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Non-invasive Cervical Vagus Nerve Stimulation Effects on Reaction Time and Valence Image Anticipation Response

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Abstract

Background: Norepinephrine (NE) driven noninvasive vagus nerve stimulation (nVNS), which improves attention and reduces reaction time, augments learning. Equally important, endogenous NE mediated arousal is highly dependent on the valence (positive or negative) of the exogenous stimulus. But to date, no study has measured valence specific effects of nVNS on both functional magnetic resonance imaging (fMRI) anticipation task response and reaction time in healthy individuals. Therefore, the aim of this pilot study was to assess whether nVNS vs sham modulates valence cortical anticipation task response and reaction time in a normative sample.

Methods: Participants received right sided transcutaneous cervical nVNS (N = 12) or sham (N = 12) stimulation during a 3T fMRI scan. Subjects first performed a continuous performance task (CPT) and then a cued anticipation task to images of positively and negatively valenced events during fMRI. Reaction times to cues and Blood oxygen level dependent (BOLD) response were examined over phase to identify effects of nVNS/sham over time.

Results: nVNS reduced reaction time for all valenced image anticipation trials. With the fMRI anticipation task, we observed a valence-specific effect; nVNS increased responsivity to images

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Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

with negative valence and decreased responsivity to images with positive valence, whereas sham showed an inverse valence response.

Conclusions: nVNS was linked to reduced reaction time during the anticipation task. In tandem, nVNS consistently enhanced responsivity to negatively valenced images and diminished responsivity to positively valenced images, suggesting specific nVNS driven endogenous neurotransmitter signaling may contribute.

Keywords

Norepinephrine; Locus Coeruleus; Attention; Arousal; Anticipation; Cervical Noninvasive Vagal Nerve Stimulation; functional magnetic resonance imaging

Introduction:

Vagus nerve stimulation (VNS) modulates human brain activity, producing enhanced arousal and attention effects that are linked to augmented reaction time and learning[1–4]. Afferent vagal fibers largely terminate in the nucleus of the solitary tract (NTS) [5–7]. Anatomical tracer studies show NTS projection fibers innervate brainstem targets including the rostral ventromedial medulla, parabrachial nucleus, raphe nuclei and locus coeruleus (LC) [8]. Locus coeruleus activation was consistently shown in preclinical vagus nerve stimulation [9–11], while temporally dependent LC activation (with auricular vagus nerve stimulation) has been measured (maxima occurring within 6–7 min post stimulation) using functional imaging[1, 12–15]. Increases in LC norepinephrine (NE) concentrations activate the prefrontal cortex as well as a broad network of cortical and subcortical circuitry projections throughout the brain [16, 17]. In addition to LC-NE circuit projection effects, high adrenergic receptor concentrations (responsive to volume transmission NE release) are localized to nodes critical in the Salience Network (SN), (including anterior insula, amygdala, hippocampus, anterior cingulate) that drive the SN network specific activation [18]. LC-NE induced changes do not necessarily directly impact decision making or reward anticipation, but rather facilitate the dynamic reorganization of neural networks designed to quickly adapt to a changing environment [19]. As such, persistent LC activated neurons electrotonically couple enabling synchronic phasic bursting that is associated with task related, novel, threat based or unpredictable stimuli [20–22]. *Additive enhancement in LC activated NE signaling directly results from increases in negatively valenced "threatening" environmental stimuli. This activated NE signaling results in*: amplified alertness and attention, enhanced visual processing speed, augmented reaction time, that jointly reinforces learning [23–27]. Put simply, as negatively valenced threat or stress increases, the human neural response (i.e. requisitely executed via LC-NE signaling) is to react quickly, thus avoiding immediate and imminent harm [23]. In conjunction, the threat-based stimuli that induces alertness and attention coactivates complex cortico-limbic regulatory pathways, thereby continuously calibrating necessary responsivity through specific anticipation circuitry [28–31].

Altered threat anticipation of future aversive events is a core feature of anxiety disorders [32, 33]. In line with this maxim, generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) can be conceptualized as altered learning states characterized by

exaggerated prediction error due to an overgeneralization, followed by an exaggerated reaction to uncontrollable or unpredictable stressors [34]. Advanced functional brain imaging protocols can quantify the neural network that categorizes subjects with general anxiety and trauma disorders (i.e., GAD and PTSD) response during negative anticipation [35, 36].

Neuroimaging affective anticipation paradigms that model threat anticipation by measuring brain response during a cued period of expectancy to negatively relative to positively-valenced images demonstrate specific node activations including: the anterior insula, the anterior cingulate cortex (ACC), the amygdala, as well as the lateral (lPFC) and medial prefrontal cortex (mPFC) [37]. The anterior insula, highly responsive in anticipation paradigms, has efferent connections with ventral frontal brain regions such as the ACC as well as other nodes, (i.e., orbital frontal cortex (OFC) and periamygdaliod areas). Conventionally, the ventral subdivision of the ACC is known to play a significant role in regulatory emotional and physiological processing (BA-24, 32). Its ventral region has reciprocal projections to the anterior insula [38, 39] and the amygdala [40–43], exerting top-down regulation on these structures [42, 43]. Consequently, the ventral ACC is involved in fear conditioning [43–45], in the pathophysiology of anxiety disorders [45, 46], in cognition that is self-relevant [47–53], and in error processing [47–49, 52]. Given the importance of the anterior insula and the ACC in the integration of physiological and psychological processes, changes in their activity are established neural biomarkers for the efficacy of pharmacotherapies. But to date, bio-electronic medicine-based therapies (i.e., nVNS, Transmagnetic Stimulation, Transcranial Electrical Stimulation, and Deep Brain Stimulation) have been largely understudied in threat anticipation. Given the presumed nVNS NE neurochemical substrate, and the well-established neural nodes responsive in threat anticipation paradigms, we proposed to compare nVNS vs sham on both: 1) task performance reaction time, and 2) cortical activation patterns during an image anticipation task, utilizing valence specific cues (negative/positive).

