Paving the Way Forward: Integrating the Senses through Phase-Resetting of Cortical Oscillations

Asif A. Ghazanfar[1],* and Chandramouli F. Chandrasekaran[1]
[1] Program in Neuroscience, Department of Psychology, Green Hall, Princeton University, Princeton, NJ 08540, USA
*Correspondence: asifg@princeton.edu

Most, if not all, of the neocortex is multisensory, but the mechanisms by which different cortical areas—association versus sensory, for instance—integrate multisensory inputs are not known. The study by Lakatos et al. reveals that, in the primary auditory cortex, the phase of neural oscillations is reset by somatosensory inputs, and subsequent auditory inputs are enhanced or suppressed, depending on their timing relative to the oscillatory cycle.

The integration of information from different sensory systems is a fundamental characteristic of perception and cognition—qualitatively different information from the various sense organs is put together in the brain to produce a unified, coherent representation of the outside world. Traditionally, it has been assumed that the integration of such disparate information was the task of highly specialized regions such as the intermediate layers of the superior colliculus or the association areas of the neocortex. Recently, however, there is mounting evidence that

much, if not all, of the brain (or at least the neocortex) is multisensory. But different brain areas may not be multisensory in the same way.

The early determination of what brain regions are multisensory was based largely on whether the spiking activity of single neurons in a given region was driven by sensory inputs from more than one modality. For example, the superior temporal sulcus of the macaque was dubbed "polysensory" because many neurons in that region were bimodal or trimodal—driven by visual stimuli as well as auditory

and/or somatosensory stimuli (Bruce et al., 1981). However, numerous human neuroimaging studies began to reveal that there were many cortical regions, including presumptive unimodal sensory areas, that seemed to be multisensory in the sense that they produced enhanced responses to bimodal stimuli relative to unimodal inputs. For example, functional imaging (e.g., Calvert et al., 1997) and, later, event-related potential (e.g., Giard and Peronnet, 1999) studies raised the possibility of audio-visual and audio-tactile interactions in human auditory

cortex. In monkeys, intracranial recordings have directly confirmed multisensory convergence (Schroeder et al., 2001) and integration (Ghazanfar et al., 2005) in multiple auditory cortical areas. Importantly, these studies examined both spiking and field potential activity which revealed that multisensory processes may not be discernable through an examination of spiking activity alone. That is, there may be bimodally induced enhancement or suppression of audio-visual responses, but no overt response to the visual modality alone. In light of this, some cortical areas may be thought of as being "driven" by multiple modalities, while others, like primary or secondary sensory areas, may be "modulated" by other modalities.

In this issue of *Neuron*, Lakatos et al. (2007) capitalize on these initial findings and use multiunit and field potential recordings to delve deeper into the mechanisms of somatosensory-auditory interactions in the primary auditory (A1) cortex of the macaque monkey. In combination with current source density analyses, their initial forays revealed that auditory "clicks" activate A1 in layer 4 (granular layer) followed by the supra- and infragranular layers (a typical feedforward pattern). In contrast, median nerve (somatosensory) stimulation activated the supragranular layers faster, and to a greater degree, than the other cortical layers. Furthermore, while clicks elicited spiking activity in all layers, somatosensory input did not in any layer. Together, these data suggest that somatosensory stimulation alone does not *drive* auditory neurons over their action-potential threshold but perhaps *modulate* auditory inputs in a manner analogous to the hypothesized role of paralemniscal thalamic pathways on general
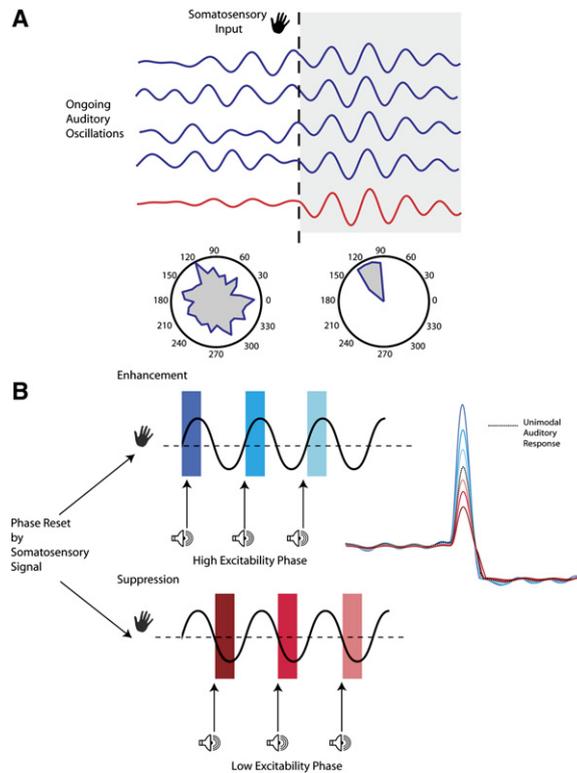

