



Original Research

# Chronicity of Stroke Does Not Affect Outcomes of Somatosensory Stimulation Paired With Task-Oriented Motor Training: A Secondary Analysis of a Randomized Controlled Trial



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## KEYWORDS

Humans;  
Occupational therapy;  
Rehabilitation;  
Transcutaneous electric nerve stimulation;  
Upper extremity

**Abstract** *Objective:* To determine whether chronicity influences outcomes of somatosensory stimulation paired with task-oriented motor training for participants with severe-to-moderate upper extremity hemiparesis.

*Design:* Spearman correlations were used to retrospectively analyze outcomes of a randomized trial.

*Setting:* University research laboratory at a rehabilitation hospital.

*Participants:* Adults, ranging between 3 and 12 months poststroke (N=55).

*Interventions:* About 18 sessions pairing either 2 hours of active (n=33) or sham (n=22) somatosensory stimulation with 4 hours of intensive task-oriented motor training.

*Main Outcome Measures:* The Wolf Motor Function Test (primary), Action Research Arm Test, Stroke Impact Scale, and Fugl-Meyer Assessment were collected as outcome measures. Analyses evaluated whether within-group chronicity correlated with pre-post changes on primary and secondary outcome measures of motor performance.

*Results:* Both groups exhibited improvements on all outcome measures. No significant correlations between chronicity poststroke and the amount of motor recovery were found.

*List of abbreviations:* ARAT, Action Research Arm Test; FMA, Fugl-Meyer Assessment; SIS, Stroke Impact Scale; SS, somatosensory stimulation; UE, upper extremity; WMFT, Wolf Motor Function Test.

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**Conclusion:** Somatosensory stimulation improved motor recovery compared with sham treatment in cases of severe-to-moderate hemiparesis between 3 and 12 months poststroke; and the extent of recovery did not correlate with baseline levels of stroke chronicity. Future studies should investigate a wider period of inclusion, patterns of corticospinal reorganization, differences between cortical and subcortical strokes, and include long-term follow-up periods.

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Neuroplasticity is the capacity for change in the central nervous system and has been shown to play a crucial role in recovery of function poststroke.<sup>1,2</sup> Motor cortical neuroplasticity can be modulated with sustained sensory activation.<sup>3-5</sup> Sensory activation via somatosensory stimulation (SS) is a therapeutic intervention that applies repetitive, transcutaneous electrical currents to peripheral nerves with the intent of activating large cutaneous and proprioceptive sensory fibers,<sup>6</sup> thereby enhancing motor cortical neuroplasticity.<sup>5</sup> Stroke studies have shown that SS can improve upper extremity (UE) motor performance, particularly when delivered as an adjunct to task-oriented motor training.<sup>7-14</sup> Although studies pairing SS with motor training have primarily been conducted in mild to moderately motor-impaired subjects,<sup>7</sup> a randomized controlled study showed that a 10-day course of SS paired with motor training can significantly improve motor function in severely motor-impaired subjects (ie, patients with almost no voluntary active UE movement poststroke).<sup>13</sup>

Recovery of motor function poststroke has long been believed to occur predominantly in the first 6 months postictus.<sup>15</sup> More recently, however, Teasell et al's<sup>16</sup> systematic review of randomized controlled trials indicated that further recovery can occur later than 6 months after a stroke. A recent study examining the effects of SS paired with intensive task-oriented motor training for participants with moderate to severely impaired UE motor function 3-12 months postictus found that SS paired with motor training led to greater motor improvement than sham SS paired with motor training.<sup>14</sup> The present study was a retrospective analysis of whether chronicity played a role in this outcome. In other words, the purpose of the present study was to evaluate if SS paired with task-oriented motor training had more benefit in early stages of recovery compared with later stages. We hypothesized that SS paired with task-oriented motor training would lead to similar improvement in outcomes regardless of the time elapsed poststroke.

