Modulation of neural oscillations by vagus nerve stimulation in posttraumatic multifocal epilepsy: case report

Adeel Ilyas, MD,^{1,3} Emilia Toth, PhD,^{2,3} Diana Pizarro, BSEE,^{2,3} Kristen O. Riley, MD,¹ and Sandipan Pati, MD^{2,3}

Departments of ¹Neurosurgery and ²Neurology; and ³Epilepsy and Cognitive Neurophysiology Laboratory, University of Alabama at Birmingham, Alabama

The putative mechanism of vagus nerve stimulation (VNS) for medically refractory epilepsy is desynchronization of hippocampal and thalamocortical circuitry; however, the nature of the dose-response relationship and temporal dynamics is poorly understood. For greater elucidation, a study in a nonepileptic rat model was previously conducted and showed that rapid-cycle (RC) VNS achieved superior desynchrony compared to standard-cycle (SC) VNS. Here, the authors report on the first in-human analysis of the neuromodulatory dose-response effects of VNS in a patient with posttraumatic, independent, bilateral mesial temporal lobe epilepsy refractory to medications and SC-VNS who was referred as a potential candidate for a responsive neurostimulation device. During stereotactic electroencephalography (SEEG) recordings, the VNS device was initially turned off, then changed to SC-VNS and then RC-VNS settings. Spectral analysis revealed a global reduction of power in the theta (4–8 Hz) and alpha (8–15 Hz) bands with both SC- and RC-VNS compared to the stimulation off setting ($p < 0.001$). Furthermore, in the alpha band, both SC- and RC-VNS were associated with greater global desynchrony compared to the off setting ($p < 0.001$); and, specifically, in the bilateral epileptogenic hippocampi, RC-VNS further reduced spectral power compared to SC-VNS ($p < 0.001$). The dose-response and temporal effects suggest that VNS modulates regional and global dynamics differently.

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KEYWORDS vagus nerve stimulator; epilepsy; mechanism; rapid cycle; case report

VAGUS nerve stimulation (VNS) can modulate dysfunctional circuits associated with select neurological and psychiatric disorders.^{5,9,19} Previous studies have demonstrated variable patient outcomes and side effects with different stimulation duty cycles; however, the neural dynamic underpinnings of this variability remain poorly elucidated.^{7,10,16} To increase understanding, a preclinical study in a nonepileptogenic rat model was conducted and showed that rapid-cycle VNS modulated hippocampal field spectral power and synchrony.¹⁷ Capitalizing on an intracranial electroencephalography (EEG) investigation performed as a workup for epilepsy surgery, we report the first in-human study demonstrating VNS duty-cycle modulation of network dynamics at meso and macro scales.

Case Report

Patient History

A 37-year-old, right-handed male was referred to our

level 4 epilepsy center for management of focal epilepsy that had been refractory to five antiseizure medications. At the age of 18, four years after a major trauma resulting in right temporal encephalomalacia, the patient developed focal seizures (2–4 seizures/month) that occasionally progressed to bilateral tonic-clonic seizures (1 seizure every 4–6 months). Seizure semiology consisted of impaired awareness, bilateral manual automatisms followed by confusion, and paraphasic errors. A VNS device (AspireSR model 106, LivaNova) was implanted at an outside facility and was initially effective for a year with a reduction in seizure frequency and severity; however, increased seizures and an episode of status epilepticus occurred later, prompting the referral.

Based on the clinical presentation and phase I investigations including scalp video-EEG, magnetoencephalography, structural evaluations (3-T MRI), and metabolic investigations (FDG-PET), a consensus was reached in our multidisciplinary epilepsy conference to perform robot-assisted (ROSA device, Medtech) stereotactic EEG

ABBREVIATIONS EEG = electroencephalography; fMRI = functional MRI; NREM = non-rapid eye movement; POD = postoperative day; RC = rapid cycle; SC = standard cycle; SEEG = stereotactic EEG; VNS = vagus nerve stimulation.

