Gap Detection in Auditory Cortex

by

ULYSSES DUCKLER

A THESIS

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Strong evidence supports that for older adults, hearing loss and difficulty with speech comprehension in noisy environments is the result of temporal processing deficits in central auditory structures such as the auditory cortex. There is a general canonical circuit model of layer by layer serial information flow through the auditory cortex from the thalamus, before information is projected back into inferior colliculus neurons. However the specific cortical circuits and cell types which regulate temporal processing through the auditory cortex are still unknown and not linked to behavior. The auditory cortex contributes to temporal acuity in receiving auditory stimuli. Temporal acuity is used, for example, for brief noise gap detection and discriminating between similar phonemes. Impairments to temporal activity can cause speech perception deficits. In this study, I tested gap detection behavior in mice. To do this, I measured how their startle responses were modulated by gaps in continuous background noise. The presence of the gap attenuates the startle response to the stimulus, so that measuring the startle response gives a measure of temporal acuity by assessing gap detection behavior. I used a technology called optogenetics to manipulate brain activity during this behavior. Optogenetics allows for the gaps to be paired with a laser pulse

that silences auditory cortex neurons and allowed me to see how gap detection is impaired by temporally precise suppression of auditory cortex. By probing cortex circuit mechanisms through layer-specific optogenetic silencing before and after gap, I found that layer-specific silencing of auditory cortex neuron populations in layers four and five suggests behavior in accordance with the canonical model.

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I would like to thank Professor Wehr and all the members of the Wehr lab, for helping me with this research through the last two years. I'd especially like to thank Dr. Mike Wehr and Aldis Weible for advising me on through the thesis writing process and helping me find direction for this study. Special thanks for Lucas Ott for assisting me with behavior trials, Christine Liu for inspiring me with her past success with the Wehr lab, and my loving girlfriend Bianca Gazzingan for supporting me. I'm very grateful to all of my family, especially my sister who visited me in lab through my last year.

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Introduction

Distinguishing speech in noisy environments can become increasingly difficult for older adults, as age-related hearing loss presents a communication challenge [1, 2]. This age-related loss of speech comprehension is the result of progressive central auditory processing disorders, which are common in people aged 65 and older. Cochlear implants are a form of surgical treatment which replace the input of lost or damaged hair cells with electrical signals to the cochleae. However, unlike deficits in peripheral auditory systems and the outer ear, as is the case with sensorineural hearing loss (cochlear damage) [3], central auditory processing disorders are caused by degeneration of central auditory structures so they cannot be treated with conventional hearing aids or cochlear implants [4-6]. Central auditory processing disorders are also caused by the degeneration of other auditory structures, including the auditory cortex of the temporal lobe and in some cases can occur without any outright measurable hearing loss (audiometric hearing loss) [7-9].

Lesion studies suggest that the auditory cortex contributes to temporal processing [10-12], which is the rate and accuracy with which we process auditory information. Loss of temporal processing acuity results in distortions and a larger window of time required for speech comprehension. A limitation of lesion studies is that the effects of specific cortical circuits, active cell types, or the dynamic processes of such circuits cannot be identified because the lesion destroys these processes. Additionally, most physiological studies of temporal processing mechanics are performed in anesthetized animals so that behavior is not accounted for [6, 13-19].

Because of this, an understanding of temporal processing mechanisms in the auditory cortex has remained unclear.

Gap detection is a well-established measure of temporal processing acuity and allows for phoneme discrimination [10-12, 20, 21]. The duration between the release of a stop consonant and the onset of vocalization, called voice-onset time, is one example of a brief noise gap which is integral to speech comprehension. Discriminating voice-onset times allow listeners to distinguish between similar consonants such as "b-" and "p-" [22]. Impaired gap detection is linked to speech perception deficits and can often occur in elderly listeners, even those with normal audiometric hearing [23-26]. Gap detection is responsible for a pre-pulse inhibition (PPI) effect, when a silent gap is inserted into continuous background noise. PPI is a sensorimotor phenomenon in which a weak pre-stimulus cue inhibits the reaction to a subsequent strong startling stimulus. In this case, gaps as brief as 2–4ms will noticeably attenuate the startle response triggered by a subsequent loud noise burst [27-29]. PPI occurs a very wide array of species ranging from mice [10], to zebra finches [30], to humans [20]. The duration of the briefest detectable gap is called the minimum gap threshold (MGT). Auditory cortex neurons respond with a burst of spiking of activity at the end of gaps, which is called the gap termination response (GTR). The GTR activity and noticeable startle attenuation share the same MGT, and both increase as gap duration increases (Figure 1). This suggests that the startle attenuation caused by the PPI phenomenon and spike of GTR activity are linked and only occur in response to perceivable gaps [10, 12, 18]. Recent studies in our lab have shown that perceptual gap detection is in fact mediated

by the GTR in auditory cortex neurons [28]. This allows startle attenuation to act as a measure of gap detection, and also as a measure of auditory cortex activity.