MATERIALS AND METHODS

Subjects

A total of 24 mentally and physically healthy, right-handed subjects (10 females and 14 males; age range 18–54 years; mean ± SD: 27 ± 8.4 years) were recruited and enrolled in the study (Table 1). A subset of the cohort was included from a prior study [54]. Exclusion criteria were prior surgery or abnormal anatomy in the anterior cervical neck region, history of neurologic disease, implanted neurostimulator or cardiac pacemaker, cardiovascular disease or carotid artery disease, metallic implants that are not MRI-safe as well as any psychiatric disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DMS-IV) Axis I. The study was approved by the University of California San Diego, Institutional Review Board (IRB#150943). All subjects provided written informed consent prior to participation.

Stimulation Paradigm

Subjects were randomized to receive either right sided transcutaneous cervical nVNS (n = 12) or sham (n = 12) stimulation during a functional magnetic resonance imaging (fMRI) scan. They were blinded to which condition they received. A pair of nonferromagnetic stainless-steel surface electrodes (1-cm diameter) were placed on the neck and secured with an adjustable Velcro strap collar, applied to either the right anterior cervical area (overlying the carotid artery) for active nVNS, or the right lateral cervical area (posterior to sternocleidomastoid) for the sham treatment. The surface electrodes were connected to the battery-powered stimulation unit by a 6-m shielded, grounded cable. Both the sham and nVNS devices delivered 1-ms duration bursts of 5 sinusoidal wave pulses at 5000 Hz with a repetition rate of 25 Hz, and a continuous train duration of 2 minutes. In both the nVNS and sham treatments, a computational fixed, initial 30-second ramp-up period (to peak voltage) was followed by 90 seconds of peak stimulation. In the nVNS treatment, the voltage was increased to 24 V, whereas in the sham stimulation it was increased to 4.5 V. Sham and nVNS devices were identical in appearance and produced similar sensations on the skin. In our previous work (pilot extension of parent study) [54] subjects were unable to differentiate sham from active nVNS. With the sham stimulation, subjects generally experience greater discomfort (because of stimulation of neck muscles), with maximal tolerable amplitude typically being only 2–8 V [2, 55]. Therefore, we employed a maximum sham voltage of 4.5 V to the far lateral neck position [2, 55]. Prior work suggests that use of the far lateral neck position with low voltage does not result in stimulation of the vagus nerve [2, 55]. Active transcutaneous cervical (20 V) nVNS is predicted to result in an electric field penetrance required to activate the vagus nerve, when the device is positioned directly over the carotid artery [56].

Neuroimaging task

Approximately forty minutes after either nVNS or sham stimulation, subjects performed a validated valenced image anticipation task that combined a Continuous Performance Task (CPT) with interspersed presentation of affective stimuli (see Fig 1) [35, 57, 58]. During the CPT, subjects pressed the ‘FIRST (index finger)’ or ‘SECOND (middle finger)’ button on a hand-held button box in response to a blue “CIRCLE” or a “SQUARE”, respectively. Simultaneously, a 250 ms long 500-Hz tone was presented every 2 s. Subjects were instructed that when the shape turned green, accompanied by a 250-Hz (low pitch) tone, a “pleasant” positively valanced image would appear, whereas when the shape turned red, accompanied by a 1000-Hz (high pitch) tone, an “unpleasant” negatively valenced image would appear. Trials with green or red shapes represented anticipation periods. Picture stimuli included 17 positive and 17 negative valenced images. Positively valenced images from the International Affective Picture System (IAPS) and proprietary negatively valenced images were used [59], and evenly distributed across the 9 min 40 sec task duration. Response accuracy and response reaction time (ms) were obtained for the CPT, anticipation of a positive image (API), and anticipation of a negative image (ANI). To examine the behavioral effect of anticipation, we examined the difference between behavioral measures during the API and ANI. No subject response was required during affective image presentation. The valenced image anticipation task was conducted during a single fMRI scan sensitive to BOLD contrast using a 3T General Electric Discovery

MR 750 scanner (GE Healthcare). Images were collected with an eight-channel head coil (T2*-weighted echoplanar imaging; repetition time, 1500 milliseconds; flip angle = 80, echo time, 32 milliseconds; 64 × 64 matrix; field of view 240mm; thirty 4-mm axial sections; 386 scans). During the same experimental session, a high-resolution T1- weighted image (spoiled gradient recalled; flip angle =12, repetition time, 8 milliseconds; echo time, 3 milliseconds; 168 sections; field of view, 256 mm; 256 × 256 matrix 1-mm^3 voxels) was obtained for anatomical reference.