Figure 1. Multisensory Integration through Phase-Resetting
(A) Before the onset of the somatosensory stimulus, the phase of the auditory cortical oscillation is random and thus their mean (red line) across trials (blue lines) is flat and their distribution in the circular plots is widely dispersed. However, once the somatosensory stimulus is delivered, the oscillations are reset and thus aligned with each other, leading to a consistent phase distribution over trials and a concentrated distribution in the circular plots.
(B) In the overall mechanism of multisensory integration, the somatosensory signal resets the phase of the ongoing oscillation (as in [A]) and when the auditory input arrives in a high-excitability phase (periods of gamma, theta, or delta) then the response is enhanced. In contrast, when the auditory input arrives in the low-excitability region of the reset oscillation (half periods of gamma, theta, or delta), then the response is suppressed. The magnitude of enhancement (shades of blue) or suppression (shades of red) still depends on the interval between auditory inputs relative to the initial somatosensory input.

cortical processing (Sherman and Guillery, 1996).

In order to characterize the putative modulatory influence of somatosensory inputs on auditory processing, Lakatos et al. varied the timing of auditory clicks relative to median nerve stimulation (the stimulus-onset asynchrony, or SOA). In doing so, they discovered a novel mechanism for multisensory integration. As predicted from the pattern of laminar activations, simultaneous presentation of somatosensory and auditory stimuli led to a nonlinear enhancement of activation in the supragranular layers and, to

a lesser degree, in the infragranular layers. No such integration was observed in the granular layer. However, when they varied the relative timing of sensory inputs beyond simultaneity, a structure emerged: in addition to the concurrent bimodal stimulation, enhanced responses (in both field potential and spiking activity) were observed at three additional SOA ranges, centered around 27 ms, 140 ms, and 781 ms. Surprisingly, these SOAs correspond to the periods of gamma, theta, and delta band oscillations that comprise the structure of spontaneous A1 activity (Lakatos et al., 2005). When SOAs of intermediate values were used, suppressed responses (relative to the unimodal auditory activation) were observed. This suggested that somatosensory inputs modulate auditory responses by changing the phase of ongoing auditory cortical oscillations.

To test this hypothesis, Lakatos et al. analyzed the oscillatory components of unimodal and bimodal responses using spectral decomposition. Although the overall pattern was similar to the unimodal auditory condition, the bimodal condition had the greatest power across the spectrum (except the delta band). Intriguingly, the unimodal somatosensory stimulation induced phase-locked oscillations that were confined to particular frequency bands (gamma, theta, and delta), and their amplitudes were much lower relative to the auditory or bimodal conditions and not significantly different from spontaneous activity. An examination of the oscillatory phase distribution pre- and postsomatosensory stimulation, however, revealed the key finding: in the gamma, theta, and delta oscillations, phase distributions were essentially random before but

were highly concentrated after somatosensory stimulation (Figure 1A). Thus, somatosensory stimulation reset the phase of oscillations in those frequencies (without a concomitant increase in power), as has been proposed in other domains of sensory or memory processing (Makeig et al., 2002; Rizzuto et al., 2003). In summary, the novel mechanism discovered by Lakatos et al. is as follows: somatosensory stimuli reset the phase of ongoing auditory cortical oscillations, and the strong phase dependence of sensory responses (Lakatos et al., 2005) subsequently results in enhanced responses when auditory inputs fall on oscillatory peaks and suppression when they fall on oscillatory troughs (Figure 1B).

The implications of these findings extend far and wide. Here are a few obvious ones. First, the data suggest a modification of the "temporal principle" of multisensory integration, which states that an interaction is most likely to be maximally effective when stimuli overlap in time (Meredith et al., 1987). While this is generally true, Lakatos et al. show that response enhancement (though to a lesser degree) is still possible well beyond the time of stimulus overlap—at particular time points on the oscillatory cycle—and that suppression is similarly timing dependent (Figure 1B). Second, at the perceptual level, the data suggest that the time window for detecting, for example, auditory-somatosensory or audio-visual asynchronies (such as in the temporal ventriloquism effect; Slutsky and Recanzone, 2001) may be more complicated than a single, short time-window. Instead, behavioral effects may depend on whether the relative timing of the auditory component of the bimodal stimuli matches the peaks/troughs of ongoing auditory cortical oscillations.

Naturally, it would be of great interest to know whether the oscillatory phase-based mechanism extends to cortical areas beyond A1 and how it would operate with ethologically relevant and other complex stimuli. For example, for highly complex, long-duration signals like faces and voices, the elegant mechanism discovered by Lakatos et al. may be insufficient to characterize face/voice integration. Unlike artificial stimuli, there is a complex interaction between the dynamics of the facial posture and the frequency and amplitude envelope of the acoustic signal. Thus, there may be more than one time point when visual and auditory information may synergize at the neural level or the dynamics of the face may reset the ongoing oscillation multiple times during an expression, complicating any straightforward prediction of when enhancement or suppression may occur. Nevertheless, the findings of Lakatos et al. provide a much-needed framework and set of clear hypotheses for investigating multisensory integration at the physiological level.

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