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Targeted neuroplasticity in rat primary auditory cortex with vagus nerve stimulation and near-threshold tones

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ABSTRACT

Vagus nerve stimulation (VNS) is a method for driving therapeutic, targeted neuroplasticity in clinical populations suffering from tinnitus and stroke. VNS facilitates specific cortical changes through the phasic release of plasticity promoting neuromodulators simultaneously paired with delivery of a sensory stimulus, such as tones or speech. Recent clinical evidence and ongoing pre-clinical experiments in rats show that VNS paired with near-threshold somatosensation of the hand/paw can significantly reduce elevated sensory thresholds resulting from neural injuries after only one week of therapy. A possible explanation for this quick and robust recovery is that VNS is more effective at driving neuroplasticity in cortical circuits when paired with stimuli just above the response threshold of neural receptive fields. To date, all auditory VNS therapies have used stimuli considerably above auditory thresholds, potentially diminishing the therapeutic effect of VNS-paired treatments. To test the effectiveness of VNS-paired, near-threshold stimuli in driving auditory neuroplasticity, unimpaired adult rats will receive VNS repeatedly paired with the brief presentation of a 10 dB SPL 9 kHz tone for one week. A cortical map of receptive field properties in primary auditory cortex will be made one day later and compared to the maps of naïve rats.

Keywords: Vagus nerve stimulation, Auditory cortex, Neuroplasticity

1. INTRODUCTION

Vagus nerve stimulation (VNS) drives phasic release of neuromodulators like norepinephrine (1), and can lead to stimulus-specific, long-term changes in auditory receptive fields when repeatedly paired with the presentation of an auditory stimulus (2–7). Pairing VNS with the presentation of a brief 9 kHz tone increases the cortical representation of 9 kHz in primary auditory cortex (A1), while pairing with a 19 kHz tone increases the representation of 19 kHz (2). Stimulus-specific plasticity has also been observed for VNS-paired speech, tone trains, and motor skill learning (3,8,9).

This ability to drive targeted neuroplasticity may enable the treatment of clinical disorders associated with maladaptive changes in neural circuitry (10,11). A VNS based tonal therapy in a rat model of tinnitus has been shown to reverse abnormal auditory processing in A1 and re-normalize behavioral correlates of tinnitus perception. The therapy consisted of repeatedly pairing VNS with the presentation of a variety of tones with frequencies surrounding (and excluding) the putative tinnitus frequency (2). A clinical trial however only found a modest improvement of VNS tonal therapy on the Tinnitus Handicap Inventory (THI) for a subgroup of chronic tinnitus patients (12). While these initial results are promising, it is expected that significant improvements in treatment can be made through the refinement of therapy design. An obvious target for further investigation is the set of tonal stimuli used during therapy, as it is unlikely that they optimally drive the necessary neuroplasticity for therapeutic benefit.

A recent case study, as well as new preclinical research, provide novel evidence that a simple change to the tonal stimulus set may enhance targeted plasticity treatment and lead to improved clinical results. During the follow-up phase of a VNS clinical trial for motor rehabilitation after stroke, a patient underwent additional tactile therapy in an attempt to ameliorate remaining sensory impairment in his hand. After only ten days of therapy, the patient had an 80% recovery in tactile threshold (13). Ongoing preclinical experiments in a rat model of sensory deficit have replicated the recovery of sensory threshold in only one week of VNS pairing (unpublished). In both cases, the tactile therapies consisted of stimuli at the threshold of sensory detection -- in effect driving activity from

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only a small subset of the neural population in primary sensory cortex. This is a key difference compared to the VNS-paired tones used in the tinnitus therapies, which were instead presented at intensities well-above auditory threshold (2,12). It is possible that pairing VNS with tones near auditory thresholds will be more effective in driving plasticity than more intense tones that already drive significant neural activity.

This study examines the effectiveness of one week of VNS paired with a near-threshold tone (9 kHz 10 dB SPL) in driving stimulus-specific plasticity in rat A1. Previous VNS tone-pairing studies have all utilized four weeks of treatment with tones well-above the rat auditory threshold (2,4–7). Therefore, it is unknown if pairing VNS with a near-threshold tone for only a single week will be sufficient to result in significant neuroplasticity of A1 in a healthy subject (as suggested by the current somatosensory results in impaired models). This is a crucial first experiment to determine the validity of potential improvements to the stimulus set of future clinical VNS-based therapies.

