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Suppressive Competition: How Sounds May Cheat Sight

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In this issue of *Neuron*, Iurilli et al. (2012) demonstrate that auditory cortex activation directly engages local GABAergic circuits in V1 to induce sound-driven hyperpolarizations in layer 2/3 and layer 6 pyramidal neurons. Thereby, sounds can directly suppress V1 activity and visual driven behavior.

Information processing in primary cortical areas is determined by many factors, including incoming sensory evidence, cortical feedback, and neuromodulatory influences, such as attention or arousal. Whereas the input to a primary sensory area has classically been considered to be largely modality specific, a fostering notion proposes a direct and more specific interplay between the early sensory cortices of different modalities (Kayser and Logothetis, 2007). Previous functional imaging work revealed how stimulation of one modality affects early sensory areas of another, and anatomical studies highlighted pathways that potentially mediate direct early crossmodal interactions (Falchier et al., 2002). However, the direct impact of individual pathways has been difficult to elucidate, especially in human cognitive studies (Schroeder and Lakatos, 2009). Now, Iurilli et al. (2012) present a technical tour de force to uncover the details of one kind of early crossmodal interaction in mice: how primary auditory cortex (A1) activation directly affects neural activity in primary visual cortex (V1).

By using in vivo whole-cell recordings, Iurilli and colleagues discovered that A1 activation elicits suppressive responses in the membrane potential of layer 2/3 pyramidal neurons in V1. This sound-induced hyperpolarization (SH) was causally related to A1 activation and scaled with sound amplitude. Specifically, replacing the acoustic stimulus by optogenetic stimulation of A1 reproduced V1 SH of similar amplitude, and pharmacological silencing of auditory cortex abolished SH. To identify the pathways involved, the authors transected the gray matter between both regions. This rather crude intervention is sure neither to ablate all corticocortical projections nor to spare all others (e.g., corticofugal pathways). However, it was sufficient to abolish SH while preserving visually evoked (i.e., thalamocortical-driven) responses in V1. Because the latency difference between sound-induced A1 activation and SH in V1 also leaves little time for additional synaptic relays, these results provide direct and comforting evidence that auditory cortex activation can causally modulate V1 neurons by virtue of direct corticocortical connectivity.

The new study also highlights some of the network mechanisms underlying the sound-induced suppression: the auditory impact on V1 seems to emerge in V1 infragranular layers and evokes feedforward GABAergic inhibition across other layers. By estimating synaptic conductances in layer 2/3 neurons during SH, the authors found that sound presentation increases inhibitory conductances and induces only little withdrawal of excitation. Subsequent pharmacological tests confirmed that SH is dependent on GABAergic transmission. From recording cells in other cortical layers, they found that SH also prevails in layer 6 pyramidal cells, whereas some layer 5 cells featured depolarizing sound-evoked responses. This led the authors to speculate that layer 5 may trigger the hyperpolarization in other cortical layers, a hypothesis that they confirmed by using optogenetic activation of cells in infragranular layers (Figure 1A). Although it is still unclear which types of interneurons mediate the SH and which cortical layers they are from, these findings provide a new insight into how crossmodal activations can affect cortical microcircuits.

By tapping into inhibitory circuits, this crossmodal suppression may engage powerful mechanisms controlling intracortical competition, information flow, and response gain in cortical microcircuits. Specifically, the recruitment of inhibition is a hallmark of recurrent cortical connectivity (Silberberg, 2008), because even weak thalamocortical inputs can evoke translaminar inhibition and competition (Adesnik and Scanziani, 2010; Kapfer et al., 2007). The possibility that crossmodal inputs engage such mechanisms is especially intriguing in light of theoretical models for multisensory integration. A recent model proposes that several aspects of multisensory computations can be implemented by a divisive normalization process (Ohshiro et al., 2011), in which one population of neurons (for example, auditory) modulates the response gain of another (for example, visual) and induces typical multisensory response patterns, such as stimulus efficacy-dependent response enhancement or suppression (Stein and Stanford, 2008). Although it remains debated whether cortical gain control is actually mediated by GABAergic inhibition (Carandini and Heeger, 2012), the new findings highlight a neural substrate that, at least in principle, may implement normalization-like crossmodal interactions in early sensory cortices.