Imaging analysis was conducted using a combination of AFNI [60] and ANTsR (https://github.com/ANTsX/ANTsR). T1 images were inhomogeneity-corrected to enhance registration using the N4 bias correction method [61]. Each subject's T1 was brain extracted, diffeomorphically registered to the 1mm mni_icbm152_nlin template, and segmented using ANTS [62, 63]. For preprocessing of the functional images, the first three EPI volumes were removed to allow for scanner equilibration. Next, EPI images were despiked, slice-time corrected, outliers were censored and N4 biased corrected. EPI images were then temporally whitened to reduce BOLD-signal temporal autocorrelation, motion corrected, detrended, the four top noise components were removed using CompCor [64], and data was spatially smoothed using Perona-Malik anisotropic diffusion [65]. Corrected EPI images were coregistered to the individual standardized T1 image using SyNBold. Forward and inverse registration transformations were concatenated and applied in a single step to minimize excess blurring of images. DVARs (>2.5) and framewise displacement (mean FD >.3mm) were identified if subjects moved however no subjects were removed. Hemodynamics were modelled (AFNI: 3dDeconvolve/TENT) during the task for valence (positive and negative anticipation blocks) and phase (phase 1 and phase 2 correspond to first half and second half of the valenced image anticipation task respectively). This two-phase model was chosen for the imaging data to retain a minimum of 8 per phase. Neural responses were measured for a duration of: 1) 6 seconds during anticipation 2) 2 seconds during the image presentation and, 3) approximately 8 seconds post image presentation; that in aggregate allow ample time for the API and ANI hemodynamic response.

To identify group and task effects on the hemodynamic response, hemodynamics for API and ANI were subjected to linear mixed-effects analysis using the R statistical package. A linear mixed-effects analysis for Group (sham and nVNS) by anticipation valence (positive and negative) by phase (phase 1 and phase 2) as fixed effects and subject as random effects, to identify task main effects. An additional linear mixed-effects analysis for Group (sham and nVNS) by anticipation valence (positive and negative) by trial (over the duration of the whole task) as fixed effects and subject as random effects, to identify task main effects. Multivoxel multiple comparisons were performed using Monte Carlo simulations (3dClustSim [bug fixed] with three-parameter noise modeling) in order to reduce potential false positives. To achieve cluster-wise threshold of $p < 0.000001$, a per-voxel thresholds of $p < .000001$ were set along with a minimum of 4 voxels per cluster. As an exploratory measure valence specific neural response (AUC) to valence specific reaction time (in phase 1 and phase 2 and from phase 1 to phase 2) correlation analyses was carried out. Statistical analyses were performed with R version 3.4.3.

Results:

Participant demographics and psychiatric assessments

Age, sex and race were similar between the nVNS and the sham groups (Table I). Subjects were healthy; anxiety, depression, or posttraumatic stress disorder (PTSD), as measured by the Beck Anxiety Index (BAI), Beck Depression Inventory 2 (BDI-2), or the PTSD Check List–Civilian version (PCL-C) were below threshold cutoffs. Accordingly, no significant difference in mean scores between groups was noted for these measures. Two subjects failed the initial screen and were excluded from the study; one potential participant had a preexisting arrhythmia disorder (Wolf-Parkinson-White syndrome) and another had dental braces (Table I). The total sample used for analysis 12 subjects in sham and 12 in the VNS group, after exclusion of the 2 subjects who failed screening, and 6 others (3 in each group) due to technical problems with the task or scan.

3.2. Continuous Image Task Performance Accuracy and Reaction Time

As expected, all participants' accuracy on the continuous performance task was high (Mean=98.7%). It did not significantly differ across conditions (Continuous Task/No Anticipation: Mean=99.1%, Positive/Affective Control Anticipation: Mean=97.3%, Negative Anticipation: Mean=99.1% ($p>.05$). Accuracy rates (correct control box button push) were also similar between groups ($p>.05$) when examined across and between phase ($p>.05$). There was a significant difference in reaction time between groups over time ($p=.01$) with the nVNS group showing greater reduction in reaction time over task duration (i.e., over phases 1–2) for CPT, positive and negative image trials (see Fig 2 and Supplemental Table 1), when compared with the sham group. Similarly, there was a significant difference in reaction time between groups over time ($p=.0009$) with the nVNS group showing greater reduction in reaction time over task duration (i.e., over trial) for CPT, positive and negative image trials (see Supplemental Table 2) when compared with the sham group.

Imaging results

Regions of Interest (ROI): The results of the whole brain analysis revealed a broad set of neural regions that demonstrate Group*Valence*Phase regions of interest. During the image anticipation task (independent of positive or negative imagery), 20 regions ($p<.000001$) met cluster thresholds (with 4 voxel minimum) in the group*valence*phase main effect derivative of the LME analyses (Table 2). Significant clusters >9 voxel in Group*Valence*Phase analysis (separated into $1^{st}/2^{nd}$ phase) demonstrates activation in the left precentral gyrus, Broadman Areas (BA) 44 and BA6, left anterior insula BA13, left anterior cingulate BA24 and BA32, and left post central gyrus BA3 ($p<.000001$). Notable clusters >4 voxels in Group*Valence*Phase analysis (separated into $1^{st}/2^{nd}$ phase) demonstrates activation in the left precentral gyrus (BA 3, 6), left orbital gyrus (BA 11), and left superior frontal gyrus (BA 6). Of note 80% (16/20) clusters identified were localized contralateral (left sided) to the nVNS (right sided). During the valence anticipation task, Group*Valence*Phase analyses (all listed ROI) of positive imagery demonstrate nVNS initial phase 1 greater response followed by consistent low response during phase 2; in converse, sham stimulation response was low during phase 1 but increased significantly during phase 2 (Fig 3). During the valence anticipation task, Group*Valence*Phase analyses

(all listed ROI) of negative imagery demonstrate an increase in response over task in the nVNS group (initial phase 1 low response followed by consistent greater response during phase 2); in converse, the sham group showed a decrease in response over task (response was greatest during phase 1 but decreased during phase 2) (Fig 3). Valence specific neural response (AUC) to valence specific reaction time (in phase 1 and phase 2 and for phase 1 transition to phase 2) correlation analyses did not demonstrate any significant correlations with Bonferroni correction for multiple comparisons (Supplemental Table 3, 4).

