CLINICAL SCIENCE

EFFECTS OF SOMATOSENSORY STIMULATION ON THE EXCITABILITY OF THE UNAFFECTED HEMISPHERE IN CHRONIC STROKE PATIENTS

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INTRODUCTION: Somatosensory stimulation of the paretic upper limb enhances motor performance and excitability in the affected hemisphere, and increases activity in the unaffected hemisphere, in chronic stroke patients. We tested the hypothesis that somatosensory stimulation of the paretic hand would lead to changes in excitability of the unaffected hemisphere in these patients, and we investigated the relation between motor function of the paretic hand and excitability of the unaffected hemisphere.
METHODS: Transcranial magnetic stimulation was administered to the unaffected hemisphere of nine chronic stroke patients. Patients were submitted to 2-h somatosensory stimulation in the form of median nerve stimulation and control stimulation using a cross-over design. Baseline Jebsen-Taylor test scores were evaluated. Resting motor threshold, intracortical facilitation, short-interval intracortical inhibition, and visual analog scores for attention, fatigue and drowsiness were measured across conditions.
RESULTS: Better pre-stimulation baseline motor function was correlated with deeper SICI in the unaffected hemisphere. We found no overt changes in any physiological marker after somatosensory stimulation. There was increased drowsiness in the control session, which may have led to changes in intracortical facilitation.
CONCLUSIONS: Our results do not support an overt effect of a single session of somatosensory stimulation of the paretic hand on motor cortical excitability of the unaffected hemisphere as measured by motor threshold, short-interval intracortical inhibition or intracortical facilitation. It remains to be determined if other markers of cortical excitability are modulated by somatosensory stimulation, and whether repeated sessions or lesion location may lead to different effects.

KEYWORDS: Rehabilitation; Afferent stimulation; Transcranial magnetic stimulation; Hemiparesis; Plasticity.

INTRODUCTION

It has been argued that the unaffected hemisphere may contribute to early recovery of motor function after stroke in humans[1] and animals.[2] A single session of somatosensory stimulation in the form of peripheral nerve stimulation improves motor function in chronic stroke.[3-5] A decrease in short-interval intracortical inhibition (SICI) in the affected hemisphere has been reported after somatosensory stimulation and motor training.[3] On the other hand, the effects of somatosensory stimulation on cortical excitability in the unaffected hemisphere are largely unknown.

Different aspects of corticomotor excitability can be evaluated using transcranial magnetic stimulation (TMS). Resting motor threshold, (i.e., the minimum intensity necessary to elicit an MEP in 50% of trials[6] in a target muscle using a single TMS pulse) is related to membrane excitability. SICI refers to a decrease in motor evoked potential (MEP) amplitude that usually occurs when a conditioning, subthreshold stimulus precedes a suprathreshold stimulus at an interstimulus interval (ISI) of 1-6 ms.[7] An increase in MEP amplitude (intracortical facilitation) occurs at greater ISIs (6-25ms). SICI and intracortical facilitation (ICF) likely

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reflect intracortical post-synaptic activity, which depends on the excitability and integrity of separate inhibitory (SICI) and excitatory ICF neurons with a possible spinal contribution to ICF.[8-9]

Our study measured SICI and ICF in the unaffected hemisphere of nine hemiparetic, well-recovered, chronic stroke patients to evaluate if somatosensory stimulation of the paretic hand was associated with excitability changes in the ipsilateral unaffected hemisphere. In addition, we evaluated correlations between hand motor function and corticomotor excitability.