## Methods

This study was conducted as a retrospective subanalysis of an institutional review board–approved randomized controlled parallel group superiority trial (N=55).<sup>14</sup> The main trial had the following inclusion criteria: (1) sustained a single ischemic or hemorrhagic stroke during the 3- to 12-month period preceding enrollment; (2) inability at the time of screening to demonstrate active extension of the

paretic metacarpophalangeal and interphalangeal joints at least 10° and the wrist, 20°; (3) baseline score of 47 or lower on the modified 30-item Fugl-Meyer Assessment (FMA) of UE motor function<sup>17</sup>; and (4) 18 years of age or older. Exclusion criteria included (1) history of carpal tunnel syndrome and/or documented peripheral neuropathy; (2) addition or change in the dosage of drugs known to exert detrimental effects on motor recovery within 3 months of recruitment<sup>18</sup>; and (3) aphasia or cognitive deficit severe enough to preclude informed consent. Outcome measures for the main trial included standardized evaluations of UE movement function at baseline and after completion of the intervention period (for further details, see Carrico et al<sup>14</sup>). Specifically, the primary outcome measure for the main trial was the Wolf Motor Function Test (WMFT), which encompasses a battery of simulated functional tasks.<sup>19</sup> Scoring calculates the mean time for completion of 15 tasks and values are denoted as log<sub>10</sub> (mean WMFT). A logarithmic transform is used in this case due to the skewness of the data. By transforming the data, a more normal distribution is achieved. The WMFT has established reliability and validity and has been extensively applied in research to evaluate UE motor capacity poststroke.<sup>19,20</sup> Secondary outcome measures included the UE motor score of the 30-item FMA, the Action Research Arm Test (ARAT), and the Stroke Impact Scale (SIS). The FMA has an extensive history of clinical and research application in stroke populations<sup>21</sup> as well as high interrater reliability (0.89~0.98 depending on the subset for lower or upper extremity) and test-retest reliability (0.99).<sup>22</sup> The FMA is a quantitative measure of motor recovery<sup>17</sup> that does not take deep tendon reflexes into account and is a unidimensional measure of volitional movement in which the highest possible motor score for a tested UE is 60.<sup>23</sup> The ARAT measures grasp, grip, pinch, and other indices of rehabilitation-related change in UE motor capacity, for which the highest possible score for a tested UE is 57.<sup>20,24</sup> The SIS is a 59-item subjective measure that assesses strength, hand function, activities of daily living, mobility, communication, emotion, memory and thinking, and participation and role function. Each item is rated on a 5-point Likert scale and scores range from 0 to 100. Several studies have proven its reliable psychometric attributes, including reliability, validity, and sensitivity to change.<sup>25,26</sup>

After baseline evaluation of motor function in the main trial, participants were randomly assigned into 2 groups, either receiving SS paired with intensive task-oriented training (experimental group) or sham SS paired with intensive task-oriented training (control group). Each

**Table 1** Baseline demographics and outcome measures

Demographics and Outcome Measures	All Participants	Experimental Group	Control Group
Age (y)	59.3±13.3 (20-86)	57.5±14.8 (20-80)	62.4±10.2 (44-86)
Time since stroke (mo)	7.4±2.4 (3-11)	7.8±2.4 (3-11)	6.7±2.3 (3-11)
Baseline WMFT	1.81±0.34 (0.96-2.08)	1.83±0.32 (0.96-2.08)	1.77±0.37 (0.98±2.08)
Baseline ARAT	13.4±13.7 (0-47)	12.2±13.0 (0-46)	15.3±14.9 (3-47)
Baseline SIS	57±11.4 (31-76)	57.3±11.7 (31-76)	56.4±11.4 (32-71)
Baseline FMA	23.7±12.5 (5-47)	23.2±12.6 (5-47)	24.6±12.7 (8-45)

NOTE. Values are mean ± SD (range).

intervention session took place 3 times per week for 6 weeks (18 total sessions) and consisted of either active or sham SS (2h duration) immediately followed by intensive task-oriented motor training (4h duration). Participants, care providers, and evaluators of movement function were blinded to group assignment. See Carrico et al<sup>14</sup> for further details of the main trial. The subanalysis reported in the present article used a Spearman correlation model, as well as Pearson correlation model, in which the pre-post changes in motor performance on WMFT, FMA, ARAT, and SIS were the dependent outcomes and chronicity (time since stroke in months) was the independent variable. Partial correlations were used to adjust for the potential confounders of severity and age. Statistical significance was prespecified as  $P < .05$ . Analyses were conducted in SAS version 9.4.<sup>a</sup>

