Discovery of Somatotopy within the Inferior Colliculus: Implications for a New Tinnitus Treatment

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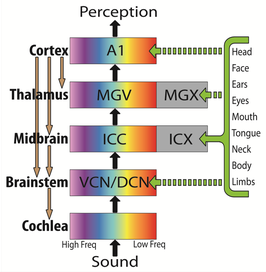
Introduction

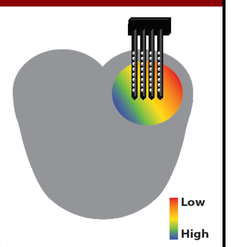
Tinnitus affects about 250 million people worldwide and is debilitating for about 1% of the world population[1]. Modulating neural activity in the central auditory pathway could alter abnormal firing patterns linked to tinnitus (hyper-synchrony, hyperactivity, altered spiking patterns), potentially suppressing the tinnitus percept[2]. The inferior colliculus (**IC**), particularly its external region (**ICX**), serves as a multimodal integration center in the auditory system with known projections from the somatosensory, visual, and limbic systems[3-8]. Somatosensory projections also modulate the auditory pathway through other auditory structures as shown below. We propose a new noninvasive tinnitus treatment utilizing multimodal integration in the IC through electrical somatic stimulation paired with acoustic stimulation to modulate neural populations with abnormal firing patterns. We call this approach Multimodal Stimulation Therapy (**MST**).



Since tinnitus is likely associated with abnormal neural patterns in only a subpopulation of neurons with locations varying between patients[9-11], one requirement for MST is for it to systematically target specific neural populations in the IC. This could be accomplished if somatotopy exists in the IC at some level. In this study, we discovered that it is possible to activate specific regions of the ICX through somatic stimulation of different body regions in guinea pigs. Additionally, activation spread can be limited through proper selection of the somatic stimulation site. We identified a systematic map across the IC showing the best stimulation site for minimal-spread activation (**MSA**) when targeting a specific IC location, which is encouraging for the implementation of MST.

Methods

Goals: (1) Determine activation threshold maps across the guinea pig IC for six different somatic stimulation sites. (2) Investigate if somatotopy exists in the IC and determine which of the six somatic sites will activate each IC recording site with minimal activation spread.



Recording Electrode Placements: A 4-shank electrode array (eight recording sites per shank, 200 µm site spacing, 500 µm shank spacing, NeuroNexus Technologies) was repeatedly inserted vertically into the IC of six ketamine-anesthetized guinea pigs in a grid-like fashion such that the shank positions spanned the IC at a 2-D spacing of 500 µm. For each animal, the order of placements was randomized (e.g. rostral to caudal for one animal and caudal to rostral for another). IC borders were determined from acoustic-driven response patterns[12].

Stimulation Paradigm: Six subdermal needle electrodes were placed in the neck, left and right shoulders, back, and left and right hind legs of the animal. Distance ratios between joints were used to ensure consistent electrode placements between animals. For each recording electrode placement, 50 trials of electrical somatic stimulation (110-710 µA in 2 dB steps for 10 total levels, 205 µs per phase pulse) were performed for each somatic stimulation site at each current level. 50 trials of spontaneous activity were also recorded, and all 3050 trials were randomized.

Activation Threshold Determination: Signal detection theory was used to determine the lowest current level that resulted in significant spike activity (d'=1) for each somatic stimulation site at each IC recording site.

IC Reconstruction: Histology was performed to pinpoint electrode placement in the right IC[13]. Electrode arrays were stained with red fluorescent dye (Di-I; Sigma-Aldrich) prior to placement, leaving fluorescent trace marks. The right IC was then cryosliced into 60 µm thick sagittal slices. Fluorescent and brightfield images of the slices were traced and aligned to generate 3-D IC models.

