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The interaction of pulse width and current intensity on the extent of cortical plasticity evoked by vagus nerve stimulation

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ABSTRACT

Background: Repeatedly pairing a tone with a brief burst of vagus nerve stimulation (VNS) results in a reorganization of primary auditory cortex (A1). The plasticity-enhancing and memory-enhancing effects of VNS follow an inverted-U response to stimulation intensity, in which moderate intensity currents yield greater effects than low or high intensity currents. It is not known how other stimulation parameters effect the plasticity-enhancing effects of VNS.
Objective: We sought to investigate the effect of pulse-width and intensity on VNS efficacy. Here, we used the extent of plasticity induced by VNS-tone pairing to assess VNS efficacy.
Methods: Rats were exposed to a 9 kHz tone paired to VNS with varying current intensities and pulse widths. Cortical plasticity was measured as changes in the percent of area of primary auditory cortex responding to a range of sounds in VNS-treated rats relative to naïve rats.
Results: We find that a combination of low current intensity (200 μA) and short pulse duration (100 μs) is insufficient to drive cortical plasticity. Increasing the pulse duration to 500 μs results in a reorganization of receptive fields in A1 auditory cortex. The extent of plasticity engaged under these conditions is less than that driven by conditions previously reported to drive robust plasticity (800 μA with 100 μs wide pulses).
Conclusion: These results suggest that the plasticity-enhancing and memory-enhancing effects of VNS follow an inverted-U response of stimulation current that is influenced by pulse width. Furthermore, shorter pulse widths may offer a clinical advantage when determining optimal stimulation current. These findings may facilitate determination of optimal VNS parameters for clinical application.

Introduction

Repeatedly pairing short bursts of vagus nerve stimulation (VNS) with sensory or motor events causes lasting changes to the cortical circuits being activated [1–5]. Depending on the type of sound paired with VNS, it is possible to change the frequency tuning, temporal following rate, or phoneme selectivity of A1 neurons [3–5]. When a single pure tone frequency is paired with VNS, the proportion of A1 neurons that respond to that frequency is increased [4,6]. When a particular movement is paired with VNS, the proportion of motor cortex neurons that generate that movement is increased [1,2]. In addition to increasing neural plasticity in normal subjects, VNS paired with motor or sensory rehabilitation can be used to enhance recovery from nervous system damage. Numerous preclinical studies have demonstrated that pairing VNS with rehabilitative training enhances recovery in animal models of stroke, traumatic brain injury, and tinnitus [4,7–10]. Recent clinical studies indicate that VNS may be a useful therapy for the treatment of chronic stroke and tinnitus [11,12]. Determining optimal stimulation parameters to maximize clinical benefit will be critical to developing its therapeutic utility.

Several studies provide evidence that varying stimulation parameters strongly influences VNS efficacy. Intensity, frequency, and pulse width are all modifiable parameters that influence the effects of VNS [6,13–18]. Among the parameters investigated, the

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influence of current intensity has been best characterized. Increasing VNS intensity enhances efficacy up to a certain point, after which higher amounts of VNS begin reducing efficacy. Increasing VNS intensity results in an inverted-U function of cortical map plasticity, in which middle intensity (400 and 800 μA) stimulation drives significantly greater plasticity than strong stimulation (1200 and 1600 μA) [6]. VNS delivered post-training enhances memory retention in both humans and rats when delivered at moderate intensities, whereas VNS delivered at higher intensities exerts little or no effect on memory performance [19–21]. Similarly, moderate VNS intensities facilitate hippocampal LTP, while higher current intensity results in significantly less facilitation [22]. Taken together, these findings suggest that exceeding the optimal simulation intensity decreases VNS efficacy. However, the lower range of effective VNS intensities has not been fully explored.

The degree of nerve activation is determined by both the stimulation intensity and pulse width. Varying the pulse width of VNS while keeping the current constant results in differential activation and deactivation of distinct brain regions [18]. The vagus nerve compound action potential (cAP) displays a standard strength-duration curve demonstrating that the intensity required to elicit a cAP decreases with increasing pulse widths [23]. Consistent with this notion, studies using 500 μs pulse widths reveal a narrower range of effective VNS intensities [19,21,22] when compared with a study using 100 μs pules widths [6]. However, the effect of varying pulse width on VNS-mediated enhancement of plasticity has not been explored within a single study.

Many of the adverse side effects associated with VNS can be mitigated by reducing the stimulation intensity, either through reductions in current amplitude or pulse width [11,24,25]. Therefore, the present study aims to investigate the lower range of effective intensities as well as the influence of pulse width on VNS-dependent plasticity. The threshold for eliciting a cAP in the vagus nerve is near 200 μA [23]. However, whether this intensity is effective for the stimulation paradigm used to enhance plasticity has not been explored. The threshold for eliciting spiking activity in the locus coeruleus (LC), an area believed to be required for VNS-dependent enhancement of plasticity, is near 200 μA when delivered at 100 μs pulse widths. However, when the same intensity was delivered at 500 μs pulse widths, LC spiking activity reached levels similar to that elicited by 800 μA VNS delivered at 100 μs [17], a parameter set previously shown to drive robust plasticity in auditory cortex [6]. Here, we evaluated the effect of 200 μA VNS, an intensity near the threshold for nerve activation, on cortical rearrangement at these two commonly-used pulse widths.