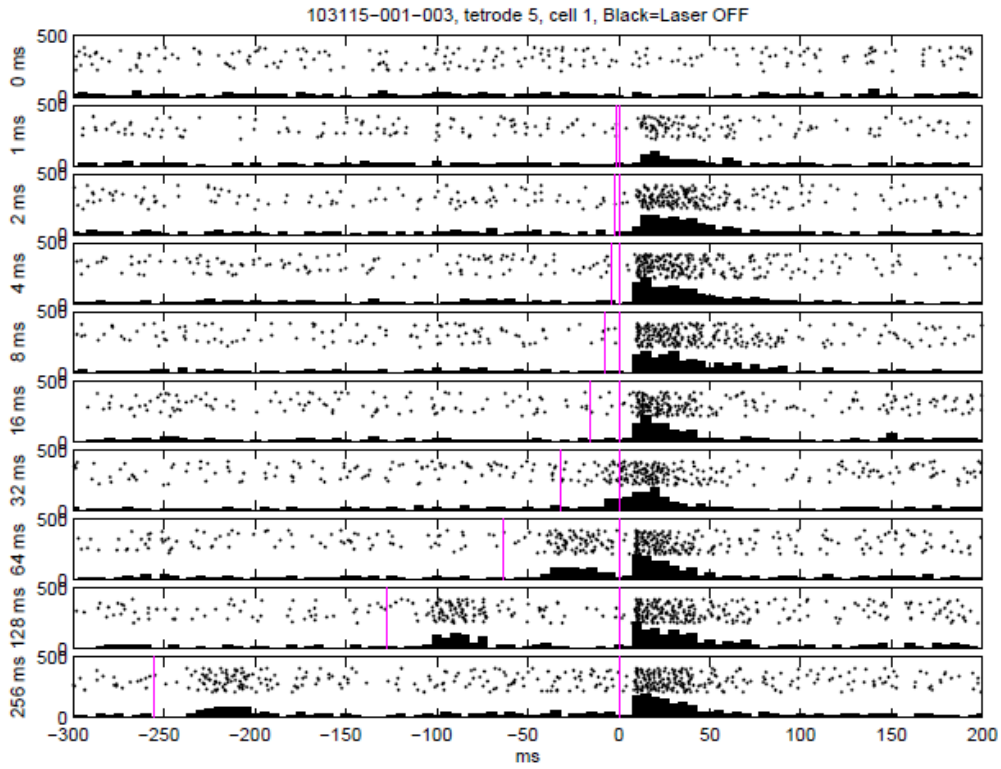

Figure 1. Gap termination response (GTR) with increasing gap duration.

The GTR activity typically appears following the gap (indicated by the purple lines) and peaks between gaps of 2-32ms. Cortical activity (black bars) is also seen following gap onset as gap duration increases. Unpublished data from single cell recordings collected by Ira Yavorska in the Wehr lab.

Interestingly, the primary auditory cortex is not necessary for many auditory tasks which govern temporal processing, including PPI of startle responses, frequency discrimination, and fear conditioning [11, 28, 31-33]. Inferior colliculus (IC) neurons can precisely encode gap stimuli and regulate PPI, yet they are not sufficient to mediate gap detection in the presence of auditory cortex lesions. Previous studies from our lab have shown that gap detection can be enhanced with fear conditioning, demonstrating

that the auditory cortex is involved with associative learning, a phenomenon termed "fear potentiation of gap detection" [27, 34]. Our broad hypothesis is that the auditory cortex's involvement with temporal processing is to assign meaning to temporally structured sounds such as phonemes in the form of associative learning. A novel aim of this study is to use optogenetics and electrophysiology in conjunction with behavioral gap detection tasks to directly test the roles of specific neurons and circuits necessary for gap detection in mice.

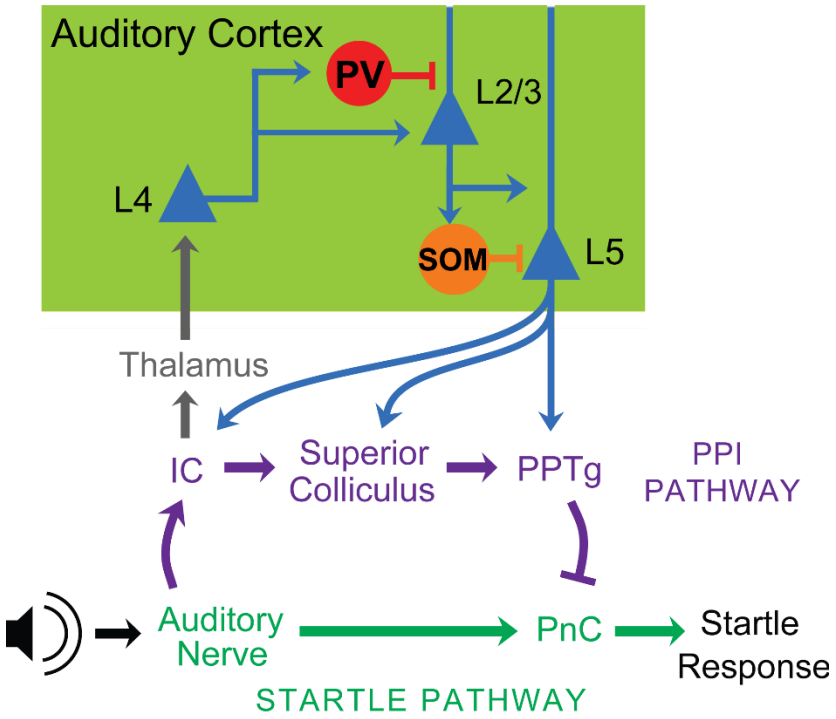

Figure 2. Candidate serial circuit model.

The current canonical model of information processing circuitry from the PPI pathway through the auditory cortex depicted as a candidate circuit model [35]. PPTg: pedunculopontine tegmental nucleus. PnC: caudal pontine reticular nucleus.

The canonical model of auditory cortex circuit signaling is that information flow is serial (i.e., following a linear sequence) (Figure 2). In this model, auditory sensory

information received from thalamic input is processed though layered auditory cortex pyramidal neurons (PNs) L4→L2/3→L5/6 before projecting subcortically back to the PPI pathway though the IC [32, 36, 37]. PV and SOM are inhibitory interneurons (INs) that are proposed to suppress L2/3 and L5 respectively [38]. An aim of this study is to determine which layered sub-populations of auditory cortex PNs are necessary for gap detection. Specifically, I am measuring the effects of optogenetically suppressing layer four and layer five neurons on gap detection performance. The canonical circuit model predicts that suppression of L2/3, L4, or L5/6 PNs should block gap detection, with equivalent effect sizes for individual suppression of each layer. This result would support the serial circuit hypothesis. Different sets of results would suggest alternate circuit pathways which could require the model to be revised (Table 1). An example would be if suppression of L4 neurons had no effect on gap detection, a result which could mean there is a pathway which bypasses L4 that is unaccounted for in the canonical model.

