Transcutaneous Cervical Vagus Nerve Stimulation Inhibits the Reciprocal of the Pulse Transit Time's Responses to Traumatic Stress in Posttraumatic Stress Disorder*

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Abstract— Research has shown that transcutaneous cervical vagus nerve stimulation (tcVNS) yields downstream changes in peripheral physiology in individuals afflicted with posttraumatic stress disorder (PTSD). While the cardiovascular effects of tcVNS have been studied broadly in prior work, the specific effects of tcVNS on the reciprocal of the pulse transit time (1/PTT) remain unknown. By quantifying detectable effects, tcVNS can be further evaluated as a counterbalance to sympathetic hyperactivity during distress – specifically, we hypothesized that tcVNS would inhibit 1/PTT responses to traumatic stress. To investigate this, the electrocardiogram (ECG), photoplethysmogram (PPG), and seismocardiogram (SCG), were simultaneously measured from 24 human subjects suffering from PTSD. Implementing state-of-the-art signal quality assessment algorithms, relative changes in the pulse arrival time (PAT) and the pre-ejection period (PEP) were estimated solely from signal segments of sufficient quality. Thereby computing relative changes in 1/PTT, we find that tcVNS results in reduced 1/PTT responses to traumatic stress and the first minute of stimulation, compared to a sham control (corrected p < 0.05). This suggests that tcVNS induces inhibitory effects on blood pressure (BP) and/or vasoconstriction, given the established relationship between 1/PTT and these parameters.

Clinical Relevance— Relative changes in 1/PTT are induced by varying vasomotor tone and/or BP – it has therefore piqued considerable interest as a potential surrogate of continuous BP. Studying its responses to tcVNS thus furthers understanding of tcVNS-induced cardiovascular modulation. The positive effects detailed herein suggest a potential role for tcVNS in the long-term management of PTSD.

I. INTRODUCTION

Severe distress negatively affects the autonomic nervous system by disrupting sympathovagal balance [1]. Heightened sympathetic ("fight or flight") arousal relative to parasympathetic ("rest and digest") activity results in
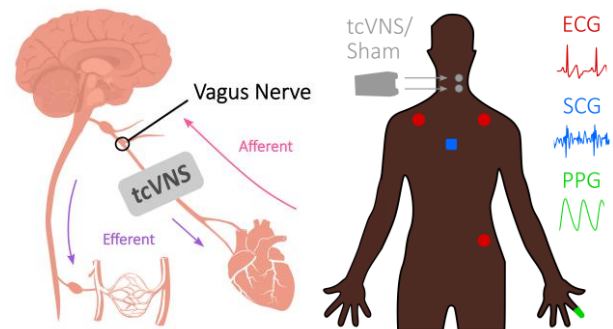

Fig. 1. **The vagus nerve and the cardiovascular system: sensing and modulation. (Left)** Transcutaneous cervical vagus nerve stimulation (tcVNS) non-invasively targets the vagus nerve with electrical stimulation, which has been found to modulate cardiovascular markers. The putative mechanism of action involves tcVNS-induced afferent signaling, followed by efferent modulation of peripheral physiology. **(Right)** Conforming to a double-blind, sham-controlled study, active or sham stimulation is delivered to the left cervical vagus. The electrocardiogram (ECG), seismocardiogram (SCG), and photoplethysmogram (PPG) are sensed at the locations indicated.

widespread effects throughout the body. These include variations in cardiovascular parameters such as vasomotor tone, cardiac contractility, and heart rate – all toward the goal of heightening cardiac output in response to the body's perceived need [2]. Two characteristic outcomes of this are peripheral vasoconstriction and increased blood pressure (BP).

The reciprocal of the pulse transit time (1/PTT) has garnered considerable interest due to its relationship to these two parameters [3]. The pulse transit time (PTT) is defined as the time taken by a pulse pressure waveform to travel between two arterial sites. Due to this time delay's relationship with arterial stiffness, which in turn affects BP, 1/PTT has the capacity for ubiquitous BP monitoring via wearable systems [4]. This potential makes it a pertinent metric not only for

remote monitoring of cardiovascular conditions such as hypertension, but also for the measurement of vagus nerve stimulation (VNS) effects on psychological stress [5].