METHODS

Nine chronic phase patients (> 6 months) with infarcts in the middle cerebral artery territory participated in this study. Inclusion criteria were hemiparesis, caused by a single ischemic cortical or subcortical infarction in the middle cerebral artery territory; age ≥ 18 years; and mild to moderate hand disability, defined in terms of ability to perform all the tasks of the Jebsen-Taylor test (JTT).[10] The JTT scores the time, in seconds, required to perform seven activities that are relevant to common daily activities. The lower the JTT score, the better the functional performance of the upper limb. Exclusion criteria were other neurological disorders, use of drugs that influence corticomotor excitability, and contraindications to TMS.[11] Patient characteristics are shown in Table 1. The protocol was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

TMS was delivered to the unaffected hemisphere at the optimal scalp position[12] to elicit motor evoked potentials in the unaffected abductor pollicis brevis (APB) through a figure-of-eight shaped coil (mean diameter, 70 mm) connected to two magnetic stimulators via a Bi-Stim 200[2] module (MagStim, UK). Electromyography (EMG) responses were amplified (x 1000), filtered (2 Hz- 2 kHz) and sampled at 5 kHz.[13] The following TMS measurements were performed before and after control or active somatosensory stimulation:

- Resting motor threshold (rMT), defined as the minimum TMS intensity required to elicit at least three out of six MEPs ≥ 50 microV in consecutive trials.[6]
- SICI and ICF, measured with paired-pulse TMS as previously described.[7-9] The conditioning stimulus (CS) intensity was set to 80% of the APB rMT. The intensity of the test stimulus (TS) was that required to evoke MEPs of approximately 0.5 to 1 mV (TS_{MEP}). The order of presentation of inhibitory (2 ms), excitatory (10 ms) and control trial intervals (test stimulus alone) was randomized. Eighteen trials were recorded for each ISI. Results are expressed as average percentages of MEP amplitudes in conditioning trials and in test trials (MEP_{CS+TS}/MEP_{TS}, %).

Patients were submitted to 2-h somatosensory stimulation, in the form of active median nerve stimulation, and to a control, consisting of subthreshold median nerve stimulation, in separate sessions, as previously described[4] in a cross-over design. Patients were blind to the experimental hypothesis. The order of the control and active somatosensory stimulation sessions was randomized and counterbalanced. Four subjects were submitted to active stimulation in the first session and five to control stimulation. The interval between active and control sessions was 19.6 ± 3.1 days (mean ± standard error).

Background EMG activity recorded from surface electrodes in the APB muscle was continuously monitored. Surface electrodes were optimally placed to stimulate the median nerve at the wrist in the paretic arm. Initially, the minimum intensity of stimulation at which patients reported paresthesias in the median nerve cutaneous territory (sensory threshold) was measured three times. One millisecond duration electrical pulses were subsequently delivered at 10 Hz (Alfamedic Ltda., São Paulo, Brazil). In the active session, stimulus intensity was increased until the maximum at which patients reported strong paresthesias in the median nerve territory in the absence of pain, while compound muscle action potential amplitudes remained below 100 microV in the APB. In the control session, stimulus intensity was kept below the sensory threshold.

Table 1 - Patient characteristics. M, male; F, female; SEM, standard error of the mean; CS, cortico-subcortical involvement of corticomotor pathways; S, exclusive subcortical involvement of corticomotor pathways; R, right; L, left; y, years; NIHSS, NIH Stroke Scale; FM*, Fugl-Meyer Assessment, motor score (% of maximum score, paretic arm); JTT(s), Jebsen-Taylor test score (in seconds). SSEPs: somatosensory evoked potentials. Latencies and amplitudes of N9, N13, N20 and P14 were evaluated

M/F	Age (y) Mean (SEM)	Time from stroke (y) Mean (SEM)	Handedness Side (R/L)	Lesion Site (CS/S)	Lesion Side (R/L)	NIHSS Median (range)	FM* Median (range)	JTT Mean (SEM)	Normal SSEPs
6/3	40.2 (4.6)	3.7 (0.7)	8/1	7/2	1/8	2 (0-5)	95.5 (66.7-100)	120.6 (35.5)	9/9

The correlation between hand motor function, evaluated by JTT scores, and TMS measurements (average of pre-somatosensory stimulation results in control and active somatosensory stimulation sessions) was assessed with the Pearson's correlation coefficient (r). TMS results were analyzed with repeated-measures ANOVA with factors time (2 levels: before stimulation and after stimulation) and condition (2 levels: control and active somatosensory stimulation). visual analog scales (VAS) to measure attention, fatigue and drowsiness were administered at the beginning of the experiments, and after each set of TMS measurements. VAS scores were analyzed with the Friedman´s test and Wilcoxon tests.

