Dissecting the Cortical Canonical Circuit of Auditory Cortex to Understand Gap Detection

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Introduction

- Auditory cortex is necessary for brief gap detection. [1]
- Cortical spiking activity during the post-gap interval is critical for attenuating startle reflex. [1]
- Goal: How does information flow through cortex to facilitate gap detection (Fig. 1).

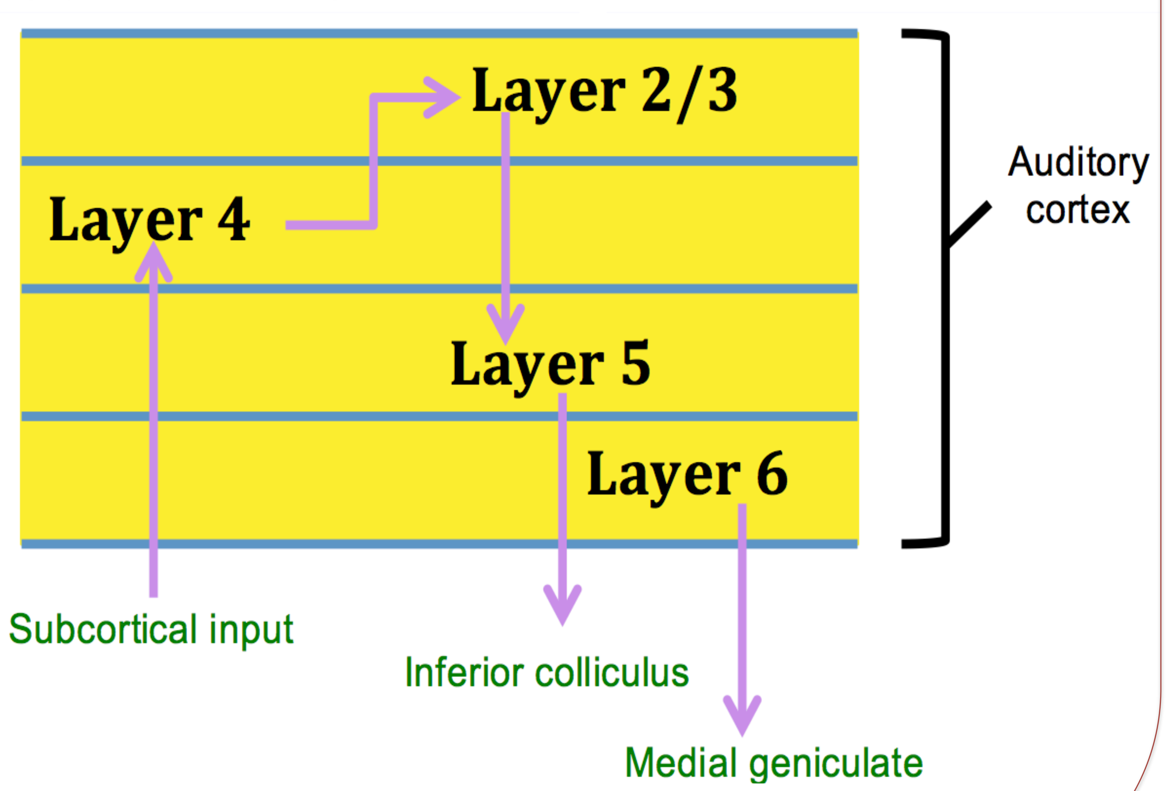


Figure 1. Simple micro-canonical circuit with input and output layers.

Methods

- Used two cre-dependent lines expressing in different cell populations: NR5A and GPR26 .
- Stimulated and suppressed principle neuron activity during the post-gap interval (PGI) via optogenetics (Channelrhodopsin (ChR2) and Archaerhodopsin (Arch)); measured startle attenuation (Fig. 2).