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(SEEG) electrode implantation into the bilateral hippocampi, amygdala, orbitofrontal gyri, anterior cingulate gyri, and right anterior insula to identify seizure foci (Fig. 1A). Overall, five electroclinical seizures were identified, three of which originated from the right and two from the left amygdala-hippocampi. These seizures rapidly propagated to the bilateral orbitofrontal gyri. Wada testing demonstrated memory support from bilateral hippocampi; therefore, the decision was made to treat the bilateral hippocampal seizures with the FDA-approved responsive neurostimulation and to consider unilateral anterior temporal lobectomy in the future based on dominant seizure laterality derived from chronic ambulatory electrocorticography.

SEEG Electrode Implantation and Data Acquisition

A total of 166 electrodes were implanted and recorded at 2048 Hz using the Natus Xtek EEG system (Quantum). Scalp EEG activity from the midline (Cz, Pz) and fronto-central (F3, F4, C3, C4) regions was recorded simultaneously. Following SEEG electrode implantation, VNS was turned off on postoperative day (POD) 1 (Fig. 1B). The VNS was activated to standard cycle (SC; 2.5 mA, 25-Hz signal frequency, 250- μ sec pulse width, 60-second stimulation on time, 108-second stimulation off time, duty cycle 38%) on POD 5 and then switched to rapid cycle (RC; 2.5 mA, 25-Hz signal frequency, 250- μ sec pulse width, 7-second on time, 18-second off time, duty cycle 44%) on POD 6, which was continued after discharge from the hospital. The decision to switch to RC was based on the partial response to seizure control with SC, and informed patient consent was obtained prior to this switch.

For each of the three VNS settings (i.e., off, SC, and RC), representative samples in the latter half of a seizure-free 24-hour recording were obtained during the awake and non-rapid eye movement (NREM) sleep states, thus yielding a total of 6 EEG samples. From these 6 representative samples, 20 randomly selected 20-second samples were selected for analysis. The criteria for selection of the representative samples were as follows. All samples were collected at least 8 hours following a VNS setting change. Simultaneous scalp video-EEG was used to identify appropriate awake and sleep states. Awake samples were obtained when the patient was resting motionlessly with a prominent underlying beta or alpha rhythm. Sleep samples were obtained during slow-wave NREM sleep.²² Based on these criteria, a total of 20, 15, and 15 minutes of EEG data were obtained for the awake stimulation off, SC, and RC states, respectively; a total of 20, 18, and 15 minutes of data were obtained for the corresponding sleep states, respectively. From these segments, 20 randomly selected 20-second samples were selected for analysis. Details regarding spectral and phase lag index (PLI) SEEG analyses and the corresponding statistics can be found in the Supplementary Material S1.

Activation of VNS Decreases Global EEG Power

During wakefulness, SC-VNS was associated with reduced overall power in all frequency bands except delta compared to the off setting, and RC-VNS was associated with reduced theta and alpha power (Fig. 2). During NREM

sleep, SC-VNS was associated with reduced power in all frequency bands except high gamma, and RC-VNS was associated with reduced power in delta, theta, alpha, and low gamma. There appeared to be a trend toward further reduction in theta and alpha power in the awake state in the RC-VNS versus SC-VNS setting. Similar trends were also seen in the insulae but not in the cingula.

Activation of VNS Increases EEG Alpha-Band Power During Sleep in the Anterior Cingulum

VNS activation was associated with increased power in the alpha band during NREM sleep in the anterior cingulum, and the effects were more pronounced with SC-VNS than with RC-VNS. In contrast, during wakefulness, RC-VNS was associated with increased low-gamma power.

VNS Modulates Neural Synchrony

Both SC- and RC-VNS were associated with decreased interhemispheric and hemispheric alpha band synchrony during wakefulness and sleep states and theta band synchrony during sleep states (Fig. 3). On the other hand, SC- and RC-VNS were associated with increased interhemispheric and hemispheric delta and beta band synchrony during wakefulness. Compared to SC-VNS, RC-VNS was associated with significantly increased interhemispheric low- and high-gamma band synchrony. Furthermore, during wakefulness, RC-VNS was associated with increased low-gamma band synchrony in the frontal lobe and decreased theta band synchrony in the temporal lobe.

