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A RANDOMIZED TRIAL OF PERIPHERAL NERVE STIMULATION TO ENHANCE MODIFIED CONSTRAINT-INDUCED THERAPY AFTER STROKE

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Abstract

Background—Constraint-based therapy and peripheral nerve stimulation can significantly enhance movement function after stroke. No studies have investigated combining these interventions for cases of chronic, mild-to-moderate hemiparesis following stroke.

Objective—Determine the effects of peripheral nerve stimulation paired with a modified form of constraint-induced therapy on upper extremity movement function after stroke.

Design—Nineteen adult stroke survivors with mild-to-moderate hemiparesis more than 12 months after stroke received 2 hours of either active (n=10) or sham (n=9) peripheral nerve stimulation preceding 4 hours of modified constraint-induced therapy (10 sessions).

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Results of this study were first presented in poster form at the 2013 International Stroke Conference in conjunction with the Travel Award for Junior Investigators.

The clinical trial registration number with clinicaltrials.gov is NCT02587234.

Results—Active peripheral nerve stimulation enhanced modified constraint-induced therapy more than sham peripheral nerve stimulation (significance at $P<0.05$), both immediately after intervention (Wolf Motor Function Test: $P=0.006$ (timed score); $P=0.001$ (lift score); Fugl-Meyer Assessment: $P=0.022$; Action Research Arm Test: $P=0.007$); and at 1-month follow-up (Wolf Motor Function Test: $P=0.025$ (timed score); $P=0.007$ (lift score); Fugl-Meyer Assessment: $P=0.056$; Action Research Arm Test: $P=0.028$).

Conclusion—Pairing peripheral nerve stimulation with modified constraint-induced therapy can lead to significantly more improvement in upper extremity movement function than modified constraint-induced therapy alone. Future research is recommended to help establish longitudinal effects of this paired intervention, particularly as it affects movement function and daily life participation.

Keywords

upper extremity; neuroplasticity; occupational therapy; humans

Introduction

Efforts to minimize neurologic damage in acute stroke have met with only limited success[1]. In turn, there is a crucial need for therapeutic interventions to enhance long-term functional recovery after stroke[2]. Neuroplastic change (reorganization of neuronal properties) has been associated with functional recovery for neurological populations, including stroke[3, 4]. Thus, interventions that harness neuroplasticity could be used to enhance recovery of function after stroke. Furthermore, sensory input has been associated with neuroplastic change and recovery of movement function following cortical lesions[5, 6]. While decrease in afferent input can reduce cortical maps of the deafferented area[7, 8], increase in afferent input can increase motor cortical excitability[9, 10]. This evidence highlights how sensory-based therapeutic interventions may enhance the potential for recovery of movement function after stroke.

A sensory-based intervention called peripheral nerve stimulation (PNS) has been shown to directly affect sensory and motor networks by increasing motor cortical excitability (an indicator of neuroplasticity) and improving post-stroke movement function, especially when delivered as a paired intervention with motor training. For example, in a sham-controlled study, Sawaki and colleagues compared the effects of PNS on voluntary movement of paretic thumb in 7 subjects enrolled at least 6 months after stroke. Results showed significantly more neuroplastic change associated with PNS than with sham conditions[11]. A study by Ikuno and colleagues enrolled 22 subjects less than 6 months post-ictus, each of whom received a 1-week block of PNS combined with intensive, task-oriented training as well as a 1-week block of training alone. Subjects were randomized to receive either the PNS-training intervention first or the training-alone intervention first. From baseline to 1 week, the PNS-training group showed more improvement in upper extremity (UE) movement function than the training-alone group as measured by the Wolf Motor Function Test (WMFT). Both groups showed significant improvements on the WMFT after their respective periods of PNS combined with task-oriented training. Authors concluded that PNS may enhance outcomes of intensive, task-oriented training for individuals less than 6

months from stroke onset[12]. A 2011 systematic review by Laufer and colleagues concluded that PNS may enhance aspects of motor recovery after stroke, especially in concert with active motor training. However, for subjects more than 12 months from stroke onset, the review indicated that no evidence exists about the effects of PNS paired with a modified form of constraint-induced therapy (CIT) in cases of mild-to-moderate hemiparesis.