RESULTS

Correlation between motor function and corticomotor excitability

There was a significant correlation between JTT scores in the affected hand and SICI in the unaffected hemisphere (r=0.73; p=0.025) (Figure 1). Patients with better performance had deeper SICI in the unaffected hemisphere. No significant correlations were found between JTT scores and rMT or ICF ($p > 0.05$).

Effects of somatosensory stimulation on corticomotor excitability

There were no significant differences in rMT and SICI after control or active somatosensory stimulation (Table 2). There were no significant effects of TIME or CONDITION alone, but there was a significant TIME x CONDITION interaction for ICF (Table 2). There was a significant increase in ICF after control somatosensory stimulation ($p<0.01$) and no significant changes after active somatosensory stimulation ($p = 0.32$). There were no significant differences in VAS scores for attention or fatigue across conditions, but there was increased drowsiness in the control session (Table 3). There was no significant correlation between changes in ICF and VAS scores for drowsiness in the CS session (rho=-0.243, p=0.53).

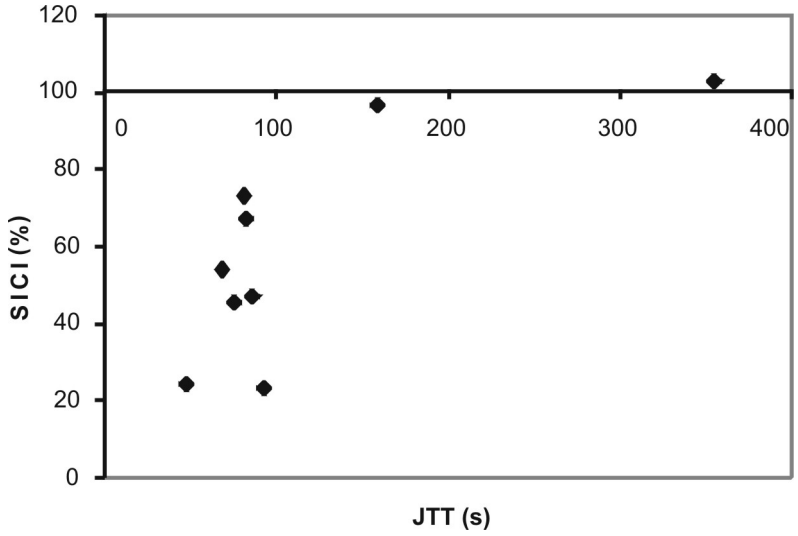

Figure 1 - Correlation between Jebsen-Taylor test (JTT) scores (in seconds) and short-interval intracortical inhibition (SICI, %)

Table 2 - Transcranial magnetic stimulation (TMS) results. CS_{bef} = before control stimulation; CS_{aft} = after control stimulation; AS_{bef} = before active stimulation; AS_{aft} = after active stimulation. F ratios and p values are shown for repeated-measures ANOVA

TMS	CS_{bef}	CS_{aft}	AS_{bef}	AS_{aft}	TIME	CONDITION	TIME x CONDITION
rMT (%)	51.8 ± 4.3	52.8 ± 4.3	54.1 ± 4.0	55.4 ± 4.3	F=2.42; p=0.16	F =3.32; p = 0.15	F = 0.11; p = 0.74
SICI (%)	59.8 ± 11.5	61.7 ± 14.0	57.5 ± 10.7	71.5±9.4	F =1.52; p= 0.25	F =0.17; p = 0.69	F = 0.74; p = 0.41
ICF (%)	147.5 ± 16.1	190.8 ± 20.8	172.3 ± 18.1	154.4 ± 15.9	F = 1.49; p = 0.26	F = 0.16; p = 0.70	F =8.48; p = 0.02

Table 3 - Visual Analog Scales (VAS) scores at the beginning of the experiment (VAS1), before somatosensory stimulation (VAS2) and after somatosensory stimulation (VAS3) in the control (CS) and active (AS) conditions. p values for the Friedman´s test are shown. Wilcoxon tests showed significant differences in drowsiness between $VAS1_{CS}$ and $VAS2_{CS}$ (p=0.033), and between $VAS1_{CS}$ and $VAS3_{CS}$ (p=0.015) but not between other measurements (p>0.05)