Discussion:

Given the known alerting effects of nVNS, our study goal was to directly assess the effects of cervical nVNS vs sham on: (1) the task performance (i.e., reaction time) and (2) the coinciding neural response during an affective anticipation task. In this healthy control cohort, results revealed a stronger task performance (i.e., greater reduction in reaction time) in the nVNS group compared to the sham group during the valence anticipation task. Coordinate cortical neuroimaging revealed a valence-specific neuromodulatory effect; nVNS increased responsivity to images with negative valence and decreased responsivity to images with positive valence), whereas sham showed an inverse valence response. In aggregate nVNS reliably reduced reaction time independent of valence, while for the first time to our knowledge this is the first report of nVNS valence specific effects on the neural substrates thought to subserve alertness, attention, and anticipation.

Potential Mechanisms of Enhancing Reaction Time and Alerting Effects Following nVNS

In this cohort, (nVNS vs sham), we observed consistent reduction in reaction time over phase. Considerable prior work provides the premise for our findings. Noradrenergic mechanisms can be modulated by stimulation (VNS) that primarily occurs through activation of the LC. This effect is supported by preclinical [10, 11, 66–68] as well as consistent clinical reports of nVNS mediated: 1) increases in salivary alpha-amylase (sAA) [69, 70], 2) pupillary change [71–73], and 3) alteration of visual evoked potential amplitude [69, 70, 74]. Multiple fMRI studies suggest nVNS results in activation of the LC [14, 15, 75] and other brainstem nuclei important in autonomic regulation [54]; in aggregate they suggest LC activation impacts nVNS effects, however change in additional neurotransmitters (GABAergic, Serotonergic, Cholinergic) may contribute as well [74]. Vagus nerve stimulation GABAergic effects are observed in the contralateral cortex to stimulation site (that correspond to ipsilateral hand) [76–78]. In our cohort, we observed a reduction of right-hand reaction time response in the right sided nVNS group. Therefore, if highly contributary, we would have expected a GABAergic mediated increase in (slowed) right hand reaction time as has been prior reported [79]. In as much, we postulate that the observed effect is likely compound, due to multiple neurotransmitters that are known to effect reaction time (Noradrenergic, Serotonergic, Cholinergic) [80–82]. Increases in LC-NE selectively activate SN nodes due to NE volume transmission amongst high density adrenergic receptors found in these regions [16, 17, 29, 83–87]. In support of this notion, nVNS reliably enhances visual search processing speed [3, 69, 87], that verify VNS as an alerting visual enhancement tool. Recent work from McIntire and colleagues (2021) support the tenet that cervical nVNS can improve attention, visual processing performance and

reaction time [4] that mirror LC-NE signaling attention effects of common stimulant drugs, such as Modafinil [88, 89] and Dextromethamphetamine [88]. Taken together, the present findings further support nVNS NE effects on reaction time, as described by other groups [3, 4, 70, 90]. In this cohort, we were likely underpowered to detect a group by valence specific reduction in the behavioral measure (i.e., reduction in reaction time see Supplemental Table 1, 2). However, we postulate that the nVNS evinced valence specific (negatively valenced image) neural (increases in cortical anticipatory node response) may also produce tangible behavioral (reduction in reaction time) effects (if adequately powered in a larger study), that are likely to be driven by additive threat and nVNS actuated LC-NE signaling. Further study, (in both pre-clinical and clinical models), is needed to determine whether negative alerting stimuli result in additive nVNS LC-NE signaling that reduce reaction time*; it may identify and translate an optimal arousal state that additively enhance nVNS effects on attention and alertness*. Moreso, preclinical and clinical work is required that may specify nVNS neurotransmitter (i.e., Noradrenergic, Serotonergic, Cholinergic) contribution to reduction in reaction time.

Effect of nVNS on Valence Image Anticipation Task

The top six clusters with a 9 voxel minimum separated by group and phase included: two in the left precentral gyrus, left superior frontal gyrus, left anterior insula, left anterior cingulate, and left post central gyrus (Fig 3). The left anterior cingulate and the left anterior insula are known SN anticipatory nodes (Fig 3 K–T) [32–36, 91–93]. The other brain areas include premotor regions that may relate to the increased task attention discussed above [94, 95]. They are important in the Ventral Attention Network (VAN), also known to be preferentially activated by LC-NE signaling (Fig 3 A–M) [28, 85, 87]. In these areas, nVNS study subjects demonstrate increased activation over time (phase-1 to phase-2) during negative valence image anticipation, but in contrast, demonstrate decreased activation over time during positive valence image anticipation, (Fig 3). Remarkably, the sham group response was the reciprocal pattern. Specifically, sham subjects demonstrated a decrease in brain activation over time during negative valence image anticipation and an increase in activation for positive valence image anticipation (Fig 3). As a core tenant, exogenous stimuli that present an immediate environmental threat incrementally increase LC-NE release in turn augmenting alertness and attention [25–27]. Consistently in clinical and neuroimaging studies, negatively valenced images provoke higher arousal than positively valenced images [96–98]. Aversive stimuli conditioning, known to result in arousal, are dependent on LC-NE signaling that counteract learning adaptation [24]. Other studies have demonstrated that healthy adults have enhanced activity in insular cortex during the anticipation of aversive events, [91–93, 99–108] and that individuals with anxiety demonstrate exaggerated anterior insula activity and altered activity in anterior cingulate during emotional processing [35, 109–111]. Both high density LC-NE and noradrenergic receptor concentrations found in the right hemisphere, (including right anterior insula) [28, 29, 85–87] may contribute to greater right anterior insula anticipatory response to negatively valenced stimuli in healthy controls [91, 93, 101, 104, 105, 107, 112] and in subjects prone to anxiety disorders [35, 110]. In addition to commonly reported right anterior insula activation, bilateral [99, 103, 106, 107, 110, 113] and left anterior insula response activation [92, 102] are also reported in anticipation response to negatively valenced stimuli. In a

