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Temporal plasticity in auditory cortex improves neural discrimination of speech sounds

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ABSTRACT

Background: Many individuals with language learning impairments exhibit temporal processing deficits and degraded neural responses to speech sounds. Auditory training can improve both the neural and behavioral deficits, though significant deficits remain. Recent evidence suggests that vagus nerve stimulation (VNS) paired with rehabilitative therapies enhances both cortical plasticity and recovery of normal function.
Objective/Hypothesis: We predicted that pairing VNS with rapid tone trains would enhance the primary auditory cortex (A1) response to unpaired novel speech sounds.
Methods: VNS was paired with tone trains 300 times per day for 20 days in adult rats. Responses to isolated speech sounds, compressed speech sounds, word sequences, and compressed word sequences were recorded in A1 following the completion of VNS-tone train pairing.
Results: Pairing VNS with rapid tone trains resulted in stronger, faster, and more discriminable A1 responses to speech sounds presented at conversational rates.
Conclusion: This study extends previous findings by documenting that VNS paired with rapid tone trains altered the neural response to novel unpaired speech sounds. Future studies are necessary to determine whether pairing VNS with appropriate auditory stimuli could potentially be used to improve both neural responses to speech sounds and speech perception in individuals with receptive language disorders.

1. Introduction

The ability to follow the rapid spectrotemporal transitions in speech is necessary for effective speech processing. Speech comprehension ability can be predicted by the temporal processing capability of the auditory cortex. For example, a decrease in the ability of auditory cortex to reliably respond to every presented sound in a rapid train of sounds is associated with poor comprehension of rapidly presented speech [1,2]. Deficits in the temporal processing of rapid sounds contribute to speech processing problems in both developmental disorders (such as dyslexia and autism) and acquired disorders (such as aphasia) [3–6]. Improvements in temporal processing are associated with improved speech processing. Auditory perceptual training can improve both the temporal following capacity of auditory cortex neurons and the accuracy of behavioral judgments [3,7–13]. Given that temporal deficits often persist even after extensive perceptual training [14,15], a method to further enhance training-induced neural plasticity could be beneficial for therapy in a variety of speech processing disorders.

Precisely timed neuromodulator release paired with sound presentation enables large-scale plasticity in the auditory cortex representation of the paired sound. Pairing nucleus basalis stimulation or vagus nerve stimulation (VNS) with a tone increases the auditory cortex response to the paired tone [16–18]. Similarly, pairing VNS with 5 pps (pulses per second) or 15 pps tone trains decreases or increases the auditory cortex response to rapidly presented sounds [19]. Pairing VNS with speech sounds strengthens the auditory cortex response to the paired speech

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sounds [20]. These findings indicate that VNS-sound pairing therapy may represent a method to manipulate temporal processing and improve speech processing.

In this study, we investigated how alterations in the temporal response properties of auditory cortex neurons affect the neural representation of rapid speech. We paired VNS with 5 pps or 15 pps tone trains and documented the primary auditory cortex (A1) response to speech sounds after 20 days of VNS pairing. We hypothesized that VNS paired with 15 pps tone trains would increase the response strength and decrease the response latency to speech sounds.

2. Materials and methods

Nineteen female Sprague Dawley rats were used in these experiments. Thirteen rats received vagus nerve stimulation paired with tone trains with a repetition rate of either 15 pulses per second, pps (n = 7 rats) or 5 pps (n = 6 rats). The remaining 6 rats were experimentally naïve controls that did not experience VNS or sound presentation. Our previous studies revealed large behavioral and neurophysiological differences when VNS was paired with sensory or motor events. However, there were no differences between experimentally naïve rats and 1) rats that received VNS which was not paired with an event or 2) rats that were exposed to sensory or motor events without VNS pairing [17,19,21–23]. As a result, the control rats in the current study did not experience exposure to sounds or exposure to VNS. The University of Texas at Dallas Institutional Animal Care and Use Committee approved all protocols and surgical procedures.

2.1. Vagus nerve surgery

Each rat was implanted with a custom made platinum iridium bipolar cuff electrode around the left cervical vagus nerve. All surgical procedures were identical to the procedures in previous studies [17–19]. Rats were anesthetized with sodium pentobarbital anesthesia (50 mg/kg), and received supplemental doses of dilute pentobarbital as needed to maintain areflexia. A bipolar cuff electrode was wrapped around the left vagus nerve and tunneled subcutaneously to a headcap connector located on top of the skull. Rats had a week of recovery from surgery, and were given oral amoxicillin and carprofen.