VAS	$VAS1_{CS}$	$VAS2_{CS}$	$VAS3_{CS}$	Friedman's test (p)	$VAS1_{AS}$	$VAS2_{AS}$	$VAS3_{AS}$	Friedman's test (p)
Attention	8.9	8	8.4	0.968	9.2	8.7	8.7	0.908
Fatigue	2.1	2.4	4.6	0.197	2.7	2.4	3.6	1.00
Drowsiness	1.2	4.7	4.6	0.032	4.1	2.7	2.2	0.255

DISCUSSION

Deeper SICI in the unaffected hemisphere was significantly correlated with better motor function of the paretic hand in chronic stroke patients. We found no overt changes in any physiological marker of unaffected hemisphere function after median nerve stimulation. Increased drowsiness in the control session may have led to changes in ICF.

Previous studies suggested that the unaffected hemisphere is not functionally relevant in stroke patients with good hand motor recovery. Decreased interhemispheric inhibition from the affected to the unaffected hemisphere may be a marker of worse recovery, or may be prejudicial to motor function.[14-17] We found a correlation between deeper SICI and better motor performance evaluated with the JTT, a widely used tool to assess hand motor ability.[10] In our study, patients exhibited slight to moderate motor disability in the chronic phase (> 6 months) after stroke. Our results indicate that increased inhibition in the unaffected hemisphere is related to better motor function in these patients. Our conclusions are in agreement with the results reported by Swayne and colleagues at 3 months after stroke.[18] Consistent with the concept that increased inhibition of the unaffected hemisphere can be beneficial while decreased inhibition may be maladaptive, Liepert and colleagues[19] reported disinihibition in the unaffected hemisphere in patients with severe upper limb impairment (strength 0-1 in the Medical Research Council Scale) in the first month after stroke.

Even though the functional role of the unaffected hemisphere in motor recovery is a matter of controversy, it has been suggested that changes in excitability can occur in the unaffected hemisphere in response to rehabilitative interventions. For instance, ICF has been found to increase in the unaffected hemisphere in chronic stroke patients submitted to constraint-induced therapy for ten days.[20] Kimberley and colleagues[1] reported improved JTT performance, and enhanced functional magnetic resonance imaging (fMRI) activity in the primary sensory cortex in the unaffected hemisphere of chronic stroke patients submitted to somatosensory stimulation in the form of electrical muscle stimulation of the forearm extensor muscles for three weeks. The increased activation in the primary sensory cortex could be related to increased sensorimotor interactions and enhanced excitability after somatosensory stimulation, but the functional relevance of this finding should be further explored.

Despite the fact that patients were asked every five minutes about the presence and intensity of paresthesias in the paretic hand in both control and active sessions, VAS scores for drowsiness increased after the control somatosensory stimulation. Therefore, it is possible that increased ICF after the control stimulation, but not after the active stimulation, could reflect differences in non-specific changes in arousal across the two conditions. There are three arguments against this hypothesis. First, a previous study reported a decrease, instead of an increase, in ICF following sleep deprivation (a condition in which drowsiness is usually increased).[21] Second, the same study reported a decrease in SICI after sleep deprivation, but, in our patients, there were no significant changes in SICI in either experimental session. Third, there were no significant correlations between VAS scores for drowsiness and ICF. However, we cannot completely rule out different non-specific effects of active and control interventions in arousal.

CONCLUSIONS

Decreased SICI (likely reflecting decreased $GABA_a$ activity) and no changes in ICF in the affected hemisphere were reported after active somatosensory stimulation in chronic stroke patients[3]. Our results do not support an overt

effect of a single session of somatosensory stimulation of the paretic hand on motor cortical excitability of the unaffected hemisphere as measured by rMT, SICI or ICF. It remains to be determined if other markers of cortical excitability[22,23] are modulated by somatosensory stimulation, and if repeated sessions or lesion location may lead to different effects.

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