Methods

Sixty 3–6 month old Sprague Dawley female rats were housed in a 12:12 h reversed light-dark cycle. All handling, housing, stimulation, and surgical procedures were approved by The University of Texas at Dallas Institutional Animal Care and Use Committee. Rats receiving tone-paired VNS were implanted with cuff electrodes around the left vagus nerve and then randomly assigned to one of 3 groups which were interleaved in time. After 20 days of VNS-tone pairing, auditory cortex recordings were performed to assess changes in auditory stimulus-evoked cortical responses. Recordings were also performed in 10 additional rats that received no VNS-tone pairing to serve as naïve controls.

Vagus nerve surgery

A custom made platinum iridium bipolar cuff electrode was implanted around the left cervical vagus nerve as described previously [2–6,8–10,26,27]. In brief, rats were anesthetized with ketamine hydrochloride (80 mg/kg) and xylazine (10 mg/kg) administered intraperitoneally and given supplemental doses as needed. Body temperature was maintained at 37 °C throughout the surgery. The vagus nerve was isolated with blunt dissection and placed in the cuff electrode. Leads from the cuff electrode were tunneled subcutaneously to interface with a headcap fixed with acrylic to 4 bone screws on the skull. Immediately following implantation, activation of the vagus nerve by the cuff electrode was confirmed by a drop in blood oxygen saturation in anesthetized rats with up to 10 s of continuous 30 Hz stimulation (800 μA, 100 μs pulse width). Nerve activation was considered to be successful if blood oxygen saturation reliably decreased by at least 5% from a stable baseline. Cefotaxime sodium (10 mg) was administered subcutaneously to prevent infection. Rats received amoxicillin (5 mg) and carprofen (1 mg) tablets for 2 days following surgery and were allowed to recover for at least 5 days before beginning VNS.

Vagus nerve stimulation and tone pairing

Rats were exposed to 500 ms, 9 kHz, 50 dB tones paired with VNS 300 times per day for 20 days as in previous studies [4,6]. To eliminate acoustic transients, 5 ms ramps were used at the beginning and end of each tone. VNS consisted of a 500 ms train of biphasic pulses at 30 Hz, with a 30 s average interval between VNS events. To prevent rats from anticipating when stimulation would occur, there was a 50% chance of stimulation every 15 s. Current amplitude was either 200 μA or 800 μA and pulse width was either 100 μs or 500 μs, as appropriate for each experimental group. Cuff impedance was monitored daily and rats who had impedance values > 10 kΩ for 2 consecutive days were removed from the study. Sixteen rats were removed from the study based on this criterion.

Auditory cortex recordings

Auditory cortex recordings were performed according to standard procedures [4,6]. 24–72 h after the last day of pairing, rats were anesthetized with sodium pentobarbital (50 mg/kg). Depth of anesthesia was monitored throughout the procedure and supplemented with additional pentobarbital as needed. A tracheal tube and cisternal drain were used to facilitate respiration and alleviate brain swelling. A section of skull was removed to expose right auditory cortex. The dura was removed and a thin layer of silicone oil was applied to the surface of the cortex to prevent desiccation. Four parylene-coated tungsten microelectrodes (1.5–2.5 MΩ, FHC) were lowered to depths of 600–700 μm below the pial surface to target layer IV. Neural signals were amplified using an RA16PA preamplifier (Tucker-Davis Technologies) and digitized at 24.414 ks/s with 16-bit resolution using an RZ5 BioAmp processor (Tucker-Davis Technologies) and subsequently filtered with a 300 to 3000 Hz bandpass filter and further amplified 20,000 times using Brainware (Jan Schnupp). A 600 mV threshold was applied to amplified voltage signals for spike detection. For electrical and acoustic isolation, recordings were conducted in a foam-lined, doubled-walled sound attenuated chamber. Pure tones spanning 81 frequencies ranging from 1 to 32 kHz and 16 intensities ranging from 0 to 75 dB were delivered via a speaker placed 10 cm from the left ear. Tones were presented every 500 ms in a randomly interleaved fashion. Multiunit neural activity was recorded using Brainware (TDT) and each recording site location was logged on a digitized photo of exposed cortex. Upon completion of the recordings, vagus nerve activation by the cuff electrode was again confirmed by observation of a decrease in blood oxygen saturation. One animal failed to exhibit a drop in oxygen saturation after