2. METHODS

2.1 Subjects

Seventeen age-matched, female Sprague-Dawley rats were randomly assigned to either naive (n=11) or VNS (n=6) groups.

2.2 Tone stimulus

VNS was paired with the brief presentation of a 500 ms, 9 kHz, 10 dB SPL tone. Previous studies suggest that a 9 kHz 10 dB tone recruits about 1/4 the amount of A1 (~10-15%) as a 9 kHz 50-60 dB tone (2,4–7).

2.3 Vagus nerve stimulation

VNS subjects had a custom, platinum-iridium bipolar cuff electrode implanted around the left cervical vagus nerve as described previously (2,4–7). Parameters used for stimulation were the same as previous studies (2). Briefly, a single stimulation event consisted of a 500 ms train of biphasic pulses (100 us pulsewidth) at a rate of 30 Hz and an intensity of 0.8 mA.

2.4 Pairing procedure

After recovering for seven days from cuff implantation, VNS subjects received five sessions of VNS tone-pairing (one session per day). Each session, the subject was placed into a wire cage inside of a double-walled, sound attenuated booth, 25 cm from a speaker calibrated to play a 9 kHz 10 dB SPL tone, and plugged into a stimulator by a free-hanging swivel. The 9 kHz tone was presented approximately every 30 seconds, paired temporally with a VNS event. Each session consisted of 300 pairings and lasted approximately 2.5 hours. At the end of a session, the subject was returned to her home cage.

2.5 Cortical mapping

Twenty-four hours after the last pairing session, a cortical map of the subject's A1 was made, as described previously (2,4–7). Briefly, the subject was anesthetized with sodium pentobarbital (50 mg/kg), and a craniotomy and durotomy was performed to expose right A1. Four parylene-coated tungsten microelectrodes were inserted into cortex approximately 600-700 um below the pial surface, and multi-unit neural activity (MUA) was recorded in response to the presentation of tones spanning 1-32 kHz and 0-75 dB SPL from a free-field speaker 10 cm from the left ear. Once recording finished, the electrodes were inserted into another cortical location. This procedure was repeated systematically until A1 was completely bordered by non-responsive and/or non-A1 auditory sites.

2.6 Analysis

Each electrode site in a subject’s map was classified as belonging to A1 or not and was considered representative of the surrounding neural area based on a Voronoi diagram of the points, as performed in previous studies (14). The average amount of A1 responding to each frequency/intensity tone pair presented during cortical mapping was then calculated based on the area represented by each electrode site and represented as a percentage.

The auditory threshold for each site was defined as the lowest intensity that evoked a reliable neural response.

3. Results

One week of VNS pairing with the near-threshold 9 kHz tone successfully drove stimulus-specific plasticity in A1 as compared to a naïve control group. The difference plot in Figure 1 shows a general increase in the amount of A1 representation for mid-frequency (4-16 kHz) tones, peaked around 9 kHz. There is also a strong increase in the representation of low-intensity (0-15 dB) tones across the 1-32 kHz frequency spectrum. These results are comparable to previous VNS tone-pairing experiments demonstrating stimulus-specific plasticity over four weeks of treatment (4–7). Figure 2 highlights the specific increase in A1 representation for 10 dB tones between 8-16 kHz for the VNS group compared to naives (unpaired t-test, $p<0.005$). The percentage area of A1 responding to 50 dB 8-16 kHz tones is also plotted for comparison. Although there is a trend for a representational increase in the VNS group compared to naives at 50dB also, it is not significant and is within the expected range of A1 representation based on data from previous studies (unpaired t-test, $p=0.06$) (4–7). Figure 3 shows the general decrease in auditory thresholds across A1 for the VNS group compared to naives (unpaired t-test, $p<0.05$).

