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Talk Louder So I Can See You

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How does one sense influence the processing of another? In this issue of *Neuron*, Ibrahim et al. (2016) demonstrate that presence of sound sharpens neural tuning in the primary visual cortex via activation of direct inputs from the primary auditory cortex.

We perceive the world through our five senses, yet we experience a holistic representation of our external world. Generating such seamless coherent percept of the sensory environment requires proper integration of information gathered through distinct sense organs. Information captured from peripheral sense organs largely travels through parallel pathways to reach the CNS. While higher-order cortical areas are mainly thought of as centers for multisensory integration, emerging evidence suggests that different senses can interact with each other even at the early stages of sensory processing, such as the primary sensory cortices (Ghazanfar and Schroeder, 2006). Previous studies have shown that primary sensory cortical neurons can influence or produce subthreshold responses upon stimulation of another sense. For example, sound produces hyperpolarizing synaptic responses in the primary visual cortex (V1) (Iurilli et al., 2012), and presenting tactile stimuli with sound has shown to reset neural oscillations measured in the primary auditory cortex (A1) (Lakatos et al., 2007). These particular studies suggested that multisensory influences occur through either direct connections from A1 to V1 (Iurilli et al., 2012) or via feedforward inputs from multisensory thalamic nuclei (Lakatos et al., 2007). Besides, there are many other potential anatomical substrates for multisensory interactions at the level of primary sensory cortices, including feedback connections from higher-order multisensory cortical areas.

While the functional circuitry involved in the direct interactions between primary sensory cortices has been suggested by several studies, how these interactions influence neural properties of primary sensory cortical neurons and the exact nature of the underlying anatomical circuit involved have not been clear. In this issue, Ibrahim et al. report how sound sharpens the tuning properties of primary visual cortical neurons, especially for low-contrast visual stimuli. Interestingly, the sharpening of neural orientation tuning by sound was restricted to the superficial layers of V1, and not in thalamorecipient layer 4 (L4), which suggests a top-down feedback circuit involved in this process. The authors further demonstrate that this interaction is largely mediated by direct projections originating from layer 5 (L5) of A1 that provide input to layer 1 (L1) and superficial layers of V1. Combining in vivo loose patch recordings, Ca^{2+} imaging, and optogenetic manipulations, the authors delineate that the sound influence on the tuning properties of V1 neurons is mediated by a combination of inhibitory and disinhibitory circuits activated by the direct inputs from A1 (Figure 1). Specifically, direct inputs originating from L5 of A1 strongly activate inhibitory neurons in L1 of V1, as well as L2/3 principal neurons. Using optogenetic silencing of V1 L1 interneurons, the authors provide a causal link between sound-induced sharpening of L2/3 pyramidal neurons and this inhibitory circuit. While L1 inhibition could explain a general decrease in response properties and narrowing of orientation tuning, it cannot by itself account for the relative increase in responsiveness to the preferred orientation. The authors propose, based on the observation that sound stimuli inhibits VIP-positive interneurons in L2/3, that there is disinhibition of the preferred orientation that allows relative enhancement of neural responses. One surprising finding made by Ibrahim et al. is that V1 L1 interneurons respond to sound alone with very short response latency, which was shorter than the responses of V1 L2/3 neurons to visual stimuli. This suggests that auditory information gains access to V1 much earlier than what is traditionally expected of a top-down modulation. Furthermore, it supports the idea that L2/3 neurons in the primary sensory cortices may be integrating multisensory information.

Then what is the function of such direct functional interaction between A1 and V1? Ibrahim et al. report that there is a threshold for how loud sound has to be in order to sharpen the orientation tuning of V1 L2/3 neurons. Also, the effect of sound was larger when visual stimuli were of lower contrast. Such properties suggest that this type of audio-visual interaction likely plays a role in sharpening vision upon highly salient sound in the environment. Since sound was not particularly localized in these experiments, it remains to be seen whether this enhancement effect is affected by the spatial location of the sound source or whether there would be selective sharpening of V1 neurons with receptive fields congruent to the sound source. Alternatively, this effect may serve to boost vision upon any loud sound that is just temporally coincident with visual stimuli.

