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Research paper

Effect of transcutaneous cervical vagus nerve stimulation on declarative and working memory in patients with Posttraumatic Stress Disorder (PTSD): A pilot study

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD) is associated with changes in multiple neurophysiological systems, including verbal declarative memory deficits. Vagus Nerve Stimulation (VNS) has been shown in preliminary studies to enhance function when paired with cognitive and motor tasks. The purpose of this study was to analyze the effect of transcutaneous cervical VNS (tcVNS) on attention, declarative and working memory in PTSD patients.

Methods: Fifteen PTSD patients were randomly assigned to active tcVNS ($N = 8$) or sham ($N = 7$) stimulation in a double-blinded fashion. Memory assessment tests including paragraph recall and N-back tests were performed to assess declarative and working memory function when paired with active/sham tcVNS once per month in a longitudinal study during which patients self-administered tcVNS/sham twice daily.

Results: Active tcVNS stimulation resulted in a significant improvement in paragraph recall performance following pairing with paragraph encoding for PTSD patients at two months ($p < 0.05$). It resulted in a 91 % increase in paragraph recall performance within group ($p = 0.03$), while sham tcVNS exhibited no such trend in performance improvement. In the N-back study, positive deviations in accuracy, precision and recall measures on different day visits (7,34,64,94) of patients with respect to day 1 revealed a pattern of better performance of the active tcVNS population compared to sham VNS which did not reach statistical significance.

Limitations: Our sample size was small.

Conclusions: These preliminary results suggest that tcVNS improves attention, declarative and working memory, which may improve quality of life and productivity for patients with PTSD. Future studies are required to confirm these results.

1. Introduction

Modern science and technology have made great advances in the diagnosis and treatment of mental health conditions; however, many patients continue to suffer from stress-related conditions including post-traumatic stress disorder (PTSD). PTSD is an extreme mental health

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condition associated with changes in multiple neurophysiological systems, including increased inflammatory and sympathetic autonomic functions as well as deficits in verbal declarative memory. Many patients have limited or no response to currently available treatments in terms of PTSD symptoms and associate cognitive dysfunction. According to the American Psychiatric Association, exposure to traumas including accidents or other life-threatening incidents can initiate the development of PTSD, a complex syndrome involving the core symptoms of hyperarousal, avoidance and re-experiencing symptoms along with associated deficits in concentration and memory (Hou et al., 2007; Williams and First, 2013). PTSD is associated with failures to resist thinking about and re-experiencing the trauma, as well as deficits in concentration, verbal declarative memory, autobiographical and finding-your way memory, which are felt to be mediated at least in part by deficits in hippocampal function (Bremner et al., 1993, 1995, 1997, 2003, 2004a, 2004b, 2021a; Bremner and Vermetten, 2012; Douglas Bremner et al., 1995; McNally et al., 1994; St. Jacques et al., 2011; Tollenaar et al., 2009).

Neuromodulation therapy is a new form of therapy that may be specifically beneficial in addressing the neuro-psychobiology of psychiatric disorders related to stress (Bremner et al., 2021b; Wittbrodt et al., 2021). Vagus Nerve Stimulation (VNS) is a form of neuromodulation approved by the Food and Drug Administration (FDA) for the treatment of epilepsy and treatment-refractory depression based on its efficacy in the treatment of these disorders. The surgically implantable vagus nerve stimulation (VNS) device is limited by its high cost and inconvenience. In contrast, a new generation of noninvasive and non-implantable handheld VNS device has a capability to be used in wide-ranging applications due to its greater convenience, cost effectiveness and ease of use. There are two vagus nerves on both left and right sides of human body, running from the brainstem through the cervical area to the chest and abdomen, as well as afferent fibers that project to the brain. The vagus nerve, the longest mixed cranial nerve, has multiple branches, including the cervical and auricular branch, and it contains both efferent (motor) and afferent (sensory) fibers, the distribution of which may differ in various locations and activation of which may produce different effects. The VNS device is applied to vagus nerve branches in the ear, which is called transcutaneous auricular VNS (taVNS), or in the neck, called transcutaneous cervical VNS (tcVNS) (Bremner et al., 2021b; Yap et al., 2020). Previous works reported that tcVNS stimulation in traumatized healthy subjects with and/or without PTSD suppressed peripheral sympathetic autonomic functions and enhanced parasympathetic functions at baseline and in response to individual trauma scripts and mental stress sources (Bremner et al., 2021b).