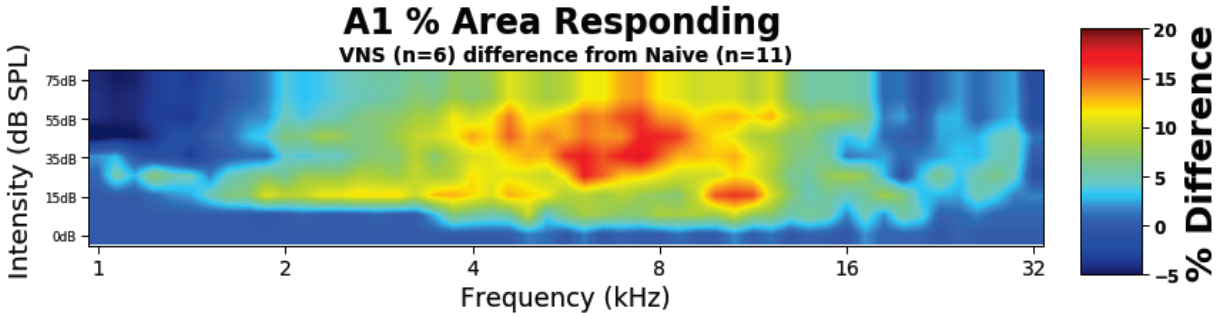

Figure 1 – Difference plot of the percentage of A1 responding between VNS and Naïve groups. The VNS group on average had more A1 sites respond with neural activity to the presentation of tones at nearly all intensities in the frequency range of 4-16 kHz. Additionally, the VNS group has a general increase in the amount of A1 responding at low intensities across all frequencies compared to Naïve. This is strong evidence that pairing a near-threshold auditory stimulus with VNS for one week is sufficient for driving stimulus-specific plasticity comparable to what is seen in previous studies.

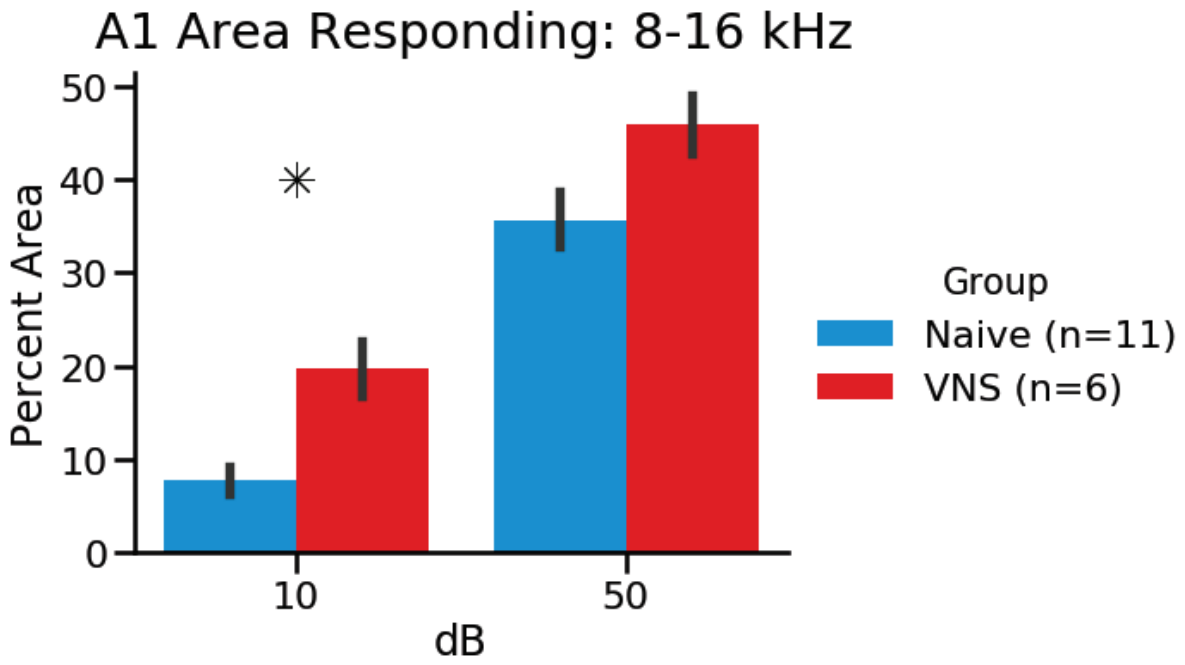

Figure 2 – Mean percentage of A1 responding specifically to 10 or 50 dB tones within the 8-16 kHz frequency range. The VNS group has more representation of 8-16 kHz at 10 dB than the Naïve group does ($p<0.005$). There is a noticeable trend for the VNS group to have more A1 representation at 50 dB also, but it does not quite exceed what might be expected from a typical Naïve subject ($p=0.06$)

