Effects of Transcutaneous Electric Nerve Stimulation on Upper Extremity Proprioceptive Function

Andrew Levitsky, Joshua Klein, Panagiotis K. Artemiadis, Christopher A. Buneo

Abstract— **Electrical stimulation of the vagus nerve has been shown to enhance cortical plasticity and may benefit upper extremity rehabilitation following stroke. As an initial step towards assessing the potential of other craniocervical nerves as neuromodulation targets during rehabilitation, we explored the ability of non-invasive stimulation of cervical spine afferents, paired with a proprioceptive discrimination task, to improve sensory function in neurologically intact human subjects. On each trial, subjects' arms were moved by a robot from a test position, along a random path, to a judgment position located 1-4 cm away. Subjects responded 'same' if the judgment position was the same as the test or 'different' if it was not. These responses were used to compute proprioceptive sensitivity and bias. Three groups of 20 subjects received transcutaneous electric nerve stimulation to the C3/C4 cervical spine at one of three frequencies (30 Hz, 300 Hz, 3 kHz) for 10 minutes prior to task performance. A fourth group served as a sham. We found a statistically significant interaction between stimulation frequency and displacement distance on proprioceptive sensitivity. In summary, stimulation of cervical spine afferents may enhance arm proprioceptive function, though in unimpaired subjects these gains depend on both stimulation frequency and discrimination distance.**

Clinical Relevance— **This study provides preliminary data on the potential for non-invasive stimulation of cervical spine afferents to enhance recovery of function following stroke and other neurological disorders.**

I. INTRODUCTION

Proprioceptive dysfunction can arise from several conditions affecting either the central or peripheral nervous system, including peripheral neuropathy, traumatic brain injury, Parkinson's disease, and stroke. Depending on the location and extent of damage to the proprioceptive system, this dysfunction can manifest as an impairment of the perception of the body's configuration and position in space and/or as difficulty in the planning and control of limb and body movement [1]. These deficits can lead to problems with performance of essential activities of daily living, negatively impacting quality of life. Despite its importance for both perception and movement control, proprioception is still poorly understood relative to other senses and the assessment and treatment of proprioceptive dysfunction remains relatively crude. Several recent studies have shown that perceptual and motor training regimens can improve proprioceptive abilities in both healthy adults and patients [2, 3]. However, variability in the effectiveness of such training regimens is large and it is unclear what conditions (e.g. feedback schedules, modes of movement (active vs passive), duration of training etc.) are necessary and sufficient for proprioceptive learning to occur. Some work suggests that training in the presence of exogenous neuromodulation of peripheral spinal nerves is beneficial for sensorimotor performance. For example, low-level electrical and mechanical noise stimulation delivered to the lower extremities has been shown to improve the control of balance in human subjects with impaired somatosensory processing due to aging, diabetes and stroke [4]. However, the optimal stimulation parameters (targets, frequencies, durations, etc.), and strategies for combining stimulation with physical training remain unknown.

More recently, transcutaneous electric nerve stimulation (TENS) delivered to cranial nerves has emerged as a potential strategy for enhancing plasticity and learning, and for treating some neurological disorders. For example, TENS of the trigeminal, vagal, and other craniocervical nerves has been shown to safely induce plasticity in healthy humans and provide therapeutic benefits for the treatment of epilepsy, depression, PTSD, and other disorders [5-7]. In the sensorimotor domain, a recent study suggests that TENS of the auricular branch of the vagus nerve combined with standard rehabilitation can improve proprioceptive and motor function following stroke [8]. This is thought to occur through activation of brainstem circuits responsible for arousal and endogenous neuromodulation of the cortex. Other craniocervical nerves such the trigeminal and cervical spine afferents also project to many of the same brainstem circuits (Fig. 1) [9, 10]. However, the therapeutic potential of these nerves with regard to improving sensorimotor function is unknown.

A recent pilot study by our laboratory assessed the effects of trigeminal and cervical spine afferent neuromodulation on upper extremity proprioceptive sensitivity, using stimulation applied *during* task performance [11]. In this experiment, the ophthalmic branch of the right trigeminal nerve, bilateral cervical spinal nerve afferents, and cutaneous afferents of the right shoulder were targeted. Subjects were assigned to one of two stimulation frequency groups (30 and 300Hz). We found no differences in proprioceptive sensitivity due to stimulation location, but did find a statistically significant effect of stimulation frequency. More specifically, while 300 Hz stimulation appeared to have no effect on task performance relative to performance without stimulation, 30 Hz stimulation applied during task performance appeared to degrade rather

