Short communication

André Salles Cunha Peres, Victor Hugo Souza, João Marcos Yamasaki Catunda,
Kelley Cristine Mazzeto-Betti, Taiza Elaine Grespan Santos-Pontelli,
Claudia Domingues Vargas, Oswaldo Baffa, Draulio Barros de Araújo,
Octávio Marques Pontes-Neto, João Pereira Leite and Marco Antonio Cavalcanti Garcia*

Can somatosensory electrical stimulation relieve spasticity in post-stroke patients? A TMS pilot study

Abstract: Evidence suggests that somatosensory electrical stimulation (SES) may decrease the degree of spasticity from neural drives, although there is no agreement between corticospinal modulation and the level of spasticity. Thus, stroke patients and healthy subjects were submitted to SES (3 Hz) for 30′ on the impaired and dominant forearms, respectively. Motor evoked potentials induced by single-pulse transcranial magnetic stimulation were collected from two forearm muscles before and after SES. The passive resistance of the wrist joint was measured with an isokinetic system. We found no evidence of an acute carry-over effect of SES on the degree of spasticity.

*Corresponding author: Marco Antonio Cavalcanti Garcia,
Departamento de Biociências e Atividades Físicas, Escola de Educação Física e Desportos – Universidade Federal do Rio de Janeiro – Avenida Carlos Chagas Filho, 540 – Cidade Universitária – Ilha do Fundão, Rio de Janeiro, RJ 21941-599, Brazil,
Phone: +55(21)3938-6824, E-mail: garcia@ufrj.br; garcia@eefd.ufrj.br.
http://orcid.org/0000-0002-8225-6573
André Salles Cunha Peres: Laboratório de Neuroimagem Funcional, Instituto do Cérebro – Universidade Federal do Rio Grande do Norte – Av. Nascimento de Castro, 2155 – Morro Branco, Natal, RN 59056-450, Brazil; and Instituto Santos Dumont, Instituto Internacional de Neurociências – Rodovia RN 160, 3001 – Distrito Jundiaí, Macaíba 59280-000, Brazil
Victor Hugo Souza and Oswaldo Baffa: Departamento de Física, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto – Universidade de São Paulo – Av. Bandeirantes, 3900 – Monte Alegre, Ribeirão Preto, SP 14040-901, Brazil.
http://orcid.org/0000-0002-0254-4322 (V.H. Souza)
João Marcos Yamasaki Catunda: Programa de Engenharia Biomédica, COPPE – Universidade Federal do Rio de Janeiro – Av.

Introduction

The physiopathology of spasticity in chronic post-stroke patients has been widely discussed. In order to improve functional condition by relieving the level of spasticity, different therapeutic approaches, including medication, are available nowadays to therapists and clinicians [9], even though there seems to be no consensus with regard to their efficacy. There is some evidence that spasticity can be caused by unbalanced excitatory and inhibitory descending drives on the motoneuron pool [3]. On this basis, a decrease of GABAergic (inhibitory) and an increase of glutamatergic (excitatory) neurotransmitters might lead to a reduction in intracortical inhibition and contribute to its manifestation in post-stroke patients [19].

The use of somatosensory electrical stimulation (SES) therapy alternatively to therapeutic approaches (e.g. botulin toxin) in treating this sensory motor disorder in post-stroke patients has been endorsed [8, 13, 22, 25, 26]. However,

Horácio Macedo 2030, Centro de Tecnologia, Bloco H, Sala 327 – Cidade Universitária – Ilha do Fundão, Rio de Janeiro, RJ 21941-914, Brazil
Kelley Cristine Mazzeto-Betti, Octávio Marques Pontes-Neto and João Pereira Leite: Departamento de Neurologia, Psiquiatria e Psicologia Médica, Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo – Av. Bandeirantes, 3900 – Monte Alegre, Ribeirão Preto, SP 14048-900, Brazil
Taiza Elaine Grespan Santos-Pontelli: Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo – Av. Bandeirantes, 3900 – Monte Alegre, Ribeirão Preto, SP 14048-900, Brazil
Claudia Domingues Vargas: Laboratório de Neurobiologia II, Instituto de Biofísica Carlos Chagas Filho – Universidade Federal do Rio de Janeiro – Av. Carlos Chagas Filho, 373 – Cidade Universitária – Ilha do Fundão, Rio de Janeiro, RJ 21941-902, Brazil
Draulio Barros de Araújo: Laboratório de Neuroimagem Funcional, Instituto do Cérebro – Universidade Federal do Rio Grande do Norte – Av. Nascimento de Castro, 2155 – Morro Branco, Natal, RN 59056-450, Brazil