In recent work, transcutaneous cervical vagus nerve stimulation (tcVNS) was found to reduce peripheral sympathetic arousal in human subjects with posttraumatic stress disorder (PTSD), as measured using non-invasive cardiovascular biomarkers [6]. These biomarkers included measures relevant to vasomotor tone and pulse pressure such as the photoplethysmogram (PPG) amplitude and pulse arrival time (PAT). Specifically, tcVNS, compared to a sham control, was shown to increase PPG amplitude and lengthen PAT.

However, given the insufficiency of 1/PAT in serving as a surrogate for 1/PTT due to variations in the pre-ejection period (PEP) [7], the absence of 1/PTT from the analysis is notable. This omission may have been due to the inherent complexity in its reliable calculation – PTT requires accurate estimates of both PAT and PEP for the same heartbeat. Therefore, confidence in the simultaneous acquisition of three quality measurements is required; without robust signal quality assessment, accomplishing this remains improbable.

We overcome this limitation herein by designing and implementing robust signal processing pipelines that incorporate automated signal quality assessment algorithms for three signals that can be jointly used to estimate 1/PTT: the electrocardiogram (ECG), the seismocardiogram (SCG), and the PPG (Fig. 1). By re-analyzing the PTSD data of [6], we uncover significant tcVNS-induced inhibition of 1/PTT increases during traumatic recall, compared to a sham control. This promisingly corroborates tcVNS use in counteracting the persistent hyperarousal symptoms associated with PTSD [8].

II. METHODS

A. Human Subjects Experiment

The data analyzed originates from a study approved by the Institutional Review Boards of the Georgia Institute of Technology (#H17126), Emory University School of Medicine (#IRB00091171), SPAWAR Systems Center Pacific, and the Department of Navy Human Research Protection Office [6]. Twenty-four human subjects (18 females) with diagnosed PTSD, mean age of 36 (SD 12) years, and body mass index of 28 (SD 6) were recruited, and written informed consent was obtained. Subjects underwent a series of 10 stimuli, as illustrated in Fig. 2. Neutral scripts involved descriptions of pleasant scenery, while traumatic stress involved personalized narrations of prior trauma.

As part of a randomized double-blind protocol (ClinicalTrials.gov NCT02992899), active tcVNS (n = 13) or sham (n = 11) stimulation was delivered cervically for 120 s at a time. Stimulation was administered after each of the four traumatic stressors, as well as twice separately to assess stimulation-specific effects. The active and sham devices (gammaCore, electroCore, Basking Ridge, NJ, USA) appeared and operated identically, differing only in stimulation parameters. For further details, the reader is referred to [6].

B. Physiological Sensing

ECG, PPG, and SCG signals were measured at the locations shown in Fig. 1 (right) from subjects in a supine
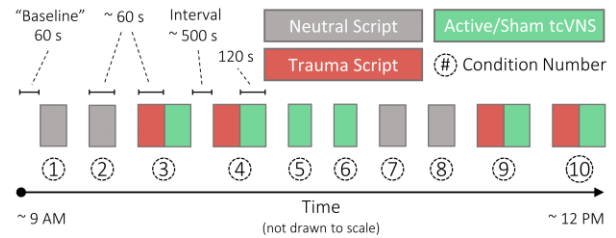

Fig. 2. Protocol diagram. The study involved 10 stimuli including neutral scripts, traumatic scripts, and active or sham transcutaneous cervical vagus nerve stimulation (tcVNS). Adapted from [8].

position using the Biopac RSPEC-R, Biopac PPGED-R (Biopac Systems, Goleta, CA, USA), and a low-noise 356A32 accelerometer (PCB Piezotronics, Depew, NY), respectively. ECG was measured using adhesive Ag/AgCl electrodes in a three-lead configuration, PPG was measured reflectively at the fingertip, and SCG was measured dorsoventrally at the mid sternum. All data were acquired at a 2-kHz sampling rate using the Biopac MP150 data acquisition system.