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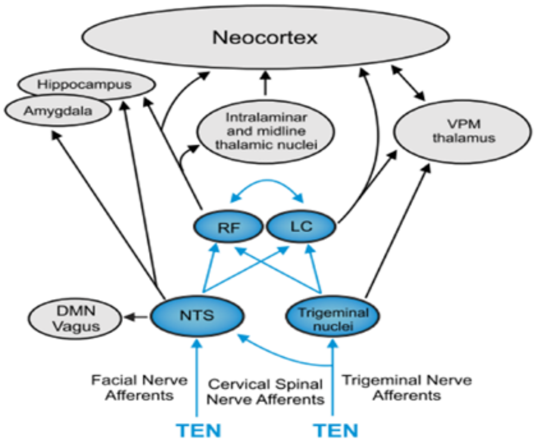

Figure 1. Neural pathways presumed to be involved in mediating TENS induced psychophysiological arousal and plasticity [11]. NTS: nucleus tractus solitarius. DMN vagus: dorsal motor nucleus of vagus nerve. RF: reticular formation. LC: locus coeruleus. VPM thalamus: ventral posteromedial nucleus of the thalamus.

than enhance proprioceptive sensitivity. Post-experiment interviews with subjects suggested that this was a distractive effect. Here we assessed the effects of cervical spinal afferent nerve stimulation delivered *prior* to task performance ('priming' stimulation) on proprioceptive sensitivity and bias. The effects of three stimulation frequencies were assessed: 30 Hz, 300 Hz, and 3kHz.

II. EXPERIMENTS

The Arizona State University Institutional Review Board approved all experimental procedures and subjects gave written informed consent prior to participating, in accordance with the Declaration of Helsinki. Eighty-two (82) subjects were initially enrolled in the study. One subject was excluded due to an adverse event and another due to a technical malfunction.

A. *Proprioceptive Assessment*

Procedures for assessment of proprioceptive sensitivity have been described in detail elsewhere [12]. In brief, subjects' right arms were coupled to a 7-DoF anthropomorphic robot arm (LWR4+, KUKA Inc.) through an arm trough that restricted wrist motion but allowed movement of the elbow and shoulder. Subjects wore headphones to block auditory motion cues from the robot and were instructed to close their eyes during task performance. On each trial (Fig. 2), the arm was moved from a 'test' position **(1)**, along a random 'distractor' path to a via point **(2)**, before stopping at a judgment position **(3)**. Subjects then responded 'same' or 'different', depending on whether they believed the judgment position was the same as the test position or not. After their answer was recorded, the arm was moved through another random distractor loop **(4)** before returning to the original test position. This procedure was repeated 30 times (15 same trials, 15 different) for a given judgment position. Four judgement positions located 1-4 cm away from the test position along a single downward direction were tested in random order for a total of 120 trials per experiment.

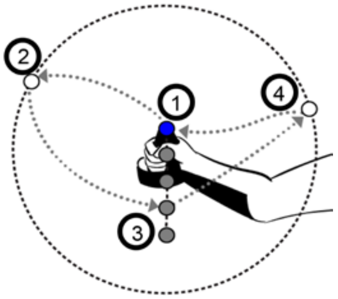

Figure 2. 'Same-different' discrimination task. The arm was moved from a 'test' position (1), along a random 'distractor' path to a via point (2), before arriving at a 'judgment' position (3). After the subject responded 'same' or 'different', the arm was moved along another random path through a 2^{nd} via point (4) before returning to the test position. Shown is a 'different' trial, i.e. the judgment position differed from the test position and required a response of 'different' to be considered correct.

Hit rates (subjects reporting 'different' when positions differed) and false alarm rates (reporting 'different' when positions were the same) were used to calculate *d'* (1), a measure of sensitivity derived from the normalized hit rates and false alarm rates:

$$d' = z\,(Hit\ Rate) - z(False\ Alarm\ Rate) \tag{1}$$

where *z()* denotes a z-score transformation. Subject responses were also used to compute *c* (2)**,** a measure of subjects' inherent biases towards responding 'same' or 'different':

$$c = -(z(Hit\ Rate)+z(False\ Alarm\ Rate))/2 \tag{2}$$

where positive values indicate a 'same' bias.

