

Dose-Response Effects of Peripheral Nerve Stimulation and Motor Training in Stroke: Preliminary Data

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Abstract— Stroke is one of the most devastating and prevalent diseases. However, efforts to limit tissue damage in acute stroke have met with only minimal success. Therefore, it is of paramount importance to establish effective therapies for use during long-term stages of recovery. Such therapy can capitalize on neuroplastic change (brain reorganization), which has been associated with recovery of function after brain lesions. Intensive, repetitive motor training is a therapeutic intervention that has been shown to support neuroplastic change and improve motor performance after stroke. Likewise, sensory input in the form of peripheral nerve stimulation (PNS) has been shown to upregulate neuroplasticity and improve motor performance after stroke. However, no studies have evaluated how pairing intensive motor training with various PNS intensities and times may affect motor performance, particularly for subjects with severe upper extremity (UE) hemiparesis after stroke. Here, we describe our ongoing study of whether various intensities and times of delivery of PNS relative to motor training will yield differential effects on UE motor function in subjects with chronic, severe motor deficit after stroke. Our results will facilitate development of a dose-response model for PNS paired with intensive, repetitive motor training, which will help optimize this combinatory intervention for stroke survivors with highest need.

Keywords— neuroplasticity; neuromodulation; robot-assisted; somatosensory; motor function

I. INTRODUCTION

Stroke continues to be a major public health concern [1]. After stroke, neuronal plasticity (enduring morphological or functional reorganization of neuronal properties [2-4]) is crucial for recovery of motor function [5-10]. The adult brain is capable of neuroplastic change to a degree formerly thought possible only during early post-natal periods [11-14,5-10]. Recent research has enabled development of rehabilitative interventions to capitalize on neuroplasticity. For example, intensive, repetitive motor training has emerged as especially effective for supporting neuroplastic change. A prominent form of this type of training is called

constraint-induced therapy (CIT). CIT for recovery after stroke consists of restraining the less-affected arm with a mitt for 90% of waking hours for 2 to 3 weeks, during which time participants engage in daily repetitive and mass practice of sensorimotor tasks. CIT has produced promising results for stroke survivors with mild-to-moderate upper extremity (UE) motor deficit [15-20]. However, CIT has not benefited those with severe UE motor deficit [21-23]. This evidence suggests that intensive, repetitive motor training *alone* is unable to significantly increase UE motor function and cortical plasticity in stroke survivors with highest need. On the other hand, pairing intensive, repetitive motor training with other techniques to upregulate neuroplasticity could prove optimal for cases of severe motor deficit.

For example, another technique to upregulate neuroplasticity is called peripheral nerve stimulation (PNS). PNS is a sensory-input based intervention that has been shown to upregulate neuroplasticity and enhance motor performance after stroke [4]. Extensive related evidence shows that sensory input can play a crucial role in motor recovery after brain lesions [24-28]. PNS delivers sensory input in the form of non-invasive, weak electrical currents. Most studies of PNS have used a single intensity of PNS—specifically, below motor threshold. No studies have evaluated the relationship between various intensities and timing of PNS, motor training, and functional gains for stroke survivors with severe hemiparesis. While it might appear intuitive that increasing the dose of PNS would correlate with increased improvement in motor recovery, neurophysiological studies have shown that excessive afferent input may overload the cortical system [29, 30]. This mechanism could presumably lessen the effectiveness of PNS interventions at higher intensities. It is also conceivable that PNS applied simultaneously with motor training would require lower PNS intensity because of lower cell membrane thresholds associated with the firing of motor neurons during voluntary contraction [31, 32]. To clarify these mechanisms, we are investigating a dose-response model coupling various PNS intensities and timing with motor training to promote

functional motor recovery for stroke survivors with chronic, severe UE hemiparesis (ie, virtually no movement in the hand or wrist).

