Nerve Stimulation Enhances Task-Oriented Training in Chronic, Severe Motor Deficit After Stroke
A Randomized Trial

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Background and Purpose—A sensory-based intervention called peripheral nerve stimulation can enhance outcomes of motor training for stroke survivors with mild-to-moderate hemiparesis. Further research is needed to establish whether this paired intervention can have benefit in cases of severe impairment (almost no active movement).

Methods—Subjects with chronic, severe poststroke hemiparesis (n=36) were randomized to receive 10 daily sessions of either active or sham stimulation (2 hours) immediately preceding intensive task-oriented training (4 hours). Upper extremity movement function was assessed using Fugl–Meyer Assessment (primary outcome measure), Wolf Motor Function Test, and Action Research Arm Test at baseline, immediately post intervention and at 1-month follow-up.

Results—Statistically significant difference between groups favored the active stimulation group on Fugl–Meyer at postintervention (95% confidence interval [CI], 1.1–6.9; $P=0.008$) and 1-month follow-up (95% CI, 0.6–8.3; $P=0.025$), Wolf Motor Function Test at postintervention (95% CI, −0.21 to −0.02; $P=0.020$), and Action Research Arm Test at postintervention (95% CI, 0.8–7.3; $P=0.015$) and 1-month follow-up (95% CI, 0.6–8.4; $P=0.025$). Only the active stimulation condition was associated with (1) statistically significant within-group benefit on all outcomes at 1-month follow-up and (2) improvement exceeding minimal detectable change, as well as minimal clinically significant difference, on ≥1 outcomes at ≥1 time points after intervention.

Conclusions—After stroke, active peripheral nerve stimulation paired with intensive task–oriented training can effect significant improvement in severely impaired upper extremity movement function. Further confirmatory studies that consider a larger group, as well as longer follow-up, are needed.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02633215.

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Key Words: occupational therapy ■ rehabilitation ■ stroke ■ upper extremity

Stroke is a major cause of death and disability.[1,2] Interventions to limit tissue damage during the acute phase of stroke have resulted in some success.[3,4] However, there is a need for further research on interventions to maximize recovery of function after acute stages of stroke,[5,6] particularly with regard to upper extremity (UE) movement function in cases of severe hemiparesis (almost no active movement).[7] These interventions may capitalize on neuroplastic change, which has been associated with functional recovery in cases of neurological impairment.[6]

Neuroplastic change and recovery of motor function after cortical lesions can be significantly influenced by sensory input.[8,9] During performance of motor tasks, repetitive activation of sensory input enhances motor cortical plasticity,

establishing a mechanism for the role of sensory input in motor skill acquisition.[10–12] A sensory-based intervention called peripheral nerve stimulation (PNS) has been shown to increase motor cortical excitability and enhance outcomes of motor training after stroke. In a study of 22 subjects <6 months after stroke, PNS paired with 1 week of intensive task–oriented UE training was associated with more significant improvement in movement function than the effects of training alone as measured by the Wolf Motor Function Test (WMFT).[13] A separate study by Sawaki et al[12] investigated the effects of PNS on voluntary movement of paretic thumb in 7 subjects at least 6 months post stroke. Significantly more neuroplastic change was associated with active PNS compared with sham conditions.

Corroborating evidence from a systematic review of randomized and quasi-randomized trials indicated that motor recovery after stroke may be enhanced with PNS, especially when PNS is delivered as an adjunct to motor training.[13,14]

A well-validated form of motor training called intensive task–oriented training has been associated with significant neuroplastic change, as well as more significant functional gains than usual and customary care, in cases of mild-to-moderate hemiparesis.[15] Further research is needed to optimize intensive task–oriented training for people with severely impaired movement function after stroke.[7] In addition, randomized controlled trials showing that PNS can enhance outcomes of task-oriented training have primarily targeted only mild-to-moderate UE impairment.[16–19] In sum, although pairing PNS with motor training can enhance motor recovery after stroke, it remains unclear how severity of motor deficit may affect responsiveness to this paired intervention.[14] To address these evidence gaps, the purpose of this study was to investigate whether active PNS paired with intensive task–oriented training would lead to significantly more improved movement function than sham PNS paired with intensive task–oriented training for subjects with chronic, severe deficit in UE movement function 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. All procedures followed in this study were in accordance with these institutions' guidelines. Subjects were recruited from Cardinal Hill Rehabilitation Hospital, University of Kentucky, and Wake Forest University Baptist Medical Center (ie, the settings where data were collected) as well as local communities.