X Blocks gap detection / No effect on gap detection	**Predicted outcome of suppressing layer**				
Alternative circuit hypothesis	L4	L2/3	$L5/6_{IC}$	L5	L6
Thal →L4→L2/3→L5/6→IC	X	X	X	/	/
Thal →L6→L5→IC	/	/	X	X	X
Thal →L4→L2/3→L5→IC	X	X	X	X	/
Thal →L4→L2/3→L6→IC	X	X	X	/	X
Thal →L6→IC	/	/	X	/	X
Thal →L4→L5→IC	X	/	X	X	/

Table 1. Alternative circuit hypothesis.

Table of alternatives to the canonical circuit model of auditory cortex signaling (column 1) depending on the results of individual layer suppression (columns 2-6).

Previous studies by our lab found that with suppression of broadly non-layer-specific CaMKII-expressing excitatory PNs in all layers of cortex, startle response was increased with suppression after gap termination (post-gap), and startle response was attenuated with suppression before-gap onset (pre-gap) [27, 28]. Gap detection reduced and enhanced respectively for post-gap and pre-gap suppression. Suppression of PV and SOM inhibitory interneurons showed the opposite results for post-gap and pre-gap suppression [28]. The suppression and analysis of these neuron populations was carried out using optogenetic techniques and behavioral trials similar to those preformed in my study.

Optogenetics is a technique that modifies neurons to express light-sensitive membrane proteins called opsins. The opsin used in this study is archaerhodopsin (Arch;[39]), a fast light-activated proton pump that suppress neuron activity when excited by a specific light wavelength. An optogenetic approach provides unparalleled spatial and temporal precision in the manipulation of mouse auditory cortex neurons by using implanted optical fibers [28]. This allows us to directly test the roles of layer-specific neurons during gap detection behavioral trials. Starting with this candidate serial circuit model hypothesis, experimental manipulations can refine this model and lead to a deeper understanding of how auditory cortex is involved in gap detection.

Experimental Design

Behavioral

Behavioral data is collected from mice performing a gap detection task in a sound-attenuating chamber in which a brief gap in continuous background noise acts as a cue for a subsequent startle noise burst. If the gap is detected, the mouse exhibits a PPI phenomenon and its following acoustic startle reflex is reduced. The mice are loosely restrained in a small perforated plastic tube which rests flat against a piezo transducer to record startle amplitude which is then amplified 200x and digitized at 10kHz (Figure 3). The mouse's head is held in a fixed position by an adjustable clamp on the mouse's cranial fiber implants. A free-field speaker directly facing the animal delivers continuous 80 dB white noise followed by the startle stimulus, a 100 dB white noise burst with duration 25ms that begins 50ms after gap termination. Each gap detection session has 20 trials for each gap duration (0-32ms) which are randomly interleaved and separated by random 15 ± 5 s intervals. The optogenetic suppression on auditory cortex activity is supplied on alternating trials. The mice show no habituation within sessions and sessions are typically separated by 24-hour periods for each mouse [27, 28].

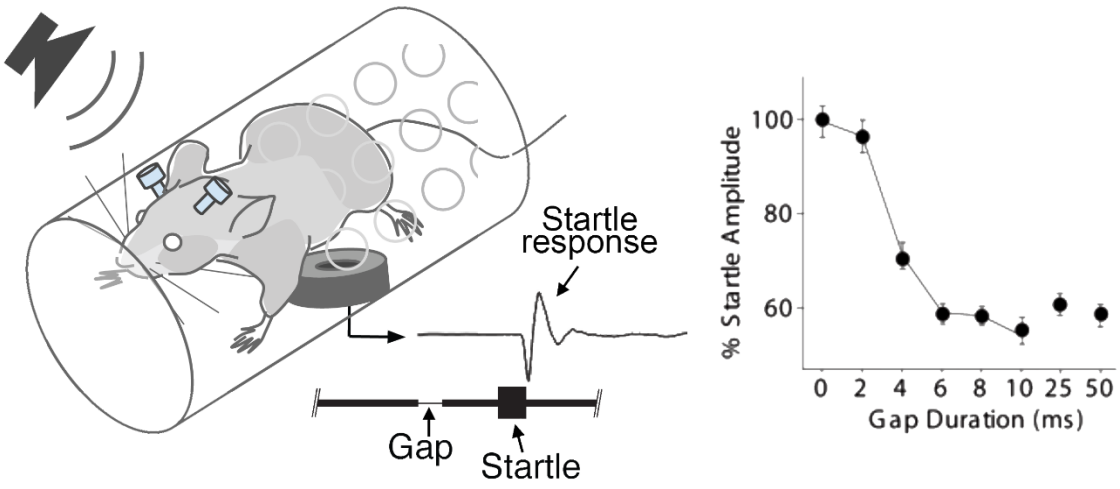

Figure 3. Behavioral trial setup.

The mouse is restrained in the plastic tube resting on the piezo transducer which records the startle response that occurs after the startle stimulus following the noise gap. The startle response decreases with gap duration [28].