unlike other electrical therapeutic modalities, which are delivered above the motor threshold (MT) and usually to the muscles opposing (antagonists) to the spastic ones, SES is commonly applied over the muscles that manifest spasticity. Since SES intensity is set below the MT, it is understood to lead to the recruitment of somatosensory receptors which mobilize neural circuitries at the spinal and brain levels [8, 13]. Accordingly, it is possible to hypothesize that the modulation of the corticospinal pathway may decrease the resistance of spastic muscles to a passive movement from neural drives. Even so, to our knowledge, no previous controlled study evaluated simultaneously the carry over effects of SES on the corticospinal excitability and on the degree of spasticity quantitatively. Additionally, we did not find any report that demonstrated agreement between corticospinal modulation and the level of spasticity.

Thus, the aim of this controlled pilot study was to evaluate whether SES therapy over the spastic forearm *flexors* modulates the corticospinal excitability of the *flexor* and *extensor carpi radialis* muscles of the affected limb in chronic post-stroke patients and if it would be accompanied by a decrease in the passive resistance of the wrist joint.

Materials and methods

Subjects

Five chronic post-stroke spastic patients (patient group, PG; Table 1) and five age-paired healthy subjects (control group, CG; 3 male; age: 60.7 ± 10.5 years; body mass: 74.6 ± 7.9 kg; height: 1.62 ± 0.04 m) asymptomatic to neurological and motor disorders participated in this study. The inclusion criteria for patients were the presence of only one stroke episode with a modified Rankin scale of at least one (P3 had lacunar strokes and only one stroke resulting in dysfunction) with spasticity in the forearm limiting wrist movements (flexion and extension) evidenced by an Ashworth scale score between "1" and "3" [2]. A modified Ashworth scale was used to assess spasticity of wrist flexors (*flexor digitorum superficialis*; *flexor digitorum profundus*; *flexor carpi radialis*; *flexor carpi ulnaris*; *palmaris longus*; and *flexor pollicis longus*). Patients were excluded if they presented scores greater than 0 in the category "Level of Consciousness" of the National Institute of Health Stroke Scale (NIHSS) or any other neurological disease. Additionally, the safety guideline for TMS applications based on Rossini et al. [24] was followed. In accordance with the Declaration of Helsinki the local ethical committee (process number: 8728/10) approved the protocol and each volunteer gave written informed consent prior to the experiment.

SES therapy

All subjects were submitted to a single session of SES therapy for 30 min with a symmetrical biphasic pulse (3 Hz, 500 µs) [13, 25].

Table 1: Demographic, clinical and neuroimaging characteristics of the patient group.

Subject	Age (years)	Sex	MPSO	NIHSS (so)	mRS	AS	Hypoesthesia	Hemiparesis	Hemineglect	Ataxia	Lesion side	LT	Lesion site	rMT (RH) (%)	rMT (LH) (%)
P1	63	M	36	7	1	1	A	P	A	A	R	IMa	In, T, F, Pu	80	75
P2	48	M	24	14	2	1	P	P	A	A	L	IMa	In, F, T, Pu	90	67
P3	68	M	31	8	1	1+	P	P	P	A	B	DMi	BG, CS, Pr	60	70
P4	60	M	29	6	1	1+	A	P	A	A	R	I	BG, In, CR, F	a	87
P5	72	M	37	4	1	1+	A	A	A	P	L	I	T, P	100	65

Current neurological deficits: P, present; A, absent; MPSO, months post-stroke onset; NIHSS(so), National Institute of Health Stroke Scale at stroke onset; mRS, current modified Rankin Scale; AS, Ashworth Scale; lesion side: R, right; L, left; B, bilateral; LT (lesion type): IMa, ischemic with macroangiopathy; DMi, diffuse cerebral microangiopathy; I, ischemic; lesion site: F, frontal; P, parietal; Pr, right parietal; T, temporal; IC, internal capsule; In, insula; CR, corona radiata; BS, brainstem; Pu, putamen; BG, basal ganglia; CS, centrum semiovale; rMT, resting motor threshold; RH, right cerebral hemisphere; LH, left cerebral hemisphere. aNot obtained.

