PROCEEDINGS of the
23rd International Congress on Acoustics

9 to 13 September 2019 in Aachen, Germany

Reversing degraded auditory processing using targeted plasticity

Yuko TAMAOKI[1], Jonathan R RILEY[1], Michael S BORLAND[1], Seth A HAYS[1], Crystal T ENGINEER[1], Michael P KILGARD[1]

[1] The University of Texas at Dallas, United States

ABSTRACT

Hearing loss is a very common and often debilitating neurological disorder, estimated to affect over 5% of the population. A major source of disability related to hearing loss stems from deficits in speech processing. Assistive devices, such as hearing aids, can yield modest improvements in speech perception, but these devices often provide inadequate utility in complex, challenging environments. We have developed a new approach to drive robust, specific plasticity that substantially enhances recovery after neurological damage. This strategy uses brief bursts of vagus nerve stimulation (VNS) paired with sound presentation. Like humans, rats are significantly impaired in their ability to accurately discriminate speech sounds following intense noise exposure. Additionally, noise trauma results in substantial maladaptive plasticity in multiple auditory structures. In these experiments, we test the hypothesis that VNS paired with sound therapy, 300 times per day for 20 days, will reverse maladaptive plasticity and restore auditory processing. Following the last day of VNS-sound pairing, the reversal of maladaptive plasticity is tested through behavioral discrimination ability, auditory brainstem responses (ABR), and auditory cortex responses. The successful development of adjuvant therapies to restore speech processing has real potential to yield tangible benefits for millions suffering from hearing loss.

Keywords: Vagus nerve stimulation, NIHL, Plasticity

1. HEARING LOSS

1.1 Hearing loss in humans

Hearing loss is the second most debilitating neurological disability. Hearing loss commonly affects many patient populations, including members of the military, children, and aging individuals (1). Patients with hearing loss exhibit abnormal neural activation in both cortical and subcortical regions of the auditory pathway (2–4). The abnormal neural activity seen in the auditory pathway affects patients' ability to hear and understand speech sounds (5). Maladaptive plasticity in the auditory network contributes to the abnormal neural activity that degrades information and impairs speech perception ability. Fortunately, through recent technologies and innovations, multiple forms of therapeutic interventions have been made available for individuals with hearing loss. However, devices such as hearing aids can sometimes only provide modest improvement in speech perception abilities.

1.2 Hearing loss in animal models

Animal models of hearing loss exhibit abnormal neurological activity and a degradation of auditory discrimination abilities (6–9). In auditory cortex, the normal orderly tonotopic map observed in experimentally naïve animals is reorganized and degraded in noise-exposed animals (7,10,11). In primary auditory cortex, rats exposed to intense noise (125 dB 1-octave band noise centered at 4 kHz) had significantly degraded responses to sound compared to non-exposed control animals (Figure 1). Moderate intensity noise-exposed animals (115 dB 1-octave band noise centered at 16 kHz) did not display significant differences in primary auditory cortex tonotopy compared to non-exposed control animals (Figure 1). This reorganization is due to maladaptive plasticity that alters neural responses due to a lack of inhibition. Similar aberrant neural responses have been observed subcortically in the inferior colliculus. These response changes in the inferior colliculus are due to hyperactivity of

[1] yxt170130@utdallas.edu

neurons, which is an effect similar to the changes observed in auditory cortex (12,13). Maladaptive plasticity in the auditory network is seen across species with hearing loss.

Hearing loss also affects the ability of animals to discriminate between human speech sounds (7). Cortical changes and behavioral changes were observed in animals noise-exposed at multiple sound frequencies and intensities (14). Rats who experienced intense noise exposure were unable to discriminate between speech sounds differing in consonant or vowel following 2 weeks of re-training. The moderate noise exposure group, however, had an initial decrease in speech discrimination ability that was able to recover. The moderate noise exposure rats fully recovered to baseline performance levels after 2 weeks of re-training. This purpose of the current study is to target maladaptive plasticity in order to recover speech discrimination ability in rats who have been exposed to more intense noise exposure parameters.