Before behavioral trials, all mice to be assessed for gap detection are implanted with a pair of 200µm optic fibers bilaterally targeting primary auditory cortex, using coordinates derived from cortical mapping experiments (implantation surgery performed by Aldis Weible in the Wehr lab) [28]. These fibers allow for suppression of layer-specific neuron activity during sessions with millisecond precision. Two different optogenetic suppression protocols are used, either post-gap suppression, which targets the interval between gap offset and startle stimulus onset, or pre-gap suppression, which begins 1000ms prior to startle onset and is terminated with gap onset. Optogenetic suppression uses a 532 nm wavelength “green” laser set to an output power of 9.7 mW. Measured from the tip of the 200 µm diameter fiber, the light intensity of 300 mW/mm2 results in suppression of excitatory activity limited to just auditory cortex (Figure 4).

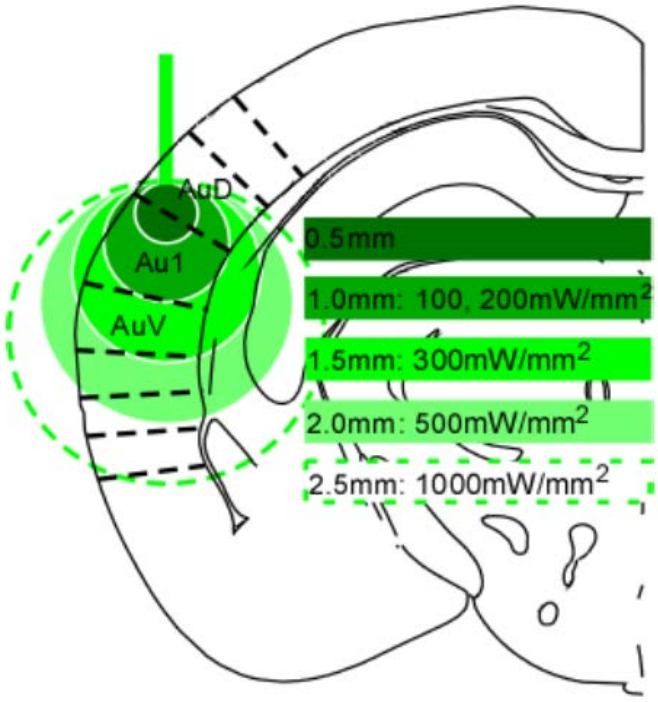

Figure 4. Effect of light intensity on optogenetic suppression.

Ideal suppression of just auditory cortex activity is reached with light intensity of 300 mW/mm2 [28].

Analysis

Startle amplitudes are measured by integrating the rectified piezo signal within the 100ms window following startle onset. Startle amplitudes are normalized within sessions based on the mean “laser off” 0ms gap startle amplitude. To ensure that each behavior trial shows if the suppression of neural activity altered gap-attenuation of startle, only data from sessions with a significant (paired t-test, $p<0.05$) attenuation of startle responses between the 0ms and the longest “laser off” gap are included in the group analyses. Data are collected from multiple sessions across multiple days for each mouse until a mouse has three trials with significance for both pre-gap and post-gap optogenetic suppression protocols.

After the final session of behavioral measurements, each mouse is then anesthetized with 30 mg/kg ketamine, 0.24 mg/kg medetomidine. Brains are fixed in 4% paraformaldehyde by perfusion and then sectioned at 100μm slices on a vibratome for histological verification. All procedures were performed in strict accordance with National Institutes of Health guidelines, as approved by the University of Oregon Institutional Animal Care and Use Committee.

Physiological

Neurons are optogenetically silenced by expressing Arch to directly suppress cortex neurons. Arch is targeted to these specific neuron populations using an established Cre-lox transgenic expression systems [27, 28, 40, 41]. This is a site-specific recombination systems that inserts targeted DNA modifications to specific cell types so that the cells are Cre dependent to express the desired sequence, which in this case encodes the Arch opsin that is then light activated to trigger silencing of the target auditory cortex neuron populations. This study uses two validated layer-specific Cre-lox lines; NR5A which targets L4 PNs and GPR26 which targets L5/6 PNs (Figure 5) [36, 37, 41].

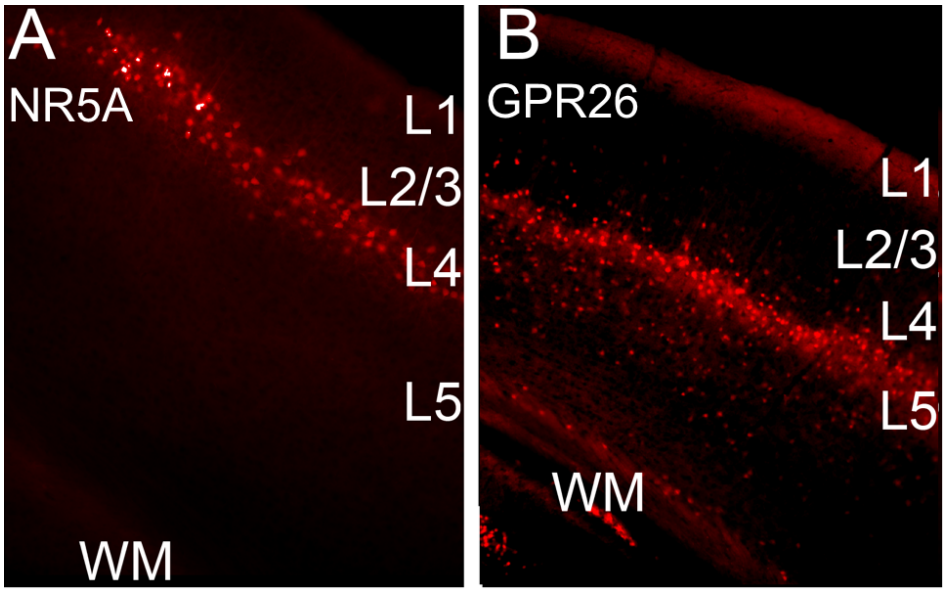

Figure 5. Histological verification of layer-specific Cre-lox lines.