C. Signal Processing and Feature Extraction

Fig. 3 depicts the high-level signal processing pipelines for ECG, SCG, and PPG. We refer the reader elsewhere for details on processing ECG to extract the final set of RR intervals [9]. SCG and PPG signals were first forward and backward finite impulse response (FIR) bandpass filtered with passbands of 2-39 Hz and 0.4-8 Hz, respectively. Both signals were then segmented into "beats," corresponding to each of the final RR intervals aforementioned. These sets of SCG and PPG beats will be denoted S_0 and P_0, respectively. S_i and P_i will denote the SCG and PPG beats, respectively, at step i. First, beats from S_0 and P_0 with outlying amplitudes were removed to circumvent subsequent template creation issues with two-stage outlier removal: all beats with amplitudes exceeding $\pm$ 5 median absolute deviations (MADs) from the medians of S_0 and P_0 were removed to form S_1 and P_1, respectively; this was followed by 30-beat moving window outlier removal using $\pm$ 5 MADs to form S_2 and P_2.

The SCG beats in S_2 were then assessed for quality using the template matching approach of [10], adapted to work for this particular dataset. Specifically, the population template set was replaced to ameliorate the assumption of relative homogeneity in the population made by [10]. Additionally, the exponential factor, λ, was doubled to 50 to generate larger separation between signal quality index (SQI) values above 0.5 – the majority case in this dataset. The remaining dynamic time feature matching steps were applied equivalently in a two stage fashion. The first stage used a 30-s moving window template, i.e., for each beat in S_2, any beats in S_2 within the previous 30 s were formed into a template using Woody's algorithm [11]. All S_2 beats with $SQI_1 > 0.53$ then formed a new set, S_3. A single template was then formed (Woody's algorithm) using all beats in S_3 for the second stage of filtering; this filtering was applied to the beats in S_2 to form S_4 as follows. Beats in $S_2 \cap S_3$ with $SQI_2 < 0.3$ were excluded from S_4, the remaining beats in $S_2 \cap S_3$ were transferred over to S_4, and beats in $S_2 \setminus S_3$ with $SQI_2 > 0.7$ were also included in S_4. This second stage remedied inadequate specificity observed for the desired sensitivity in certain subjects' data;
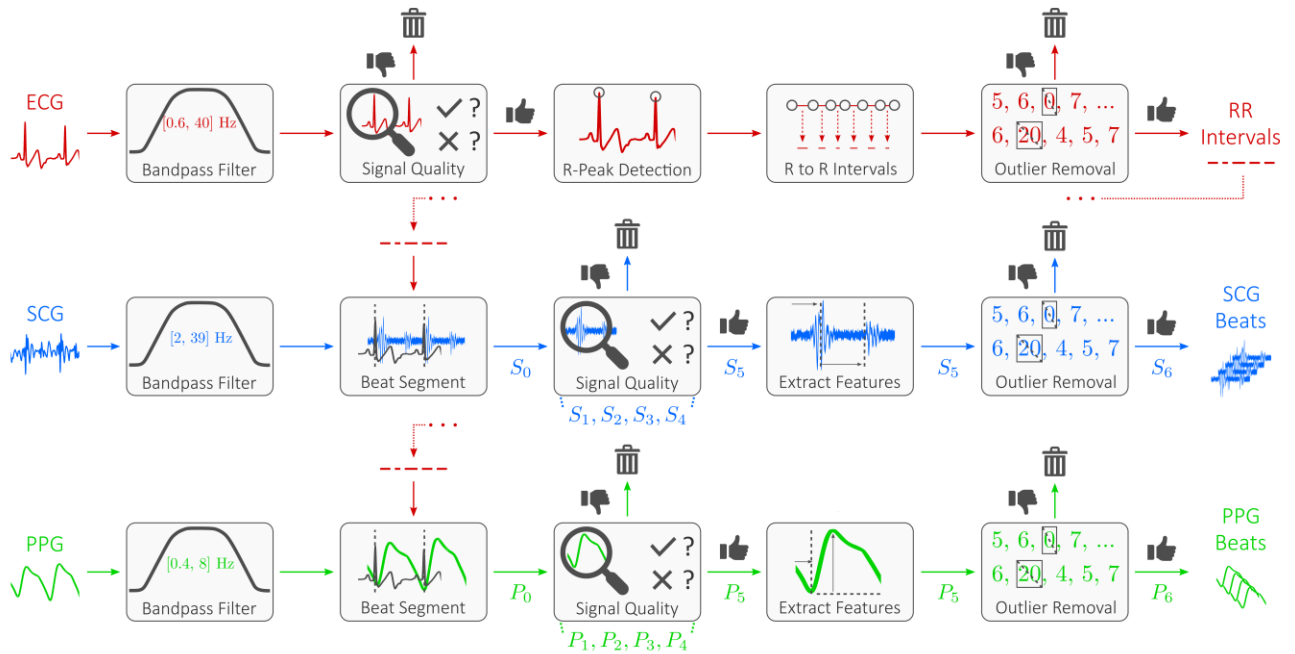
Fig. 3. High-Level signal processing and feature extraction block diagram. Using state-of-the-art quality assessment and feature extraction algorithms, the electrocardiogram (ECG), seismocardiogram (SCG), and the photoplethysmogram (PPG) were processed to obtain quality R peak to R peak intervals (RR intervals), SCG segments corresponding to heart beats (i.e., SCG beats), and PPG beats. S_i and P_i correspond to the sets of beats detailed in the text.

