Transcutaneous Median Nerve Stimulation Regulates Peripheral Skin Temperature During Cold Pressor: A Sham-Controlled Study

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***Abstract*—Cold exposure activates thermoregulatory processes through the autonomic nervous system that, while maintaining homeostasis, reduce peripheral blood flow and dexterity in the extremities. Transcutaneous median nerve stimulation (tMNS) represents a promising method for autonomic regulation through activation of parasympathetic vagal nerve afferents to the brain. However, the effect of this type of non-invasive therapy has not been investigated thoroughly in the context of thermoregulation. We analyzed peripheral skin temperature data in an ancillary study from a cohort of 19 participants who underwent two study visits of a protocol, each involving a dose-response activity, a cold pressor activity, and either tMNS or sham stimulation. Data from each protocol segment was averaged and then normalized as a percent difference from a baseline rest section. Paired t-tests and Pitman-Morgan tests were run on data from the cold pressor and dose-response activities respectively to determine statistical significance. We found that tMNS had a significant ($p = 0.036$) effect of blunting peripheral skin temperature drops during cold pressor recovery as compared to sham stimulation. Additionally, tMNS had a general regulatory effect on skin temperature change during the dose-response activity, with significantly less variance than sham stimulation ($p < 0.05$). These results indicate that possible regulation of peripheral skin temperature with tMNS can serve as a therapy for cold exposure. Future work should investigate this mechanism in a larger cohort with a protocol designed to assess reactivity in temperature and dexterity to both cold and heat exposure.**

***Index Terms*—transcutaneous median nerve stimulation, cold pressor, non-invasive therapy, wearable-compatible**

I. Introduction

Cold exposure activates thermoregulatory responses in the body that are mediated through sympathetic activation in the autonomic nervous system. These responses, including peripheral vasoconstriction, shivering, and thermogenesis through brown adipose tissue, are important adaptations for maintaining homeostasis [1]. However, reduced peripheral blood flow due to these adaptations leads to declining manual dexterity in the periphery, which can be particularly dangerous in critical scenarios such as military applications or cold-weather outdoor emergency medical responses [2]–[5].

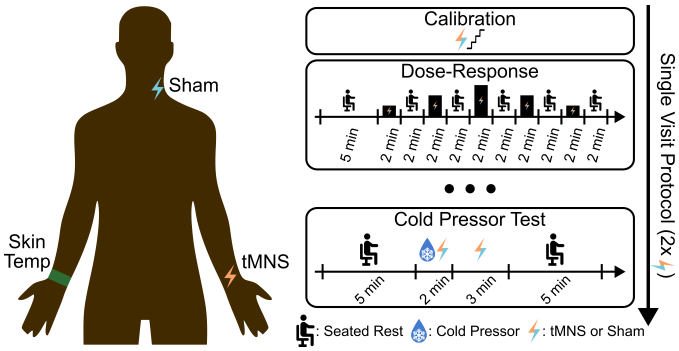

Fig. 1. Sensor Placement and Protocol Diagram. Subjects underwent two study visits during which peripheral skin temperature data was collected, once with tMNS and once with sham stimulation. Each visit comprised of a calibration period for the stimulation, as well as dose-response and cold pressor activities.

Non-invasive peripheral nerve stimulation represents an emerging area of research focused on wearable-compatible regulation of the autonomic nervous system. In particular, transcutaneous cervical vagus nerve stimulation (tcVNS) has shown promise in reducing the deleterious effects of excessive bouts of sympathetic activation. Prior work in subjects with post-traumatic stress disorder and opioid use disorder has shown that tcVNS is effective in reducing cardiac sympathetic activation related to traumatic recall and cue-induced withdrawal symptoms in those populations respectively [6], [7]. Related studies on brain activity indicate that tcVNS may improve autonomic regulation through parasympathetic afferents of the vagus nerve to the brain [8]–[10]. Transcutaneous median nerve stimulation (tMNS), a less extensively studied form of non-invasive peripheral nerve stimulation, also shows promise for sympathetic regulation. tMNS has been shown to reduce blood pressure in hypertensive humans and to

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reduce the cardiovascular effects of acute mental and physical stressors in healthy subjects [11]–[13]. The autonomic effects of tMNS are likely modulated through overlapping vagus nerve afferents to the brain, suggesting a similarity in function between tcVNS and tMNS [14].