Previous studies show that VNS may be helpful for enhancement of neurocognitive abilities such as attention, recalling ability, memory capacity, cognitive flexibility and planning, and executive functioning (Boon et al., 2006; Broncel et al., 2017; Clark et al., 1999; Driskill et al., 2022; Ghacibeh et al., 2006; Kaan et al., 2021; McIntire et al., 2021a; McIntire et al., 2019; McIntire et al., 2021b; Sun et al., 2017; Vonck et al., 2014). An initial study to investigate the improvement in working memory was presented by (Sun et al., 2017) in epilepsy patients, where implant VNS was used with a computer-based visual attention test. Noninvasive transcutaneous VNS was also explored to study on verbal or item order memory on healthy young adults (Kaan et al., 2021), where stimulation was applied during the entire duration of this study. Most of the methods suffered with either of the following: were less accurate and showed no consistency in performance, were not focused on PTSD or other acute distress syndromes, and relied on invasive VNS techniques causing inconvenience to the patients. The tcVNS neuromodulation treatment can help reducing forgetfulness, strengthening memory, and enhancing attention, possibly in part by suppressing stress reactivity of sympathetic and inflammatory systems in PTSD. Memory is classified into three types: sensory or iconic memory, short-term memory, and long-term memory (Camina and Güell, 2017). Short-term, or episodic or declarative memory refers to the ability to remember facts or lists, such as a number of items to buy at the grocery store. Working memory is closely related to short-term memory and refers to a part of the brain system responsible for providing temporary storage and tweaking the information necessary for some complex cognitive tasks. In cognitive neuroscience and psychology, short-term memory assessment is performed using recall tests in which participants are given with specific stimuli and then, after a delay, are analyzed by their responses of recalling as many of that stimuli as possible (Goldstein, 2014). Memory performance of a participant can be evaluated by estimating the percentage of stimuli he/she was able to remember. Working memory is assessed with tasks that require an individual to analyze multiple pieces of information at the same time.

The aim of this study was to assess attention, short-term and working memory during noninvasive tcVNS stimulation in patients with PTSD. Patients with PTSD underwent stimulation with double-blind active or sham tcVNS paired with short term declarative memory tasks including paragraph encoding followed by recall and N-back tests. We analyzed the effect of active/sham tcVNS during paragraph encoding and working memory tasks (N-1 back) of PTSD patients and assessed paragraph recall and N-1 back performance. It was hypothesized that the active tcVNS group would perform better in both memory assessment tests after a period of two months or more of treatment.

2. Materials and methods

2.1. Participants

The current research was approved by the Institutional Review Boards of Emory University (#IRB00091171), Georgia Institute of Technology (#H17126), and the Space and Naval Warfare Systems Command (SPAWAR), Center of the Pacific and the Department of Navy Human Research Protection Program. PTSD Patients were investigated from February 2019 to March 2020 at the Emory University School of Medicine (ClinicalTrials.gov #NCT02992899). Individuals gave written informed consent before participating in the study. We enrolled physically healthy subjects, aged 27–53, having any exposure of prior psychological trauma and current clinical diagnosis of PTSD. Subjects were excluded from the study if they were diagnosed with schizophrenia, bipolar disorder, schizoaffective disorder, bulimia or anorexia as determined by The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Williams and First, 2013). Subjects were also excluded with traumatic brain injury (TBI), current pregnancy, meningitis, current evidence or history of serious clinical or neurological illness. A total of 64 subjects were screened for eligibility; out of them, 15 subjects were enrolled and randomly chosen for active ($N = 8$) or sham ($N = 7$) VNS stimulation. PTSD patients represent a subset of a previously reported cohort and details of the entire protocol are provided in a previous publication (Bremner et al., 2021b). A baseline demographic of both active and sham groups is presented in Table 1.

The participants were randomly selected into active or sham groups in a double blinded approach. The tcVNS devices were randomly allocated by personnel who were not involved in the research. The researchers and subjects were blinded to the type of stimulus. Statistical analyses were performed by a bio-statistician who did not get involved

Table 1
Baseline demographics in active and sham VNS groups for the longitudinal study.