## Results

The date range defining the periods of data analysis for the main trial was July 2008 to February 2015. The date range defining the period of data subanalysis was May 2017 to June 2018. Table 1 shows baseline demographics and outcome measures. Improvements were observed for both groups on all outcome measures, shown in table 2. Individual changes on outcome measures as a function of time since stroke is shown in fig 1. Table 3 shows the Spearman correlation coefficients between chronicity and changes in outcome measures. Table 4 shows the Spearman partial correlation coefficients between chronicity and changes in outcome measures that have been adjusted for the potential confounders of severity and age. Pearson correlation coefficients were found to be similar to the Spearman correlation coefficients, though were deemed less appropriate due to outliers in the data. Therefore, the Pearson correlation coefficients are not reported. No statistically significant correlations between chronicity and changes in

motor function were found, whether with or without adjustment for severity and age.

## Discussion

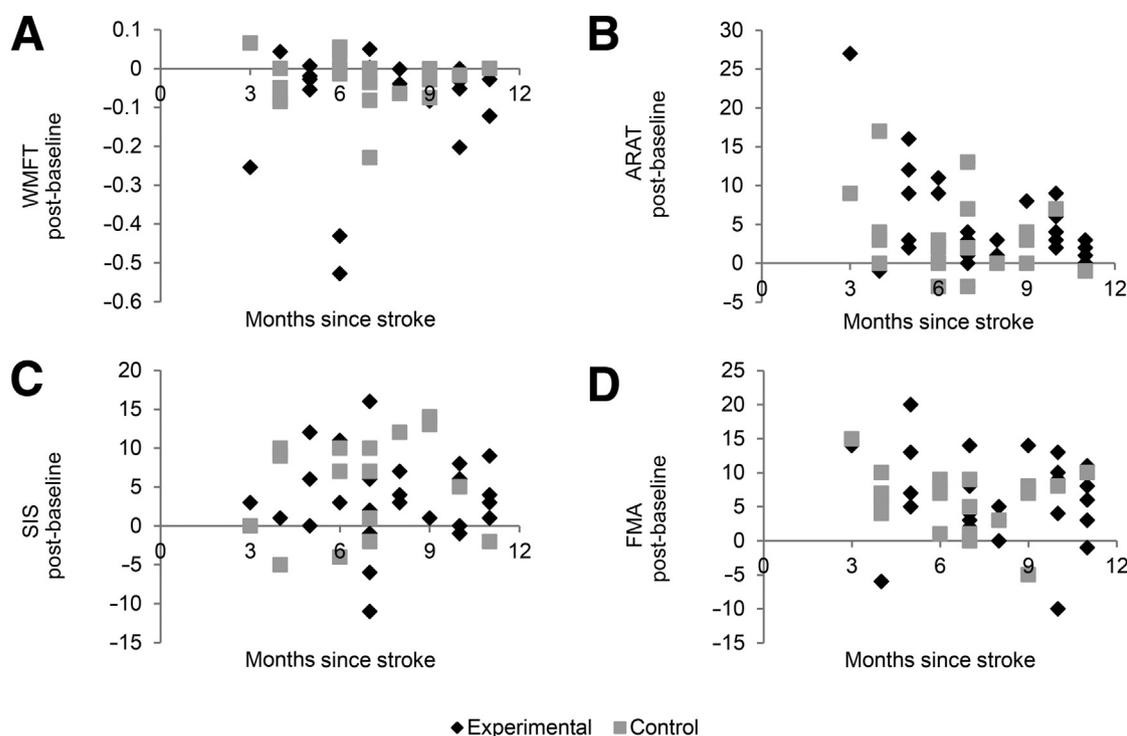
The present study extends the evidence base about how SS paired with task-oriented motor training can drive motor recovery poststroke. Past evidence has shown that SS paired with motor training has benefit in later recovery after severe stroke. Specifically, a study of 36 participants at 12 or more months postictus showed significant improvement in UE motor function in response to 10 daily 2-hour sessions of either active or sham SS paired with 4 hours of intensive task-oriented training.<sup>27</sup> The present study extends these findings to participants at earlier stages of recovery—specifically, results of the present study showed that chronicity did not significantly predict response to SS paired with task-oriented motor training for participants with moderate-to-severe impairment in 3-12 months poststroke. That is to say, participants enrolled close to a year poststroke had similar responses to SS paired with motor training compared with participants enrolled 3 months poststroke.