II. METHODS

Projected recruitment for this ongoing study is $n=60$. Here, we present data from 28 subjects (Table 1) who participated in 2 evaluations (at baseline, and immediately following completion of all intervention) and 10 consecutive weekday sessions of intervention. We evaluated motor performance using the UE portion of the Fugl-Meyer Assessment (FMA; primary outcome measure) and the Stroke Impact Scale (SIS). Inclusion criteria: We recruited subjects with chronic (i.e., >1 year post-stroke), severe UE motor deficit after a single stroke. We defined “severe” as that which would normally exclude the subject from CIT (i.e., inability to extend the affected metacarpophalangeal joints at least 10° ; and the wrist, 20°) [33]. We set age range as at least 18 years of age with no upper age limit. We obtained past data, including radiographic studies and medical history, in order to confirm diagnosis, site, volume, and type of lesion. We conducted routine neurological evaluation during the screening of potential subjects. Each individual received a verbal and written explanation of the purposes, procedures, and potential hazards of the study; and written consent was obtained. Our study was approved by the institutional review boards of the University of Kentucky and Cardinal Hill Hospital. Exclusion criteria: a) within 3 months of recruitment, addition or change in the dosage of drugs known to exert detrimental effects on motor recovery, including alpha-adrenergic antagonists or agonists, phenothiazines, phenytoin, benzodiazepines, muscarinic receptor antagonists, dopaminergic antagonists, or other neuroleptics; b) untreated depression; c) history of multiple strokes; d) history of head injury with loss of consciousness; e) history of severe psychiatric illness or alcohol or drug abuse; f) positive pregnancy test or being of childbearing age and not using appropriate contraception; g) presence of ferromagnetic material in the cranium except in the mouth, including metal fragments from occupational exposure, and surgical clips in or near the brain; h) cardiac or neural pacemakers or implanted medication pumps; or i) fixed UE contractures that would interfere with participation in the motor training protocol. After baseline evaluation, we

randomly assigned subjects to 1 of 5 groups: 1) “Low/Before”: low-intensity PNS, delivered before intensive, repetitive UE motor training; 2) “High/Before”: high-intensity PNS, delivered before intensive, repetitive UE motor training; 3) “Low/During”: low-intensity PNS, delivered during intensive, repetitive UE motor training; 4) “High/During”: high-intensity PNS, delivered during intensive, repetitive UE motor training; or 5) “Sham”: PNS at 0V, delivered during intensive, repetitive UE motor training. “Low” denotes PNS at sensory threshold; “high” denotes PNS at a level approaching motor threshold; “before” denotes PNS delivered immediately before motor training; and “during” denotes PNS delivered concurrent with motor training. In each intervention session, we administered 100 minutes of PNS and 2 hours of intensive, repetitive UE motor training.

To deliver PNS, we attached adhesive disposable surface electrodes over the belly of deltoid, triceps, and biceps muscles. We determined the optimal position to stimulate axillary, radial, and musculocutaneous nerves with trains of electrical stimulation at 1Hz through an isolation unit connected to a S88 square pulse stimulator (Grass stimulator, Astro-Med, Inc, West Warwick, RI). Each train consisted of 5 single pulses of 1ms duration, 100ms apart (50% duty cycle) [34-37] at 10Hz. Electromyographic (EMG) activity was amplified and bandpass filtered from 10 to 3000Hz by a biosignal amplifier (World Precision Instruments, Sarasota, FL), then recorded using a data collection program written in LabView (National Instruments, Austin, TX). We delivered individual PNS pulses with an offset of 15ms between each stimulation channel to prevent blocking of distal nerve stimulation by stimulation of more proximal nerves (a phenomenon known as “collision” in nerve conduction studies) [38, 39].

All motor training took place on an InMotion2 (Interactive Motion Technologies, Cambridge, MA). This robot-assisted training device constrains the non-paretic UE while the hemiparetic UE is used to complete virtual tasks (Fig. 1). Tasks occur with progressive-yet-achievable challenge, and a robotic mechanism provides movement assistance as needed. Subjects, evaluators, and trainers overseeing robot use remained blind to PNS condition.