Details	Active VNS	Sham VNS	Overall
Total involved subjects	8	7	15
Gender (M/F)	5 M, 3 F	5 M, 2 F	10 M, 5 F
Age (yrs)	39.43 ± 11.44	41.53 ± 14.45	40.41 ± 12.98
Weight (lbs)	192 ± 60.44	187.14 ± 45.19	189.73 ± 53.92
Height (inches)	67.06 ± 4.33	67.43 ± 4.34	67.23 ± 4.33
BMI	29.47 ± 6.95	28.68 ± 4.89	29.1 ± 6.09

Demographic variables are in the format of mean ± standard deviation.

in data acquisition or its processing. Both stimulation groups were unblinded for statistical analyses.

2.2. Study design

The participants shared their traumatic experiences, and personalized traumatic scripts were generated out of them to increase their stress levels during the study. In the first day, six traumatic scripts (each of 1 min. approximately) and six neutral scripts (to induce neither positive or negative feelings), were provided through headphones. As the traumatic stress recording ended, active or sham tcVNS stimulation was applied on the left-side of the neck by the researcher. In the current study for memory assessment tasks, the participants were stimulated for 2 min. during encoding, which was when they were hearing the paragraph. Thereafter, paragraph recall test followed by N-back test were performed. Stimulation was also delivered during performance of the N-back. After each task, behavioral ratings were also provided using Visual Analogue Scales (VAS) rating. On the same day, two active or sham VNS were applied without using any stressor. Blood draws were also collected on starting of the day (called baseline) and at different timepoints after. Patients were followed up for three months periodically in 7, 34, 64 and 94 days, and all the same study protocols were followed for memory assessments. Participants were provided with the device for self-administration at their home. The instruction was given to stimulate for 2 min on the left side of the neck, then a 1 min rest, followed by 2 min. on the right side, and to repeat this once at morning time and once during night. They were suggested further to perform stimulation when personalized trauma scripts were listened two times in a week. They carried on VNS stimulation twice in a day for 3 months and returned once in a month for behavioral assessments. After a period of three months, participants were provided an active VNS device and suggested to keep on twice daily VNS modulation.

2.3. Transcutaneous cervical vagus nerve stimulation

Both active and sham tcVNS stimulations were administered using small handheld devices that aim to modulate the cervical vagus nerve from the skin surface noninvasively (GammaCore, ElectroCore, Basking Ridge, New Jersey). The device uses stainless steel electrodes with an electrically conductive gel mounted on the left side of the neck area near thyroid cartilage. The placement area is determined by perceiving palpations on the carotid artery (Fig. 1). Active VNS device generates an alternating voltage signal comprising of five sine bursts of 5 kHz (1 ms of 5 sine waves having 40 ms pulse width) at a frequency of 25 Hz envelopes. The rate of 25 Hz was selected based on previous research works demonstrating to optimize the effects on neurobiological autonomic functions and other related measures at this rate (Bremner et al., 2021b). However, the sham devices generate an alternating and biphasic voltage signal comprising of 0.2 Hz square pulses with a 5 s pulse width that induces a mild sensation. Amplitudes of the peak voltage for active and sham VNS device were set to 30 v and 14 v, respectively. Applying these voltage levels directly to the skin activates skin nociceptors causing a sensation feeling. Hence, these levels are considered to be sufficient to blind the participants about the stimulus type. Earlier research works have reported that anatomical location left or right cervical vagus nerve does not matter for stimulation, the effects in the brain are bilateral (Chen et al., 2015, 2016). Also, performing right and left VNS stimulation one after another, 2 min. for each, significantly reduces mean Cortical Spreading Depression (CSD) frequency (Chen et al., 2016). Thus, in our study, participants were instructed for twice daily self-stimulation for 2 min on the left side of the neck, then a 1 min. pause, followed by 2 min. on the right side. However, they were stimulated on the left side for 2 min. during the memory assessment tests.