however, to keep this stage from undoing quality filtering, if $|S_3| > |S_4|$, then $S_5 = S_3$; $S_5 = S_4$ otherwise.

PEP was then extracted from each beat in S_5 utilizing the simplified consistent peak tracking algorithm employed in [12]. This initial extraction was used for outlier-based beat removal, employing, again, two-stage outlier removal with $\pm$ 5 MAD thresholds. Beats in S_5 with PEP flagged as outlying were removed to form the final set of SCG beats, $S^* = S_6$, from which the final time series of PEP values were extracted.

The PPG beats in P_2 were quality assessed analogously to the SCG beats in S_2. First, the template matching approach of [13] was applied as is to the beats in P_2 with an SQI threshold of 0.6; this produced P_3. From P_3, a new template was formed (Woody's algorithm) for a second stage of filtering with upper and lower thresholds of 0.7 and 0.35, respectively. This resulted in the set P_5 (please see analogous SCG steps for details). PAT was then extracted from the beats in P_5 using the intersecting tangents method [14]; this first extraction was, again, for outlier removal purposes, utilizing the exact same two-stage process as for PEP-based outlier removal for SCG. The resultant set of PPG beats formed $P^* = P_6$, from which the final time series of PAT values were extracted.

For every RR interval with both a corresponding SCG beat in S^* and PPG beat in P^*, 1/PTT was finally calculated by subtracting the PEP from the PAT and taking the reciprocal.

D. Active vs. Sham Statistical Analysis

Similar to [6], the time periods of interest included the first 30 s of traumatic recall, last minute of stimulation, and one minute from post-stimulation (3 minutes after stimulation stopped); the first minute of stimulation was additionally included based on the dynamics of tcVNS effects discovered in prior work [15]. All 1/PTT values were normalized relative to subject-specific baselines (average across first minute of

protocol); percent differences were obtained by subtracting and then dividing by baseline 1/PTT. Responses with no immediately preceding stressors (stimuli 5 and 6) were analyzed separately from those involving traumatic stress. To obtain one value per subject, values of the same interval type were averaged. The active and sham groups were then compared for each of the intervals in question.

Upon discovering differences between the groups (see Results), the 1/PTT responses to two additional intervals were studied: the neutral scripts prior to any stimulation (stimuli 1 and 2) and the remaining neutral scripts (stimuli 7 and 8). The first two neutral scripts were investigated to observe whether group differences unrelated to traumatic stress could be ascertained prior to any stimulation, while the remaining two neutral scripts addressed curiosities regarding any significant lingering explanatory effects of active or sham tcVNS.

Normality and homoscedasticity of data was checked using the Shapiro-Wilk and Levene tests, respectively. Two-tailed Mann-Whitney U tests or independent t-tests were employed for nonnormally and normally distributed variables, respectively; lack of uniform normality in interval data prevented the use of multivariate analysis of variance. For normally distributed variables that rejected homoscedasticity, Welch's independent t-test was used; Student's t-test was used otherwise. Bonferroni-Holm corrections accounted for familywise error due to related comparisons, where all reported p-values are adjusted. A significance threshold of α = .05 was used. Effect sizes were computed using Cohen's d or the common language effect size, f, as appropriate.