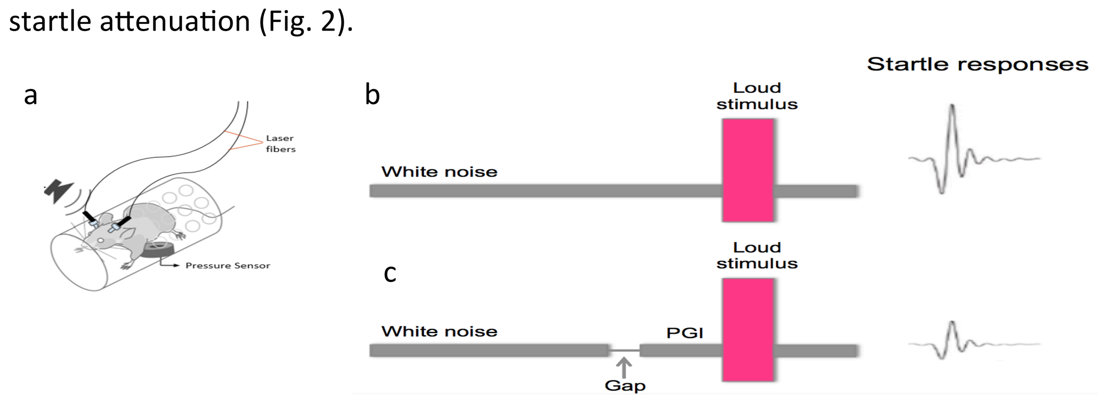


Figure 2. Behavior set-up. a) Measured startle attenuation via pressure sensor. b) Presentation of a loud stimulus during 80dB white noise. c) Inserted a short gap 50ms before the loud stimulus. Insertion of gap leads to increased cortical activity during PGI, corresponding to smaller startle response.

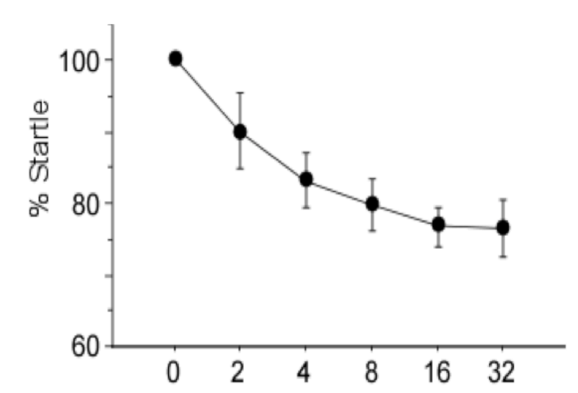


Figure 3. Decreased startle response with increased gap length.

- Anatomy studies done by taking coronal sections of brain for the cre-dependent lines (Fig. 4)

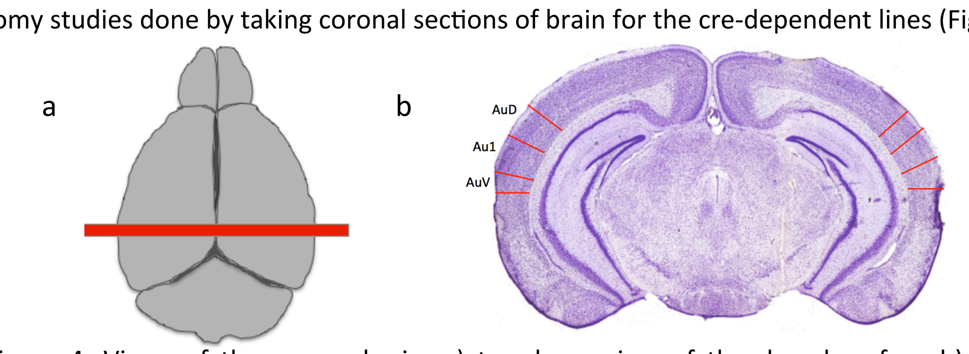


Figure 4. Views of the mouse brain. a) top-down view of the dorsal surface b) coronal section through the brain including auditory cortex. Red bar in panel a illustrates position of section in panel b. Red sections in panel b represent dorsal (AUD), primary (Au1) and ventral (AuV) auditory cortex.

- Compared laminar distributions of cre-positive cells and endogenous output neurons labeled using fluorescent-retrobead injections in inferior colliculus and medial geniculate, the two major outputs of auditory cortex.
- Cells were quantified from both hemispheres.