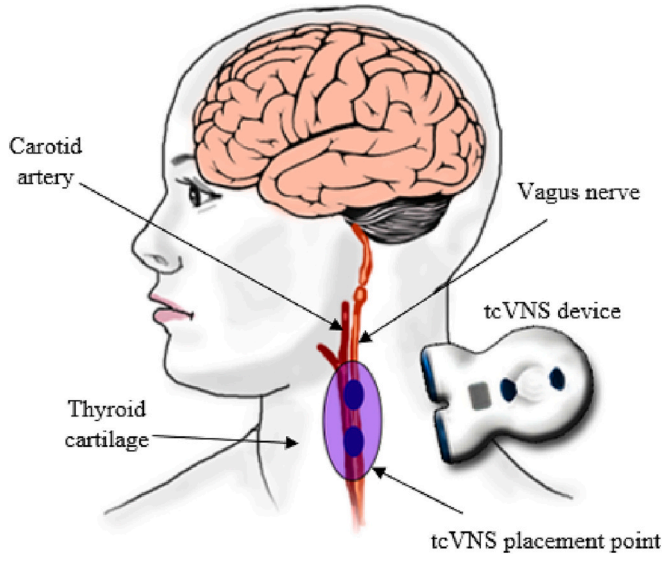

Fig. 1. Device placement for tcVNS on the neck near the vagus nerve as it runs through the carotid sheath.

2.4. Memory assessment tests: paragraph recall and N-back studies

Two memory recall and working memory tests were performed in the study, namely paragraph recall and N-back tests. Participants initially underwent testing with the Wechsler Memory Scale (WMS) at baseline in which participants read a paragraph from a story, and then were asked to remember the paragraphs with immediate recall and delayed recall. Paragraph recall was then performed on PTSD patients on successive day visits (7, 34, 64). In each visit, a paragraph (standardized by (Craft et al., 1996)) was recited to them verbally in conjunction with the stimulation. The study is illustrated by a flow chart in Fig. 2(A). Based on their recalled word count, a score was given. For a day-visit or session-wise performance evaluation, recall scores were collected and

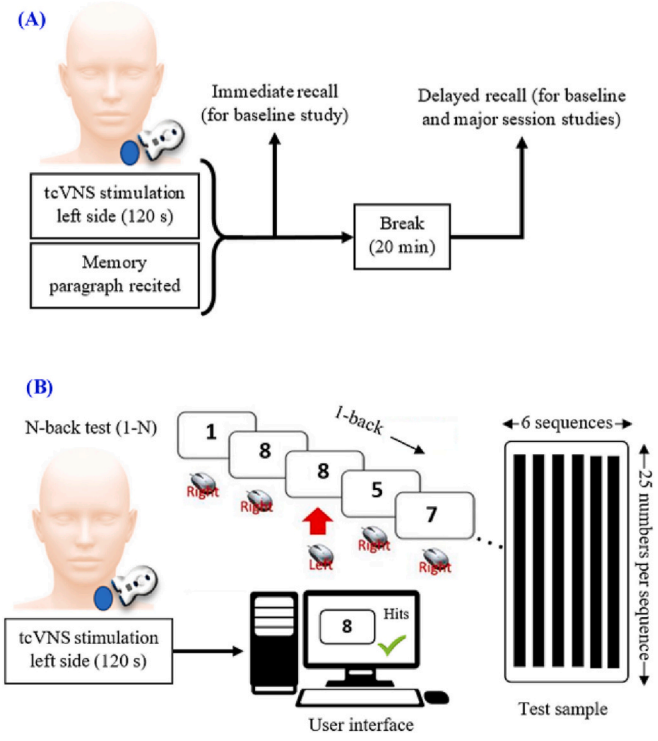

Fig. 2. Flow chart showing study protocol for (A) paragraph memory recall, and (B) N-back test.

statistically analyzed for active and sham groups for all sessions/day-visits of participants. The variation in session-wise performance were also studied by computing the average scores for each session for active and sham groups, and determining mean score difference of a specific session (or day-visit) to the 7th day. In addition, baseline study was also performed without any vagus nerve stimulation. The performance for two different stories were evaluated at 0 min. delayed recall. Due to the nature of the study protocol, patients performed both immediate and delayed recall at baseline using the WMS but only delayed recall after stimulation was paired with encoding on days 7, 34, and 64. Therefore the baseline WMS could be used to show no differences at baseline in verbal declarative memory between the groups but not as a baseline for subsequent paragraph administrations. However, we were able to compare groups and progression over time on days 7, 34 and 64 on which days participants received novel paragraphs that had been validated as matching in word frequency, syllable and length using methods previously described (Bremner et al., 2004b, 2004c). Independent two-tailed *t*-tests were used to compare the performance characteristics for the active tcVNS and sham stimulation groups. Paired two-sample t-tests were applied to compare the responses of memory assessment before and after the treatment with $p < 0.05$ showing statistically significant.