Acknowledgments

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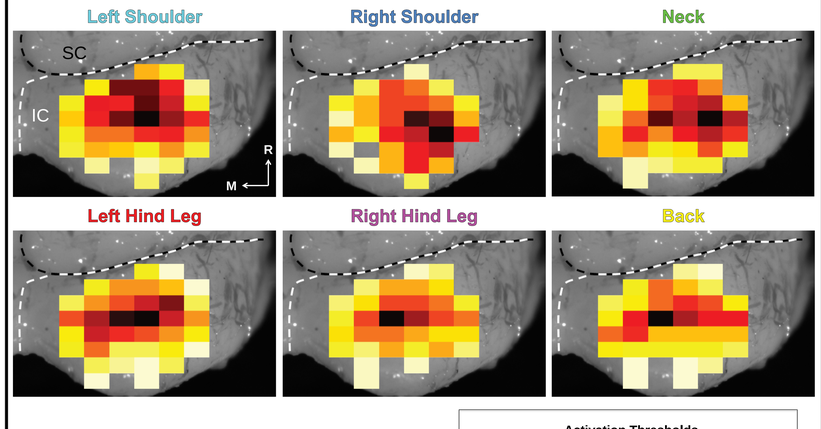
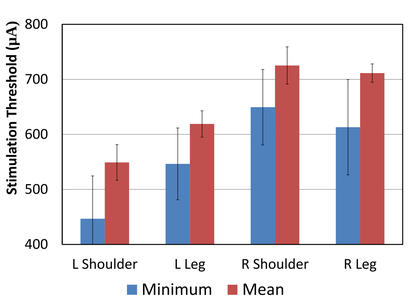
[1] American Tinnitus Association. *http://www.ata.org/research/resources-researchers.*
[2] Moller, AR, et al. *Textbook of Tinnitus,* 2011.
[3] Huffman, RF, et al. *Brain Res Rev,* 15:295-323, 1990.
[4] Gruters, KG, et al. *Front Neural Circuits,* 6:96, 2012.
[5] Schofield, BR, et al. *Hear Res,* 279:85-95, 2011.
[6] Aitkin, LM, et al. *J Comp Neurol,* 196:25-40, 1981.
[7] Winer, JA, et al. *Hear Res,* 212:1-8, 2006.
[8] Marsh, RA, et al. *J Neurosci*, 22:10449-60, 2002.
[9] Ma, WL, et al. *Hear Res,* 212:9-21, 2006.
[10] Bauer, CA, et al. *J Neurosci Res,* 86:2564-78, 2008.
[11] Eggermont, JJ, et al. *Trends Neurosci,* 27:676-82, 2004.
[12] Lim, HH, et al. *J Neurosci,* 27:8733-43, 2007.
[13] Markovitz, CD, et al. *Front Neural Circuits,* 6:39, 2012.

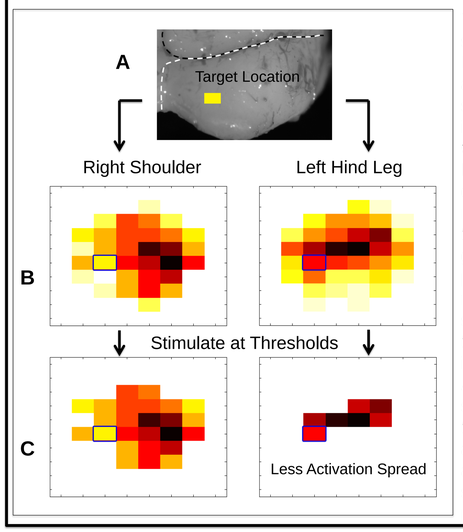
Somatotopy and Activation Analysis

For each IC recording site, the activation threshold for each somatic stimulation site was determined. 3-D reconstructions of the IC revealed the location of each electrode placement, and activation threshold maps were plotted for each somatic stimulation site. For a simpler visualization of the maps, the lowest threshold of the eight recording sites along a given shank was used to represent that shank location. These thresholds were then averaged across all six animals to create one 2-D threshold map for each somatic stimulation site (shown below). The caudal portion of the superior colliculus (**SC**) is also shown in each plot for reference.



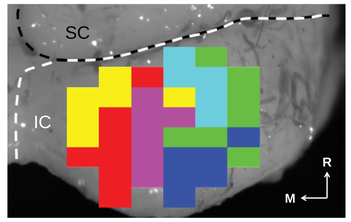


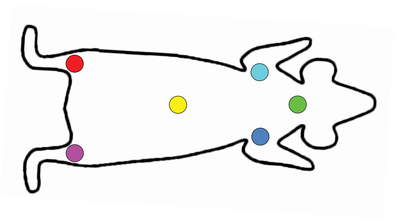
For each map, the darkest color represents the minimum threshold across all recording locations for the given somatic stimulation site. These thresholds are illustrated in the bar graph to the left, along with the mean thresholds across all activated recording sites, for four stimulation sites. Interestingly, left body locations demonstrated lower thresholds than right body locations. This indicates the prevalence of contralateral somatic projections over ipsilateral projections into the IC.