VNS Decreases Hippocampal EEG Alpha-Band Power and Spike Counts

In both awake and sleep states, RC- and SC-VNS were each associated with reduced power in the alpha frequency band in the bilateral hippocampi compared to the off setting (Fig. 2). Compared to SC-VNS, RC-VNS further reduced power in the alpha band in the bilateral hippocampi. In addition, RC-VNS decreased hippocampal spike counts compared to the off setting in the sleep state, and there was a similar trend in the awake state (Fig. 4).

Discussion

In this study, we assessed how two VNS duty cycles sequentially activated over 24-hour periods affected global and local neural dynamics. An increase in the duty cycle from 38% to 44% decreased the cumulative VNS on time from 8.56 hours/day (SC) to 6.72 hours/day (RC). The acute responses following this increase in duty cycle were as follows: 1) selective decrease in EEG power in the alpha band in the epileptogenic hippocampi but not in the cingulum where there was an increase in alpha-band power—particularly by SC-VNS; 2) decreased interhemispheric and hemispheric alpha band synchrony that was independent of behavioral state (awake or sleep); and 3) increased interhemispheric and hemispheric gamma band synchrony during wakefulness. Activation of (RC) VNS decreased spike count within the epileptogenic hippocampus. Overall, our case demonstrates that titration of the VNS stimulation duration does not monotonically increase (or decrease) the

FIG. 1. Diagram (A) illustrating the entry sites and target locations of the 12 symmetrically implanted electrodes targeting the limbic structures bilaterally. Timeline of clinical course (B), highlighting the interval when seizures were captured and EEG activity was sampled relative to SEEG electrode implantation, anticonvulsant medication titration, SC-VNS, RC-VNS, and SEEG electrode explantation. AED = antiepileptic drug; D1, . . . , D7 = day 1, . . . , day 7. Figure is available in color online only.

FIG. 2. Spectral analysis of the global, bilateral hippocampal, bilateral cingular, and bilateral insular electrodes in the awake and sleep states. Figure is available in color online only.

stimulation effects but rather modulates the regional and global dynamics differently.

The variable effects in global and regional cortical dynamics associated with different VNS stimulation parameters have been reported using functional imaging studies (e.g., functional MRI [fMRI]).^{13,18,20} For example, interleaved VNS-fMRI data demonstrated significant differences in activation patterns with stimulation at 20 Hz compared to stimulation at 5 Hz in patients with depression.¹⁸ However, cortical physiological studies evaluating

VNS dose-response effects are lacking. Prior studies have analyzed scalp and intracranial EEG characteristics to differentiate VNS responders from nonresponders and found that decreased global delta and alpha band synchrony was associated with an improved response to VNS therapy.^{2,3}

The reduction in hippocampal EEG power with SC- and RC-VNS likely reflects a suppression of synaptic potentials and modulation of hippocampal excitability. The thalamus has been proposed to generate and modulate EEG alpha rhythm.^{25,26} Previous functional imaging

FIG. 3. Phase lag index analysis of the interhemispheric, bilateral hemispheric, bilateral frontal, and bilateral temporal electrodes in the awake and sleep states. Figure is available in color online only.

studies have demonstrated that VNS, in particular, RC-VNS, decreases thalamic metabolic activity.²⁴ Our finding of decreased hippocampal EEG power and decreased synchronization in the alpha band suggests that RC-VNS modulates thalamus and thalamocortical loops.²⁴ Anecdotal reports suggest that daytime vigilance is improved following VNS therapy in patients with epilepsy.⁸ The increased synchrony in delta and gamma oscillations during wakefulness by RC-VNS suggests the potential of VNS in augmenting higher-order cognitive functions such as

attention, motivation, and memory.^{12,14} Indeed, activation of VNS modulates the limbic network and has been demonstrated to improve performance of working memory by augmenting arousal and attention.^{4,23} Although the mechanistic underpinnings are not completely understood, stimulation of the vagus nerve has been shown to alter both the electrophysiological and metabolic profile of the forebrain, suggesting that the peripheral state of the body influences cognition.^{4,15,21}

