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Research Article

The Role of Proprioception in Transcallosal Interaction: A Pilot Study on Immobilization of the Upper Limb

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Abstract

Introduction: The strength of the transcallosal fibers connecting the two primary motor cortices (M1) seems to depend on the motor activity of the controlled limb and its contralateral counterpart. This study verifies cortical excitability in healthy subjects with the right hand immobilized for ten hours and the left hand free.

Objectives: The activity of the cerebral cortex M1 was analyzed in two different groups of subjects: the G1 subjected to prolonged immobilization without activity and/or stimuli and the G2 subjected to prolonged immobilization during which stimuli were provided at predefined intervals.

Materials: The study participants were divided into two groups (G1 and G2) that differed in that in G2, during the hours of immobilization, a vibration protocol was also applied. The vibration protocol stabilizes transcallosal inhibitions by simulating the normal use of the immobilized upper limb.

Results: In G1 and G2, after immobilization, the excitability of the left and right motor cortex changed, but in very different percentages depending on the type of activity carried out during the immobilization period.

Conclusion: The non-use caused by immobilization reduces the excitability of the left M1 and decreases the inhibitory effect on the right M1 but by applying a vibration, transcallosal inhibitions stabilize simulating normal use of the arm.

Keywords: *Transcallosal Inhibition; Immobilization; Vibration*

Introduction

In the human brain, homologous regions of the primary motor cortex (M1s) are connected through transcallosal fibers [1]. These connections appear to be to a greater extent inhibitory and can be measured by evaluating interhemispheric inhibition (IHI) by transcranial stimulation (TMS) [2]. Transcallosal inhibitions presumably involve GABAergic inhibitory interneurons, since the corpus callosum consists of glutamatergic excitatory fibers [3,4].

Experiments have shown that interhemispheric communications between the primary motor cortices play a major role in controlling the movements of a hand and that the strength of these communications is dependent on the use made of the limb. In fact, during the

unilateral execution of movements made with the fingers, the contralateral M1s profoundly inhibits the ipsilateral M1s through transcallosal pathways [5], inducing a reduction in the excitability of the ipsilateral cortex [6], moreover, studies on patients with STROKE in the motor cortex have shown an increase in the activity of unharmed M1s [7] and an irregular increase in IHI from the healthy motor cortex to that presenting with a stroke, i.e. it was more evident when the impairment included a greater motor area [8]. It is not clear, however, whether these changes within the cortex are attributable to disuse of the suffering hand or excessive use of the healthy hand [7,9]. These results raised the hypothesis that reduced excitability in the healthy hemisphere may lead to improvements to damaged motor neurons [9]. Previous studies on healthy volunteers have shown that decreasing excitability in a motor cortex, with repeated TMS, results in an increase in the excitability of the contralateral motor cortex and an improvement in the activity of motor neurons that control the ipsilateral hand [10-12].

To study the cortical changes induced by an abnormal and asymmetric use of the limbs we carried out an experiment based on a short-term approach in which we immobilize a hand of completely healthy volunteers. In fact, recent studies have shown that even a short period of immobilization of the upper limb leads to a reduction in the cortical activity of contralateral M1s [13]. In addition, the extent to which cortical changes may be linked to the use of the non-immobilized limb has yet to be evaluated.

Pursuing this goal, we studied the excitability of the two primary motor cortices and their transcallosal interactions on healthy subjects, in which the right hand was immobilized and the left hand left completely free, moreover, to a part of them (Group 2) during the hours of immobilization, we carried out a vibration protocol. The short time of non-use, therefore, should have induced the downregulation of the contralateral M1s, the upregulation of the ipsilateral and a modification of the interhemispheric interactions between the two M1s, moreover, we expected that the results would be different between the G1 (with the left arm free but without vibration) and the G2 (with the left arm free and the vibration on the first dorsal interosseous (FDI) of the right hand which provided a proprioceptive stimulus), In particular, in vibrated subjects we should have detected values very similar to the measurements made in pre-immobilization.

Materials and Methods

Materials

For this study, 18 subjects were called, divided into 2 groups (G1, 12 subjects; G2, 6 subjects), homogeneous by age (G1 mean age, 25.4 ± 3.0 years; G2 mean age 22.5 ± 1.5 years) and sex (G1: six males, six females; G2: three males, three females). All subjects were right-handed as established by the Ediburgh Handedness Inventory [14], without neurological or orthopedic problems in the right limb, without contraindications for TMS, and all enrolled with informed consent.

Methods

Immobilization procedure: All subjects had their right hand immobilized for 10 hours (8:00 a.m. - 6:00 p.m.) (Figure 1a) by means of a soft brace, with concomitant support of the forearm.

Vibration protocol: The proprioceptive stimulus was applied on the tendon of the first dorsal interosseous (FDI) (Figure 1b), with the help of "Vibralgic 5" (Electronic Conseil) capable of producing a range of vibrations between 30 and 285 Hz (Figure 2a), modular thanks to eleven customizable vibration programs. The protocol of this study, number 3 called "tendinites" (vibration at 70 Hz at 80%) which produced an illusion of movement, accompanied by the voluntary closure of the eyes of the "vibrated" subject, performed every 30 minutes for the 10 hours of immobilization for the duration of 1 minute of vibration with 30 seconds of pause.