Inclusion Criteria

Participant recruitment targeted adults (aged ≥21 years) with chronic (at least 12 months after stroke), severe UE motor deficit (the inability to extend the affected metacarpophalangeal joints at least 10° and the wrist, 20°[20,21]) after a single stroke. Targeting the chronic phase reduced the likelihood that spontaneous motor recovery would be a confounding factor.

Exclusion Criteria

The exclusion criteria are as follows: (1) History of carpal tunnel syndrome and documented peripheral neuropathy; (2) within 3 months of recruitment, addition of or change in dosage of drugs known to exert detrimental effects on motor recovery or interfere with neuroplasticity, such as monoamine oxidase inhibitors, α-adrenergic antagonists, benzodiazepines, muscarinic receptor antagonists, and dopaminergic antagonists[22–24]; and (3) aphasia or cognitive deficit severe enough to preclude informed consent.

For the trial design, a parallel-group block design was used within the conceptual framework of a superiority trial. All subjects were given a verbal and written explanation of the purposes, procedures, and potential hazards of this study before providing written informed consent to the principal investigator. After screening and enrollment by the principal investigator, baseline UE movement function was evaluated. This evaluation was repeated immediately after the intervention period and at 1-month follow-up. After baseline evaluation, the principal investigator used a computer-generated randomizer program to govern group assignment. This program generated a simple random allocation sequence (1:1) for assigning subjects into 2 equal-sized groups (ie, either active PNS paired with intensive task–oriented training; or sham [control] PNS paired with intensive task–oriented training). The order of randomization was in strict
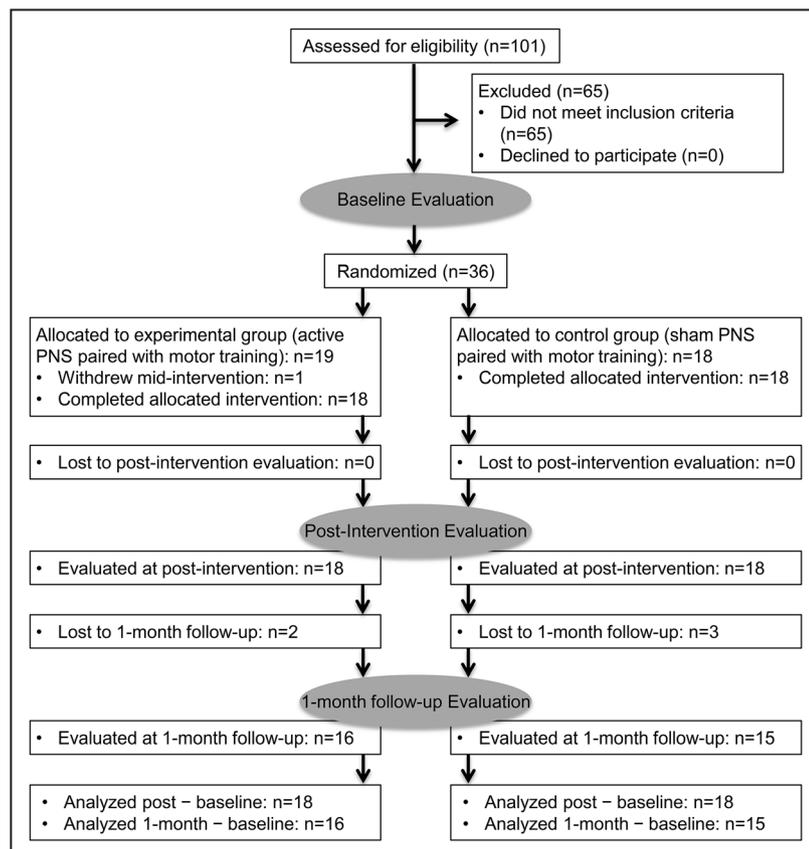

Figure 1. Participant flow. PNS indicates peripheral nerve stimulation.