Results

Behavior

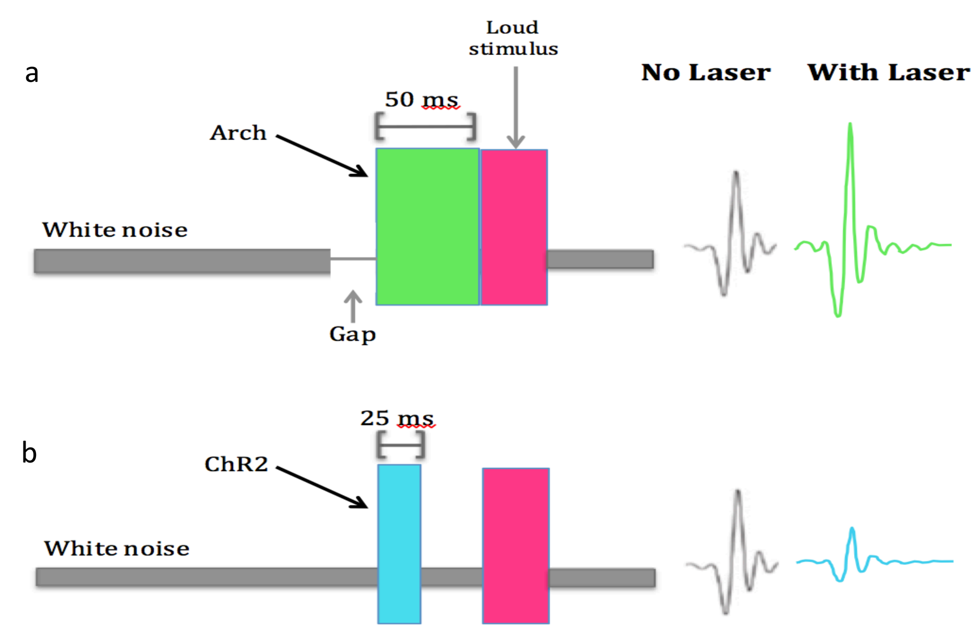


Figure 5. Expected startle responses to optogenetic manipulation. a) cortical neuron inhibition with Arch (green laser) b). cortical neuron stimulation with ChR2 (blue laser)

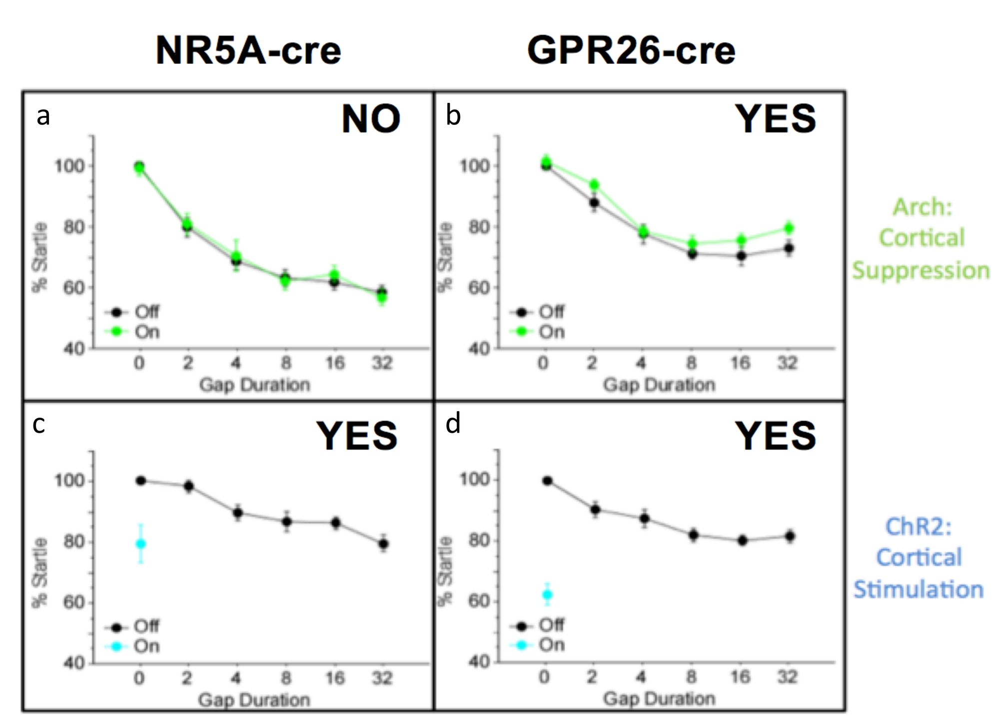


Figure 6. Effects of stimulation (ChR2) or inhibition (Arch) of cortical cells. a) No change in startle attenuation in NR5A inhibition; b) decreased startle attenuation in GPR26 inhibition; c-d) increased startle attenuation with phantom gap. Cortical stimulation attenuates the startle as if a long gap has been presented, an effect we refer to as Phantom Gap detection.

