Reversing degraded auditory processing using targeted plasticity

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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

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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 pairing 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.

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REFERENCES