N-back test is a continuous performance task for the assessment of working memory and its capacity. In our study, participants were presented a list of numbers from 0 to 9 in a long sequence, and asked to judge whether the current number had a match with the number displayed N numbers ago. Participants were subjected for '1-N' N-back test in which they had to remember the position of the item, one turn back. The test was performed in different sessions or day visits (1, 7, 34, 64, 94) immediately after stimulation. In each visit, six sets of sequences, each containing 25 numbers, were presented to the participants through a user interactive screen one after another. They were asked to respond by hitting a specific button for a 1-back match. It is demonstrated in Fig. 2(B). Thus, patient responses collected for 6 sequence sets in each session were analyzed statistically to show the performance of both active and sham groups.

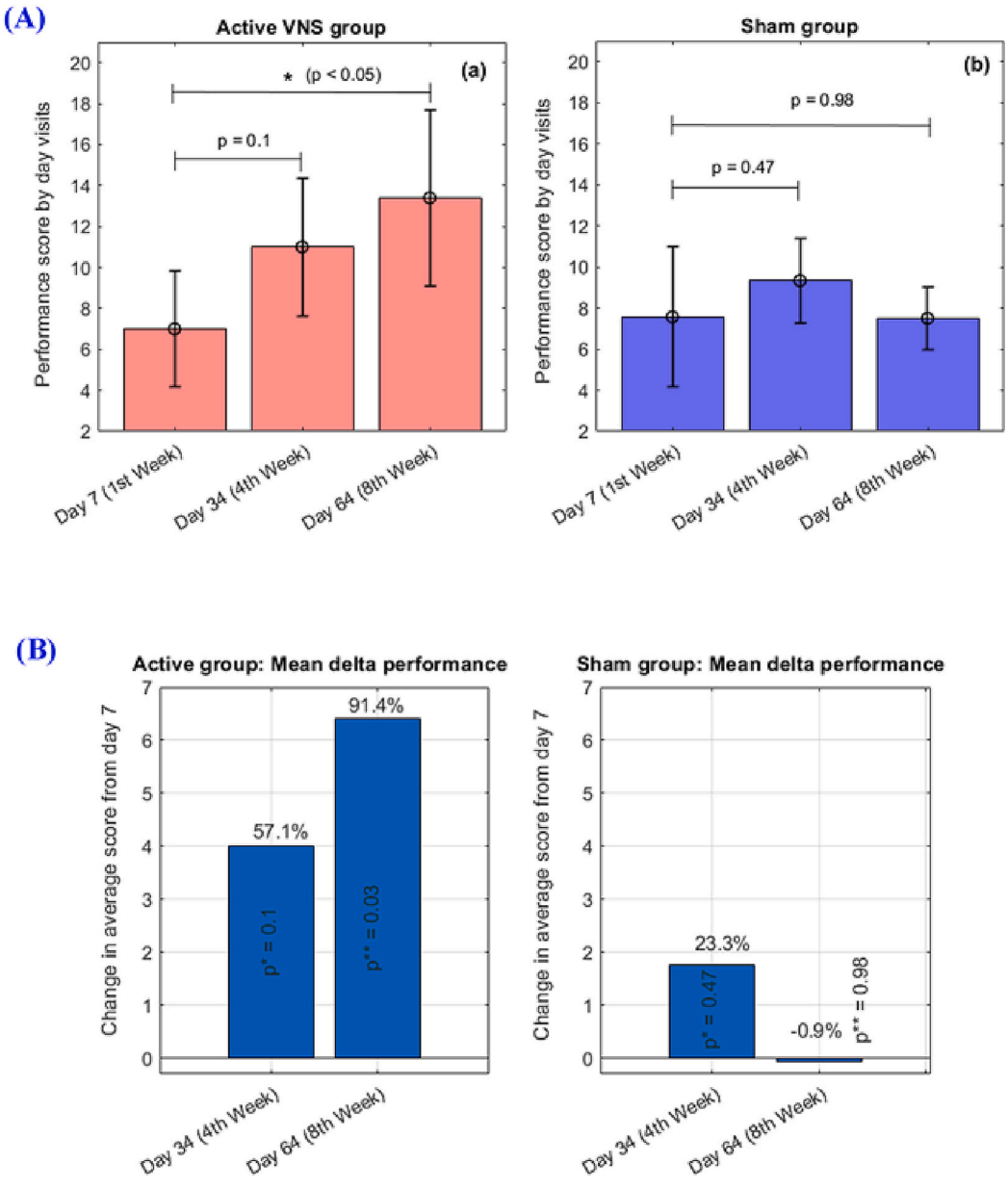

Fig. 3. Effect of active VNS and sham on paragraph recall performance in 7th, 34th and 64th days of participants' visits during their acute stress treatment. Panel (A): Recall performance scores for (a) active VNS group in red bars, and (b) sham group in blue bars. Black vertical lines with circles and bars represent mean and standard deviation of scores on specific days, respectively. Panel (B): Change in average performance score from day 7. Day-wise paragraph recall performance on longitudinal PTSD data (Note that p* and p** denote significance in performance difference of day 7th with 34th and 64th days, respectively). With the VNS stimulation, a significant improvement in the performance is observed in day 64 by 91.4 % from day 7 ($p < 0.05$). While sham group does not perform well with their treatment sessions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

In this study, we present longitudinal assessment of the effects of stimulation on declarative and working memory of both active tcVNS ($N = 8$) and sham ($N = 7$) groups. The participant stimulation groups were similar in sex, age, body mass index (BMI), number of subjects, height, and weight as shown by Table 1.

3.1. Paragraph recall performance