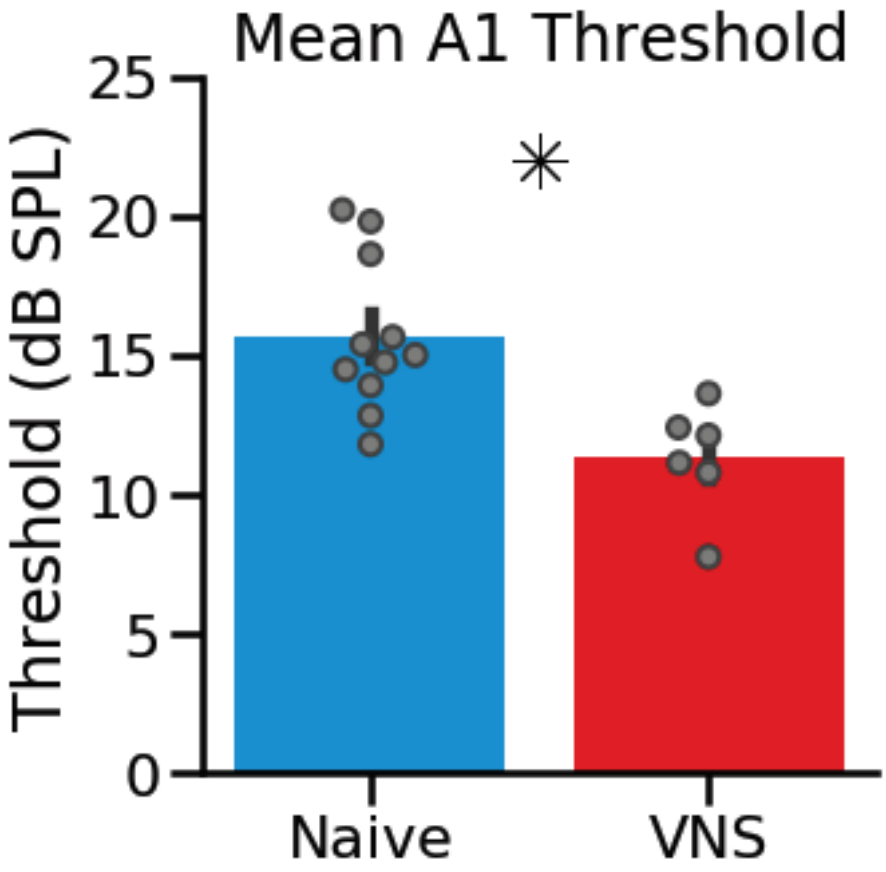

Figure 3 – VNS pairing with a near-threshold stimulus reduces overall auditory thresholds in A1 ($p<0.05$)

4. CONCLUSIONS

Vagus nerve stimulation (VNS) is a potential clinical therapeutic tool for treating a wide range of disorders associated with maladaptive plasticity, such as tinnitus, through its ability to drive targeted, stimulus-specific neuroplasticity. Although there has been modest success treating tinnitus in initial clinical trials, both the number of patients successfully treated, and the amount of benefit gained from treatment may be improved with changes to the therapy stimulus set. Recent evidence suggests that pairing VNS with stimuli near the threshold of neural receptive fields can drive significant neuroplasticity in only one week and may be a better therapeutic approach than using stimuli well above thresholds. The current study demonstrates that one week of pairing VNS with a near-threshold 9 kHz 10 dB tone drives stimulus-specific plasticity comparable to previous studies using much more intense auditory stimuli over four weeks of treatment. Future work will focus on comparing these results with one week pairing of other stimuli to see if the results are specific to the use of a near-threshold tone.

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