Stimulation parameters were determined from other studies that observed positive clinical results and/or neuromodulatory effects [1, 12, 23, 27]. Stimuli were delivered with a custom-made current stimulator, by means of surface self-adhesive electrodes (5×5 cm; model: CF5050, AXELGAARD Manufacturing CO., LTD., Denmark) positioned between the wrist and the elbow joints, over the ventral forearm surface (flexor muscles). All subjects were asked to stay relaxed, sit comfortably and to keep the stimulated forearm in a prone position. SES was applied to the impaired forearm in patients (most prominent side for P3) and the dominant forearm in healthy controls. SES intensity was kept constant and below the MT without pain and without any adjustment of the sensory threshold.

Motor potentials evoked by TMS

Motor evoked potentials (MEPs) were extracted from surface electromyograms acquired with a BIOPAC system (Model: MP1500 BIOPAC Systems, Inc., USA; A/D converter: 16 bits; dynamic range: 10 V; sampling frequency: 15 kHz; 4th order band pass filter; range: 100–5000 Hz and gain: 2000). Two muscles were assessed: *flexor* (FCR) and *extensor carpi radialis* (ECR) from the impaired (PG) and dominant (CG) forearms. Surface BIOPAC reusable electrodes (Ag/AgCl; diameter: 8 mm) were placed over each muscle belly, following recommendations of the project Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) [15].

MEPs were elicited with a figure eight TMS coil positioned over the primary motor cortex (M1). The FCR hot-spot position was considered as the site over the scalp to produce the highest MEP and the resting MT was the TMS pulse amplitude capable of evoking five out of ten MEP with amplitudes greater than 50 µV [18]. At least ten magnetic stimuli were delivered with a MagPro R30 stimulator (MagVenture, Farum, Denmark) with a time interval of 5–10 s between pulses. The stimuli intensity was adjusted at 20% above the FCR MT.

Corticospinal excitability was estimated as the peak-to-peak MEP amplitudes (MEP_{P-P}) [14] by using the free software *Signal Hunter* (https://github.com/biomaglab/signalhunter). MEPs were recorded immediately before and after SES therapy. Visual feedback of the electromyograms was provided to the experimenters throughout the TMS session to assist certification that subjects were relaxed.

Measurement of passive resistance of wrist joints

The passive resistance of the impaired and non-impaired wrist joints were measured using a custom-made isokinetic system (Figure 1), which measures the passive joint torque at the individual limits of range of motion [4], after MEP recordings (before and after SES). Thus, the passive torque of cyclical movements was measured from passive wrist extension and flexion within individual range limit. Root mean square (RMS) of the passive torque magnitude (gf.cm) was calculated at an angular velocity of 10 degrees per second to avoid a stretch reflex [21].

Data and statistical analyses

Prior to testing the hypothesis of SES effects upon the corticospinal excitability, all the MEP_{P-P} values recorded before and after SES for
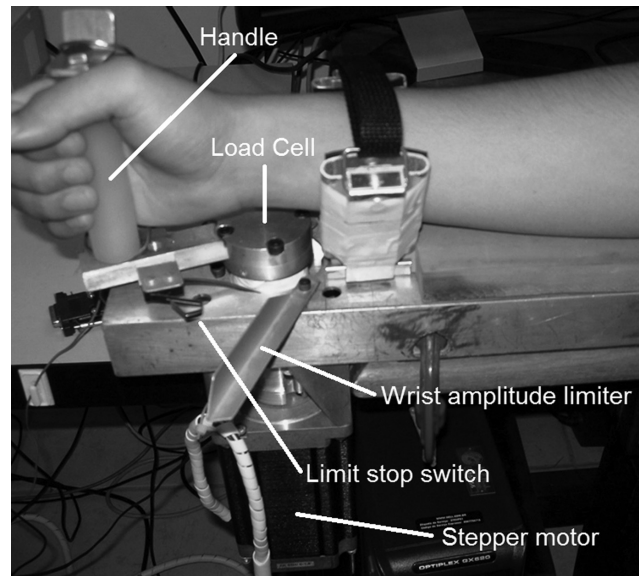

Figure 1: Details of the custom-made isokinetic device used to measure the passive resistance of the wrist joints of both groups according to Garcia et al. [13].
The individual limits of range of motion were controlled by setting the wrist amplitude limiter and the limit stop switch. In detail, the positioning adopted by the forearm and hand. It provides the passive torque and angle data from cyclical wrist extensions with constant angular speed and range of movement.