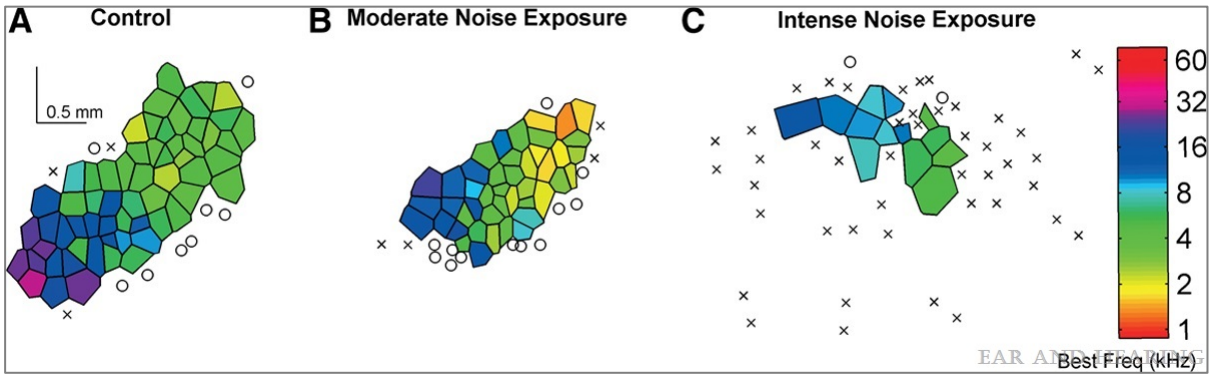

Figure 1. Moderate and intense noise exposure altered the tonotopic organization of responses in the primary auditory cortex. Each polygon represents a single electrode penetration into the auditory cortex. The color of the polygon represents the characteristic frequency of each penetration. Sites marked with an "o" were assigned to fields other than A1; sites marked with an "x" were classified as nonresponsive to tones. Reproduced with permission from (15).

2. VNS-SOUND PAIRING IMPROVES AUDITORY PROCESSING

Vagus nerve stimulation (VNS) paired with a sensory event releases neuromodulators involved in plasticity, including acetylcholine, norepinephrine, and serotonin, activates the neural regions that respond to the sensory event (16). For example, when VNS is paired with a tone, the proportion of primary auditory cortex that responds to the paired tone frequency is increased (10,11,17–19). Similarly, when VNS is paired with speech sounds, there is an increase in the A1 response strength to the paired speech sounds (20). Likewise, VNS paired with fast or slow tone trains can increase or decrease the primary auditory cortex response strength to rapid sounds (21). VNS can alter both the spectral and temporal aspects of the neural response to sound in primary auditory cortex.

VNS paired with tones has also been examined in a rat model of tinnitus in order to improve the degraded auditory processing observed in this model (10). These rats were exposed to 16 kHz noise at 115 dB, and one month after noise exposure, the Turner gap detection method was used to identify the perceived tinnitus frequency of each rat. VNS was paired with multiple tone frequencies that were distinct from the perceived tinnitus frequency, 300 times per day for 20 days. Both the behavioral and neural effects of noise exposure were reversed following one month of VNS-tone pairing. This VNS-tone therapy, which was first tested in a rat model of tinnitus, has recently been shown to provide long-lasting improvement in tinnitus intensity and tinnitus distress in chronic tinnitus patients (22–24).

3. VNS-SOUND PAIRING IN A RAT MODEL OF HEARING LOSS

Based upon the success of these previous studies, the objective of the current study is to test the ability of VNS paired with the presentation of sounds to enhance the precision of spared auditory inputs and substantially improve speech processing in noise-exposed rats. Rats received an auditory

brainstem response (ABR) recording prior to noise exposure to test the hearing (Figure 2). Groups of rats were noise exposed to different intensity-frequency noise combinations for one hour. The intensity of the noise exposure ranged from 115 to 125 dB SPL and the center frequency of the 1 octave band-passed noise ranged from 4 to 22 kHz. Following a one-month break, rats received a vagus nerve cuff and ABR to assess hearing loss from noise damage. In short, the VNS implantation procedure involved placing a chronically implanted bipolar cuff electrode around the left cervical branch of the vagus nerve. Subcutaneous leads were routed to a stimulator interface on the skull. The rats received 300 VNS-sound pairing presentations per day over 20 days. VNS stimulation parameters for the VNS-sound paring sessions were 500 ms bursts of 100 us biphasic pulses with 33 ms between pulses at an amplitude of 0.8 mA. The VNS stimulation occurred at the same time that the sounds were presented. The sounds paired with VNS stimulation were either speech sounds shifted into the rat hearing range or tones spanning the rat's hearing range. Following the last day of VNS-sound pairing therapy, in a manner consistent with prior experiments (15), physiological recordings were acquired from the right auditory cortex and inferior colliculus of noise induced hearing loss animals. Tungsten microelectrodes were used to record multiunit responses from the respective fields to a variety of sound stimuli including tones spanning 1-32 kHz from 0 to 85 dB SPL, speech stimuli (both novel and VNS-paired sounds), and noise burst trains.