For the paragraph recall performance evaluation, session-wise analysis was performed on scores obtained by specific day-visit of a patient. The performance is visualized in terms of mean ± standard deviation for each day-visit as shown by error bar plot in Fig. 3(A). It shows the effect of tcVNS on declarative memory when paired with memory encoding for patients with PTSD measured by paragraph recall performance. In Fig. 3(A)(a), graph suggests a statistically significant increment in the performance from day 7 to day 64 within the active tcVNS stimulated group ($p < 0.05$), while no such trend can be observed within the sham group. Additionally, changes in average performance scores were analyzed by evaluating mean score difference of a specific day visit to 7th day performance. It is illustrated in Fig. 3(B), which shows a significant improvement in the performance in day 64 by 91.4 % from day 7 ($p < 0.05$); while the performance becomes poor in the sham group. The performance results suggested that active VNS group developed a better paragraph recall ability over time as compared to sham. Also, a baseline study was performed in which an average performance for two different stories was evaluated under immediate and 20 min. delayed recall. The baseline results are listed in Table 2. Since there were no stimulation applied, the performance results for both the groups were similar and comparable on immediate recall ($p = 0.87$) and 20 min. delayed recall ($p = 0.69$).

3.2. N-Back performance

The N-back tests were performed with 6 active VNS and 7 sham participants from the same population we used for the paragraph recall test. In each session (or day-visit), participant responses were collected for 6 sequence sets, each consisting of 25 numeric entries ranging from 0 to 9. These matching responses were analyzed using the statistical metrics such as accuracy (*Acc*), precision (*Pr*), and recall (*Re*). These measures can be expressed as follows:

$$\mathrm{Acc} = \frac{\mathrm{TP} + \mathrm{TN}}{\mathrm{TP} + \mathrm{TN} + \mathrm{FP} + \mathrm{FN}}$$

$$Pr = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FP}}$$

$$Re = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}}$$

Table 2
Baseline paragraph recall performance of active and sham VNS population, when stimulation was not supplied.

Details	Active (recall type, story A & B)		Sham (recall type, story A & B)	
	Immediate	20 min delayed	Immediate	20 min delayed
Total involved subjects	7	7	7	7
Average performance	17.93	16.29	18.71	14.57
Standard deviation	8.31	7.57	8.63	8.11
Median performance	18	15	17.5	12