CIT is a form of motor training that has recently emerged to prominence in stroke rehabilitation research[12]. This approach compels intensive, task-oriented use of the affected limb while the non-affected limb is constrained. CIT developed from groundbreaking studies in which unilaterally deafferented monkeys regained use of their affected limbs after restraint of the non-affected limbs[13]. Translated to humans, the original CIT protocol (ie, 6 hours daily; 10-12 consecutive weekdays) can significantly improve UE movement function in cases of neurological impairment, even in long-term stages of recovery following stroke[14, 15]. Moreover, CIT can have superior, more lasting benefit for UE movement function than standard stroke rehabilitation[12, 16]. Modified forms of CIT (less training time, duration, or intensity than original CIT) have also been shown to lead to significant improvement in UE movement function after stroke[17].

CIT-based protocols (e.g., original CIT; modified CIT) rely on the premise that motor learning involves entrainment of cortical motor neurons via intensive, repetitive practice of functional tasks[3, 18]. CIT can lead to significant neuroplastic change after stroke, including enlarged cortical motor maps as measured by transcranial magnetic stimulation[16, 19]. Additionally, in a pre-post comparison of the effects of CIT, Laible and colleagues found that increases in affected UE motor capacity (as measured by WMFT) were closely related to changes in ipsilesional S1 activation peaks (as measured by functional magnetic resonance imaging (fMRI)) in subjects with moderate UE hemiparesis more than 12 months after stroke[20]. Furthermore, Hamzei and colleagues found that CIT-related activation changes in sensorimotor cortex (as measured by fMRI) are highly similar to changes resulting from a modified form of CIT[21] in subjects with moderate UE hemiparesis more than 24 months after stroke. In sum, research has shown that changes in sensory and motor networks are associated with motor gains induced by CIT or modified CIT in subjects with moderate hemiparesis in long-term stages of recovery following stroke.

The present study adds novel findings by reporting on an investigation of the following central hypothesis: subjects who receive *active* PNS paired with a modified form of CIT will have significantly more improved UE movement function than subjects who receive *sham* PNS paired with the same training protocol (ie, a modified form of CIT). The present article reports on the aim to assess effects of intervention on activity-based measures of UE movement function for subjects with mild-to-moderate UE hemiparesis more than 12 months after stroke.

Methods

In accordance with the Declaration of the World Medical Association (www.wma.net), this study was approved by the authorized institutional human research review boards at the institutions governing the research (ie, the University of Kentucky and Cardinal Hill

Hospital in Lexington, KY). The research setting was a neurorehabilitation research lab located on the premises of Cardinal Hill Hospital in Lexington, KY. The date range defining the periods of data collection was 11/21/06-02/23/10. All procedures followed in this study were in accordance with institutional guidelines. Subjects were recruited from local and regional communities, including local hospitals and clinics. *Inclusion Criteria*: Recruitment targeted subjects with mild-to-moderate UE motor deficit after a single ischemic stroke. "Mild-to-moderate" was defined according to standard eligibility criteria for CIT[12] (ie, able to extend the affected metacarpophalangeal and interphalangeal joints at least 10°; and the wrist, 20°). Targeted subjects were adults (ie, 18 years of age and older) at least 12 months from stroke onset. Targeting this phase helped mitigate the potential confound of spontaneous motor recovery, which usually occurs within the first 12 months after stroke onset.

Exclusion criteria were established to minimize potential confounding variables. These criteria included a) history of carpal tunnel syndrome and documented peripheral neuropathy; b) within 3 months of recruitment, addition or change in the dosage of drugs known to exert detrimental effects on motor recovery[22]; and c) aphasia or cognitive deficit severe enough to preclude informed consent.

Figure 1 details the workflow of the study. As required by the authorized institutional human research review boards at the institutions where the research was conducted, all subjects provided written informed consent after receiving a verbal and written explanation of the purposes, procedures, and potential hazards of this study. This study used a parallel-group block design within the conceptual framework of a superiority trial. After enrollment, subjects were evaluated with regard to UE movement function at baseline, after completion of the intervention period, and at 1-month follow-up. Following baseline evaluation, a computer-generated randomizer program was used to generate the simple random allocation sequence (1:1) of subjects into 2 groups (ie, either active PNS paired with a modified CIT protocol, or sham (control) PNS paired with a modified CIT protocol). The PI used an experimental design generator and randomizer program for simple random allocation of subjects into equal-sized groups. The PI generated the random allocation sequence, enrolled subjects, and assigned subjects to interventions. Each intervention session consisted of either active or sham PNS (2 hours) immediately preceding modified CIT (4 hours). PNS was the only independent variable. Subjects, care providers, and assessors of movement function were blinded to group assignment in that they were not made aware of which PNS condition any subject received. Additionally, personnel administering PNS did not administer modified CIT. Subjects were ordered by the randomizer in strict accordance with the order of enrollment.