These findings can be considered in light of other studies of stroke chronicity as related to motor recovery. Stinear et al<sup>28</sup> conducted a retrospective analysis of longitudinal data collected from 46 participants during the first 6 months poststroke. At baseline, participants had predominantly subcortical damage and mild-to-severe motor impairment based on National Institutes of Health Stroke Scale. Within 2 weeks poststroke occurrence, UE motor performance was assessed using FMA and ARAT, and transcranial magnetic stimulation was used to measure neuroplasticity in cortical UE areas. Participants completed a standardized course of 30-minute sessions of UE therapy each weekday for 4 weeks and had follow-up assessments at 6, 12, and 26 weeks poststroke. Contrary to the present subanalyses, results revealed significant correlations

**Table 2** Changes in outcome measures

Outcome Measure	All Participants	Experimental Group	Control Group
ΔWMFT	-0.06±0.11 (-0.09 to -0.02)	-0.07±0.13 (-0.12 to -0.02)	-0.03±0.07 (-0.06 to -0.0002)
ΔARAT	4.4±5.8 (2.8-6.1)	5.0±6.1 (2.8-7.2)	3.5±5.2 (1.0-6.0)
ΔSIS	4.1±5.7 (2.4-5.8)	3.3±5.3 (1.3-5.3)	5.5±6.2 (2.3-8.7)
ΔFMA	6.3±5.5 (4.8-7.9)	6.6±6.0 (4.4-8.8)	5.9±4.5 (3.8-8.1)

NOTE. Values are mean ± SD (95% confidence interval).



**Fig 1** Scatterplots of outcome measures. No clear correlations are visible for any of the 4 outcome measures.

between chronicity and recovery of UE motor function.<sup>28</sup> More specifically, the greatest improvement in clinical function occurred within 6 weeks poststroke. However, attributing this improvement solely to intervention would be difficult, because this time period is also when spontaneous recovery is a significant determinant of change in motor performance.<sup>28,29</sup> On the other hand, and similar to findings from the present study, a separate meta-analysis of 3 studies showed that chronicity poststroke did not significantly predict response to constraint-induced movement therapy as measured with WMFT in 43 participants more than 10 months poststroke (mean chronicity:  $4.3 \pm 3.9$  y post) with mild to moderate UE motor impairment at baseline.<sup>30</sup> Our study adds to the body of evidence that fails to find a significant correlation between stroke chronicity and recovery in moderate to severely impaired participants.

It is also important to understand clinical improvement in the context of neuroplastic changes, because neuroplasticity

is the mechanism by which motor recovery occurs.<sup>31-33</sup> Although the present subanalysis revealed comparable patterns of motor recovery regardless of chronicity, it is still conceivable that motor cortical activation patterns may vary with chronicity. Most of the relevant studies on this topic have enrolled subjects with mild-to-moderate motor impairment. For example, Kokotilo et al<sup>34</sup> conducted a systematic review to evaluate differences in brain activation patterns in acute and chronic phases poststroke. They found that there is increased activation of secondary motor areas such as contralateral hemisphere in early stages postrecovery, but recruitment of these areas decreases as functional improvement occurs. On the other hand, a separate study by Sawaki et al<sup>33</sup> evaluated 26 participants with mild-to-moderate UE motor impairment at baseline. About 17 participants were 3-9 months poststroke (*early group*) and 9 were more than 12 months poststroke (*late group*). Intervention consisted of 10 consecutive weekdays of constraint-induced movement therapy. Findings demonstrated no statistical differences in

**Table 3** Spearman correlation coefficients for changes in outcome measures and chronicity

Outcome Measure	All Participants			Experimental Group			Control Group		
	Spearman Coefficient	P Value	Sample Size (n)	Spearman Coefficient	P Value	Sample Size (n)	Spearman Coefficient	P Value	Sample Size (n)
$\Delta$ WMFT vs chronicity	-0.083	.57	49	-0.051	.79	30	-0.123	.62	19
$\Delta$ ARAT vs chronicity	0.244	.09	50	-0.326	.07	31	-0.215	.38	19
$\Delta$ SIS vs chronicity	-0.061	.69	46	-0.039	.84	29	0.214	.41	17
$\Delta$ FMA vs chronicity	-0.128	.36	50	-0.156	.40	31	-0.165	.50	19

NOTE. No statistically significant correlations were demonstrated between stroke chronicity and pre-post changes in UE motor function for all participants, for participants in the experimental group, or for participants in the control group.