Table 1.   Baseline Characteristics: Descriptive Statistics

Baseline Characteristics	Active	Sham
Fugl–Meyer Assessment	25.7±13.3 (18)	22.8±15.0 (18)
Wolf Motor Function Test	1.71±0.41 (18)	1.84±0.40 (17)
Action Research Arm Test	13.9±12.3 (18)	10.4±11.2 (18)
Age	58.7±12.1 (18)	65.4±10.8 (18)
Time since stroke (mo)	39.2±34.6 (18)	25.7±17.7 (18)
Handedness before stroke (right/left)	17/1	15/3
More-affected upper extremity (right/left)	12/6	11/7

Sample mean±SD (sample size).

accordance with the order of enrollment. Each intervention session consisted of either active or sham PNS (2 hours) immediately preceding motor training (4 hours). PNS was the only independent variable. Blindedness was ensured in that subjects, care providers, and evaluators of movement function were not informed of PNS condition assignment. Furthermore, the principal investigator did not administer outcome measures or interventions; and personnel delivering PNS did not administer intensive task–oriented training. The intervention period lasted for 10 consecutive weekdays.

Sample Size

Sample size was determined using results from a previous study evaluating the effects of PNS paired with motor training (n=3). The mean Fugl–Meyer Assessment (FMA) difference (completion minus baseline) for the active PNS condition was 11 (SD, 6.4); and for the sham PNS condition, 4. To detect a similar effect size in the present randomized trial as that observed from the previous study with 90% power, assuming a similar SD in the change, it was determined that a sample size of 18 evaluable subjects per group would be required.

Evaluation and Outcome Measures

The primary outcome measure was FMA. The FMA quantitatively measures motor recovery, sensation, coordination, and speed of movement, which has high inter-rater reliability and test–retest reliability,[25] and it has been used extensively in stroke.[26] The highest possible FMA motor score for a tested UE is 66. The minimal clinically important difference (MCID) for FMA is 9 to 10 points; and the minimal detectable change (MDC) is 5.2.[27]

Secondary outcome measures included the timed portion of WMFT (more-affected UE only) and the Action Research Arm Test (ARAT; more-affected UE only). The WMFT is a time- and function-based assessment of motor capacity that has established reliability, validity, and history of use in research to evaluate UE motor capacity.[28] The MCID for WMFT is 1.5 to 4 s; and the MDC is 12 s.[27] The ARAT measures rehabilitation-related changes in UE motor capacity[29] and has measures for grasp, grip, pinch, and gross movement. The highest possible ARAT score for a tested UE is 57. The MCID for ARAT is 5.7 points; and the MDC is 3.5.[27]

Intervention Component 1

Peripheral Nerve Stimulation

PNS was delivered using parameters that have been shown to target upstream synaptic plasticity by preferentially activating large cutaneous and proprioceptive sensory fibers.[30] There is no evidence that these parameters are associated with overstimulation.[12,31–34] PNS was delivered for 2 hours in each session. Optimal positions to stimulate Erb's point, radial, and median nerves were determined by applying a surface bar electrode (for details see the online-only Data Supplement).[30,31] For active PNS, the stimulus intensity was adjusted to elicit small compound muscle action potentials of ≈50 to 100 μV.[31] For sham PNS, an identical protocol was implemented except that the amplitude was set to 0 V.

Intervention Component 2

Intensive Task–Oriented Training

Immediately after each session of PNS, each subject participated in 4 hours of intensive task–oriented training. Training occurred in a 1:1 therapist:subject ratio. No physical constraint of the less-affected UE was applied, but training compelled highly repetitive use of the

Table 2.   Demographic and Clinical Characteristics of the Study Sample

Group	Sex	Stroke Type	Stroke Site
Active (A)	M	Ischemic	Middle cerebral artery territory (MCA)
A	F	Hemorrhagic	Parietal lobe/basal ganglia
A	M	Ischemic	MCA
A	M	Hemorrhagic	MCA
A	F	Ischemic	MCA
A	F	Ischemic	MCA
A	M	Ischemic	MCA
A	M	Ischemic	MCA
A	F	Hemorrhagic	MCA
A	F	Hemorrhagic	MCA
A	M	Ischemic	MCA
A	F	Ischemic	MCA
A	M	Ischemic	MCA
A	F	Hemorrhagic	Basal ganglia
A	F	Ischemic	MCA
A	M	Ischemic	MCA
A	F	Ischemic	MCA
A	M	Hemorrhagic	MCA
Sham (S)	F	Ischemic	MCA
S	M	Ischemic	Basal ganglia
S	F	Ischemic	MCA
S	F	Ischemic	Basal ganglia
S	F	Ischemic	MCA
S	M	Ischemic	MCA
S	M	Ischemic	Corona radiata
S	F	Ischemic	Pons
S	F	Hemorrhagic	MCA
S	M	Ischemic	MCA
S	M	Ischemic	MCA
S	M	Hemorrhagic	MCA
S	F	Ischemic	MCA
S	F	Hemorrhagic	MCA
S	F	Ischemic	Internal capsule
S	M	Ischemic	Basal ganglia/Corona radiata
S	M	Ischemic	MCA
S	M	Ischemic	MCA