one single subject were normalized by dividing them by the highest MEP_{P-P} value from each subject. A two-way (factors: *muscles* and *before and after SES*) ANOVA of repeated measures was used to evaluate the corticospinal excitability from each group (PG and CG) separately. We also compared the individual MEP_{P-P} within each subject using the Mann-Whitney U-test. Similarly, a two-way (factors: *wrist movement direction* and *before and after SES*) ANOVA of repeated measures was also used to evaluate the torque from passive wrist movements from each group (PG and CG) separately. The RMS values of passive wrist torques in flexion and extension movements were compared among before and after SES by using the Wilcoxon test. The level of significance (α) was set at 5%.

Results

Figure 2A and B shows the results obtained for normalized MEP_{P-P} amplitude from each muscle before and after SES and for each subject (horizontal axes) in both groups. There were no significant statistical differences in FCR and ECR muscles in either group (PG: p = 0.179; CG: p = 0.353) although individual significant differences (p < 0.05) were observed in FCR for three patients (P2, P4 and P5) and one patient (P1) for ECR. In turn, there were significant differences (p < 0.05) in FCR for one healthy volunteer (C3) and three (C1, C2 and C3) for ECR.
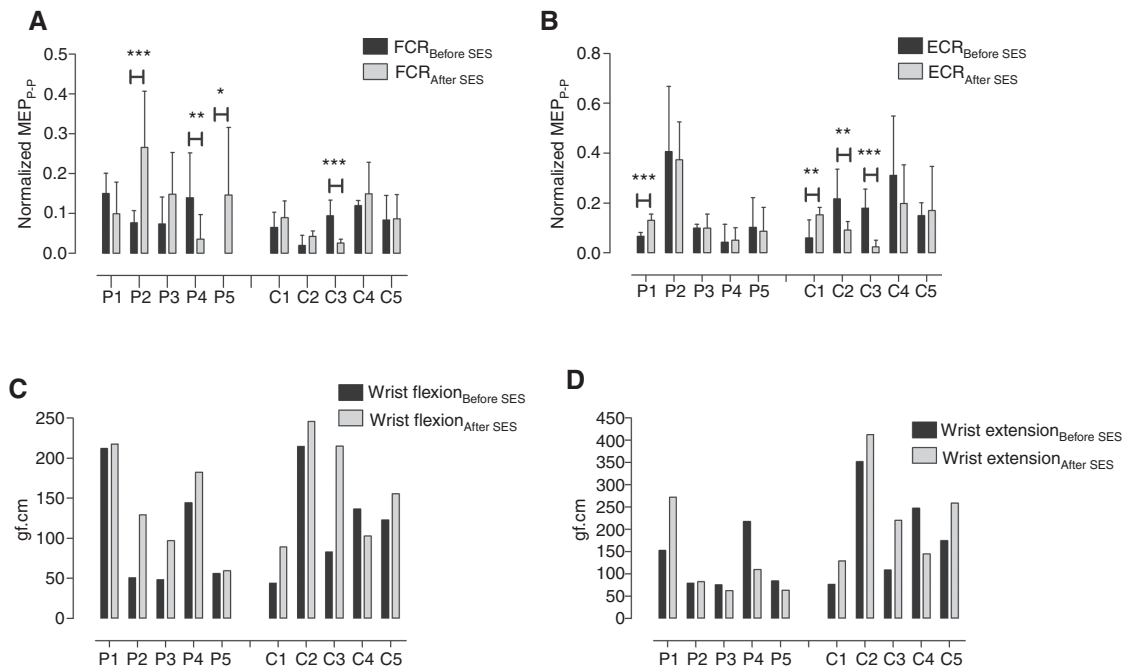
Figure 2: Normalized MEP$_{P-P}$ amplitudes ($\overline{x} \pm$ standard deviation) obtained from each individual TMS trial and each volunteer (P, patients; C, healthy subjects) collected before (Before SES) and after (After SES) SES from FCR (A) e ECR (B) muscles.
Individual RMS passive torque values reached by each volunteer (P, patients; C, healthy subjects) on wrist flexion (C) and extension (D) passive movements collected before (Before SES) and after (After SES) SES. Even though there were not significant statistical differences ($p < 0.05$) for groups, there were for particular volunteers (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

Passive torque data from passive wrist flexion (Figure 2C) and extension (Figure 2D) also did not show any significant difference in both groups (GP: $p = 0.996$; GC: $p = 0.418$).