The vagus nerve is also believed to play a role in thermosensation and thermoregulation. In particular, it is thought to mediate thermal reflexes of visceral organs in response to changes in temperature [15]. However, its exact role in this process is unclear. It is theorized that the vagus nerve's influence on thermoregulation is an indirect by-product of its role in energy expenditure and metabolism [15], [16]. The role of the median nerve and effect of tMNS on body temperature regulation is likewise unclear. One study has found that tMNS delivered to the right palmar wrist resulted in an increase in both mechanical and thermal sensory perception thresholds in the ipsilateral and contralateral palms [17]. However, there is no study, to our knowledge, on the effects of tMNS versus sham stimulation on peripheral skin temperature during cold exposure. In this sham-controlled ancillary study, we analyze changes in skin temperature in the presence of tMNS or sham stimulation during a dose-response activity and in the context of a cold pressor. Our analysis provides a basis for future work on the effectiveness of tMNS on improving dexterity in cold exposure environments.

II. Materials and Methods

A. Data Collection

The study protocol was approved by the Institutional Review Board of the Georgia Institute of Technology (Protocol Number: H18452) and the U.S. Navy Human Research Protection Office. This work was an ancillary study as part of a larger crossover investigation into the effectiveness of several types of non-invasive peripheral nerve stimulation for the reduction in cardiovascular and sudomotor reactivity to acute mental and physical stressors. A more detailed description of the full study is given in prior work [12]. We obtained written consent from 24 healthy participants with no history of cardiovascular or neuropsychiatric disorder and who were not on medications for those disorders. Additionally, participants with prior familiarity with neuroanatomy and neuromodulation were excluded. Five subjects dropped out before completing both visits for the study, resulting in a cohort of 19 subjects which consisted of 10 females and 9 males. The final cohort had a mean ± standard deviation age of 21 ± 2 years, height of 169 ± 11 cm, and weight of 64 ± 12 kg.

The sensor setup and protocol are depicted in Figure 1. Participants completed two study visits, which were identical apart from the type of stimulation that the participant received. During one visit, participants received tMNS at the left palmar wrist, and during the other visit, participants received sham stimulation at the sternocleidomastoid muscle of the neck. Participants also completed two additional identical visits with other types of stimulation in the full study which are not analyzed here. The order of the four visits were randomized, and the study was conducted in a single-blind process, as described

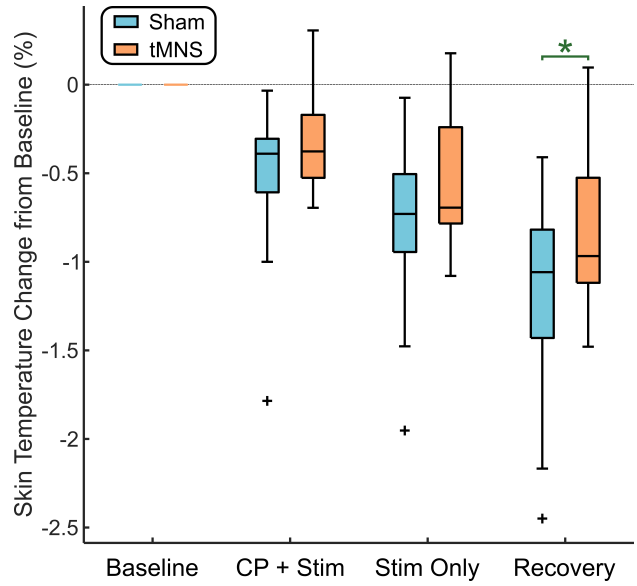

Fig. 2. Results depicting percent changes in peripheral skin temperature from baseline during the cold pressor activity. * indicates statistical significance of difference in means. Blue (left): sham stimulation, orange (right): tMNS

in prior work [12]. Both tMNS and sham stimulation were provided by a bench-top DS8R current stimulator (Digitimer, Broadway, Letchworth Garden City, UK). During both visits, skin temperature was recorded at a sampling rate of 4 Hz and with a resolution of 0.02°C from the right wrist using an E4 wristband (Empatica, Cambridge, MA, USA) [18].