large (N=965 individuals) meta-analysis [114], bilateral anterior insula uniformly activate in anticipation to negatively valenced stimuli. In that study, the non-uniform population included both healthy and anxious individuals, that may have contributed to their bilateral anterior insula finding. Future studies and metanalyses that covary the population (healthy and anxious or PTSD), may further support lateralized activation in aversive anticipation (right vs left anterior insula activation). Comparable to the anterior insula, anterior cingulate activation is universally reported: left, [92, 102, 106], right [115] and bilaterally [99, 103, 112, 113, 116] in aversive anticipation paradigms; likewise meta-analysis reports of bilateral anterior cingulate activation may indicate non-uniform population effects (i.e., inclusion of healthy and anxious individuals) in that study [114]. The observed (in our cohort) left anterior insula and anterior cingulate areas otherwise known to highly relate to cardiac parasympathetic responsivity, [117–119], potentially point to nVNS modulation of a valence specific autonomic arousal set point specific to our healthy control cohort. In our healthy control cohort, right sided cervical nVNS was carried out on all subjects. Canonical pre-clinical work by Randich and colleagues, (1990) [120], consistently instantiate VNS to LC projection cortical effects are predominantly contralateral to the site of stimulation, possibly explaining our observed left side (anterior insula, anterior cingulate, frontal cortex) effects. However, other as yet unstudied mechanisms may contribute in mental health populations (anxiety prone, GAD, PTSD) and therefore are not generalizable. Taken together, we hypothesize that in the nVNS group the intrinsic arousal associated with negative image anticipation met an additive threshold reciprocally activating SN nodes including the anterior insula and anterior cingulate. To our knowledge, the present study is the first to suggest that cervical noninvasive VNS improved reaction time by enhancing attentional networks during the valenced image (i.e., affective) anticipation task.

Limitations

There are limitations that need to be addressed. First, we do not have a direct measurement of vagus nerve activity. Prior work utilizing the same cervical nVNS device have found neural evidence supporting stimulation of the vagus with similar stimulation-specific sensory evoked potentials as implantable devices [121–123] and changes consistent with increases in p300b amplitude indicative of noradrenaline specific effects (auricular vagus nerve stimulation) [69, 70, 123], while one study failed to do so [124]. Future studies are planned to objectively acquire fMRI scan evoked potential measures and peripheral and central noradrenaline biomarkers (salivary alpha amylase, plasma and cerebrospinal fluid norepinephrine) that may evince parameter specific change in noradrenaline pre-to-post nVNS. Second, we do not have direct measures of skin impedance during the stimulation as the procedures were carried out in the fMRI suite; therefore, we did not calculate the current imparted at the anterior cervical skin. Future studies will calculate current and as well as complete finite element modeling to identify current density at the cervical vagus nerve. Although the target of this stimulator is the vagal nerve, cutaneous afferents to the skin and innervation of the underlying tissue may have been stimulated as well. Baseline reaction times (prior to sham or nVNS) were not measured. Future work will incorporate a within subject design that allows for measures of pre-to-post intervention reaction time. We do not have direct measure of blindness between sham and active stimulation. Future within subject study will measure pre-to-post blindness. Although substantial data support

the anticipation protocol employed in this study (>300 subjects across studies) [58, 125–132]; color (red vs green) and tone (250 Hz vs 1000Hz) effects of the anticipation stimuli may have contributed. And, although the hemodynamic response measured includes the anticipation and image presentation, future work may disambiguate the which components, i.e., color, tone, or image contribute to the observed group by phase effects. This study was carried out in healthy control subjects and as yet cannot be extrapolated to disease state populations. As this was a pilot study, the small sample size was modest and may not adequately represent a larger population, thus results should be considered preliminary. However, the positive findings observed in this small cohort of healthy control subjects were robust and significant, warranting further investigation in a larger cohort, as well as in patients with mental health disorders (Posttraumatic Stress, Depression and Generalized Anxiety Disorder) or cognitive deficits (due to traumatic brain injury, stroke, dementia, etc.). Further, the valence image anticipation task was administered 40 minutes after nVNS; dose response and duration of effects were not assessed. Prior work demonstrates LC activation maximal response at 7 minutes post nVNS stimulation. The lack of LC activation response in the current cohort is likely due to the long post stimulation scan window, i.e., 40 min post stimulation. Additional work is needed to address these methodological considerations and to evaluate whether nVNS has only short-term effects or whether longer-term improvements, through noradrenergic driven facilitation of arousal-based learning acquisition and or consolidation, can be achieved. Accumulating work from Bremner et al., (2021) provide substantial evidence of nVNS improved learning in clinical populations with PTSD over a three-day period [133–136]. The study task, a self-motivated personalized traumatic script, when coupled with nVNS likely increased perceived control contributing to enhanced extinction learning; the authors observed a reduced SN (including anterior insula, anterior cingulate) response [136]. In contrast to the self-motivated personalized traumatic script task, valence anticipation paradigms provide a model of reduced perceived control that demonstrates a clear link between anxiety proneness and exaggerated anterior insula activity [35, 108]. These task paradigm differences (self-motivated vs reduced perceived control) likely contribute to the inverse effects observed in our studies [133–136]. Although promising, more work is clearly needed that may identify optimal arousal levels titrated for disease specific (i.e., PTSD, Generalized Anxiety Disorder, Anorexia) enhanced learning.