Sample Size

Prior to the present study, a proof-of-concept study was conducted to compare outcomes of PNS paired with modified CIT (n=3) versus modified CIT only (n=2). Thus, the present study required a sample size of 10 evaluable subjects per group to detect the same effect size as that observed in the proof-of-concept study with 80% power, assuming a similar standard deviation in the change. This estimate was felt to be conservative since the variance was

estimated from the change in a group that received an intervention and appeared to have an average effect. In the present study, 21 subjects were enrolled. Nineteen subjects completed baseline and post evaluations; 17 of the 19 went on to complete 1-month follow-up evaluations.

Evaluation and Outcome Measures

The WMFT served as the primary outcome measure. The WMFT is a time- and function-based assessment encompassing a battery of 17 tasks that simulate functional tasks and that are ordered according to complexity [12]. The non-timed subcomponents of the WMFT comprise 1) a lift portion, which measures the maximum amount of weight the tested individual can lift to a height requiring 90° shoulder flexion; and 2) grip force dynamometer measurements. The WMFT has established reliability and validity and has been extensively applied in several CIT studies to evaluate UE motor capacity[12]. Secondary outcome measures included the Fugl-Meyer Assessment Scale (FMA; UE motor score only) and the Action Research Arm Test (ARAT). The FMA is a quantitative measure of motor recovery, balance, sensation, coordination and speed and is based on the principle that motor recovery occurs in a predictable progression[23]. The inter-rater reliability (=0.886~0.984 according to the subset for lower or UE) and test-retest reliability (=0.99) of FMA are also high[24]. FMA is extensively applied in cases of stroke; it is feasible for use with this condition[23]. The highest possible FMA UE motor score for a tested UE is 66. The ARAT was developed specifically to measure rehabilitation-related changes in UE motor capacity[25] and has measures for grasp, grip, pinch, and gross UE motor capacity. The highest possible ARAT score for a tested UE is 57.

Intervention Component 1: PNS

PNS was delivered in 120-minute sessions each day during a period of 10 consecutive weekdays. Optimal positions to stimulate the posterior interosseous, median, and ulnar nerves were determined by applying a surface bar electrode with the cathode placed distally on the affected UE. To stimulate each nerve trunk, gold-plated stimulating electrodes were placed with the cathode positioned proximally over each of the optimal positions identified by the bar electrode[26]. Disposable surface EMG electrodes were placed over the belly of the extensor digitorum communis, abductor pollicis brevis, and abductor digiti minimi muscles. EMG activity was amplified and filtered (bandpass, 10-3000Hz) and recorded using a data collection program written in LabVIEW (National Instruments, Austin, TX). For active PNS, the stimulus intensity was adjusted to elicit small compound muscle action potentials of approximately 50 to 100μV without the absence of visible muscle movements [26]. This low stimulus intensity and the stimulus duration of 1ms has been shown to preferentially activate large cutaneous and proprioceptive sensory fibers[27]. For sham PNS, an identical protocol was implemented except that the amplitude was set to 0V. Since attention appears to play an important role in neuroplastic change[9], subjects were required to stay awake during PNS.

Intervention Component 2: Modified CIT

Each subject participated in 4 hours of modified CIT immediately following PNS. An occupational therapist blinded to PNS condition administered the training, which included

rest breaks and grading of activities according to subject fatigue. Per the original CIT regimen, subjects were requested to wear a padded constraining mitt for at least 90% of waking hours on the non-affected extremity as well as fill out a diary to monitor the time spent wearing the mitt. Also in keeping with original CIT, the protocol focused on constraining the non-affected extremity while compelling highly repetitive use of the affected extremity in task-oriented motor activities [12]. Tasks with progressive difficulty were applied where the extended motor ability was kept just beyond the performance already achieved (shaping). Tasks were repeatable and targeted functional goals of importance to each subject (such as activities of daily living) or prerequisites to function (eg, releasing; grasping; reaching; supination). For example, an individual who had difficulty with thumb movement performed activities that required use of the thumb and second digit in order to strengthen thumb movements in activities identified as meaningful by the individual (eg, fastening jewelry; handwriting; manipulating coins). Verbal or visual (graph) positive feedback was provided after small improvements beyond the already achieved skill level. Rest breaks were provided, lasting no longer than the practice segment. The number of repetitions for each designated task were documented to evaluate the effort of each patient. The target range for repetitions of any given task was 10 to 50 according to the demands of the task as well as reported levels of fatigue and engagement of each subject with a given task. Transfer package was not provided in this study. Therapy took place in a 1:1 therapist-to-subject ratio.