F indicates female; and M, male.

Table 3. Estimated Means (SE), 95% Confidence Intervals, and *P* Values Corresponding to Mean Change in Score on Each Outcome Measure

Outcome Measure	Postintervention—Baseline			1-Mo Follow-Up—Baseline		
	Active	Sham	Active–Sham	Active	Sham	Active–Sham
Fugl–Meyer Assessment	7.4 (1.0); (5.4, 9.5); *P*<0.0001	3.4 (1.0); (1.4, 5.5); *P*=0.002	4.0 (1.4); (1.1, 6.9); *P*=0.008	7.2 (1.3); (4.6, 9.8); *P*<0.0001	2.8 (1.4); (−0.02, 5.6); *P*=0.052	4.4 (1.9); (0.6, 8.3); *P*=0.025
Wolf Motor Function Test	−0.18 (0.03); (−0.25, −0.11); *P*<0.0001	−0.06 (0.03); (−0.13, 0.01); *P*=0.068	−0.12 (0.05); (−0.21, −0.02); *P*=0.020	−0.14 (0.03); (−0.21, −0.07); *P*=0.0002	−0.07 (0.04); (−0.14, 0.01); *P*=0.075	−0.07 (0.05); (−0.17, 0.03); *P*=0.157
Action Research Arm Test	6.4 (1.1); (4.1, 8.7); *P*<0.0001	2.3 (1.1); (0.1, 4.6); *P*=0.044	4.1 (1.6); (0.8, 7.3); *P*=0.015	6.9 (1.3); (4.2, 9.7); *P*<0.0001	2.4 (1.4); (−0.4, 5.2); *P*=0.089	4.5 (1.9); (0.6, 8.4); *P*=0.025

more-affected UE.[35] Subjects attempted tasks with progressive difficulty, meaning each task elicited a skill level just beyond the level already achieved (shaping).[15] No transfer package was provided.

Statistics

For each outcome of interest, a longitudinal repeated measures model was used that accounts for time, trial arm, and their interaction. Each model incorporates an unstructured working covariance matrix, and the Kenward and Roger[36] 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. For more detail, the separate impacts of each trial arm on the mean change of each outcome are presented. Longitudinal repeated measures ANCOVA models were also fit for each outcome because of slight imbalances at baseline. However, results were similar and thus are not presented. All available data were used for analyses. All tests were 2-sided, with statistical significance prespecified as *P*<0.05. Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC).

Results

The participant flow of the study is shown in Figure 1. Table 1 shows that baseline characteristics were similar between the 2 trial arms. Table 2 summarizes demographic and clinical characteristics of the sample.

No treatment complications or serious adverse events occurred during recruitment and follow-up (March 2005 through December 2013). One subject could not perform WMFT at any time point because of severity of motor impairment. Losses to 1-month follow-up occurred because of either transportation constraints or subjects' enrollment in other research studies immediately after postintervention evaluation. One subject was withdrawn midintervention because of noncompliance with the study schedule. The trial ended because the desired sample size was achieved.

Table 3 summarizes estimated means and SEs, 95% confidence intervals (CIs), and *P* values corresponding to mean change in score on each outcome measure. Table 4 shows the proportion of subjects who showed an improvement, along

with corresponding exact CI. Analysis was carried out by original assigned groups. No evidence of unintended effects (ie, unforeseen outcomes associated with intervention) was found in either group. With regard to within-group change (Table 3), all measured outcomes at all time points after intervention reflected statistically significant improvement associated with the active PNS condition. The sham PNS group showed statistically significant improvement on the FMA and the ARAT immediately after intervention but no statistically significant improvement on any outcome measure at 1-month follow-up. At postintervention, the estimated mean FMA change for the active PNS group (ie, 7.4; Table 3) exceeded MDC level (5.2[27]). At 1-month follow-up, ARAT change for the active PNS group (ie, 6.9; Table 3) exceeded both MDC and MCID levels (3.5 and 5.7,[27] respectively). No other association was evident between intervention and mean change at MCID or MDC levels for either group.