All visits took place in a controlled laboratory environment with the thermostat set to 73°F. During each visit, the E4 wristband and stimulation electrodes were first placed on the participant. Then, the participant went through a calibration stage, during which the stimulation intensity was increased in steps until the participant indicated that it was at the maximum tolerable level. Perceptual threshold (PT) was then defined as 66.7% of this level. Participants then underwent a dose-response activity, during which the participants first sat at rest for five minutes to establish a baseline, followed by five two-minute sections of stimulation at 50% PT, 100% PT, 150% PT, 100% PT, and 50% PT respectively. Each stimulation section was followed by a two-minute period of sitting at rest without any stimulation. After other activities not analyzed in this study, participants underwent a cold pressor test. They first sat at rest for five minutes to establish a baseline. Then, for two minutes, the participants submerged their left foot in a

TABLE I
Results of Statistical Analyses of Differences in Mean Between tMNS and Sham on Skin Temperature Changes During Cold Pressor

	CP + Stim	Stim Only	Recovery
p	0.055	0.068	0.036*
μ (%)	0.19	0.24	0.31
σ (%)	0.40	0.52	0.59
Cohen's d_z	0.48	0.46	0.54

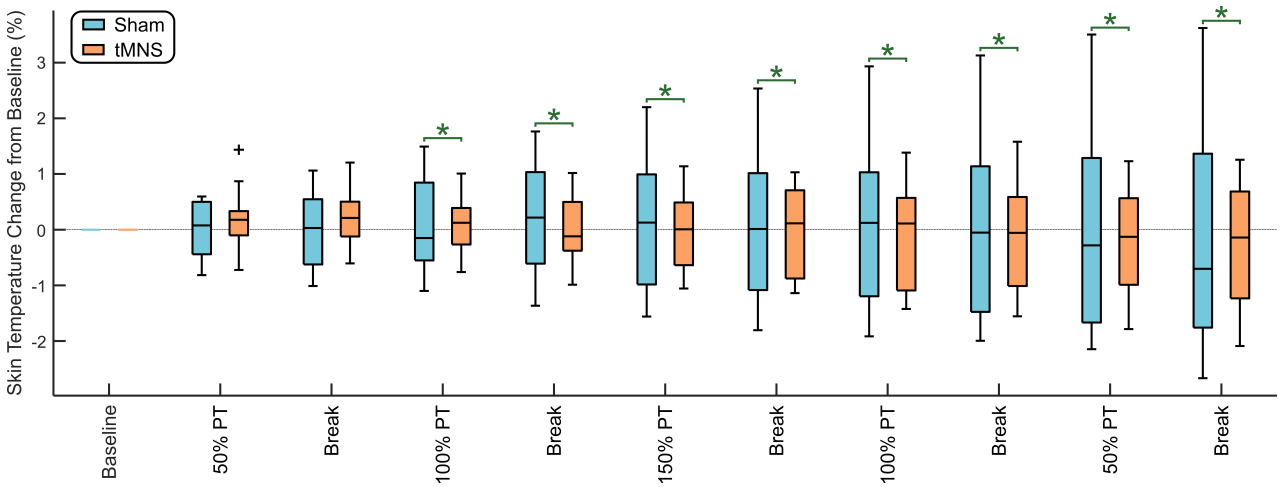

Fig. 3. Results depicting percent changes in peripheral skin temperature from baseline during the dose-response activity. * indicates statistical significance of difference in variance. Blue (left): sham stimulation, orange (right): tMNS

bucket of ice water while receiving stimulation ("CP+Stim"), followed by a three-minute period of stimulation only ("Stim Only"). Finally, the participants recovered from the stressor during a five-minute period of sitting at rest ("Recovery").

B. Data Processing and Statistical Analysis

For each participant and visit, skin temperature data samples were first averaged within each protocol segment to obtain a representative marker of the participant's temperature during each segment. Then, each of these markers were normalized to their respective subject-specific baseline in order to obtain temperature changes across the activities as a percent change from baseline. The five-minute rest sections at the beginning of each activity (i.e., dose-response and cold pressor) were used as the baseline for their respective activity sections.

The resultant distributions from each protocol segment were then statistically tested for differences between tMNS and sham stimulation. For the cold pressor activity, Shapiro-Wilk tests were run on the distributions of paired differences between tMNS and sham. As all tests indicated normality, paired t-tests were then run to assess differences in means between the tMNS and sham distributions. Post-hoc analyses were run to determine the achieved power of the statistical tests for both the CP+Stim and Stim Only sections.

For the dose-response activity, Shapiro-Wilk tests were run on the distributions of paired differences between tMNS and sham to check for normality. Subsequently, as all tests indicated normality, paired t-tests were run to assess differences in means between the tMNS and sham distributions. Additionally, Shapiro-Wilk tests were also run on the distributions of paired sums between tMNS and sham to check for normality. As these tests, as well as the previous Shapiro-Wilk tests on the distributions of paired differences, all indicated normality, Pitman-Morgan tests were run to assess differences in variance between the tMNS and sham stimulation. The two-tailed significance level used for all statistical tests across both activities was $\alpha = 0.05$.