Co-localization of tdTomato florescence in auditory cortex PNs for NR5A to layer 4 (A) and GPR26 to layer 5 (B). A is a Cre-reporter tdTomato cross stain [40], and B is a HA antibody tag stain [42]. WM: white matter. Laminar boundaries established from [43].

Histological

Fiber placements and genotype are verified though histological analysis on each mouse's brain sections. GFP fluorescence expression at the appropriate location of the optic fiber tracks is confirmed using secondary antibody staining. The specificity of Arch expression along the correct layer of the auditory cortex is observed using the co-localization of native GFP. This also confirms mice as double positive for their reported genetic line. Mice which are not double positive through this analysis are analyzed as controls.

Results

Gpr26 (layer 5 PNs)

In the behavioral trials, Arch x Gpr26 mice showed significant differences in startle amplitude for post-gap and pre-gap optogenetic suppression compared to control trials (without suppression). Suppressing layer five PNs during the post-gap interval significantly increased the startle responses following gaps, indicating reduced gap detection (Figure 6A).

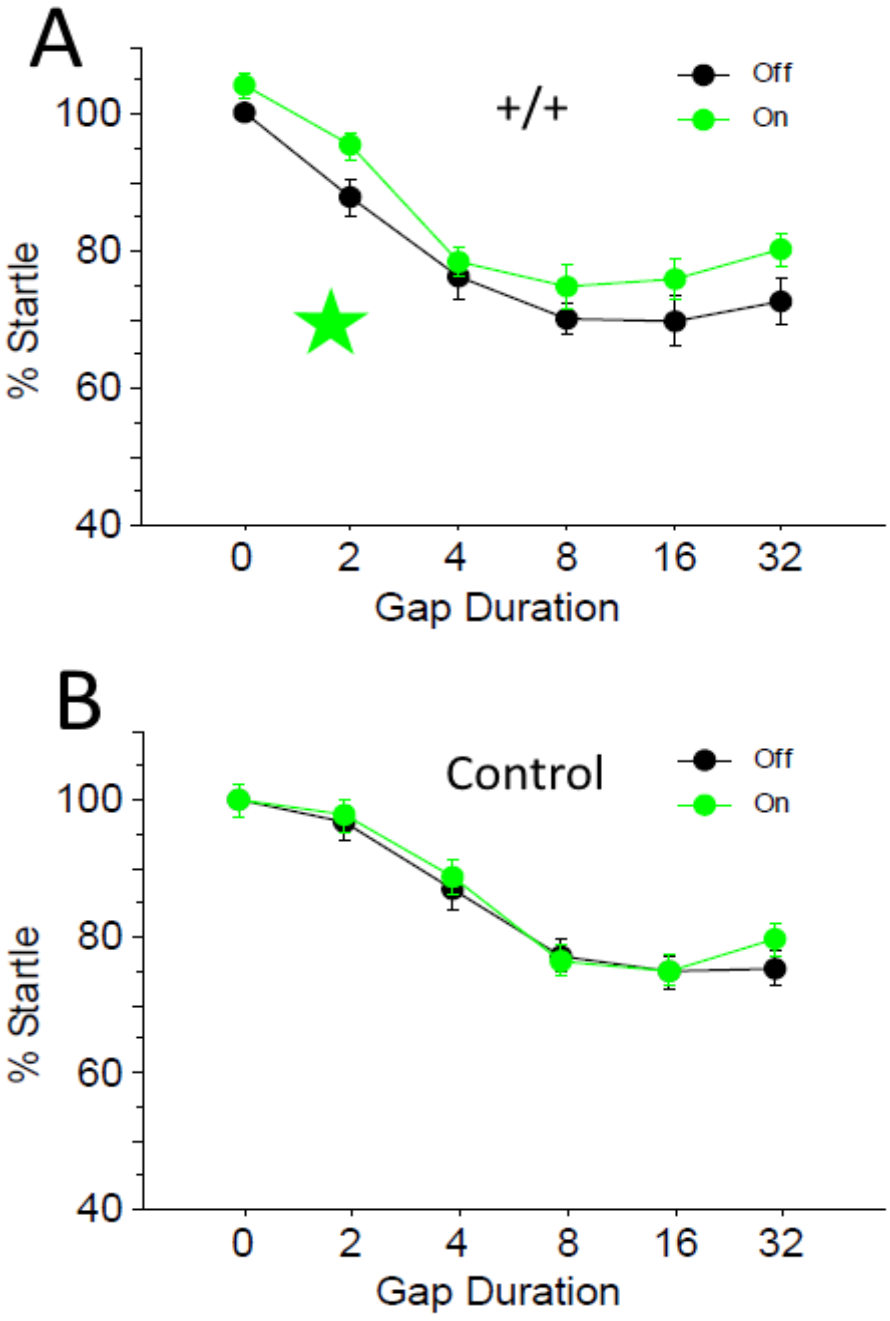

Figure 6. Arch x Gpr26 L5 post-gap suppression.

A) Behavioral trials with post-gap optogenetic suppression active (green) show significantly greater startle (reduced gap detection) then trials without optogenetic suppression (black) with mice double positive for Arch x Gpr26. Significance was derived from a factorial ANOVA [p=0.0405; 4 mice, 14 sessions]. **B**) Control mice (no Arch x Gpr26 expression) showed no effect [p=0.6283, 5 mice, 23 sessions].

Suppressing layer five PNs during the pre-gap interval significantly attenuated the startle responses following gaps, indicating enhanced gap detection (Figure 7A). Alarm over the surprising difference in startle response at 0ms gap duration for suppression on/off was discounted by observing similar raw voltage for 0ms gap (Figure 7C-D).