Statistics

For each outcome of interest, a longitudinal repeated measures model that accounts for time, trial arm, and their interaction was fit. Each model incorporates an unstructured working covariance matrix, and the Kenward and Roger[28] degrees of freedom method was used for inference. These analyses correspond to the use of repeated measures MANOVA, but with the allowance of missing data. Primary interest was in the comparison of mean changes in outcomes from baseline to immediately post-intervention and to 1-month follow-up for the 2 trial arms. Corresponding results are presented in Table 2. For more detail from the models, the separate impacts of each trial arm on the mean change of each outcome are presented. All available data were utilized for analyses. All tests were 2-sided, with statistical significance pre-specified as $P<0.05$. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

Analysis was by original assigned groups. Table 1 summarizes demographics of the sample. No significant difference existed between groups on any outcome measured at baseline, as determined by simple unpaired t-testing. No treatment complications or serious adverse events occurred during the study. Two subjects were withdrawn from the study after baseline testing and prior to post-intervention evaluation. One of these 2 subjects was assigned to the active PNS group and was subsequently withdrawn due to non-compliance with the study protocol (inconsistent attendance during the intervention period). The other subject was assigned to the sham PNS group and subsequently requested to withdraw secondary to sequelae of a fall sustained at home. This fall was determined by the study doctor to be a

non-serious adverse event unrelated to the study procedures. Two other subjects were lost to 1-month follow-up testing as a result of transportation issues. Both of these subjects had been assigned to the sham PNS group. The trial ended because funding was completed.

For the active PNS group, score changes for the affected UE were significantly greater than score changes for the sham PNS group on the WMFT timed and lift portions (Figure 2); the UE motor portion of the FMA (Figure 3); and the ARAT (Figure 4). These significant differences between groups were evident on all outcome measures immediately post-intervention. Significant differences between groups were also evident at 1-month follow-up except for FMA (Table 2). No significant difference between groups was evident at any timepoint after intervention with regard to the grip portion of the WMFT (Figure 2; Table 2). However, mean changes were significant in the active PNS group, and estimated mean changes were more favorable than for the sham PNS group. For both groups, the WMFT showed non-significant changes in the less affected UE; the ARAT showed no change in this regard. No evidence of unintended effects in each group was found.

Discussion

Because results indicated that active PNS can enhance a modified form of CIT significantly more than sham PNS can, it appears that PNS has enormous promise as a clinical intervention to enhance outcomes of motor training for stroke survivors with mild to moderate hemiparesis. Additionally, that the active PNS group showed more significant improvement than the sham PNS group 1 month after intervention had ended (ie, on the WMFT timed portion) highlights the potential translational value of this study. More specifically, this evidence suggests that compared with the sham PNS group, the active PNS group may have made more extensive use of the more affected upper extremity in settings outside the lab, such as in activities of daily living. Future studies are recommended to provide conclusive evidence in this regard.

The lack of more significant improvement for the active PNS group compared with the sham PNS group on WMFT grip was somewhat surprising, particularly in consideration of a 2002 study by Conforto and colleagues that showed improvement in pinch force associated with 2 hours of PNS to median nerve (no motor training provided) for subjects more than 12 months post-stroke (n=8) [29]. Likewise, a separate study by Klaiput and colleagues reported gains in pinch force associated with 2 hours of dual PNS to median and ulnar nerve (without motor training) for 20 subjects less than 6 months following stroke[30]. On the other hand, in 2010, Conforto and colleagues showed a lack of effects on pinch force associated with different intensities of single nerve (median) PNS paired with motor training in 22 subjects at 2 months or less since stroke[31]. Additionally, Sawaki and colleagues showed that while there was a trend towards improved WMFT grip associated with CIT, no significant between-groups difference was evident in comparing early with late phase of recovery (ie, less than 9 months post-stroke versus greater than 12 months post-stroke)[32]. Taken together, these inconsistent findings with regard to WMFT measurement of isometric force may reflect the lack of homogeneity in PNS protocols and/or phases of recovery across these cited studies.