Anatomy

- Cell expression of NR5A and GPR26 line are mostly non-overlapping (Fig. 7).

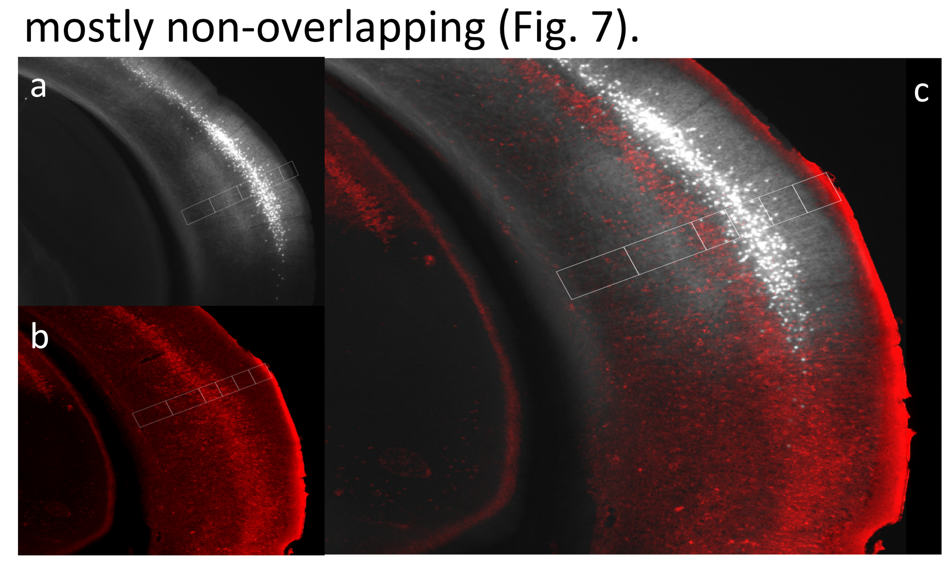


Figure 7. Expression of cre-positive lines. a) NR5A x AI14 cell population expression, layer 3; b)GPR26 x AI14 cell population expression, layer 4; c) Overlap of NR5A and GPR26, non-overlapping.

- Principle neuron projection (Fig. 8).

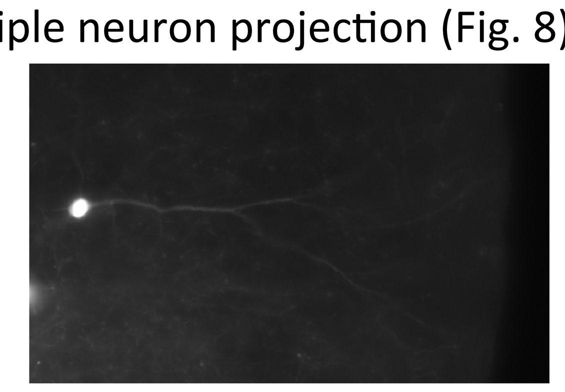


Figure 8. Projection of principle neuron in NR5A to superficial layers.

- We partitioned auditory cortex into sublamina for quantification (Fig. 9)

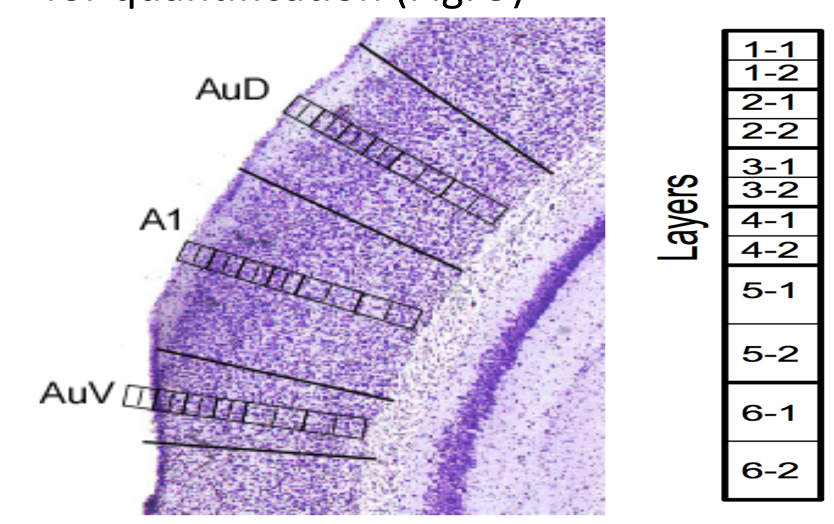


Figure 9. Division of auditory cortex and quantification of cells[2]