Would such suppressive and mostly subthreshold crossmodal influences affect behavior? Iurilli et al. (2012) show that, along with V1 suppression, acoustic stimuli also affected the behavior of the mouse. Mice aversively conditioned to respond to a visual stimulus exhibited reduced behavioral responses when the visual stimulus was paired with a sound (Figure 1B). Hence, in the specific context of these experiments, sounds reduced both neural and behavioral responses evoked by a visual stimulus. This behavioral effect is reminiscent of crossmodal competition, a flavor of crossmodal interaction whereby different senses compete for attentional resources or memory access (Talsma et al., 2010). The results of Iurilli and coworkers concord well with crossmodal competition, because the authors not only tested the impact of auditory activation on visual cortex, but they also demonstrated the general prevalence of crossmodal inhibition: sounds also induced hyperpolarization in somatosensory cortex, and whisker stimulation induced hyperpolarization in auditory and visual cortices. This widespread crossmodal inhibition might well reflect a generic competition for resources across modalities, a hypothesis that fits well with the presented behavioral and neural data.

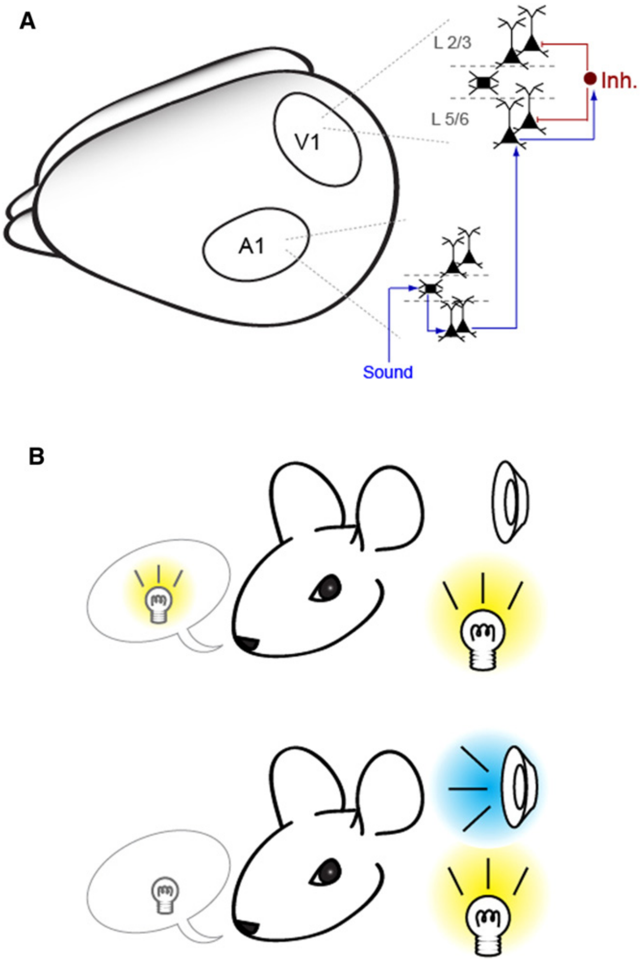

Figure 1. Auditory Cortex Activation Reduces Light-Evoked Neural Responses in V1 and the Behavioral Detection of Visual Stimuli

(A) Schematic of the cortical microcircuitry studied by Iurilli et al. (2012). Sounds activate primary auditory cortex (A1), which in turn excites some neurons in primary visual cortex (V1). Within V1, sound presentation engages translaminar inhibitory circuits (red), which cause sound-driven hyperpolarizations and reductions in firing rates of layer 2/3 and layer 5/6 neurons. The location and type of interneurons remain uncertain.

(B) Behavioral results. Animals aversively conditioned to detect a visual target (top) failed more frequently to detect the visual target when presented with a sound (bottom).