Conclusion

This study revealed two major findings. First, when compared to sham, the nVNS group reaction time was consistently reduced for all (CPT, positive and negative) image anticipation trials. Second, we observed a valence specific nVNS neural effect; nVNS uniformly increased responsivity to negatively valenced images and decreased responsivity to positively valenced images, consistent with an extant nVNS literature suggesting that endogenous NE signaling may contribute. Future studies will be necessary to determine if the observed nVNS effects can be specifically calibrated in healthy control and mental health populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- nVNS effects, (increase in arousal and reduction in reaction time) is in part ascribed to (LC-NE) cortical signaling.
- In this study, nVNS (in contrast to sham) reduced reaction time across all valenced anticipation tasks.
- In contrast to sham, nVNS: 1) increased responsivity to images with negative valence and 2) decreased responsivity to images with positive valence.
- nVNS additive response during the negatively valenced (arousing) image anticipation tasks may have additively reduced reaction time across all valenced anticipation tasks.

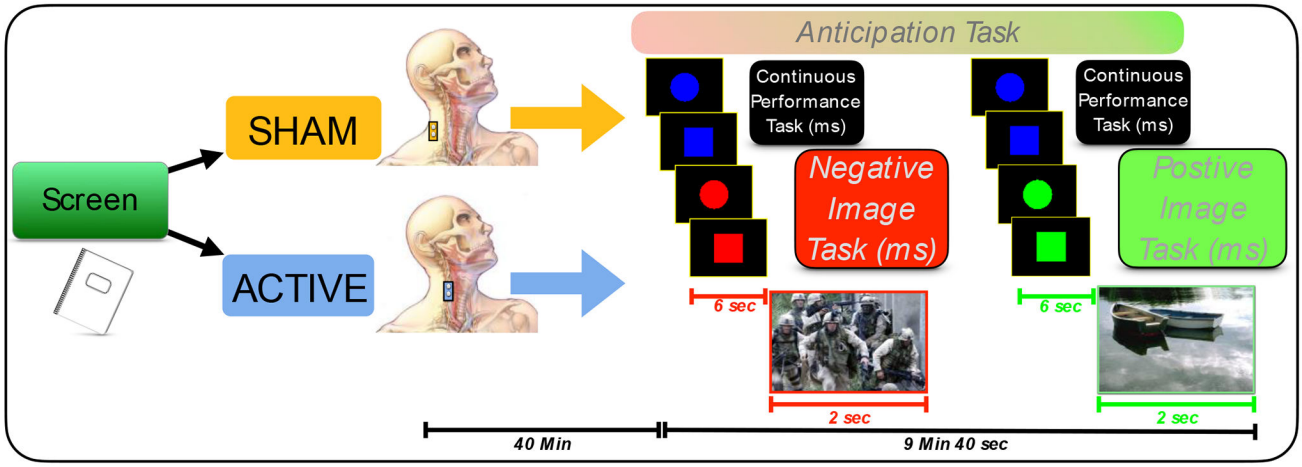

Figure 1.

Noninvasive Vagus Nerve Stimulation Study Design. Subjects were screened and randomized to either the sham treatment or nVNS group. Sham stimulation was carried out posteriolateral to the sternocleidomastoid. In the nVNS group, stimulation occurred anteromedial to the sternocleidomastoid and lateral to the trachea. 40 min after completion of stimulation (sham or nVNS), subjects participated in the functional magnetic resonance imaging anticipation task. This task combines a continuous performance task (CPT) with the interspersed presentation of affective stimuli. Subjects were asked to press a button based on a type of shape (circle or square). They were instructed that a green shape accompanied by a low pitch tone indicated a positive image would appear (6 sec). In contrast, a red shape accompanied by a high pitch tone signaled an impending negative image (6 sec). Images displayed (2 sec) in this paradigm were taken from the International Affective Picture System (IAPS) [59].