where TP, TN, FP and FN denote true positive, true negative, false positive, and false negative in the response of participants. The performance metrics (Acc, Pr and Re) evaluated session-wise for each subject were averaged for all 6 sets of sequences. Then, delta (difference of) performances of days 7, 34, 64, 94 from first day performance were estimated for each subject. Thereafter, groupings of performances were made for each of the sessions. Finally, for each of the metrics, mean and standard deviation of delta scores were evaluated day-wise and represented through error-bar plots for accuracy in Fig. 4(A), precision in Fig. 4(B), and recall in Fig. 4(C). From these quantitative measures, it can be observed that the differences of performance metrics of specific sessions (7, 34, 64, 94) with respect to first day performance show positive deflections for the active VNS group that correspond to improvements in their working memory performance, whereas the working memory performance tended to be worse for the sham stimulation group as shown by negative or zero differences mostly. This relation is found true and consistent for all three performance-metrics across all longitudinal sessions and both active tcVNS and sham groups as shown by Fig. 4. Active tcVNS group had a pattern of better performance (average differences in ΔAcc from active to sham in all 4 sessions with respect to day 1 are 3.22, 4.39, −0.06, and 3.4) that did not reach statistical significance due to small sample size.

4. Discussion

This pilot study showed that tcVNS had a positive effect on declarative and working memory in patients with PTSD as measured with the paragraph recall and the N-back tests when tcVNS stimulation was paired with paragraph encoding and N-back performance, respectively. The results showed that the active tcVNS group performed better in both memory assessment tests. Over the course of three months of twice daily home-based tcVNS self-administered treatments the active group developed better attention and recall of paragraphs encoded with stimulation as well as for working memory tasks as compared to sham. This longitudinal study shows benefit for cognitive symptoms associated with PTSD and suggests that tcVNS may improve work and social functioning for patients with PTSD.

The effects of tcVNS on declarative and working memory in PTSD patients may have broader implications for interventions for PTSD. Prior studies have shown that VNS has effects on neural plasticity, fear circuits in the brain, learning and memory, and autonomic function that may be beneficial in PTSD (Noble et al., 2019, 2017; Peña et al., 2014, 2013; Player et al., 2014). Animal studies show beneficial effects of VNS on neural plasticity, when paired with an auditory tone in animal models of tinnitus (Engineer et al., 2015, 2011; Li et al., 2015; Shim et al., 2015). And studies in patients with tinnitus show similar benefit when VNS is paired with a tone (Shim et al., 2015). Animal studies also show improvement in motor function when paired with training following a stroke affecting motor function (Hays, 2016; Hays et al., 2016, 2014; Khodaparast et al., 2016; Liu et al., 2016; Porter et al., 2012; Pruitt et al., 2016). VNS also promotes learning and memory in patients with Alzheimer's disease (Jacobs et al., 2015; Merrill et al., 2006; Sjogren et al., 2002). VNS enhances memory with a U-shaped curve n (Clark et al., 1998, 1995; Smith et al., 2006, 2005; Williams and Jensen, 1993) acting through afferent fibers of the vagus and the locus coeruleus, noradrenergic neurons, and beta-adrenergic receptors in the hippocampus to enhance synaptic transmission, long-term potentiation and neurogenesis (Clark et al., 1998; Hassert et al., 2004; Revesz et al., 2008; Shen et al., 2012; Ura et al., 2013; Zuo et al., 2007). This research design may show usefulness of VNS for improvement of deficits in hippocampal-based declarative memory as well as working memory deficits in PTSD. Additionally, VNS-induced promotion of hippocampal plasticity may be beneficial for the relief of symptoms of PTSD as well as depression (Diamond et al., 1995; Duman, 2004; Duman et al., 2001, 1997; Santarelli et al., 2003).