Figure 2 and Table 3 summarize between-groups comparisons. For the active PNS group, score changes on all outcome measures from baseline to immediately post intervention were significantly greater than score changes for the sham PNS group (FMA 95% CI, 1.1 to 6.9; *P*=0.008; WMFT 95% CI, −0.21 to −0.02; *P*=0.020; and ARAT 95% CI, 0.8 to 7.3; *P*=0.015). Statistically significant differences between groups persisted to 1-month follow-up on all outcome measures except for WMFT (FMA 95% CI, 0.6–8.3; *P*=0.025 and ARAT 95% CI, 0.6–8.4; *P*=0.025).

Discussion

For stroke survivors with chronic, severe impairment in movement function, active PNS paired with intensive task–oriented training can effect significant improvement in UE movement function. For both the groups in this study, intensive task–oriented training was associated with significant benefit immediately after intervention. These findings seem to counter previously published review evidence that stroke survivors with severe hemiparesis cannot benefit from intensive task–oriented training as a singular intervention delivered

Table 4. Individual Effects of Active Peripheral Nerve Stimulation (PNS) Paired With Intensive Task–Oriented Training (Exploratory Analysis)

	Fugl–Meyer Assessment	Wolf Motor Function Test	Action Research Arm Test
Postintervention—baseline	17/18=0.94 (0.73, 0.999)	17/18=0.94 (0.73, 0.999)	16/18=0.89 (0.65, 0.99)
1-mo follow-up—baseline	15/16=0.94 (0.70, 0.998)	14/16=0.88 (0.62, 0.98)	16/16=1.00 (0.79, 1.00)

The proportion of subjects who showed an improvement, along with the corresponding exact confidence interval, is shown.
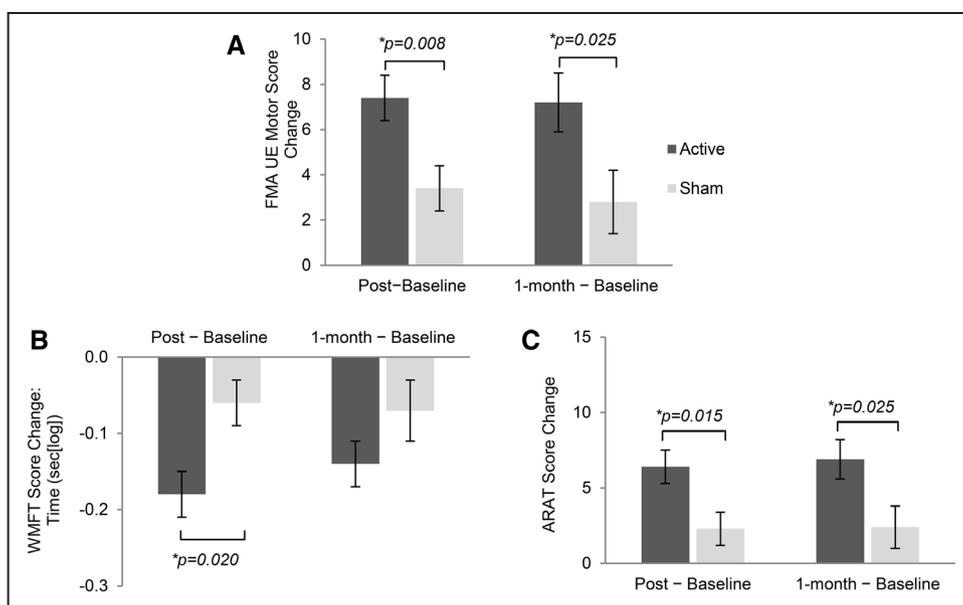
Figure 2. Peripheral nerve stimulation (PNS) combined with intensive task–oriented training improves upper extremity (UE) movement function in chronic, severe hemiparesis after stroke. All plots display the change in score with respect to baseline. **A**, Increase in Fugl–Meyer Assessment (FMA) score indicates improvement. The active PNS group showed significantly more improvement than the sham PNS group at both evaluation time points after intervention. **B**, Decrease in Wolf Motor Function Test (WMFT) score indicates improvement. The active PNS group showed more improvement than the sham PNS group at all time points after intervention—significantly more at immediately post intervention. **C**, Increase in Action Research Arm Test (ARAT) score indicates improvement. The active PNS group showed significantly more improvement than the sham PNS group at both evaluation time points after intervention.