- Penetrance of NR5A and GPR26 cell lines show GPR26 expressed deeper in the auditory cortex than NR5A (Fig. 10)

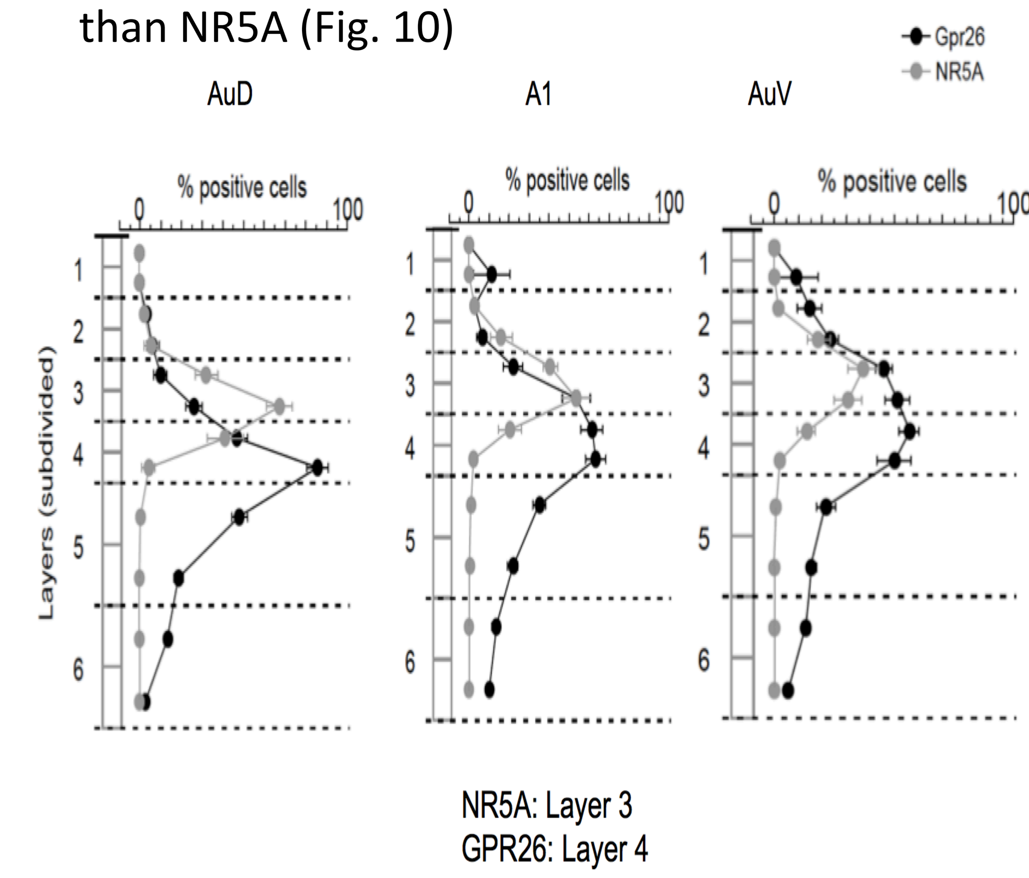


Figure 10. Penetrance of NR5A and GPR26 cell lines. Across auditory cortex, NR5A is more superficial than GPR26. Additionally, there is incomplete penetrance of principle neurons.

- Retrograde transport from inferior colliculus (IC) and medial geniculate (MG) to the output layers of auditory cortex show layer 5 output to IC and layer 6 output to MG.