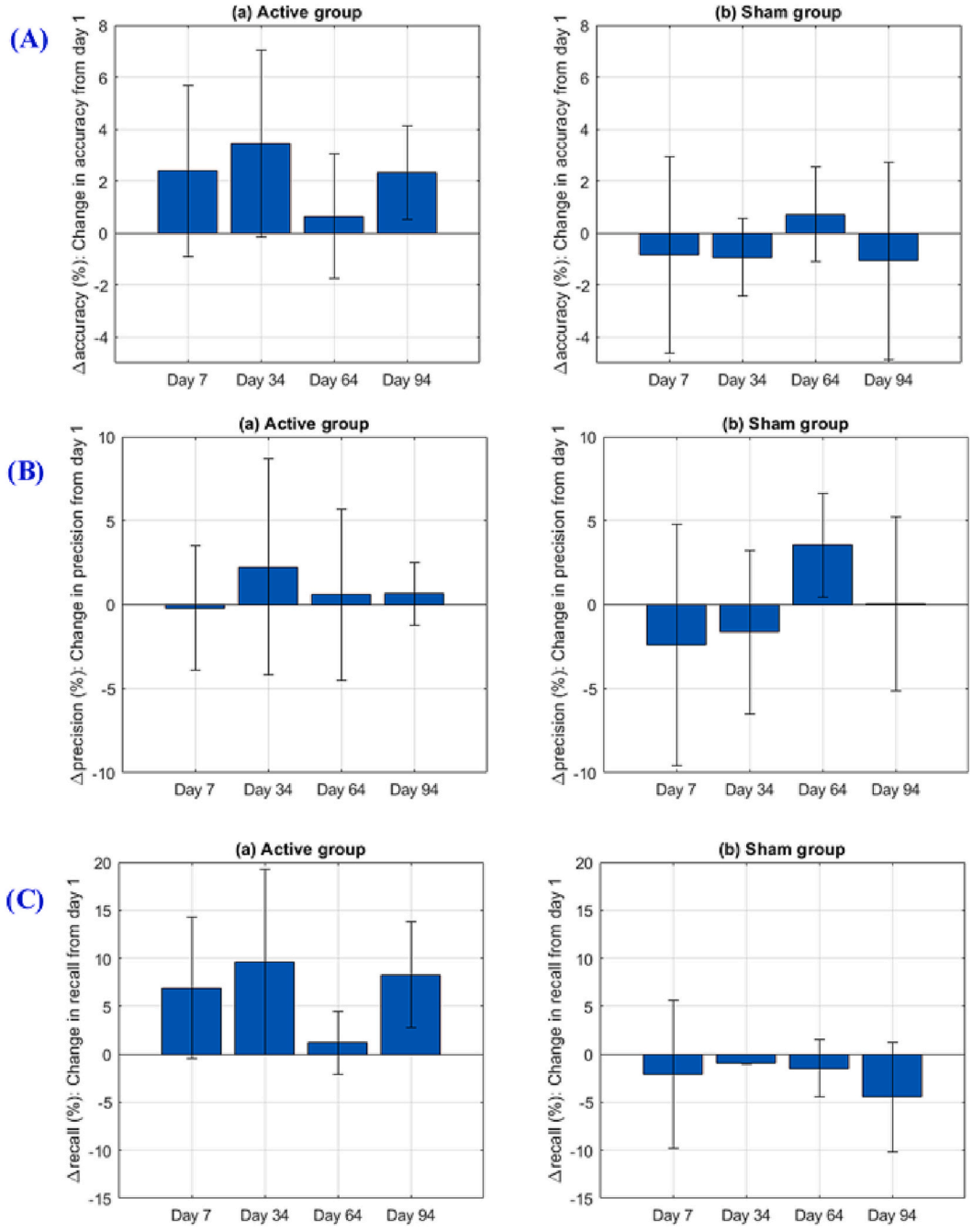

Fig. 4. Change in day-wise accuracy measures from day 1. Active VNS group, showing positive deflections in (A) ΔAcc, (B) ΔPr, and (C) ΔRe, performed better in the N-back study.

This study has several limitations. The sample size was small and assessments were missing at some time points. Paragraph recall at baseline was tested with the Wechsler Memory Scale which involves both immediate and delayed recall. Since the subsequent paragraph encoding and recall tests were performed only with delayed recall, we were unable to use the WMS paragraphs as baseline. Nevertheless, this study showed an improvement in paragraph recall over the course of treatment as well better recall in the active versus the sham group at each point of the study while the baseline pre-treatment performance on the WMS was identical between the two groups. The current study needs to be validated with a comprehensive large sample size for a better generalizability. The active and sham devices were designed to perform a similar sensation of stimulation. However, a limitation was that we did not collect data on the participants perception of whether they were receiving active or sham treatments so we could not determine if they were able to accurately guess the treatment. Future studies are needed to replicate these results and determine if the effects of tcVNS on cognition and memory are applicable to healthy subjects and other patient groups.

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CRediT authorship contribution statement

T.C. performed research analysis and wrote the manuscript; J.D.B., O.I., M.E., and N.E. helped in designing research, and read and approved the final manuscript; N.G., A.R. and M.W. contributed in data collection, interpretation and manuscript reading. V.V. and A.S. read, suggested feedbacks, and approved the final manuscript.

Declaration of competing interest

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