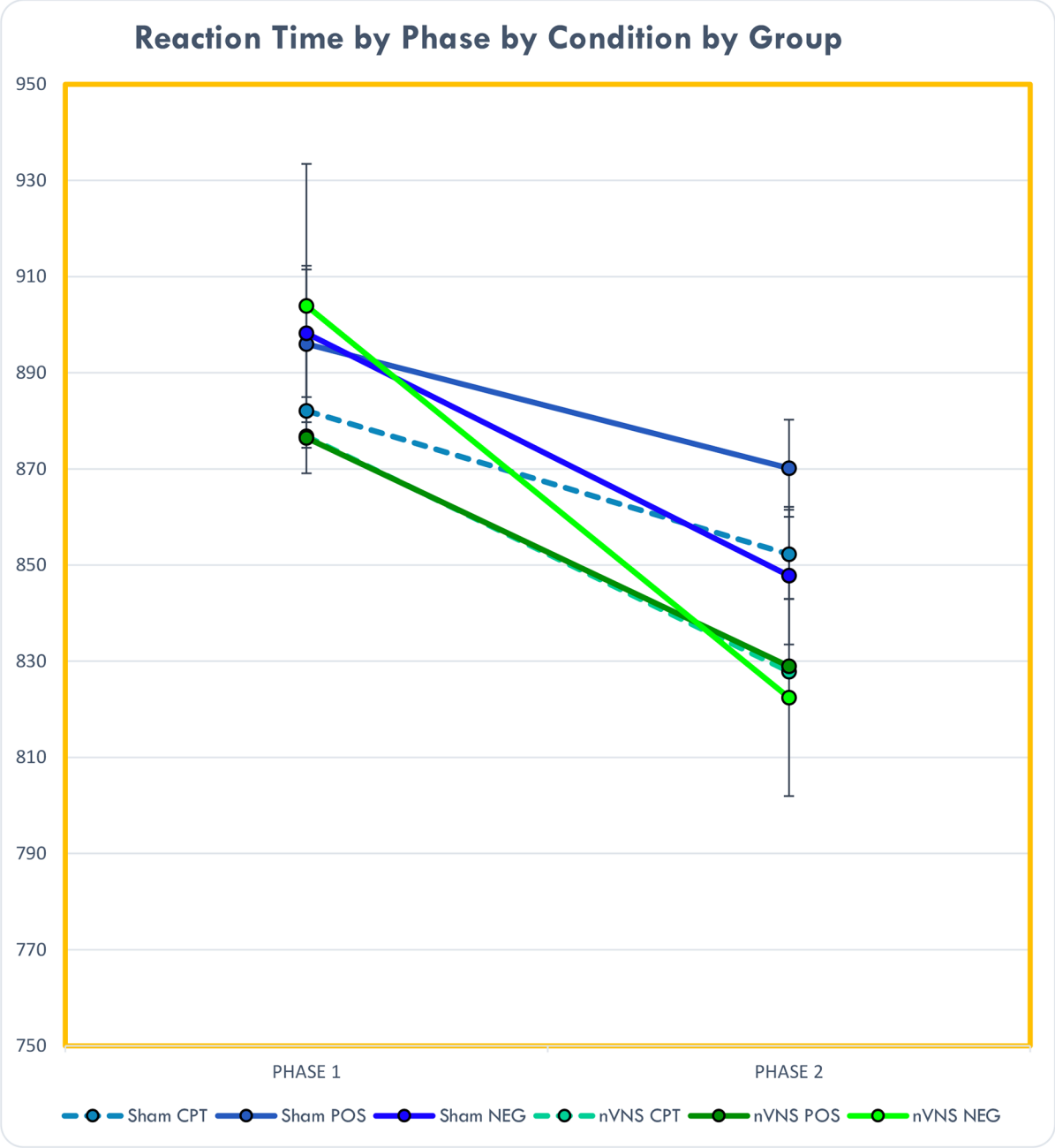

Figure 2.

Reaction time across phases (1–2) demonstrate a group*phase (p=.01) significant effect; the nVNS group showed greater reduction in reaction time over the duration (phase 1–2) of the image task when compared to sham for Continuous Performance Task (CPT), as well as for the positive and negative imagery. Reaction time for all image tasks over all phases (i.e., CPT, positive and negative, for phase 1–2) improved in the nVNS group. (+/− is reported as Standard Error, CPT=Continuous Performance Task, POS=positive image task, NEG=negative image task, nVNS=Non-invasive Vagus Nerve Stimulation, Sham=sham device, Phase 1=1st 1/2nd of task duration Phase 2=2/2nd of task duration).