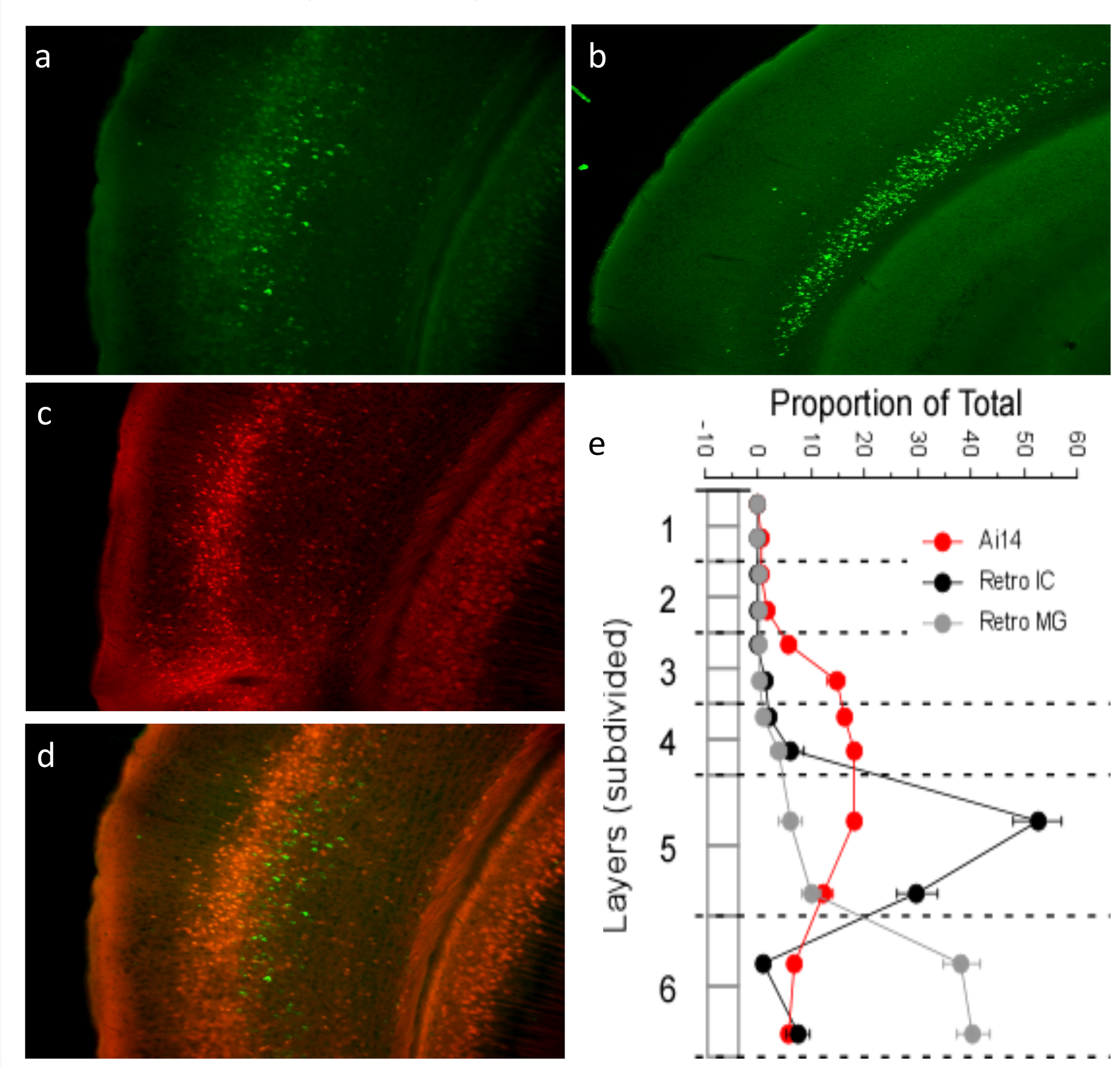


Figure 11. Retrobead projections from IC (a) and MG (b); c) GPR26 cell population expression; d) overlap IC retrobead and GPR26; IC receives output mostly from layer 5, MG receives output mostly from layer 6.

Conclusion

- Stimulation of cortical neurons mimics gap detection, the Phantom Gap effect.
- Inhibition of cortical neurons decreased gap detection in GPR26 line but not NR5A line.
- GPR26 found to be predominantly layer 4 input line and NR5A is layer 3.
- No change in startle attenuation in NR5A may be due to incomplete penetrance or no involvement of this population in the gap detection circuit.

Future Directions

- Determine how single neurons respond to gaps.
- Further break down of circuit by analyzing different cell populations.
- Further behavior studies by linking gap detection with a behavioral task for mice to perform to see what the mice are perceiving (Fig. 12).