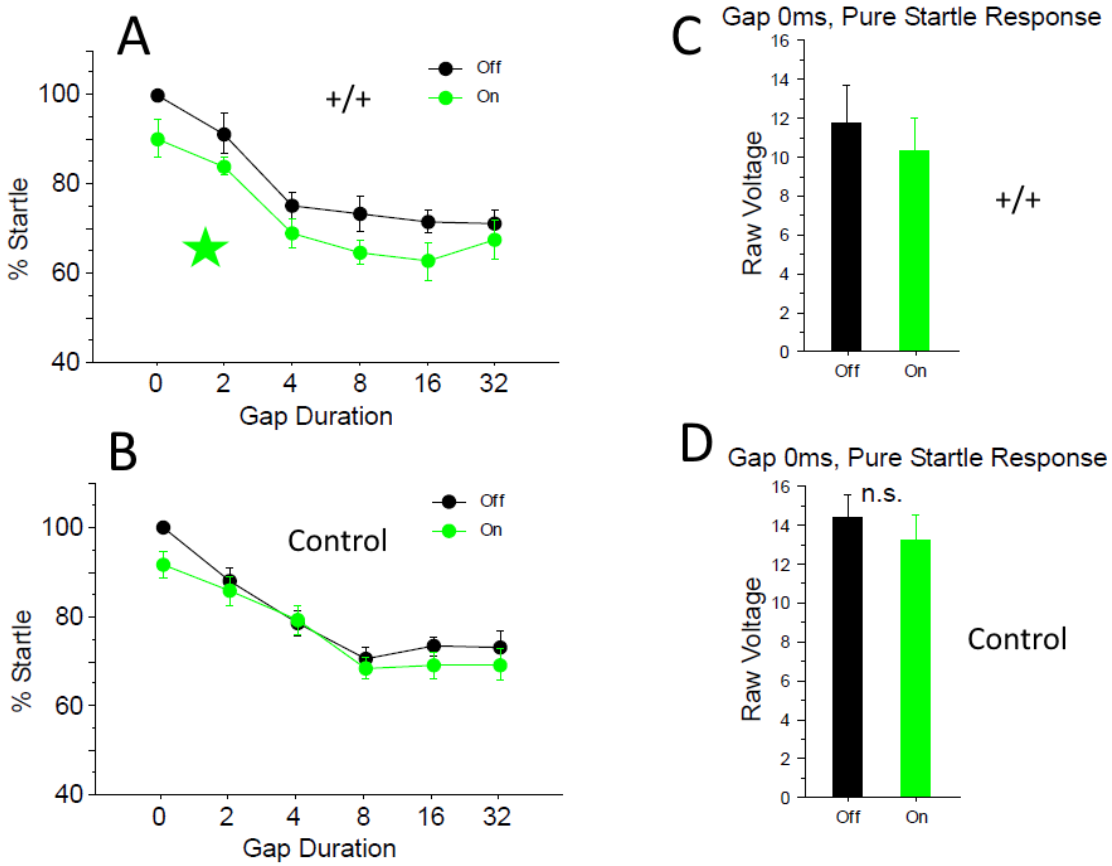

Figure 7. Arch x Gpr26 L5 pre-gap suppression with raw voltage data.

A) Behavioral trials with post-gap optogenetic suppression active (green) show significantly attenuated startle (enhanced gap detection) compared with trials without optogenetic suppression (black) with mice double positive for Arch x Gpr26. Significance was derived from a factorial ANOVA [p=0.0456; 5 mice, 10 sessions]. **B**) Control (no Arch x Gpr26 expression) mice showed no effect [p=0.2690, 4 mice, 13 sessions]. **C-D**) Similar raw voltage data of 0ms gap duration startle for suppression on/off explain the unexpected difference in % startle at 0ms gap duration for figures 7A-B

Gap detection in the control mice was unaffected by suppression during the post-gap or pre-gap interval as expected (Figures 6B, 7B).

NR5A (layer 4 PNs)

In the behavioral trials, Arch x NR5A mice showed significant differences in startle amplitude for pre-gap optogenetic suppression compared to absence of suppression. Suppressing layer four PNs during the post-gap interval had no significant effect on the startle response (Figure 8A).