III. Results

The results from the statistical analysis of the cold pressor activity are depicted in Figure 2. The means (μ), standard deviations (σ), and effect sizes (Cohen's d_z) of the distributions of paired differences between tMNS and sham, as well as the significances of the paired t-tests, are tabulated in Table I. Only the recovery section demonstrated a significant difference between the tMNS and sham distributions. The trends for the CP+Stim and Stim Only sections were consistent with the Recovery section, but the difference was not significant. Post-hoc tests revealed an achieved power of $1 - \beta = 0.51$ and $1 - \beta = 0.47$ for the tests of the CP+Stim and Stim Only sections respectively.

The results from the statistical analysis of the dose-response activity are depicted in Figure 3. The μ and σ of the separate tMNS and sham distributions, as well as the significances of the Pitman-Morgan tests, are tabulated in Table II. No significant differences in means were found between the tMNS and sham distributions. However, significant differences in variance were found between the tMNS and sham distributions during all sections after the break following the first 50% PT stimulation, where tMNS significantly reduced the variance.

IV. Discussion

The results from our analysis of the cold pressor activity indicate that tMNS had a regulatory effect by counteracting the drop in skin temperature induced by the cold pressor as compared to sham stimulation. This effect was found to be statistically significant during the Recovery section following the CP+Stim and Stim Only sections. However, the effect also neared significance during CP+Stim and Stim Only, with a moderate effect size ($d_z \approx 0.5$) observed during both of these sections. A post-hoc analysis of the achieved power revealed that our study was underpowered ($1-\beta < 0.8$), indicating that a follow-up study with a larger sample size would be required to better capture the thermoregulatory effects of tMNS. Cold

TABLE II
RESULTS OF STATISTICAL ANALYSIS OF DIFFERENCES IN VARIANCE BETWEEN tMNS AND SHAM DURING DOSE-RESPONSE

	50% PT	Break	100% PT	Break	150% PT	Break	100% PT	Break	50% PT	Break
p	0.90	0.15	0.016*	0.027*	0.014*	0.028*	0.028*	0.030*	0.025*	0.033*
μ (%)	0.16, 0.016	0.16, 0.026	0.063, 0.093	0.044, 0.17	-0.042, 0.11	-0.051, 0.062	-0.12, 0.047	-0.16, -0.076	-0.23, -0.22	-0.32, -0.36
σ (%)	0.46, 0.47	0.46, 0.63	0.46, 0.81	0.59, 0.95	0.66, 1.10	0.76, 1.22	0.87, 1.41	0.93, 1.51	0.98, 1.64	1.06, 1.74

exposure results in reduced peripheral blood flow, which is related to a reduction in manual dexterity performance [2]–[4]. As such, our results suggest that tMNS may be a promising non-invasive therapy for the improvement of dexterity performance in cold environments. tMNS is particularly well-suited for such a therapy due its anatomical location's proximity to wearable devices (i.e., wristwatches) that can measure skin temperature, accelerometry, and other valuable signals. We have demonstrated in prior work that tMNS can be feasibly and effectively delivered in a wearable wrist-worn form-factor for the mitigation of acute stress [13].

Statistical analysis was subsequently run on the dose-response activity to further elucidate the mechanism of the effect of tMNS on peripheral skin temperature outside of the context of the cold pressor. All paired t-tests run on this section indicated that there was no difference in means between the tMNS and sham distributions. However, based on the results of the Pitman-Morgan tests, tMNS compared to sham led to a significant reduction in variance for all sections after the break following the first 50% PT section. Furthermore, the difference in variance between the two distributions increased as the dose-response activity progressed. These results may indicate that tMNS has a general thermoregulatory effect on skin temperature at the contralateral wrist (i.e., tMNS regulates both increases and decreases from a baseline temperature). However, as this work was a small ancillary study, future studies are warranted to verify the results with a larger cohort and a protocol designed to analyze skin temperature changes during both cold and heat exposure as well as with extended stimulation times to elucidate longitudinal effects and activities such as the Box and Block Test to assess dexterity [19].

V. CONCLUSIONS AND FUTURE WORK

This work represents the first study, to our knowledge, of the effects of tMNS on contralateral peripheral skin temperature during cold pressor. Our results indicate the potential of tMNS as a non-invasive method for thermoregulation and enhancement of dexterity during cold exposure and underscore the need for future work in larger cohorts.

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