Typically, phase synchronization is measured on short-

FIG. 4. Hippocampal spike count analysis in the awake and sleep states. Figure is available in color online only.

er intervals than the 20-second interval used in our analysis. A longer time interval was chosen because the present case was focused on the analysis of effects that persist beyond the duration of stimulation (i.e., tonic effects). On the other hand, phasic effects would occur on the order of milliseconds—certainly within the subsecond time frame. The use of very long time intervals (e.g., 60 seconds) can result in unreliable results.¹¹ Therefore, selection of the temporal window duration is a tradeoff between reliable output and the duration of the event of interest.

Limitations

These results, having been derived from a single patient, may not generalize to all VNS implant patients. In addition, the neuromodulatory effects of SC- and RC-VNS were assessed in the acute inpatient setting; however, long-term follow-up is needed to determine the anticonvulsive effects of RC-VNS in this patient. The limited availability of EEG data presents the potential for sampling bias despite adherence to strict behavioral and EEG criteria for selection of awake and sleep states. Unfortunately, longer durations of sampling were unobtainable as a consequence of these criteria. Nonetheless, the samples obtained for analysis were noncontiguous, which decreases the risk of sampling bias. Furthermore, whereas the typical long-range conduction delay is on the order of tens of milliseconds, our use of longer segments for analysis is likely to detect sustained synchronization, which is of interest in this study as the SC- and RC-VNS are each a continuously

cycling stimulus.⁶ We performed a focused spectral analysis of the hippocampi, cingula, and insulae as the patient's seizures originated from the bilateral hippocampi and VNS has been shown to modulate the limbic network. In addition, the hippocampus plays a crucial role in temporal lobe epilepsy; therefore, we investigated the dose-response effects of VNS on the hippocampus.¹

Spikes may result in spurious oscillations, thereby leading to significant change in synchrony measures. However, spikes last less than a second (< 70 msec). To reduce the confounding effects of spikes, we selected EEG segments that lack any periodic runs of spikes. In addition, we visually screened the epileptogenic zones to select spike-free epochs for analysis. Despite our efforts, a few spikes may have been present in some of the epochs, but these are unlikely to have a confounding effect given that spikes are transient and we selected multiple noncontiguous 20-second epochs.

It is important to consider that our findings may reflect the cumulative effects of VNS rather than the effects of the change in VNS parameters from SC to RC. In other words, we assessed the combined dose-response and temporal effects of VNS on neural modulation. It is interesting to note that not all effects were monotonic. Thus, if the observed changes were secondary to cumulative stimulation effects alone, then it would imply that VNS reverses both global and regional power and synchrony in certain frequency bands in a time-dependent manner. Unfortunately, our trial was not designed to specifically test this hypothesis, which would be better tested with a crossover design.

Conclusions

VNS may induce a complex modulation of the cortico-subcortical network with titration of duty cycles. RC-VNS can induce robust suppression of EEG power in epileptogenic hippocampi and insulae and global and hemispheric alpha band desynchronization. Further studies are needed to investigate the mechanism behind VNS neural modulation.

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Disclosures

Dr. Pati has been a consultant for NeuroPace.

Author Contributions

Conception and design: Ilyas, Toth, Pati. Acquisition of data: Ilyas, Toth, Pati. Analysis and interpretation of data: Ilyas, Toth. Drafting the article: Ilyas. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ilyas. Statistical analysis: Ilyas. Administrative/technical/material support: Riley, Pati. Study supervision: Riley, Pati.

Supplemental Information

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Correspondence

Adeel Ilyas: University of Alabama at Birmingham, AL. adeelilyas@uabmc.edu.