in a hands-on fashion (as opposed to robot-assisted therapy).[7] However, this review was predicated on studies spanning acute to chronic stages of stroke, unlike this study.

In this study, only the active PNS condition was associated with (1) statistically significant benefit at 1-month follow-up and (2) improvement exceeding MDC, as well as MCID, on ≥1 outcome measures at ≥1 time points after intervention. A statistically significant difference between groups favored the active PNS group on both the evaluation time points after intervention. Taken together, these findings highlight that in cases of chronic, severe poststroke impairment, outcomes of intensive task–oriented training can be significantly enhanced, both statistically and clinically, with active PNS. To help substantiate whether these effects persist longitudinally, further research using 6-month follow-up or longer is recommended.

A possible trial limitation is that although preparatory techniques were used to reduce spasticity during intervention, spasticity may have affected evaluation. Specifically, on 1-month between-groups analysis, the only outcome that reflected no statistically significant difference between groups was WMFT. As WMFT is a time-dependent measure, and because abnormal spasticity is a velocity-dependent mechanism, it is conceivable that WMFT may be particularly suited to measure change in populations in which speed of movement is unlikely to trigger a level of spasticity that interferes with functional performance. Future studies incorporating objective measures of spasticity are recommended to build on the results of this study.

Benefits of intervention were not sufficient to effect full recovery of movement function for study participants. Further research is needed to establish (1) what other interventions would augment these benefits for the target population as well as (2) optimal parameters of PNS intervention. It is conceivable

that delivering PNS to Erb's point alone, in conjunction with motor training, would effect desired change. This streamlined setup would potentially increase ease of clinical use by minimizing the number of needed electrodes. Similarly, establishing optimal dose–response and timing parameters would enhance the translational potential of PNS paired with motor training. Finally, to enhance generalizability of this trial's findings, studies are recommended to help establish whether PNS may enhance outcomes of intensive task–oriented training during other phases (eg, subacute) or contexts (eg, activities of daily living in home and community) of recovery after stroke.

Disclosures

Dr Sawaki serves as a consultant to HealthSouth Cardinal Hill Rehabilitation Hospital.

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Nerve Stimulation Enhances Task-Oriented Training in Chronic, Severe Motor Deficit After Stroke: A Randomized Trial

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SUPPLEMENTAL MATERIAL

Supplemental methods: For peripheral nerve stimulation (PNS), gold-plated stimulating electrodes were placed with the cathode positioned proximally over each of the optimal positions[1, 2]. EMG electrodes were placed over the bellies of the deltoid, triceps, and abductor pollicis brevis muscles. Trains of electrical stimulation were delivered 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) at 10Hz [2]. EMG activity was amplified and filtered (bandpass, 10-3000Hz) and recorded using a data collection/analysis program written in LabVIEW (National Instruments, Austin, TX). Individual PNS pulses were delivered with an offset of 15ms between each stimulation channel to prevent stimulation of distal nerves from being blocked by stimulation of more proximal nerves (i.e., collision [3]). For task-oriented training, tasks targeted occupations (such as activities of daily living) and prerequisites to function (such as release, grasp, or supination). For example, subjects practiced self-feeding using the more-affected UE to stabilize a plate while the less-affected UE used utensils to scoop food. Alternately, the occupational therapist used hand-over-hand assistance, as well as adaptive equipment, to engage the more-affected upper extremity (UE) in task practice. Other preparatory techniques to reduce spasticity (e.g., intermittent stretching; weight-bearing) were used as needed to optimize participation. The target range for repetitions of any given task was 10 to 50 according to the demands of the task. Subjects were asked to report of sense of effort for each task according to a scale of 1-10.

SUPPLEMENTAL REFERENCES

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