B. *Stimulation Protocol*

Stimulation was provided by a custom-built stimulator designed by the laboratory of William J. Tyler at Arizona State University (Fig. 3). Two (2) 1.25" conductive cloth neurostimulation electrodes (PALS, Axelgaard Manufacturing Co. Ltd.) were placed on the cervical spine at the level of C3/C4. Twenty (20) subjects were randomly assigned to each of four stimulation frequency groups (30Hz, 300Hz, 3kHz, or sham). Thirty (30) Hz stimulation was chosen because frequencies in this range are associated with high degrees of cortical plasticity changes in animal experiments [13] and have been used in previous studies of stroke patients [8, 14]. Higher frequencies were included based on their use in other cranial nerve studies [9, 15] and observations that these frequencies

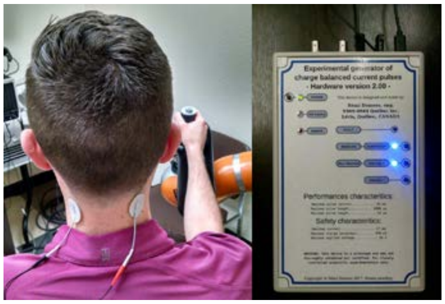

Figure 3. Left: Electrode configuration and initial arm position during the discrimination task. Right: Custom stimulator designed by William J. Tyler and colleagues.

are better tolerated by subjects and therefore could potentially allow stimulation at higher intensities. Here stimulation intensity and pulse-width were fixed in all groups at 4mA and 150µS, respectively. Subjects were only stimulated for a 10-minute block prior to task performance. No stimulation occurred during task performance.

C. *Data Analysis*

Calculation of sensitivity, bias, hit rates and false alarm rates was performed using custom code developed in MATLAB (The MathWorks, Inc.). Two-factor mixed ANOVAs were performed on each of these dependent variables in SPSS Version 25 (IBM Corp.) with displacement distance (1-4 cm) as a within-subjects variable and stimulation frequency as a between-subjects variable. A significance level of $\alpha = 0.05$ was used.

III. RESULTS

Hit rates and false alarm rates varied with distance from the test position but did not vary with stimulation frequency. Figure 4 shows the average hit rates and false alarm rates (+/- SEM) for each stimulation group and distance. As observed in previous studies without stimulation [12], hit rates increased monotonically with distance and false alarm rates decreased in all stimulation groups. However, there were no observable effects of stimulation frequency on either hit rates or false alarm rates. This was confirmed by ANOVA, which showed a statistically significant effect of discrimination distance on hit rates but no main effect of frequency (p=0.354) and no frequency x distance interaction (p=0.386) for hit rate. Similarly, there was a significant effect of distance on false alarm rate but no effect of frequency (p=0.493) and no frequency x distance interaction (p=0.699).

Bias also varied with displacement distance but did not vary with frequency. Figure 5 shows the mean values of bias (*c*) +/- SEM for each stimulation group and distance. At smaller distances, (1-2 cm) bias was generally positive, indicating that most subjects tended to respond that the test and judgment positions were the same. For larger distances (3-4 cm) bias decreased precipitously, approaching zero at 4 cm. This trend was expected as it indicates that as the proprioceptive signal strengthened, subjects' responses became less biased [12]. Regarding effects of stimulation, although there was some tendency for bias to be lower for the 3kHz stimulation group across all distances, this trend was not confirmed by statistical analysis. An ANOVA revealed a statistically significant effect of discrimination distance on bias but no main effect of frequency (p=0.158) and no frequency x distance interaction (p=0.911).

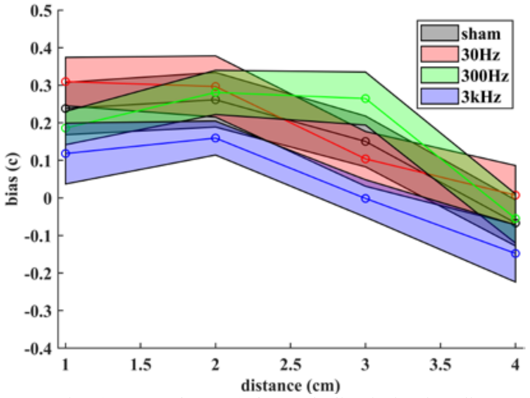

Figure 5. Bias (means +/- SEM) for each discrimination distance and all stimulation groups. Bias generally decreased with distance but did not vary with stimulation condition.

