Current Biology 24, 1447–1455, July 7, 2014 ©2014 Elsevier Ltd All rights reserved http://dx.doi.org/10.1016/j.cub.2014.05.031

Article

Perceptual Gap Detection Is Mediated by Gap Termination Responses in Auditory Cortex

Aldis P. Weible,[1] Alexandra K. Moore,[1] Christine Liu,[1] Leah DeBlander,[1] Haiyan Wu,[1] Clifford Kentros,[1,2] and Michael Wehr[1,*]
[1]Institute of Neuroscience, University of Oregon, Eugene, OR 97405, USA
[2]Kavli Institute, 7491 Trondheim, Norway

Summary

Background: Understanding speech in the presence of background noise often becomes increasingly difficult with age. These age-related speech processing deficits reflect impairments in temporal acuity. Gap detection is a model for temporal acuity in speech processing in which a gap inserted in white noise acts as a cue that attenuates subsequent startle responses. Lesion studies have shown that auditory cortex is necessary for the detection of brief gaps, and auditory cortical neurons respond to the end of the gap with a characteristic burst of spikes called the gap termination response (GTR). However, it remains unknown whether and how the GTR plays a causal role in gap detection. We tested this by optogenetically suppressing the activity of somatostatin- or parvalbumin-expressing inhibitory interneurons, or CaMKII-expressing excitatory neurons, in auditory cortex of behaving mice during specific epochs of a gap detection protocol.
Results: Suppressing interneuron activity during the postgap interval enhanced gap detection. Suppressing excitatory cells during this interval attenuated gap detection. Suppressing activity preceding the gap had the opposite behavioral effects, whereas prolonged suppression across both intervals had no effect on gap detection.
Conclusions: In addition to confirming cortical involvement, we demonstrate here for the first time a causal relationship between postgap neural activity and perceptual gap detection. Furthermore, our results suggest that gap detection involves an ongoing comparison of pre- and postgap spiking activity. Finally, we propose a simple yet biologically plausible neural circuit that reproduces each of these neural and behavioral results.

Introduction

Understanding speech in noisy environments, such as a crowded restaurant, often becomes increasingly difficult with age. Age-related speech processing deficits can occur even with completely normal audiometric hearing and are instead associated with temporal processing deficits [1, 2]. In contrast to declines in audiometric hearing, which are associated with the peripheral auditory system [3], age-related temporal processing deficits involve higher-order structures [4–6]. Lesion studies suggest that auditory cortex is essential for temporal acuity [7–9]. However, lesions cannot reveal the contributions of specific cortical circuits or cell types, nor can they reveal any of the dynamic processing by which these circuits mediate temporal processing. Moreover, most neurophysiological studies of temporal processing have been only correlative. As a result, the mechanisms underlying temporal processing in cortex are not well understood.

A well-established measure of temporal processing in both humans and animals is gap detection. In this variant of prepulse inhibition, a silent gap is inserted into continuous background noise. The gap acts as a cue that reduces the startle response evoked by a subsequent loud noise burst. Gaps as brief as 2–4 ms measurably attenuate the startle response in species as diverse as mice [7], zebra finches [10], and humans [11]. Cortical deactivation studies have shown that auditory cortex is necessary for the detection of brief gaps ($\leq$50 ms), but not for long gaps (75–100 ms; [7, 9]). The duration of the briefest detectable gap is referred to as the minimum gap threshold (MGT). Auditory cortical neurons respond to the end of the gap with a characteristic burst of spikes called the gap termination response (GTR). The cortical GTR has an MGT similar to that of behavioral startle attenuation, and both grow with increasing gap durations [7, 9, 12]. The cortical GTR has therefore been proposed as a neural correlate of brief gap detection [12, 13].