Nevertheless, multisensory perception, especially in humans, does bestow many behavioral benefits that contrast with these new findings (Stein and Stanford, 2008). For example, human observers show enhanced visual contrast detection or orientation discrimination in multisensory contexts when visual targets are accompanied by uninformative sounds. This points to an increased, rather than decreased, excitability of visual cortex in response to crossmodal inputs, a hypothesis that recently received additional support. Romei et al. (2009) measured visual cortical excitability in humans by using transcranial magnetic stimulation (TMS) to induce visual phosphenes, and they found stronger visual phosphene perception following the presentation of sounds—hence demonstrating sound-induced enhancement of visual perception. However, whether V1 is really the key area critically affected by TMS in that study remains uncertain, and perception ultimately depends on multiple sensory areas and their collective interplay. Hence, the specific contributions of crossmodal activations in individual areas and their causal relation to behavior remain to be elucidated. In addition, it remains to be seen whether the reported SH in V1 can support some of the functional specificity of crossmodal interactions reported in previous studies. For example, in the TMS study, certain sounds (for example, looming) caused stronger excitability than simple noises (Romei et al., 2009), revealing specificity with regard to the acoustic input. And in a visual perceptual learning experiment, sounds were found to enhance learning in a spatially restricted region of the visual field, pointing to specificity locally within visual retinotopic maps (Beer and Watanabe, 2009).

Ongoing work suggests that rodents can display similar behavioral crossmodal benefits as humans. Rats trained and tested by using operant conditioning on an audio-visual detection task that uses food reward (rather than aversive conditioning) show better and faster detection as found in corresponding human psychophysical studies (Gleiss et al., 2012, Cosyne, abstract). This suggests that the behavioral findings of Iurilli et al. (2012) do not result from a species-specific stereotype but are better interpreted in the context of crossmodal competition induced and emphasized by the behavioral paradigm of aversive conditioning. Recent work shows that aversive conditioning engages neuromodulatory feedback on primary sensory cortices through the translaminar activation of layer 2/3 pyramidal neurons by reducing the tonic inhibition of local interneurons (Letzkus et al., 2011). Hence, whereas aversive learning seems to enhance neuronal responses to the aversive-associated stimulus (here, visual), crossmodal activations (here, auditory) can reduce these. The new findings therefore also predict that the acquisition of aversive-associative learning should be slowed in a multisensory context. Still, additional studies would be required to elucidate in detail how the behavioral task context affects the behavioral and neural patterns of crossmodal interactions.

Anatomical studies have highlighted the direct connectivity between early sensory cortices of different modalities (Falchier et al., 2002). The new study in mice not only reveals the prominence of sound-induced changes in V1, but also reports that visual stimulation has a weaker effect on auditory or somatosensory cortex than vice versa. One may speculate that this asymmetry results from a rodent's reliance on tactile and auditory over visual information, hinting on a more general pattern of asymmetry in crossmodal interactions. This may explain why finding sound-induced activations in V1 of primates has proven surprisingly difficult (Wang et al., 2008) and suggests that crossmodal interactions may be adapted to a particular ecological niche. To conclude, the new results of Iurilli and colleagues not only demonstrate the power of rodent models in conjunction with multiple experimental techniques, but they also promote speculations and future studies on the brain's multisensory faculty.

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Axonal mRNA Translation: An Unexpected Link to Axon Survival and the Mitochondrion

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Localized mRNA translation plays roles in dendrites and axons, but the regulatory mechanisms and downstream pathways are not well understood. An article in *Cell* by Yoon et al. (2012) shows that lamin B2, well known as a nuclear protein, undergoes regulated synthesis in axons, promoting mitochondrial function and axon survival.

Eukaryotic cells are organized into functionally distinct subcellular regions, and proper localization of proteins is usually essential for function. While many proteins possess amino acid sequences that target them to specific locations, it is becoming increasingly clear that mRNA transport and local translation play a widespread role in protein localization (Holt and Bullock, 2009; Swanger and Bassell, 2011).

Neurons present an extreme example of cell compartmentalization where protein synthesis can differ not only between axons and dendrites, but also between different regions of a dendrite or axon. In dendrites, local translation is regulated by synaptic activity and plays a role in plasticity. In axons, protein synthesis can be regulated in the growth cone in response to guidance cues and this can contribute to growth cone turning, collapse, or change in responsiveness. Local protein synthesis has also been implicated in axon regeneration (Holt and Bullock, 2009; Swanger and Bassell, 2011).

Although a large number of mRNAs have been found to localize within the axon, we still have limited knowledge about the roles of individual locally translated mRNAs: either the axonal functions of specific mRNAs, or which of them may be regulated in response to extracellular cues. In the February 17th issue of *Cell*, Christine Holt and colleagues report the unexpected discovery that a major protein subject to translational regulation within the axon is a member of the lamin B family—proteins known for decades