2.2. Sound stimuli

The tone trains paired with VNS in this study were identical to the trains used in previous studies [19,24]. The tone repetition rate was either 5 pps or 15 pps. Each train was made up of six tones, and each tone was 25 ms in duration. The carrier frequency of the tones that made up each train was one of seven frequencies distributed across the rat hearing range (1.3, 2.2, 3.7, 6.3, 10.6, 17.8, or 29.9 kHz). The carrier frequency of the tones in each train was randomized from trial to trial but the repetition rate was always the same for an individual rat.

The speech sounds presented during the terminal neurophysiology component of the study were words presented in a CVC (consonant-vowel-consonant) context and were identical to the sounds used in previous studies [25–28]. The words 'bad', 'dad', 'sad', 'wad', and 'yad' were spoken by a female native English speaker, and will be referred to as "speech sounds". To better match the rat hearing range, each word was frequency shifted up by one octave using the STRAIGHT vocoder [29,30]. Each word was adjusted so that the peak intensity (loudest 100 ms of the vowel) was normalized to 60 dB. The words were concatenated to create the word sequences 'sad wad bad yad' and 'sad wad dad yad' (Fig. 1), which will be referred to as "word sequences". These word sequences were then compressed to 70%, 50%, 30%, 20% and 10% of their original length (2.9, 4, 6.7, 10, and 20 syllables per second, sps) using the STRAIGHT vocoder. Conversational syllable rates in English are estimated to be between 3.5 and 7 sps [31–33]. The words 'bad' and 'dad' were also presented in isolation at 100% of their original length (500 ms) and temporally compressed to 50% and 30% of their original length (250 and 150 ms).

2.3. Vagus nerve stimulation – sound pairing

Vagus nerve stimulation was paired with tone train presentation approximately 300 times per day for 20 days, as in previous studies [17–20]. The VNS + 5 pps paired group experienced an average number of stimulations per day of 314.5 ± 3.5, while the VNS + 15 pps paired group experienced 314.8 ± 2.0 stimulations per day, which was not significantly different ($p = 0.94$). The onset of VNS was simultaneous with the onset of the third tone in the train of six tones. The VNS was a 500 ms pulse train at 30 Hz with an intensity of 0.8 mA and a biphasic pulse width of 100 μs The average interval between sounds was 30 s, with an average session length of 2.5 h. Rats were awake and unrestrained during the pairing sessions that took place in a 25 × 25 × 25 cm^3 wire cage. The tone trains were delivered free-field from an Optimus Bullet Horn Tweeter speaker positioned 20 cm above the cage.

2.4. Electrophysiology recordings

Following 20 days of VNS sound pairing, primary auditory cortex multiunit responses were recorded, as in previous studies [17,25,34]. Responses were recorded from 262 A1 sites in seven VNS + 15 pps paired rats, 157 A1 sites in four VNS + 5 pps paired rats, and 170 A1 sites in six experimentally naïve control rats. Recording sites were chosen to evenly sample A1 while avoiding blood vessels. There was no significant difference in the number of A1 sites between each of the experimental groups ($F(2,14) = 0.89$, $p = 0.43$). There was no significant difference in the sampled characteristic frequency ranges between each of the experimental groups ($F(2,14) = 2.69$, $p = 0.10$). In addition, there was no significant difference in the recording site density between each of the experimental groups ($F(2,14) = 0.76$, $p = 0.49$). Rats were anesthetized with pentobarbital using the same protocol as the vagus nerve surgery. A tracheotomy was performed and a humidified air tube was provided in order to facilitate breathing. A cisternal drain was opened in order to reduce brain swelling. A craniotomy and durotomy were performed over right auditory cortex, and 4 Parylene-coated tungsten microelectrodes (FHC Inc., 1–2 MΩ impedance) were simultaneously lowered to layer IV/V of primary auditory cortex. At each recording site, tones were randomly interleaved and presented, ranging in frequency from 1 to 48 kHz in 0.0625 octave steps and ranging in intensity from 0 to 75 dB in 5 dB steps. Following tone presentation, tone trains were presented at 70 dB with 2 s of silence between each train. Tone trains were randomly interleaved and presented at 11 repetition rates (3, 5, 7, 9, 10, 11, 13, 15, 17, 20, and 25 pps). The carrier frequency of the tones was the paired carrier frequency that was the closest to the characteristic frequency of the recording site. Following tone train presentation, speech sounds were presented both in isolation ('bad' or 'dad') and as word sequences ('sad wad bad yad' or 'sad wad dad yad'), at varying presentation rates from 2 sps to 20 sps.

2.5. Data analysis

The response strength evoked by speech sounds was quantified in each group using both the total number of driven spikes as well as the peak firing rate. Response latency was quantified as the peak firing latency. Neural discrimination accuracy was quantified using a nearest-neighbor classifier [25,27,35,36]. The classifier was provided

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