**Table 4** Spearman partial correlation coefficients for changes in outcome measures and chronicity

Outcome Measure	All Participants		Experimental Group		Control Group	
	Spearman Coefficient	P Value	Spearman Coefficient	P Value	Spearman Coefficient	P Value
ΔWMFT vs chronicity	−0.12	.46	−0.07	.71	−0.12	.66
ΔARAT vs chronicity	−0.19	.23	−0.30	.13	−0.25	.37
ΔSIS vs chronicity	−0.07	.64	−0.08	.70	0.22	.42
ΔFMA vs chronicity	−0.06	.69	−0.13	.53	−0.05	.87

NOTE. These coefficients have adjusted for the potential confounding factors severity and age. No statistically significant correlations were found for any outcome measures.

motor map volume evoked by transcranial magnetic stimulation in early compared to late groups. On the other hand, a case study by Chelette et al<sup>35</sup> documented neuroplastic change for an individual with severe poststroke motor impairment at baseline. This individual had a variable course of intervention over several neuromodulation studies as well as standard-of-care clinical rehabilitation and continued to display significant ipsilesional cortical reorganization as long as 21 months postictus.

### Study limitations

The primary limitation of this study is a lack of statistical power. It is possible that the lack of significant correlations is due to the relatively small sample sizes. In light of limitations of the present study, future studies should include a larger sample size, long-term follow ups, and measurement of indices of neuroplasticity. In addition, research on the effects of SS intervention before 3 months postictus could shed particular light on how to accelerate the effect of early spontaneous recovery. Finally, future research should focus on participants with the most severe motor impairments to address the population segment with highest need.

### Conclusions

Chronicity did not significantly predict pre-post response to SS paired with task-oriented motor training for participants with moderate-to-severe motor impairment in the 3- to 12-month period poststroke.

### Supplier

a. SAS version 9.4; SAS Institute.

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### References

1. Nudo RJ, Plautz EJ, Frost SB. Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle Nerve* 2001;24:1000-19.
2. Wolpaw JR. Harnessing neuroplasticity for clinical applications. *Brain* 2012;135:e215 [author reply e216].
3. Pavlides C, Miyashita E, Asanuma H. Projection from the sensory to the motor cortex is important in learning motor skills in the monkey. *J Neurophysiol* 1993;70:733-41.
4. Sakamoto T, Arissian K, Asanuma H. Functional role of the sensory cortex in learning motor skills in cats. *Brain Res* 1989;503:258-64.
5. Sawaki L, Wu CW, Kaelin-Lang A, Cohen LG. Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. *Stroke* 2006;37:246-7.
6. Kaelin-Lang A, Luft AR, Sawaki L, Burstein AH, Sohn YH, Cohen LG. Modulation of human corticomotor excitability by somatosensory input. *J Physiol* 2002;540:623-33.
7. Laufer Y, Elboim-Gabyzon M. Does sensory transcutaneous electrical stimulation enhance motor recovery following a stroke? A systematic review. *Neurorehabil Neural Repair* 2011; 25:799-809.
8. Ikuno K, Kawaguchi S, Kitabepu S, et al. Effects of peripheral sensory nerve stimulation plus task-oriented training on upper extremity function in patients with subacute stroke: a pilot randomized crossover trial. *Clin Rehabil* 2012;26:999-1009.
9. McDonnell MN, Hillier SL, Miles TS, Thompson PD, Ridding MC. Influence of combined afferent stimulation and task-specific training following stroke: a pilot randomized controlled trial. *Neurorehabil Neural Repair* 2007;21:435-43.
10. Kim TH, In TS, Cho HY. Task-related training combined with transcutaneous electrical nerve stimulation promotes upper limb functions in patients with chronic stroke. *Tohoku J Exp Med* 2013;231:93-100.
11. Fleming MK, Sorinola IO, Roberts-Lewis SF, Wolfe CD, Wellwood I, Newham DJ. The effect of combined somatosensory stimulation and task-specific training on upper limb function in chronic stroke: a double-blind randomized controlled trial. *Neurorehabil Neural Repair* 2015;29:143-52.
12. Dos Santos-Fontes RL, Ferreira de Andrade KN, Sterr A, Conforto AB. Home-based nerve stimulation to enhance effects of motor training in patients in the chronic phase after stroke: a proof-of-principle study. *Neurorehabil Neural Repair* 2013;27:483-90.
13. Carrico C, Chelette KC 2nd, Westgate PM, Salmon-Powell E, Nichols L, Sawaki L. Randomized trial of peripheral nerve stimulation to enhance modified constraint-induced therapy after stroke. *Am J Phys Med Rehabil* 2016;95:397-406.
14. Carrico C, Westgate PM, Salmon Powell E, et al. Nerve stimulation enhances task-oriented training for moderate-to-severe hemiparesis 3-12 months after stroke: a randomized trial. *Am J Phys Med Rehabil* 2018;97:808-15.