The rats' neural responses and ABRs varied from group to group depending on what noise exposure they received. Rats who received noise exposure at 115 dB SPL had less cortical reorganization compared to rats who received more intense noise exposure at 120 dB SPL and higher (Figure 3). Rats receiving higher frequency noise exposure preserved more neural responses than the group of rats receiving lower frequency exposure. Noise exposure intensity and sound frequency influenced the preservation of cortical responses. A similar pattern of response preservation was observed in the ABRs of the different exposure groups (Figure 4).

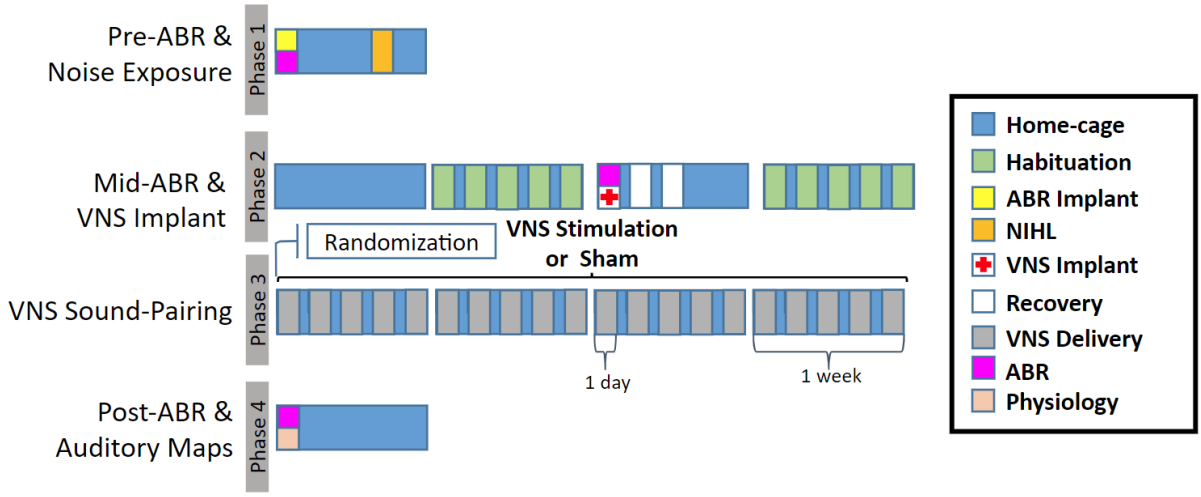

Figure 2. Study timeline: Auditory brainstem responses (ABR) were collected prior to the induction of noise induced hearing loss, following noise induced hearing loss, and following VNS-sound pairing. Approximately 1 month after noise induced hearing loss, animals received 20 days of VNS-sound pairing. Following VNS-sound pairing neural responses were collected from the primary auditory cortex and the inferior colliculus.