Based on their findings, Ibrahim et al. propose L1 inhibitory/disinhibitory circuit acts as a "hub" for top-down control of cortical function. This is a tantalizing proposal considering that many higher-order inputs arrive through L1 and the superficial layers. The inhibitory/disinhibitory circuit found in the current study is similar to those reported in several recent studies, albeit the specific inhibitory neuronal types involved are not identical. Bernardo

Rudy's group showed that disinhibitory circuit exists for motor cortex (M1) to barrel cortex interactions. In that study, M1 inputs activate VIP interneurons in the superficial layers of barrel cortex, which then inhibit somatostatin (SOM)-positive interneurons to cause disinhibition of pyramidal neurons (Lee et al., 2013). A similar VIP to SOM to pyramidal disinhibitory circuit was described in V1 to mediate enhancement of visual responses upon locomotion (Fu et al., 2014), and activating this disinhibitory circuit recovered ocular dominance plasticity in adult V1 (Fu et al., 2015). Taken together with the results from the current study, these findings suggest that multiple disinhibitory neural circuits may exist in the superficial layers of cortices. It would be of interest to examine whether distinct disinhibitory networks are recruited by different long-range cortical interactions to serve specific functional purposes. Furthermore, the L1 inhibitory neurons that were shown to causally mediate the sound-induced sharpening of V1 tuning express 5-HT3a receptors, which are often used as markers to identify these neurons and respond to serotonin as well as acetylcholine to some degree (Rudy et al., 2011). Whether or not neuromodulators influence the inhibitory/disinhibitory circuit identified here would be of interest and would open up the possibility that this circuit may be regulated by neuromodulatory tone accompanying behavioral states.

Another open question is whether the direct functional projection between A1 and V1 would exhibit plasticity upon alterations in vision and/or audition. Recent studies highlight that loss of a sensory modality leads to distinct synaptic plasticity across different primary sensory cortices (Goel et al., 2006; Jitsuki et al., 2011; Petrus et al., 2014). In particular, losing vision produces functional strengthening of feedforward synapses (i.e., thalamocortical to L4 and L4 to L2/3 synapses), as well as circuit refinement, in the primary sensory cortices of the spared senses (Meng et al., 2015; Petrus et al., 2014, 2015). In principle, direct projections from A1 to V1 could allow functional interaction between the two senses needed for crossmodal plasticity. Or they themselves may undergo plasticity in response to loss of vision and/or audition. On a similar note, whether these synaptic connections could be altered by audio-visual learning paradigms would be of interest. In any case, it is becoming clear that even primary sensory cortices do not play alone.

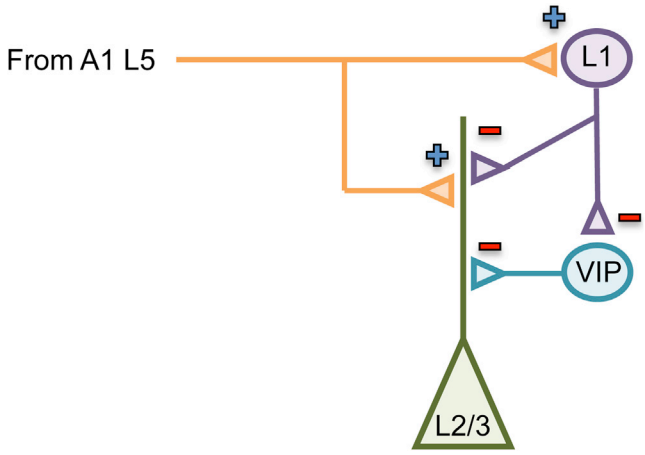

Figure 1. Proposed Inhibitory/Disinhibitory Circuit in V1 that Mediates Sharpening of Visual Cortical Neuronal Responses with Sound

Auditory information arrives through A1 L5 axonal projections to L1 and L2/3 of V1, which synapse strongly onto L1 inhibitory neurons and L2/3 pyramidal neurons. L1 inhibitory neurons suppress L2/3 activity but also disinhibit them via inhibition of VIP inhibitory neurons. L1-mediated inhibition acts to sharpen the orientation tuning of L2/3 neurons, while disinhibition through VIP neurons is thought to preferentially enhance the response to preferred orientation. Such dual adaptation allows loud sound to refine V1 L2/3 orientation tuning. +, excitatory synapses; −, inhibitory synapses.

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