15. Jorgensen HS, Nakayama H, Raaschou HO, Vive-Larsen J, Stoier M, Olsen TS. Outcome and time course of recovery in stroke. Part ii: time course of recovery. The Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1995;76:406-12.
16. Teasell RW, Murie Fernandez M, McIntyre A, Mehta S. Rethinking the continuum of stroke rehabilitation. *Arch Phys Med Rehabil* 2014;95:595-6.
17. Woodbury ML, Velozo CA, Richards LG, Duncan PW. Rasch analysis staging methodology to classify upper extremity movement impairment after stroke. *Arch Phys Med Rehabil* 2013;94:1527-33.
18. Goldstein LB. Pharmacology of recovery after stroke. *Stroke* 1990;21(11 Suppl):III139-142.
19. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 2006;296:2095-104.
20. Lemmens RJ, Timmermans AA, Janssen-Potten YJ, Smeets RJ, Seelen HA. Valid and reliable instruments for arm-hand assessment at ICF activity level in persons with hemiplegia: a systematic review. *BMC Neurol* 2012;12:21.
21. Gladstone DJ, Danells CJ, Black SE. The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties. *Neurorehabil Neural Repair* 2002;16:232-40.
22. Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. *Phys Ther* 1983;63:1606-10.
23. Woodbury ML, Velozo CA, Richards LG, Duncan PW, Studenski S, Lai SM. Dimensionality and construct validity of the Fugl-Meyer assessment of the upper extremity. *Arch Phys Med Rehabil* 2007;88:715-23.
24. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res* 1981;4:483-92.
25. Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the stroke impact scale. *Arch Phys Med Rehabil* 2003;84:950-63.
26. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med* 2010;362:1772-83.
27. Carrico C, Chelette KC 2nd, Westgate PM, et al. Nerve stimulation enhances task-oriented training in chronic, severe motor deficit after stroke: a randomized trial. *Stroke* 2016;47:1879-84.
28. Stinear CM, Petoe MA, Byblow WD. Primary motor cortex excitability during recovery after stroke: implications for neuromodulation. *Brain Stimul* 2015;8:1183-90.
29. Plautz EJ, Barbay S, Frost SB, et al. Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurol Res* 2003;25:801-10.
30. Gauthier LV, Mark VW, Taub E, et al. Motor recovery from constraint induced movement therapy is not constrained by extent of tissue damage following stroke. *Restor Neurol Neurosci* 2014;32:755-65.
31. Nudo RJ. Functional and structural plasticity in motor cortex: implications for stroke recovery. *Phys Med Rehabil Clin N Am* 2003;14:S57-76.
32. Hallett M. Plasticity of the human motor cortex and recovery from stroke. *Brain Res Brain Res Rev* 2001;36:169-74.
33. Sawaki L, Butler AJ, Leng X, et al. Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. *Neurorehabil Neural Repair* 2008;22:505-13.
34. Kokotilo KJ, Eng JJ, Boyd LA. Reorganization of brain function during force production after stroke: A systematic review of the literature. *J Neurol Phys Ther* 2009;33:45-54.
35. Chelette KC, Carrico C, Nichols L, Sawaki L. Long-term cortical reorganization following stroke in a single subject with severe motor impairment. *NeuroRehabilitation* 2013;33:385-9.