The threshold maps above reveal some somatotopic organization within the IC. However, there is significant overlap in activity across the IC for different somatic sites. For the success of MST, we are interested in activating a given IC location with minimized activation elsewhere in the IC. For a given recording location, we determined what percentage of other recording locations across IC had activation thresholds at or below the threshold for a given somatic stimulation site. This percentage indicates the fraction of recording locations that are activated if this somatic stimulation site is used to activate the desired recording location. For example, if the target recording location is indicated in **A**, and **B** shows the activation maps of two somatic stimulation sites for that location, then **C** shows which IC locations will be activated if the target recording location is activated at its threshold for each somatic stimulation site. For data analysis, we performed this with all six stimulation sites.

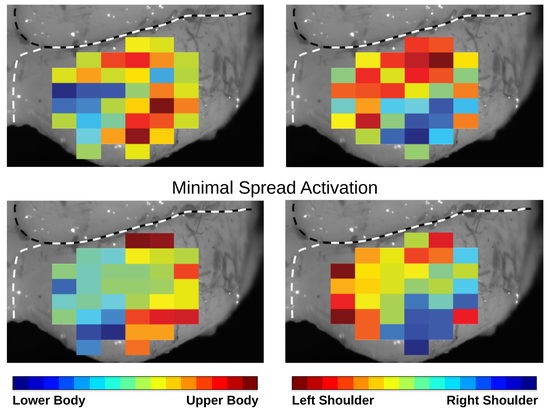
Minimal-Spread Activation Maps





In the above MSA map, each IC recording location is represented by the best stimulation site that induced responses with minimal activation spread. In general, recording sites with the same best stimulation site are localized to a specific area of the IC. Additionally, somatic groups of recording sites seem to be organized in groups of similar somatic locations (e.g. locations which respond to neck stimulation are near those which respond to stimulation of the shoulders). There are also trends corresponding to left-to-right and upper-to-lower body representations.

The figures below compare upper body vs. lower body stimulation (left figures) and left shoulder vs. right shoulder stimulation (right figures). The top figures show differences in thresholds and the bottom figures show differences in the activation spread as calculated for the MSA figure above. For example, for the upper left figure, we identified the lowest threshold across all upper body sites (neck and shoulders) and the lowest threshold across all lower body sites (back and hind legs) for each IC location. We then took the differences in these thresholds for all IC locations and used them to generate the colormap in which the colors represent the somatic region that had a lower threshold (less activation spread for lower figures). This method more clearly reveals the somatotopic organization across the IC. Upper body regions have more significant projections to lateral IC locations while lower body regions to medial locations, and the right shoulder region has more significant projections that are caudolateral to those of the left shoulder. In short, a map of the body of the guinea pig appears to be superimposed onto the IC in a head-to-toe orientation from the rostro-lateral to the caudomedial direction. These trends are also apparent in the six threshold maps shown in the Somatotopy and Activation Analysis section.



Conclusions

We have discovered somatotopy in the guinea pig IC. Despite significant overlap in IC responses between somatic stimulation sites, it is possible to active a specific IC location while minimizing activation of other IC locations by appropriately selecting the stimulation site. Since we only investigated six somatic sites, even greater localization might be possible if more somatic sites are used. Based on the MSA results, it may be possible to adjust the timing of stimulation of multiple somatic sites to activate a specific IC location in a synchronized manner while only activating other locations in a temporally diffuse and weak pattern. Interestingly, contralateral somatic projections are more prevalent than ipsilateral projections to the IC. This is expected since most somatic sensory fibers decussate in the spinal cord and medulla before they reach the midbrain.

Clinically, our findings are encouraging for MST as a treatment for tinnitus. Somatotopic organization in the IC provides the opportunity to specifically modulate multimodal neurons and potentially fix pathogenic auditory populations that could be driving the tinnitus percept. Future studies must evaluate how to systematically stimulate across multiple somatic locations to sufficiently alter abnormal auditory activity and suppress tinnitus. Since somatic stimulation can be achieved with noninvasive and inexpensive stimulators, MST could be tested directly in patients.