In order to maximize adjuvancy of PNS with CIT or its modified forms, further research is recommended to optimize parameters of multiple nerve stimulation sites (ie, proximal vs distal; multiple versus single). The literature reports only 1 study that, similar to the present study, applied simultaneous stimulation of median, radial, and ulnar nerves[33]. (However, in delivering PNS at the elbow, this protocol differed from the present study, which delivered multiple nerve stimulation more distally. Additionally, the present study delivered individual PNS trains with an offset of 35ms between each stimulation channel to prevent stimulation of distal nerves from being blocked by stimulation of more proximal nerves, a phenomenon known as "collision" in nerve conduction studies [34, 35].) Fleming and colleagues administered 2 hours of PNS immediately prior to 30 minutes of task-specific training for 33 subjects with chronic stroke[33]. At post-intervention, more significant improvement on the ARAT was evident for the active PNS group compared with the sham PNS group; but no significant between-groups difference was evident on secondary measures (ie, FMA; Motor Activity Log; Goal Attainment Scale) or at long-term follow-up.

Other future investigations are recommended to help establish strategies for translating intervention used in the present study, as well as other PNS-based interventions, to settings beyond research. Examples would include PNS paired with standard occupational therapy or PNS paired with daily living tasks in in the home and community. Studies are also recommended to determine the effect of PNS paired with different CIT-based protocols (ie, various frequencies or durations). Such studies would build on the systematic review and meta-analysis by Peurala and colleagues[17] regarding optimal parameters of different CIT-based protocols targeting various outcomes (eg, functional independence; reduction of motor impairment).

Because the reduced training time, duration, or intensity of modified forms of CIT may have greater insurance-related compatibility than CIT[36], studying how PNS enhances different CIT protocols could help optimize the intervention for settings that may not support protracted therapy. To this end, the modified CIT in the present study required comparatively less daily time than CIT. However, full clinical translation would require establishing the minimum time required for efficacy of this paired intervention.

The main possible limitations to the present study included small sample size and need for longer-term follow-up. Other possible limitations included lack of multiple baselines. Additionally, the customization of motor training to each subject could be considered a lack of standardization, even though this tailored approach was associated with improvement for both groups. Finally, the present study, as well as the other PNS/motor training studies we have cited here, did not focus on stroke survivors with severe motor deficit (ie, almost no finger or hand movement) more than 12 months post-stroke. Future studies in this regard would establish the generalizability of findings from the present study to other stroke sub-populations in great need of effective interventions.

Conclusions

All outcome measures in this study reflected improvement in behavioral measures of UE activity for both groups after intervention. However, significantly more improvement was

evident for the active PNS group compared with the sham PNS group. Overall, the results of this study provide a strong rationale for a full-scale investigation of the effects of PNS paired with a modified form of CIT for stroke survivors with chronic, mild-to-moderate UE hemiparesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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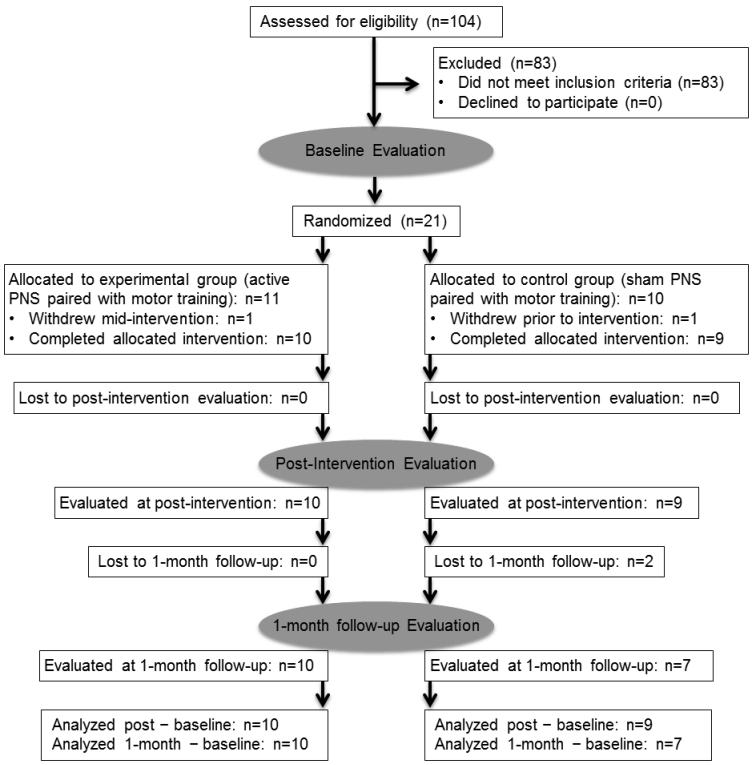

Figure 1.
Diagram of Study.