III. RESULTS

Fig. 4 (a) depicts the active vs. sham comparison results during and after traumatic recall. During traumatic stress and the first minute of stimulation, relative 1/PTT was
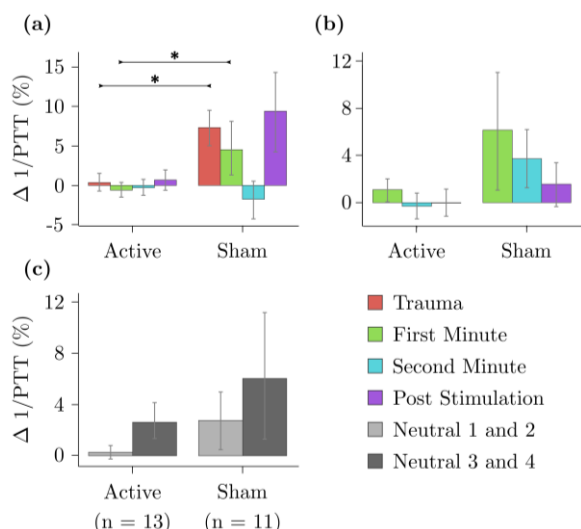
Fig. 4. Active vs. sham 1/PTT responses. Each bar represents the mean of the group for that corresponding interval, and the error bars represent standard error of the mean (SEM). * denotes statistical significance ($p < 0.05$ (corrected)). **(a)** Relative 1/PTT responses to stimulation following traumatic recall. **(b)** Responses to stimulation without preceding traumatic stress. **(c)** Responses to the first and last pair of neutral scripts, shown in light and dark gray, respectively. Notably, no significant differences existed under stress-free conditions.

significantly lower for active compared to sham tcVNS ($p = .020$, U = 27, f = .19; $p = .048$, U = 34, f = .24, respectively). No significant differences existed during the second minute and post stimulation ($p = .52$; $p = .08$, respectively).

Fig. 4 (b) displays the comparison results for the stimulation administrations with no preceding traumatic stress (stimuli 5 and 6). No significant differences existed between the groups for the first minute, second minute, or post stimulation ($p = .72$; $p = .21$; $p = 1.0$, respectively). Fig. 4 (c) demonstrates this as well for the first and last two neutral scripts ($p = .66$; $p = .78$, respectively).

IV. DISCUSSION

Fig. 4 illustrates that tcVNS reduces the reactivity of 1/PTT in response to traumatic stress in this sample of PTSD patients. These differences were only observed during and immediately after traumatic recall, when sympathetic arousal is the greatest. Importantly, these stress related differences were not explained by disparities external to traumatic recall conditions, suggesting that tcVNS may have a protective effect against acute increases in arterial stiffness in response to traumatic stress. For those suffering from vascular complications related to PTSD-induced hyperarousal, this could imply potential therapy through long-term stimulation.

Assuming the relationship between 1/PTT and BP holds in this case, the implications extend further to comorbid hypertension and the like. However, it is important to note that smooth muscle contraction can also affect PTT [3]. Thus, future investigations of tcVNS effects on traumatic stress should include continuous BP responses to address this vasoconstriction confound and further enlighten.

This analysis is not without limitation. By averaging over repeated measures, the instantaneous and cumulative differences between tcVNS and sham cannot be differentiated; statistical power may also be reduced. Although this did not

hinder the present investigation, additional differences may exist that require mixed modeling to discover. Future efforts to validate these findings in a larger sample are also encouraged.

V. CONCLUSION

In this work, end-to-end SCG and PPG signal processing pipelines were elucidated for robust 1/PTT extraction from a dataset of 24 PTSD subjects, 11 of which received sham stimulation instead of tcVNS in a double-blind study. In response to traumatic stress, active tcVNS reduced the reactivity of PTSD subjects' relative 1/PTT responses by ~7% in comparison to sham stimulation (corrected $p < 0.05$); relative 1/PTT responses were also ~5% lower for the active group during the first minute of stimulation (corrected $p < 0.05$). Given the BP and vasoconstriction related implications of 1/PTT, the results suggest possible long-term use of tcVNS in reducing stress-induced sympathetic hyperarousal in patients with PTSD – a vital step toward enhancing quality of life for those suffering from trauma.

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