Demonstrating a causal link between the cortical GTR and perceptual gap detection requires manipulating the GTR itself. The challenge lies in manipulating neural activity only during the brief interval (50 ms) when the GTR occurs, between the gap termination and the onset of the startle stimulus. Here we used optogenetic suppression to specifically manipulate the GTR. We measured gap detection in transgenic mice expressing archaerhodopsin (Arch; [14]) in one of three different neuronal populations: parvalbumin-expressing (PV) GABAergic interneurons, somatostatin-expressing (SOM) GABAergic interneurons, or CaMKII-expressing pyramidal neurons (PNs). Both PV and SOM interneurons have a predominantly inhibitory role, reducing excitatory PN activity [15–19]. We predicted that suppressing the activity of these inhibitory cells during the postgap interval would increase the GTR and enhance gap detection. Conversely, we predicted that suppressing CaMKII-expressing pyramidal neurons during the same interval would decrease the GTR and reduce gap detection. We also tested the effects of cortical manipulation during other epochs of the task to determine the specificity with which the GTR is responsible for brief gap detection, and how it interacts with activity during other epochs of the task.

We found that suppressing SOM- or PV-expressing inhibitory interneurons (INs) immediately following brief gaps enhanced gap detection. Suppressing CaMKII-expressing excitatory neurons during this period reduced gap detection. This demonstrates for the first time the functional relationship between cortical GTRs and perceptual gap detection. By contrast, suppression limited to the pregap interval elicited the opposite behavioral effects. Prolonged suppression throughout both pre- and postgap intervals had no effect on gap detection. Taken together, these data indicate that gap detection involves a comparison between pre- and postgap neuronal activity. We illustrate this idea with a simple neural

*Correspondence: wehr@uoregon.edu

circuit model that implements such a comparison and reproduces our neural and behavioral results.

Results

We tested the ability of mice to detect gaps of 2, 4, 6, 8, 10, 25, and 50 ms embedded in continuous 80 dB white noise. Gap detection was measured by the attenuation of the startle response evoked by a 100 dB burst of noise, presented 50 ms after the gap. On alternating trials, we suppressed the activity of SOM- or PV-expressing inhibitory interneurons or CaMKII-expressing excitatory PNs during (1) the 50 ms interval between gap termination and startle onset, which includes the GTR ("postgap" suppression); (2) the 940 ms interval preceding gap onset ("pregap" suppression); or (3) the entire 1,000 ms preceding startle onset ("prolonged" suppression both before and after the gap). In separate experiments in anesthetized mice, we determined the optimal coordinates for optical fiber placement (see Figure S2 available online), measured the spread of suppression at different laser intensities (Figure S3), and electrophysiologically verified the efficacy of optogenetic suppression. We also verified in awake mice the electrophysiological effects of suppression directly on the GTR (Figure S4). We used two laser intensities: 300 mW/mm^2, which affected only auditory cortex and provided moderate suppression, and 1,000 mW/mm^2, which provided more robust suppression in auditory cortex but may have affected adjacent cortical and subcortical regions (Figure S3).

Effects of SOM Interneuron Suppression

Auditory cortex is necessary for brief gap detection, and the amplitude of the cortical GTR is correlated with both detection threshold and the degree of startle attenuation [7, 9, 12]. SOM interneurons are found throughout the depth of cortex and therefore could be highly effective in suppressing auditory cortical activity [20–22]. We verified that SOM cells expressed Arch (Figure 1A), that their laminar distribution was consistent with previous reports (Figure 1B; [20–22]), and that suppression of SOM cells significantly increased PN spiking activity (Figure 1C). If a causal link exists between the GTR and gap perception, we hypothesized that suppression of SOM activity during the postgap interval would increase the GTR and result in greater attenuation of the startle reflex. Consistent with this prediction, suppression during the postgap period significantly attenuated startle responses following gaps $\leq$ 25 ms, but not gaps of 50 ms (Figure 1D). In other words, detection was improved for brief gaps. This effect was more pronounced with the higher laser intensity (1,000 mW/mm^2; Figure 1E). The MGT was 4 ms and was not affected by SOM suppression at either intensity. SOM suppression in the 0 ms gap condition had no effect, indicating a specific effect of suppression on gap detection. Moreover, the laser had no effect in Arch-negative SOM littermate controls (Figure 1H).