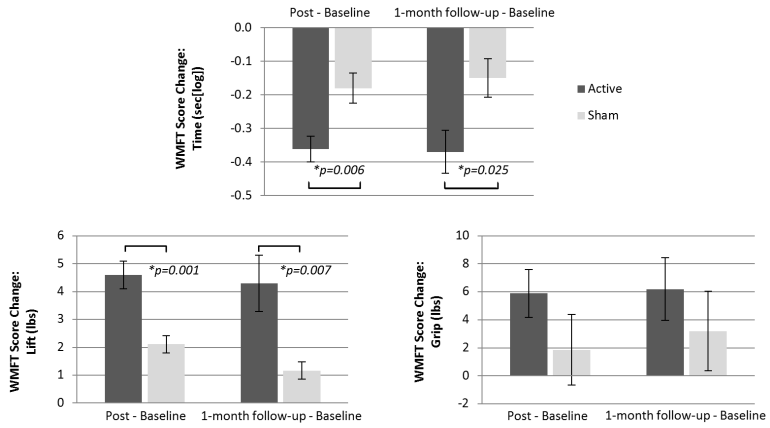

Figure 2.

Comparison of Groups' Score Changes on Wolf Motor Function Test (WMFT). Results of the WMFT (primary outcome measure) show that active peripheral nerve stimulation (PNS) can enhance outcomes of a modified form of constraint-induced therapy (CIT) significantly more than sham PNS. Score decrease on the timed portion of the WMFT, as well as score increase on the lift and the grip portions, indicate improvement in affected upper extremity (UE) motor capacity. Immediately post-intervention, as well as at 1-month follow-up, there was a significant difference between groups on the timed portion (upper image) and the lift portion (lower left image). No significant difference emerged between groups on the grip portion (lower right image).

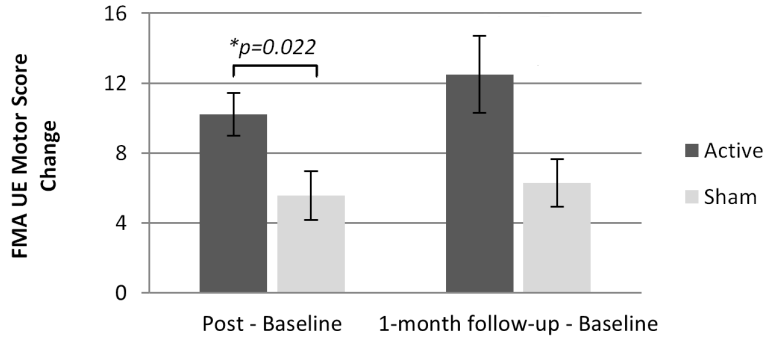

Figure 3.

Comparison of Groups' Score Changes on Upper Extremity (UE) Motor Score of the Fugl-Meyer Assessment (FMA). Increase in FMA score indicates improvement in affected UE motor function. Results at immediately post-intervention show that active peripheral nerve stimulation (PNS) can enhance outcomes of a modified form of constraint-induced therapy (CIT) significantly more than sham PNS.

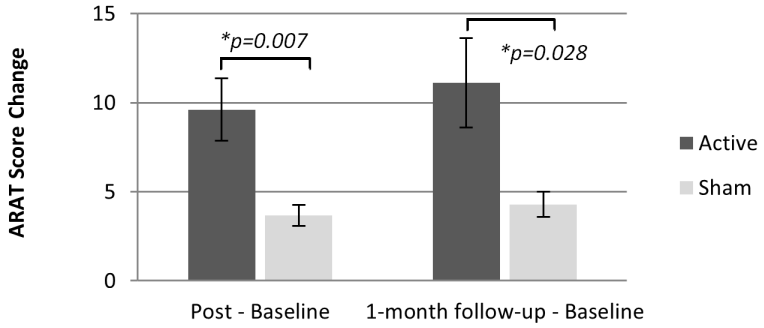

Figure 4.