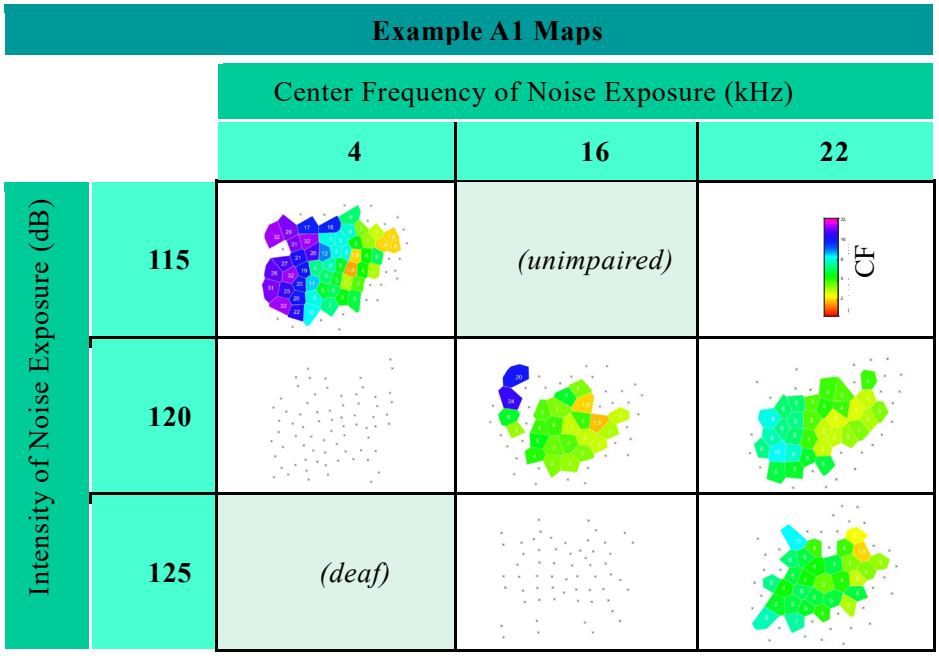

Figure 3. Example maps from the primary auditory cortex of animals with noise induced hearing loss. Noise exposures were conducted for one hour to 1-octave band-passed noise centered on 4, 16, or 22 kHz. The intensity of the sound was either 115, 120, or 125 dB SPL. Animals were not exposed to 16 and 22 kHz noise at 115 dB SPL nor to 4 kHz at 125 dB. Each polygon represents a single electrode penetration into the auditory cortex. The color of the polygon represents the characteristic frequency of each penetration. Sites marked with an "x" were classified as nonresponsive to tones.

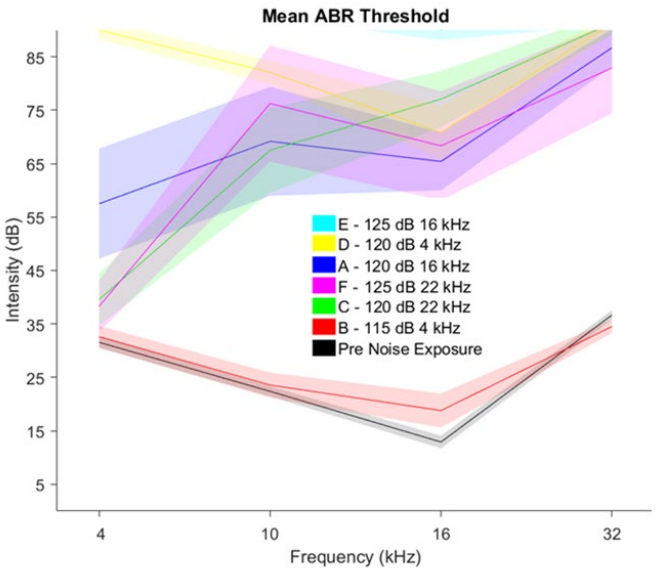

Figure 4. Mean ABR thresholds following noise exposure but prior to VNS-sound pairing.

4. CONCLUSIONS

Noise induced hearing loss degrades both neural and behavioral auditory processing. While auditory training can improve neural and behavioral auditory processing in some rat models of hearing loss, it can be insufficient to restore auditory processing in other more intense noise exposure models. Ongoing work involves pairing vagus nerve stimulation with sound presentation in rat models of hearing loss to improve both sound discrimination ability and the neural processing of sounds.

ACKNOWLEDGEMENTS

The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office. This work was supported by the Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, through the FY17 Hearing Restoration Research Program/Translational Research Award under Award No. W81XWH-18-1-0399. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense. In conducting research using animals, the investigator(s) adheres to the laws of the United States and regulations of the Department of Agriculture.