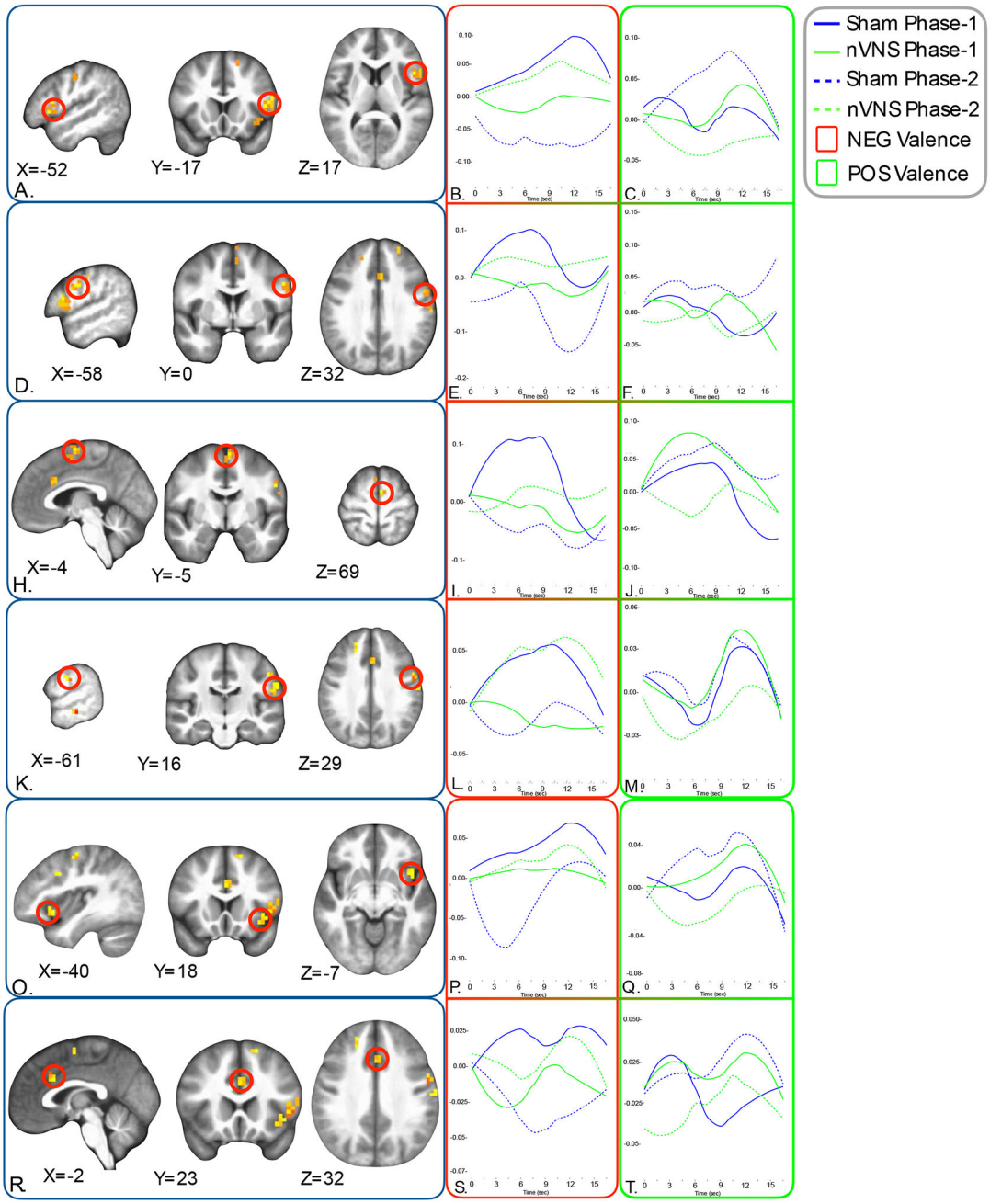

Figure 3.

Group*Valence*Phase analysis separated into 1st (solid line) and 2nd phase (dashed line) demonstrate left precentral gyrus, Broadman Areas (BA) 44, (A), and BA6 (D, H), left post central gyrus BA3 (K), left anterior insula BA13 (O) and left anterior cingulate BA32 (R), ($p<.000001$). During the valence anticipation task, Group*Valence*Phase analyses of negative imagery (red box) demonstrate nVNS phase 1 low response followed by consistent greater response during phase 2; in converse, sham stimulation response was greatest during phase 1, but decreased during phase 2 (B, E, I, L, P, S). During the valence anticipation task, Group*Valence*Phase analyses of positive imagery (green box) demonstrate nVNS initial

phase 1 greater response followed by consistent low response during phase 2; in converse, sham stimulation response was low during phase 1, but increased significantly during phase 2 (C, F, J, M, Q, T) for all ROI.

Table 1.

Demographic and affective measurement in nVNS and Sham groups.

	nVNS	**Sham**	
Age (years)	25 (18, 31)	28 (18, 54)	0.410[a]
Sex	8M:4F [66%, 33%]	7M:5F [58%: 41%]	0.673[b]
Race			
Asian	4 [33%]	4 [33%]	
Black	0 [0%]	1 [8.3%]	0.428[b]
White	7 [58%]	7 [58%]	
Other	1 [8.3%]	0 [0%]	
BAI	2.41 (0.0, 13.0)	2.58(0.0, 12.0)	0.79[a]
BDI-2	3.25 (0.0, 17.0)	2.91 (0.0, 14.0)	0.97[a]
PCL-C	18.5 (17.0, 28.0)	19.75 (17.0, 28.0)	0.19[a]

BAI = Beck Anxiety Inventory; BDI-2 = Beck Depression Inventory 2; PCL-C = Posttraumatic Stress Disorder Check List–Civilian version.

a=Mann Whitney U statistical test.

b=Log-Likelihood.

() connote data ranges, [] connote percentile of overall group.

Table 2.

Whole-brain linear mixed effects results.

Voxels	x	y	z	F-Value	Region	BA
32	−52	17	9	33.413	Left Precentral Gyrus (44)	44
11	−58	0	32	32.404	Left Precentral Gyrus	6
10	−40	18	−7	28.586	Left Anterior Insula, Inferior Frontal Gyrus	13, 47
10	−61	−16	29	30.671	Left Postcentral Gyrus	3
10	−2	23	32	34.006	Left Cingulate Gyrus	24, 32
9	−4	−5	69	33.424	Left Superior Frontal Gyrus	6
8	39	−58	−38	28.673	Right Tuber	NA
6	−12	38	−28	30.781	Left Orbital Gyrus	11
6	−45	9	39	34.136	Left Middle Frontal Gyrus	9
6	−53	−13	45	27.827	Left Precentral Gyrus	3
6	5	11	69	28.536	Right Superior Frontal Gyrus	6
5	−25	56	28	31.947	Left Superior Frontal Gyrus	10
5	−42	−11	59	31.193	Left Precentral Gyrus	6
4	−26	−42	−38	30.217	Left Cerebellar Tonsil	NA
4	−64	−26	−12	40.139	Left Middle Temporal Gyrus	21
4	−47	37	−12	27.946	Left Inferior Frontal Gyrus	47
4	20	41	33	27.842	Right Superior Frontal Gyrus	9
4	−5	2	61	27.306	Left Superior Frontal Gyrus	6
4	−15	18	61	28.665	Left Superior Frontal Gyrus	6
4	8	−22	82	30.788	Right Paracentral Lobule	NA

Note: Abbreviations: Broadman Area = BA. *F*-value reflects peak, *F*-Value within the cluster. Voxel- size = 4 mm^3. Cluster-thresholded, $p <$ .000001; F-Value threshold was 24.22, with whole-brain cluster-corrected < 0.000001 ($k > 4$ voxels).