Discussion

Previous studies [6, 8, 20] support the hypothesis that even one single session of peripheral electrical stimulation mediates long term potentiation (LTP) or depression (LTD) at the spinal and other levels of the central nervous system (CNS), which might minimize temporarily the level of spasticity and would help clinicians as a prior step, for instance, to kinesiotherapy. Therefore, based on these and other studies [1, 8, 12, 23, 25, 27], we hypothesized that low frequency SES could result in a short-term restoration of the cortical excitability in affected motor areas with a subsequent acute minimization of spasticity in post-stroke patients. Even though we did not observe significant statistical differences for both groups in corticospinal excitability, we should highlight the positive and negative deviations from the MEP$_{P-P}$ data collected before SES in both muscles and groups. For instance, subjects from both groups (P1, P3, P4, C2, C4 and C5) seemed to

undergo reciprocal agonist and antagonist inhibition/facilitation, the underlying mechanisms of which were already reported [27]. Reciprocal agonist and antagonist inhibition and facilitation are well described mechanisms where lower motoneurons from opposing muscles or muscle groups are inhibited by interneurons connected to muscle spindles [16]. In addition, these motoneurons are modulated by descending pathways [16]. Therefore, although it may be recognized that such mechanisms are determined at two levels of the CNS, SES might produce modulatory effects at the cortical level [27]. According to Veldman et al. [28], we also suggest that the level and direction of SES effects on M1 excitability depend particularly on the stimulation intensity, which may vary considerably. This means that depending on the step increment in SES intensity from the perceptual threshold, M1 excitability may vary between depression and facilitation. Even so, it is interesting to note that previous studies reported an acute increase in spasticity after applying electrical stimulation above the MT over spastic muscles [7, 10, 29]. In contrast, other investigators [5, 11, 17] succeeded in relieving this sensory motor impairment by using SES set below or at the MT also over spastic muscles.

Distinct deviations in MEP amplitudes in our study could probably be caused by inappropriate SES intensity

adjustment, i.e. without any fine tune adjustment from multiples of sensory threshold. Therefore, even though the recent literature [13, 16] corroborates the hypothesis that the intensity of stimulation may lead to distinct effects on corticospinal modulation, the excitability of this neural pathway may be affected by other parameters such as pulse width, waveform, frequency and application time. Moreover, it seems reasonable to conjecture that not every resultant modulatory effect on corticospinal excitability (positive or negative deviations from baseline) will lead to the same effect on spasticity even in stroke patients with similar clinical signs. Consequently, we reinforce that each parameter of stimulation may contribute differently in modulating the corticospinal excitability even though, to our knowledge, there seems to be no consensus regarding these methodological aspects.

Passive torque measurements also did not show any effect of SES therapy in both PG and CG groups. Moreover, there seems to be no evidence of an agreement between the direction of SES effects on M1 excitability and wrist passive torque even for the wrist flexion, which seemed to increase in both the groups. In turn, the present results might be restricted to the sample characteristics. Since only patients with mild spasticity (1 – 1+) were included in the study, according to the Ashworth Scale, it might be possible that SES produced better effects on patients with more severe spasticity. Thus, although we cannot ascertain an agreement between corticospinal modulation and the level of spasticity, it must be taken into account that non-neural/biomechanical muscle properties, mainly in chronic patients, should be unaffected by SES and therefore to mask its likely potential carry over effects upon spasticity [30].

Conclusion

Previous findings [8, 22, 25] sound encouraging in terms of SES as an adjunctive therapy alternative to botulinum neurotoxin in relieving spasticity in post-stroke patients, even from one single session followed by a short-term decrease in peak passive torque responses [8, 17]. Our results suggest no clear group evidence of a carry-over effect of SES set at 3 Hz and applied for 30 min with a symmetrical biphasic pulse (500 µs) on the degree of spasticity, although we must recognize that the results are from a small sample. However, it is worth mentioning that there is still no consensus on how different SES parameters modulate brain activity, and this matter requires further investigation. Finally, we reinforce the need for special attention by therapists and clinicians to setting SES parameters when SES is used as an alternative therapy in the treatment of spasticity in chronic post-stroke patients.

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