Demographics	Low/Before	High/Before	Low/During	High/During	Sham
Age	68.7 ±3.2	60.8±2.3	68.5±4.1	61.9±4.5	62.8±3.0
Years after stroke	3.63±0.9	3.5±0.8	8.3±2.2	6.8±1.4	3.9±1.3
Gender (female/male)	2/4	1/4	3/4	3/4	1/6
Handedness (right/left)	6/0	4/1	6/1	6/1	7/0
Affected brain (right/left)	2/4	3/2	5/2	5/2	3/4
Lesion (cortical/subcortical)	4/2	3/2	5/2	5/2	5/2
Type (ischemic/hemorrhagic)	4/2	5/0	6/1	4/3	4/3

Table 1. Subject demographics.



Fig. 1. Peripheral nerve stimulation (PNS) delivered during intensive, repetitive upper extremity (UE) motor training on a robotically assisted device.

We compared baseline measures for the 5 groups to assess group differences prior to the intervention. Analysis of variance (ANOVA) model was fitted to each dependent variable to evaluate group changes (i.e., post-intervention compared to baseline) main effects (groups). Significance was accepted at $\alpha < 0.05$. Statistics were calculated using StatView software.

III. RESULTS

At baseline, all groups had comparable total motor scores on the FMA. Additionally, Table 1 shows that baseline demographic characteristics were comparable between groups. However, more time had elapsed since stroke onset for the “Low/During” group than all other groups, although this difference was not significant. Fig. 2 shows that in a pre – post comparison, “Low/During” showed more improvement in FMA total motor score than all other groups. Significance was reached in comparison to “Low/Before” (mean difference: 5.3, $p=0.004$), “High/During” (mean difference: 3.4, $p=0.039$), and “Sham” (mean difference: 3.6, $p=0.027$). Likewise, on the FMA shoulder-elbow subcomponent score (which focuses on the body segments trained in this protocol), “Low/During” showed the most improvement. SIS scores generally followed the same pattern as FMA scores, with “Low/During” showing significantly more improvement than “Sham” (mean difference 7.6, $p=.045$).

IV. DISCUSSION

Our preliminary results suggest that for stroke survivors with chronic, severe UE hemiparesis, PNS improves outcomes of intensive, repetitive UE motor training. Furthermore, in this combinatory intervention, outcomes vary according to PNS