Comparison of Groups' Score Changes on Action Research Arm Test (ARAT). Increase in ARAT score indicates improvement in affected upper extremity (UE) motor capacity. Results at immediately post-intervention, as well as at 1-month follow-up, show that active peripheral nerve stimulation (PNS) can enhance outcomes of a modified form of constraint-induced therapy (CIT) significantly more than sham PNS.

Table 1

Demographics of sample.

Age (y)	Group	Sex	Time Since Stroke (months)	Stroke Type	Stroke Site	Handedness Before Stroke	More Affected Upper Extremity
50	Sham	F	26	Ischemic	Middle cerebral artery (MCA) territory	Right	Right
35	Sham	F	29	Ischemic	MCA territory	Right	Right
65	Sham	M	15	Ischemic	MCA territory	Right	Left
63	Sham	M	20	Ischemic	Basal ganglia	Right	Right
62	Sham	M	22	Ischemic	MCA territory	Right	Right
58	Sham	F	84	Ischemic	Basal ganglia	Right	Left
54	Sham	M	21	Ischemic	MCA territory	Right	Right
61	Sham	M	41	Ischemic	Corona radiata	Right	Right
43	Sham	M	64	Hemorrhagic	MCA territory	Left	Right
66	Active	M	12	Ischemic	Basal ganglia	Right	Right
58	Active	F	60	Ischemic	MCA territory	Right	Left
48	Active	M	12	Ischemic	Corona radiata	Right	Right
61	Active	M	12	Ischemic	Basal ganglia	Right	Right
61	Active	F	60	Ischemic	MCA territory	Right	Left
52	Active	F	52	Hemorrhagic	MCA territory	Right	Left
56	Active	F	24	Ischemic	MCA territory	Right	Right
65	Active	F	24	Ischemic	MCA territory	Right	Left
62	Active	F	21	Ischemic	Basal ganglia	Right	Left
38	Active	F	18	Ischemic	MCA territory	Right	Left

Table 2

Estimated means, 95% confidence intervals, and p-values corresponding to mean change.

Outcome Measure	Test Portion	Post-intervention – Baseline			1-month follow-up – Baseline		
		Active	Sham	Active - Sham	Active	Sham	Active - Sham
Wolf Motor Function Test (WMFT; primary outcome measure)	Timed (log): more affected upper extremity (UE)	−0.36 (−0.45, −0.28) $p<0.001$	−0.18 (−0.27, −0.09) $p=0.001$	−0.19 (−0.31, −0.06) $p=0.006$	−0.37 (−0.49, −0.24) $p<0.001$	−0.14 (−0.29, 0.004) $p=0.056$	−0.23 (−0.42, −0.03) $p=0.025$
	Lift: more affected UE	4.60 (3.72, 5.48) $p<0.001$	2.11 (1.19, 3.03) $p<0.001$	2.49 (1.22, 3.76) $p=0.001$	4.30 (2.50, 6.10) $p<0.001$	0.30 (−1.78, 2.39) $p=0.763$	4.00 (1.24, 6.75) $p=0.007$
	Grip: more affected UE	5.89 (1.56, 10.22) $p=0.011$	1.86 (−2.70, 6.42) $p=0.402$	4.03 (−2.26, 10.32) $p=0.194$	6.19 (1.36, 11.03) $p=0.015$	1.61 (−3.56, 6.78) $p=0.521$	4.59 (−2.49, 11.66) $p=0.189$
Fugl-Meyer Assessment (FMA; secondary outcome measure)	Motor: more affected UE	10.20 (7.52, 12.88), $p<0.001$	5.56 (2.73, 8.38) $p=0.001$	4.64 (0.75, 8.54) $p=0.022$	12.50 (8.61, 16.39) $p<0.001$	6.58 (1.89, 11.26) $p=0.009$	5.92 (−0.16, 12.01) $p=0.056$
Action Research Arm Test (ARAT; secondary outcome measure)	More affected UE	9.60 (6.79, 12.41) $p<0.001$	3.67 (0.70, 6.63) $p=0.018$	5.93 (1.84, 10.02) $p=0.007$	11.10 (7.10, 15.10) $p<0.001$	4.29 (−0.13, 8.72) $p=0.057$	6.81 (0.83, 12.78) $p=0.028$