REFERENCES

1. Yankaskas K. Prelude: noise-induced tinnitus and hearing loss in the military. Hear Res. 2013 Jan;295:3–8.
2. Melcher JR, Sigalovsky IS, Guinan JJ, Levine RA. Lateralized Tinnitus Studied With Functional Magnetic Resonance Imaging: Abnormal Inferior Colliculus Activation. J Neurophysiol. 2000;83(2):1058–72.
3. Ghazaleh N, Zwaag W van der, Clarke S, Ville D Van De, Maire R, Saenz M. High-Resolution fMRI of Auditory Cortical Map Changes in Unilateral Hearing Loss and Tinnitus. Brain Topogr. 2017;0(0):0.
4. Smits M, Kovacs S, de Ridder D, Peeters RR, van Hecke P, Sunaert S. Lateralization of functional magnetic resonance imaging (fMRI) activation in the auditory pathway of patients with lateralized tinnitus. Neuroradiology. 2007 Aug;49(8):669–79.
5. Moore BCJ. The role of temporal fine structure processing in pitch perception, masking, and speech perception for normal-hearing and hearing-impaired people. J Assoc Res Otolaryngol. 2008 Dec;9(4):399–406.
6. Kimura M, Eggermont JJ. Effects of acute pure tone induced hearing loss on response properties in three auditory cortical fields in cat. Hear Res. 1999;135(1–2):146–62.
7. Reed AC, Centanni TM, Borland MS, Matney CJ, Crystal T, Kilgard MP, et al. Moderate or Intense Noise Exposure in Rats. Vol. 35. 2015. 1–33 p.
8. Eggermont JJ. Animal models of spontaneous activity in the healthy and impaired auditory system. Front Neural Circuits. 2015;9(April):1–11.
9. Eggermont JJ, Roberts LE. Tinnitus: animal models and findings in humans. Cell Tissue Res. 2015;361(1):311–36.
10. Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, et al. Reversing pathological neural activity using targeted plasticity. Nature. 2011 Feb 3;470(7332):101–4.
11. Borland MS, Engineer CT, Vrana WA, Moreno NA, Engineer ND, Vanneste S, et al. The Interval Between VNS-Tone Pairings Determines the Extent of Cortical Map Plasticity. Neuroscience. 2018 Jan 15;369:76–86.

12. Wang J, Ding D, Salvi RJ. Functional reorganization in chinchilla inferior colliculus associated with chronic and acute cochlear damage. Hear Res. 2002 Jun;168(1–2):238–49.
13. Pollak GD, Xie R, Gittelman JX, Andoni S, Li N. The dominance of inhibition in the inferior colliculus. Hear Res. 2011 Apr;274(1–2):27–39.
14. Reed AC, Centanni TM, Borland MS, Matney CJ, Engineer CT, Kilgard MP. Behavioral and neural discrimination of speech sounds after moderate or intense noise exposure in rats. Neuroscience.
15. Reed AC, Centanni TM, Borland MS, Matney CJ, Engineer CT, Kilgard MP. Behavioral and neural discrimination of speech sounds after moderate or intense noise exposure in rats. Ear Hear. 2014 Jul 28;35(6):e248-61.
16. Hays SA. Enhancing Rehabilitative Therapies with Vagus Nerve Stimulation. Neurotherapeutics. 2016 Apr;13(2):382–94.
17. Buell EP, Loerwald KW, Engineer CT, Borland MS, Buell JM, Kelly CA, et al. Cortical map plasticity as a function of vagus nerve stimulation rate. Brain Stimul. 2018;11(6):1218–24.
18. Borland MS, Vrana WA, Moreno NA, Fogarty EA, Buell EP, Sharma P, et al. Cortical Map Plasticity as a Function of Vagus Nerve Stimulation Intensity. Brain Stimul. 2015 Sep 9;9(1):117–23.
19. Buell EP, Borland MS, Loerwald KW, Chandler C, Hays SA, Engineer CT, et al. Vagus Nerve Stimulation Rate and Duration Determine whether Sensory Pairing Produces Neural Plasticity. Neuroscience. 2019 Mar 20;
20. Engineer CT, Engineer ND, Riley JR, Seale JD, Kilgard MP. Pairing speech sounds with vagus nerve stimulation drives stimulus-specific cortical plasticity. Brain Stimul. 2015;8(3):637–44.
21. Shetake JA, Engineer ND, Vrana WA, Wolf JT, Kilgard MP. Pairing tone trains with vagus nerve stimulation induces temporal plasticity in auditory cortex. Exp Neurol. 2012 Jan;233(1):342–9.
22. Tyler R, Cacace A, Stocking C, Tarver B, Engineer N, Martin J, et al. Vagus Nerve Stimulation Paired with Tones for the Treatment of Tinnitus: A Prospective Randomized Double-blind Controlled Pilot Study in Humans. Sci Rep. 2017 Sep 20;7(1):11960.
23. De Ridder D, Vanneste S, Engineer ND, Kilgard MP. Safety and efficacy of vagus nerve stimulation paired with tones for the treatment of tinnitus: a case series. Neuromodulation. 2014 Feb;17(2):170–9.
24. De Ridder D, Kilgard M, Engineer N, Vanneste S. Placebo-controlled vagus nerve stimulation paired with tones in a patient with refractory tinnitus: a case report. Otol Neurotol. 2015 Apr;36(4):575–80.