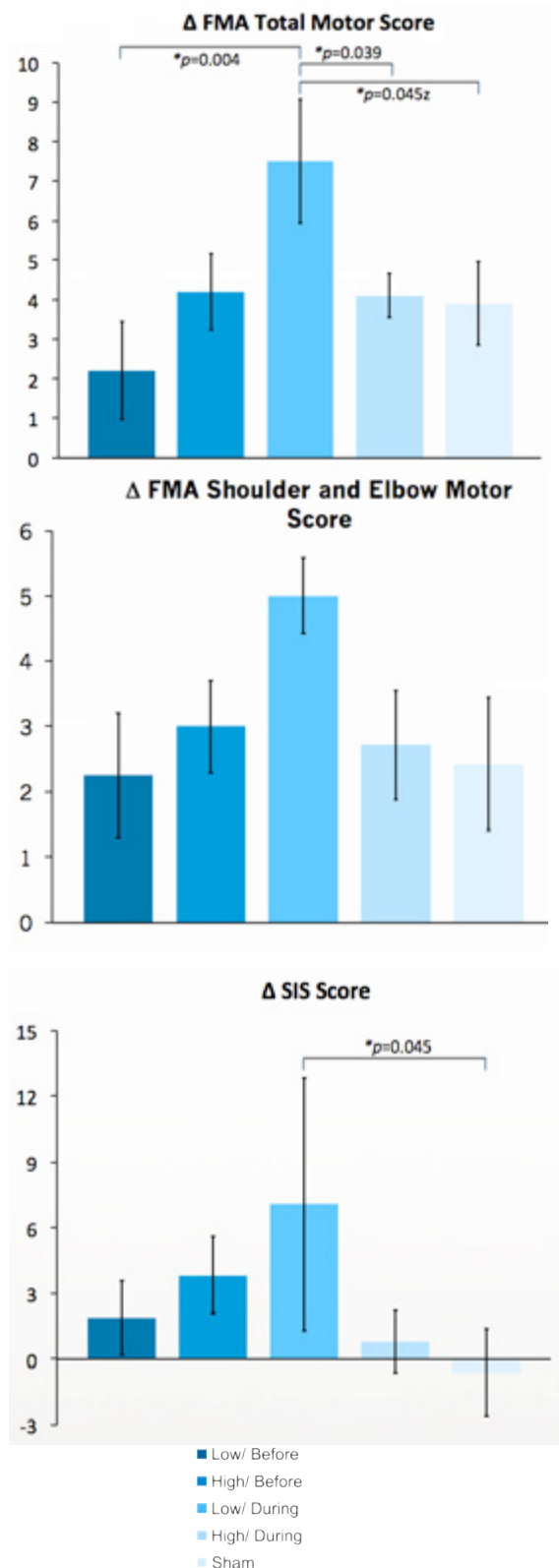


Fig. 2. Change in upper extremity motor function measured by Fugl-Meyer Assessment (FMA; total motor score and shoulder-elbow score) and Stroke Impact Scale (SIS). On all measures, score increase indicates improvement. On all measures, subjects in the “Low/During” group (center bar) showed more improvement than subjects in other groups.

timing/intensity configurations. At this early stage in our investigation, it appears that PNS at or below sensory threshold, delivered during motor training (“Low/During”), is optimal in cases of severe motor deficit. Although the most time had elapsed since stroke for the “Low/During” group, this group showed the most improvement of all groups. This finding indicates that chronicity does not negatively impact potential benefit from this study’s intervention.

It is conceivable, though unproven, that PNS applied simultaneously with motor training would require lower stimulus intensity because of lower cell membrane thresholds associated with the firing of motor neurons during voluntary contraction^{8, 9}. Our data thus far support investigating this hypothesis in that various parameters have different effects on motor function (Figure 2). More specifically, it appears that the higher PNS intensity is optimal when PNS is delivered prior to motor training. On the other hand, lower PNS intensity appears optimal for concurrent motor training. We anticipate that the trends we have observed will become more pronounced as we complete subject enrollment. Given that we achieved promising results even with a small sample size, a full-scale investigation based on our feasibility study is warranted. Only a full-scale randomized study will offer sufficient data to support progress towards optimization of our novel, paired intervention. To this end, we recommend using expanded outcome measures (eg, neuroplastic change as measured by transcranial magnetic stimulation; longer-term follow-up evaluations).

Translation of interventions using PNS to enhance motor recovery after stroke is a timely, compelling endeavor that addresses several gaps in current research. Evidence has been found supporting the increased effectiveness of sub motor threshold stimulation intensities relative to those above motor threshold in patients who suffered a mild to moderate stroke no greater than 2 months prior to the study [40]. Presently; however, little evidence generalizes to those among the neediest of stroke survivors—namely, those living with severe hemiparesis. Furthermore, additional evidence is needed to elucidate which cortical areas engage in recovery of motor function for this subpopulation. Additionally, if we are able to demonstrate that PNS delivered during motor training is equally or more effective than PNS delivered immediately prior to motor training, we will be able to dramatically decrease intervention time. By discovering interventions to bolster health and participation for people with severe motor deficit after stroke, we will be able to transform prevailing, pre-conceived notions of recovery, independence, and capability in society after stroke.

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