateral (Li et al., 2016) inactivation. Guo et al. (2014) also found that vibrissal primary somatosensory cortex (vS1) was necessary for stimulus sensing. Gilad et al. (2018) made inactivations by (AAV)-CAG-ArchT-GFP, as well as VGAT-ChR2-EYFP, where they found multiple causally linked areas for stimulus sensation and memory in secondary motor cortex (M2) or lateral posterior areas (P). Interestingly, area P only had a causal role during the delay period for animals using a passive body movement strategy (Gilad et al., 2018).

While previous work indicated that sensory processing and/or memory was causally linked to selective cortical areas, the use of wide-field functional imaging indicates that the response to even brief sensory stimuli, such as whisker deflections, tones, or tactile stimuli, are distributed across wide cortical networks (Ferezou et al., 2007; Mohajerani et al., 2013).

Pinto et al. (2019) describe how the causal role of brain areas can change across similar tasks with different cognitive demands. They suggest that previously reported localized effects could be due to task simplicity and short delay periods and might not generalize. The authors' VGAT-ChR2 bilateral-inactivation strategy probed whether a wide number of bilateral cortical points were necessary for task performance (total 29, ~2 mm radius, Figure 1, size of spots indicates sensitivity to inactivation). They chose three different tasks in a VR T-maze, which was divided into two regions: 2 m cue region (~4 s) where towers can appear on left/right side and a 1 m delay region (~2 s) where no cues are shown. First, in the accumulating-evidence task,