In contrast to the other dependent variables examined, sensitivity varied with stimulation frequency, but in a distance-dependent manner. Figure 6 shows average sensitivities (*d'*) +/- SEM for each stimulation group and distance. At the 1 cm distance, sensitivity was near zero for all stimulation groups, indicating approximately chance performance. However, at 2 cm sensitivity improved in all groups except sham, with the 30 Hz group showing the greatest gains. At 3 cm, sensitivity increased again in all groups but differences across frequencies were less apparent. Sensitivity was greatest in all stimulation groups at 4 cm (where the proprioceptive signal was strongest), but was noticeably weaker for the 3 kHz group. As with the other dependent variables, an ANOVA showed a statistically significant effect of discrimination distance. No main effect of frequency was found (p=0.11) but there was statistically significant frequency X distance interaction. Post hoc Tukey's tests indicated that the sensitivity for 30 Hz was

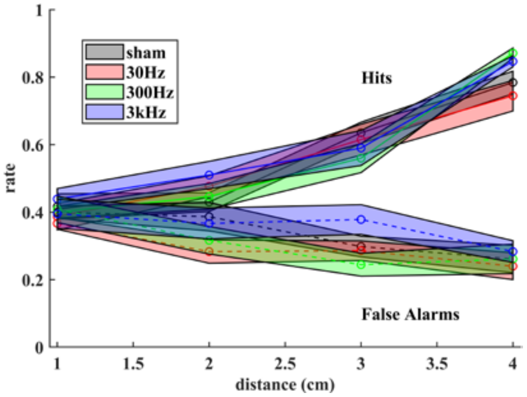

Figure 4. Hit rates and false alarm rates (means +/- SEM) for each discrimination distance and all stimulation groups. Hit rates increased and false alarm rates decreased with distance but neither rate varied with stimulation condition.

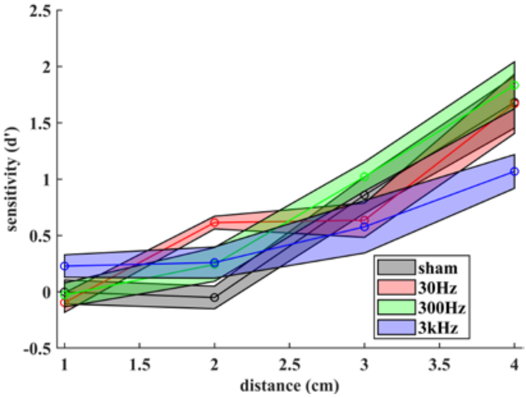

Figure 6. Sensitivity (means +/- SEM) for each discrimination distance and all stimulation groups. Sensitivity varied with stimulation frequency, but in a distance-dependent manner.

significantly different than the sensitivity for sham at 2cm. No other significant differences were found.

IV. DISCUSSION

Previous studies have suggested that electrical stimulation of vagal nerve afferents combined with physical training can enhance sensory and motor function. Here we characterized the potential of cervical spine afferent stimulation to enhance sensory function. We found that TENS delivered to these afferents prior to performance of a proprioceptive discrimination task enhanced sensitivity relative to sham though these effects were dependent upon stimulation frequency and discrimination distance.

In this study, 30 Hz stimulation was the most advantageous for improving proprioceptive sensitivity. This finding is consistent with recent studies exploring the potential of combined VNS and physical training for stroke rehabilitation. For example, Kilgard and colleagues found that invasive VNS stimulation delivered at 30 Hz was associated with improved somatosensory function in a patient with severe sensory impairment due to stroke [14]. Similarly, a study of twelve stroke patients that received auricular VNS at 25 Hz during performance of a motor task found that most patients showed post-intervention increases in sensory function [8].

The observation that 30 Hz TENS was only effective at improving proprioception at discrimination distances of 2 cm may indicate that this neuromodulation approach is beneficial only when signals are detectable but weak, and not otherwise. Our previous work [12] has shown that at 1 cm, proprioceptive sensitivity (d') generally fluctuates around zero, indicating approximately chance performance. This is likely due to the fact that at this discrimination distance the proprioceptive signal is too weak to be detected, thus subjects simply guess at whether the positions are different or not. Performance at greater than chance levels only begins to occur at 2-3 cm while at 4 cm performance is generally very good, presumably because the proprioceptive signal is strong enough to be reliably detected by most subjects. Thus, the finding that effects of stimulation were greatest at 2cm could mean that stimulation is most effective under conditions where proprioceptive signals are detectable but generally weak or otherwise impaired, e.g. following damage to the nervous system or with aging.

V. CONCLUSION

Delivery of TENS to the cervical spine prior to performance of a proprioceptive discrimination task increased sensitivity in a frequency and distance dependent manner. The nature of the effects suggest that this approach might be helpful for rehabilitation of proprioceptive dysfunction arising from neurological damage or aging. Future work should focus on exploring the stimulation parameter space more completely, e.g. frequencies, locations, durations and timing of TENS application. In addition, novel training regimens that can be combined with neuromodulation to optimally enhance cortical plasticity and learning are needed.

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