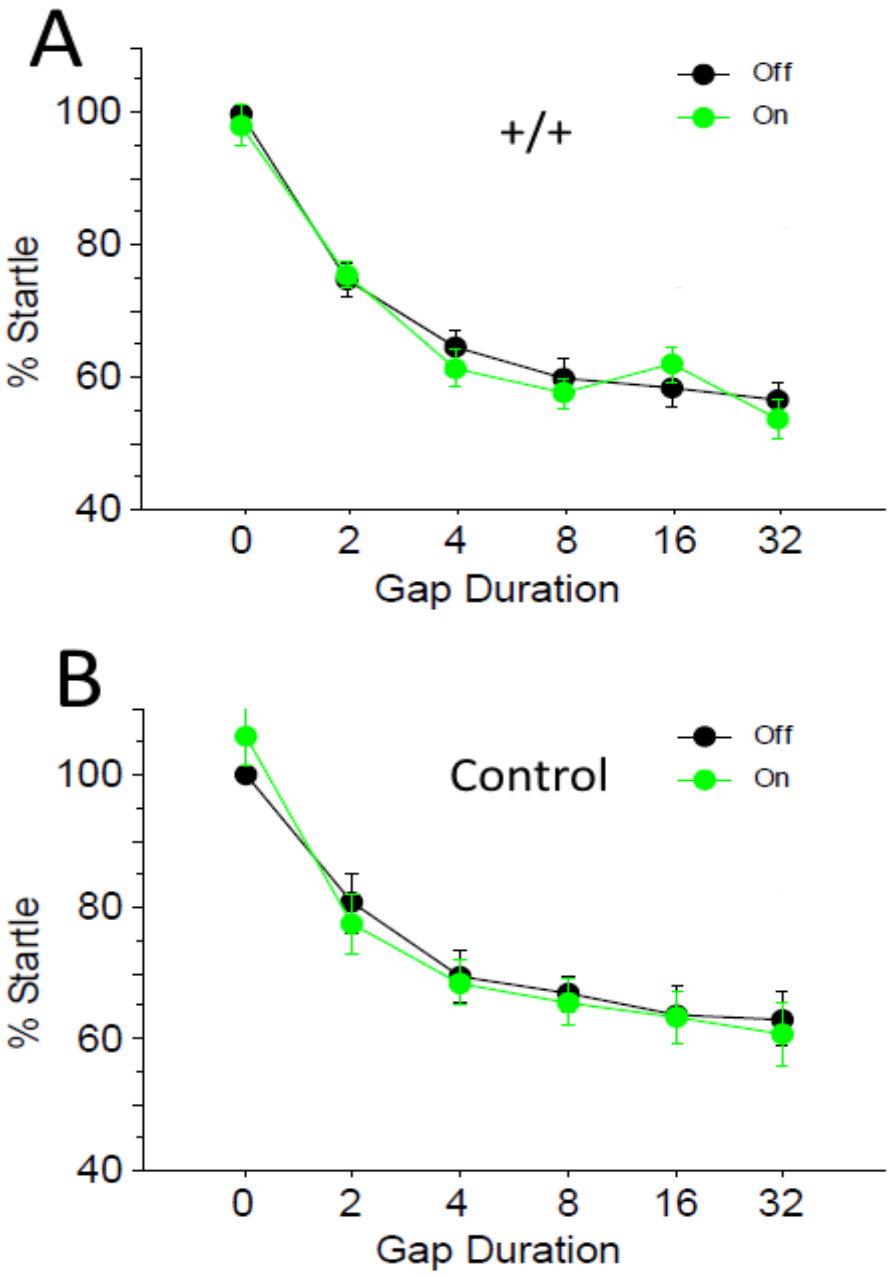

Figure 8. Arch x NR5A L4 post-gap suppression.

A) Behavioral trials with post-gap optogenetic suppression active (green) showed no effect on startle compared to trials without optogenetic suppression (black) with mice double positive for Arch x NR5A [p= 0.6987; 7 mice, 22 sessions]. B) Control mice (no Arch x NR5A expression) also showed no effect [p=0.9428, 4 mice, 14 sessions].

Suppressing layer four PNs during the pre-gap interval significantly attenuated the startle responses following gaps, most notably for gap durations 2ms and 32ms, indicating enhanced gap detection (Figure 9A). Gap detection in the control mice was unaffected by suppression during the post-gap or pre-gap interval as expected (Figure 8B, 9B).

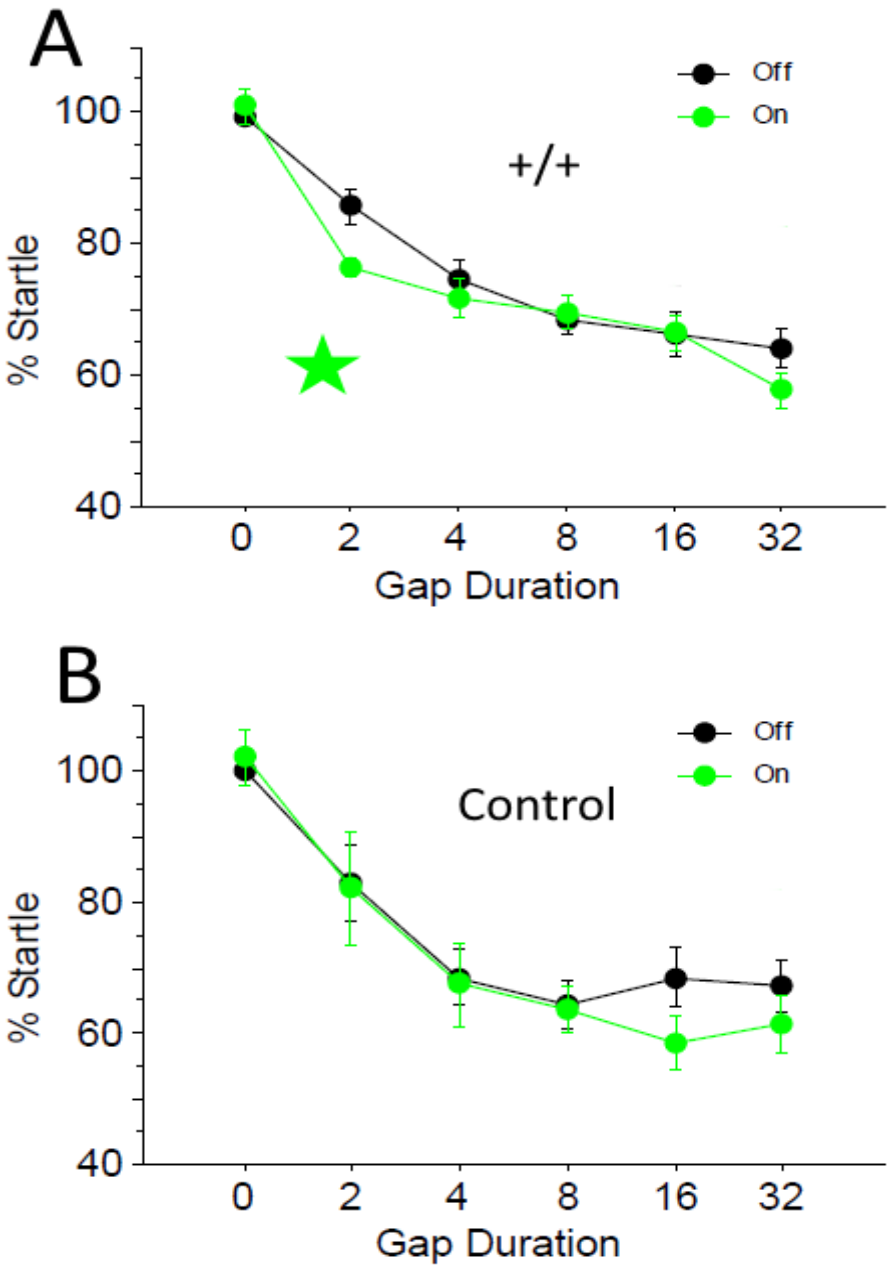

Figure 9. Arch x NR5A L4 pre-gap suppression.