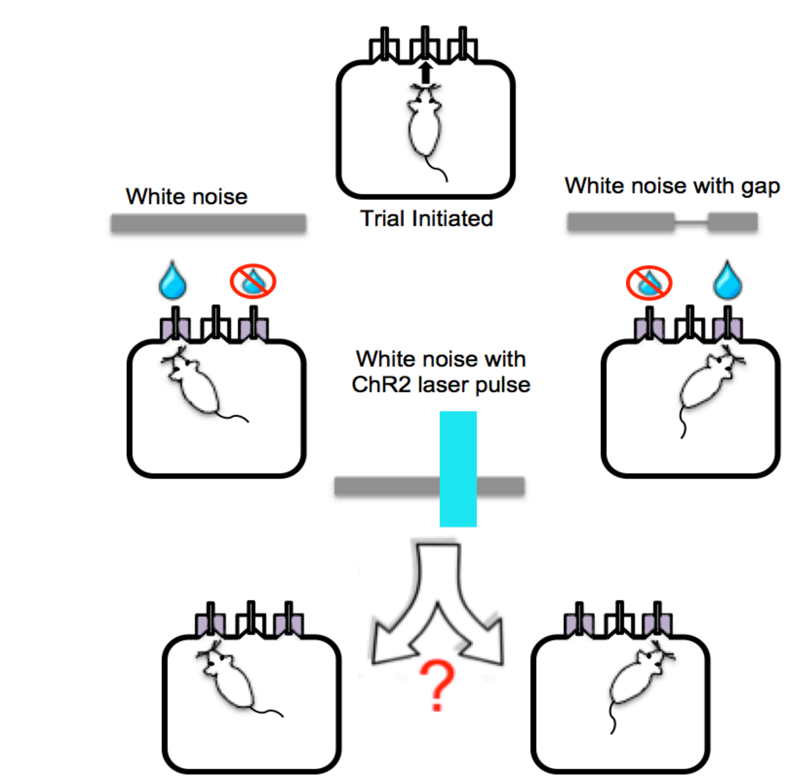
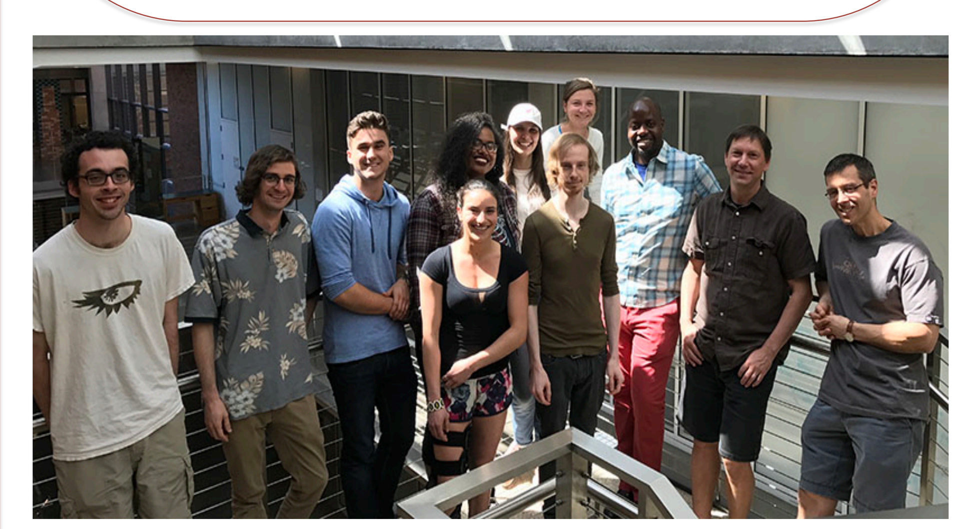


Figure 12. Trial initiates when mouse presses center port. A 500ms burst of white noise plays. If there is no gap in burst of noise, mouse goes to left to get water reward. If there is a gap and mouse perceives gap, mouse should go to right for water reward. If mouse goes to wrong port, no water is given. Will cortical stimulation in the ChR2 cross, eliciting the Phantom Gap effect, elicit behavioral gap detection?



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References

1. Weible, A., Moore, A., Liu, C., deBlander. L., Wu, H., Kentros, C., Wehr, M.2014. Perceptual Gap Detection is Mediated by Gap Termination Responses in Auditory Cortex. *Curr. Bio.* 24(13):1447-55.
2. Anderson, L.A., Christianson, G.B., Linden, J.F. 2009. Mouse auditory cortex differs from visual and somatosensory cortices in the laminar distribution of cytochrome oxidase acetylcholinesterase.1252: 130-42.