We next suppressed SOM interneurons during other temporal epochs of the gap detection protocol. Surprisingly, suppressing SOM activity in the pregap period increased startle amplitudes (Figure 1F), indicating a decrease in gap detection. Even more interestingly, when we instead suppressed SOM interneurons uniformly across both the pregap and postgap intervals ("prolonged suppression"), there was no effect on startle responses (Figure 1G). These two results suggest the existence of a dynamic comparison between pregap and postgap spiking activity.

Effects of PV Interneuron Suppression

PV-expressing interneurons also inhibit pyramidal neurons and have distinct neurochemical, morphological, and electrophysiological phenotypes compared to SOM interneurons [22–25]. We therefore expected that, like SOM interneurons, suppressing this population would improve gap detection. Here, too, our expectations were confirmed, although the effect was less robust. We first verified that PV cells expressed Arch (Figure 2A), that their laminar distribution was consistent with previous reports (Figure 2B; [26]), and that suppression of PV cells significantly increased PN spiking activity (Figure 2C). Postgap suppression of PV cells significantly reduced startle amplitudes following gaps $\leq$ 10 ms but had no effect for gaps of 25 ms or 50 ms (Figure 2D). As with the SOM animals, the effect was more robust with the higher laser intensity (1,000 mW/mm^2; Figure 2E). The MGT was reduced from 4 ms to 2 ms at the higher intensity ($df = 179$, $t = 3.83$, $p = 0.0002$) but was unaffected at the lower intensity.

No significant effect was seen with pregap PV suppression, although as with SOM suppression, the trend was in the direction of increased startle amplitudes (Figure 2F). Prolonged PV suppression, in turn, had no effect on gap detection (Figure 2G). Illumination again had no effect in Arch-negative PV littermate controls (Figure 2H).

Finally, to test whether the effects of interneuron suppression were specific to gap detection or more generally affected the gain of startle response circuitry, we measured conventional prepulse inhibition (using white-noise bursts as the prepulses, presented in a silent background). PV and SOM suppression had no effect on prepulse inhibition (Figure S5), indicating that the effects we observed were specific for gap detection.

Effects of CaMKII Pyramidal Neuron Suppression

We verified that CaMKII cells expressed Arch (Figure 3A), that their laminar distribution was consistent with previous reports (Figure 3B; [27]), and that suppression of CaMKII cells significantly reduced PN spiking activity (Figure 3C). Suppressing SOM or PV inhibitory neurons during the postgap interval improved gap detection. We predicted that suppressing pyramidal neurons during this interval would have the opposite effect. Indeed, postgap suppression of CaMKII neurons following gaps $\leq$ 10 ms significantly reduced startle attenuation (i.e., impaired gap detection; Figure 3D). No effects were seen following gaps of 25 ms or 50 ms. The effect was more pronounced with the higher laser intensity (1,000 mW/mm^2; Figure 3E). The MGT of 4 ms was not affected at either intensity. Conversely, suppressing CaMKII neurons during the pregap interval decreased startle amplitudes (Figure 3F), indicating improved gap detection. Prolonged suppression again produced no effect (Figure 3G). Laser illumination had no effect on Arch-negative CaMKII littermate controls (Figure 3H).

A Circuit Model for Gap Detection

We found that increasing or decreasing the activity of pyramidal neurons during either the pregap or postgap periods caused opposing effects on gap detection, whereas prolonged suppression throughout the pre- and postgap period had no effect. This suggests the existence of a process that compares postgap activity to pregap activity. One simple yet biologically plausible mechanism that could perform such a comparison is a circuit that subtracts the recent history