A) Behavioral trials with post-gap optogenetic suppression active (green) show significantly attenuated startle (enhanced gap detection) compared with trials without optogenetic suppression (black) with mice double positive for Arch x NR5A. Significance was derived from a repeated measures ANOVA. [p=0.0266; 7 mice, 29 sessions]. **B**) Control mice (no Arch x NR5A expression) showed no effect [p=0.5955, 4 mice, 10 sessions].

Discussion

Gap detection acts as a model of speech perception in that the detection of brief noise gaps is analogous to the discrimination of phoneme peaks in speech. Perceptual gap detection is mediated by the auditory cortex GTR, so knowledge of the cortical circuit is necessary to understand exactly how the auditory cortex is involved in mediating temporal processing. Here, I built upon previous studies that looked at the influence of optogenetic suppression of CaMKII-expressing PNs in all layers of auditory cortex on gap detection [28]. For this study, I used layer-specific optogenetic suppression of cortical PNs to further elucidate the influence of individual neuron layers on gap detection.

My data for optogenetic suppression with Arch of Gpr26-expressing layer five PNs in mice gave similar results as those in previous studies of the suppression of widespread CaMKII-expressing PNs [28]. Startle response was increased by suppression during the post-gap interval, and startle response was attenuated by suppression during the pre-gap interval. For optogenetic suppression with Arch of NR5A-expressing layer four PNs in mice, startle response was unaffected by suppression during the post-gap interval. Similar to layer five suppression, startle response was attenuated by suppression during the pre-gap interval for layer four, but the attenuation was less significant except for on gap durations 2ms and 32ms (Table 2). This does not support the serial canonical circuit model, which predicts that both layer neuron populations are equally necessary for gap detection.

	Post-gap Suppression	**Pre-gap Suppression**
		
Gpr26 (Layer 5)	Increases Startle	Decreases Startle
NR5A (Layer 4)	No Observed Effect	Decreases Startle
Effect on Gap Detection	Reduced Gap Detection	Enhanced Gap Detection

Table 2. Behavioral summary by suppression protocol.

Increased startle means an absence of PPI behavior indicating that mice are not perceiving the gaps. Startle attenuation indicates typical PPI behavior that is associated with active gap detection.

These results further evidence that gap detection involves a comparison between post-gap and pre-gap neuronal activity due to the opposing effects on startle response post-gap and pre-gap suppression of layer five neurons. This is seen in the increase of the startle response caused by suppression during the pre-gap interval of layer five neurons. Suppression of the neurons at any interval would be expected to attenuate startle instead and reduce gap detection, if not for this temporal comparison process. An explanation is that an absence of recent cortical activity during the pre-gap interval strengthens the following GTR, thus increasing startle response. This “rebound effect” seen in pre-gap suppression is the result of cortex increasing post-gap activity to adjust for a lack of pre-gap activity.

For layer four neurons, the weak significance of startle enhancement for pre-gap suppression and lack of effect for post-gap suppression is unexpected. It does not fully suggest an alternative circuit pathway (Table 1), which would require no effect on gap detection with suppression for either suppression protocol, nor does it fit with the serial

conical model which would suggest that layer four and layer five neuron suppression share identical results. A likely explanation for this is that NR5A-expressing neurons do not account for the entirety of the layer four neuron population. It is possible that NR5A-expressing neurons play a specific role in the aforementioned post-gap and pre-gap neuronal activity comparisons, which might explain why only pre-gap interval suppression of NR5A-expressing neurons shows an effect. It is also possible that optogenetic suppression of more encompassing neuron populations of layer four would show results similar to layer five and support the serial canonical model of the auditory cortex circuit.

Future Directions

The next step of this study would be to repeat this experiment with other neuron populations for both layers four and five, as well as eventually layers two, three, and six. This will continue to test the canonical circuit model and paint a fuller picture of the dynamic process in auditory cortex circuit signaling. Future studies could benefit from additional suppression protocols, such as suppressing neurons across both pre-gap and post-gap intervals, and suppression only during the gap duration itself. Increasing laser intensity can also ensure greater penetrance of suppression for layer-specific neuron populations, at the risk of light leakage into other cortex layers (Figure 4). Another avenue for future studies is excitation of layer-specific neuron populations using channelrhodopsin2 to test if layered neuron populations are sufficient for gap detection. The end goal is to repeat this experiment with mice successfully trained in phoneme discrimination in order to see if optogenetic shutdown affects more nuanced forms of learning and other aspects of temporal processing.

As a preliminary foray into layer-specific optogenetic suppression of auditory cortex PNs, this study found that the results of layer four and layer five suppression were for the most part in line with the canonical circuit model and similar to previous non-layer-specific studies. However, these results are still limited in the scope of auditory cortex signaling and overlook many other possible alternative pathways to the canonical model. Further testing of other layer-specific neuron populations are necessary to determine with greater certainly if the auditory cortex follows the canonical circuit model or if alternative circuit pathways exist.

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