Electromyographic registration: EMG was performed with silver surface electrodes, placed bilaterally on the belly and tendon of the first dorsal interosseous (FDI). The ground electrode was placed on the styloid process of the ulna. The signal from the electrodes was amplified and filtered (from 20 Hz to 1 kHz) with the D360 amplifier.

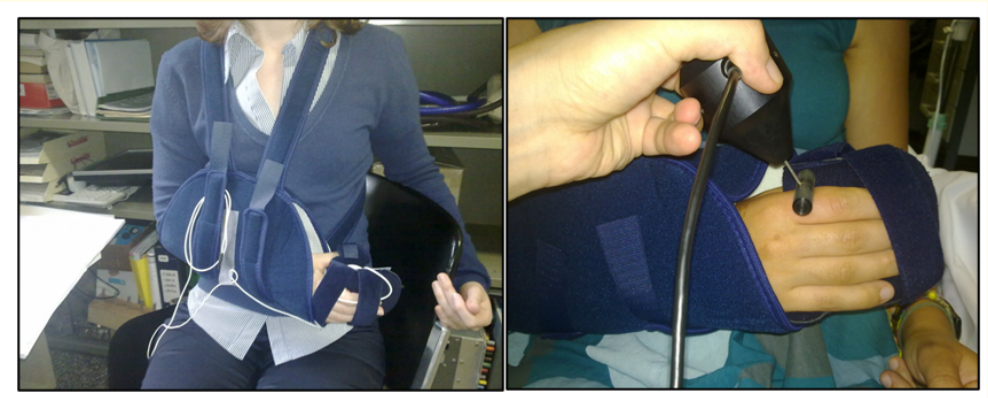

Figure 1: *(a) Immobilized right arm (b) proprioceptive stimulus was applied to the tendon of the first dorsal interosseous (FDI).*

Transcranial magnetic stimulation: The excitability of the left and right motor cortex was tested, studying the recruitment curve (RC) and interhemispheric communications between the two M1s evaluating the IHI. TMS was performed the day before and immediately after 10 hours of immobilization, both around 6:00 p.m.

For the study of CR, TMS was performed with a single magnetic stimulator (Magstim 200 from the Magstim Company) (Figure 2b) connected to a coil in the shape of "eight" with a wing of 70mm diameter. For the IHI study, TMSwas carried out using two Magstim 200 stimulators, one connected to an "eight" shaped coil with a 70 mm diameter wing (test stimulus) and the second was connected to an "eight" shaped coil with a 50 mm diameter wing (conditioning stimol).

Figure 2: *(a) Swave of "Vibralgic 5", manufactured by Electronic Conseil, which can produce a vibration range between 30 and 285 Hz. (b) For the study of CR, TMS was performed with a single magnetic stimulator (the Magstim 200 of the Magstim Company) connected to a "eight" shaped coil with a 70mm diameter wing., for the IHI study, instead, TMS was carried out through two Magstim 200 stimulators, one connected to a "eight" shaped coil with a 70mm diameter wing (test stimulus) while the second was connected to a "eight" shaped coil with a 50 mm diameter wing (conditioning stimulus).*

The coils were positioned tangentially to the scalp, with the handle facing posteriorly and laterally 45° with respect to the sagittal plane, thus inducing a postero-anterior stimulus to the encephalon; This is due to the fact that a lower threshold of motor neurons can be recorded in the presence of an induction of electric current perpendicular to the line of the groove [15]. The optimal position for the activation of the right and left FDI was obtained by moving the coils of 0.5 cm around the area of the motor cortex that affected the hand. The activation threshold of motor neurons was determined with a stimulus of minimum intensity that produced MEPs of at least 0.05 mV in 5 or 10 consecutive tests. RCs were tested in all G1 and G2 subjects while IHI was studied on 9 subjects in G1 and all in G2.

3 G1 subjects were excluded from the IHI study because after immobilization we did not find an inhibition of at least 50% and therefore it would have been difficult to evaluate the possible changes in IHI after immobilization.

The recruitment curve (RC): Rc was evaluated by measuring the amplitude, expressed in mV, of motor neuron potentials (MEPs), induced by stimulation of intensity equal to 5, 10, 15, 20 and 25% above the threshold. Ten tests were recorded for each stimulus intensity on which the average was then calculated.

Interhemispheric inhibition (IHI): IHI can originate from the left hemisphere ending in the right hemisphere (LtoR) or, vice versa, arise in the right and head to the left (RtoL). To measure IHI we tested the M1s after performing random conditioning tests [2].

The conditioning stimulus (CS) was given in one hemisphere before the "test" stimulus (TS) reached the contralateral motor cortex. The TS was calibrated by producing MEPs of 1mv amplitude. The Cs has been set at 130% of the threshold.

To measure the IHI we put both coils on the subject's scalp, alternating test 1 (in which only the coil test stimulated) with test 2 (in which at a distance of a few milliseconds (ISIs) first stimulated the conditioning coil and then in coil test). Two recordings were made: first LtoR and then RtoL. In both, 20 tests 1 and 50 tests 2 were performed. IHI was calculated as the average between MEPs measured with test 1 and MEPs measured with test2.

Results

All subjects tolerated TMS, vibration performed and prolonged immobilization.

Cortical excitability in the left cortex in G1 and G2

In G1 and G2, after immobilization, the excitability of the left motor cortex changed, but in different percentages (Figure 3 and 4). Analyzing the following data, it is possible to note that the activation threshold expressed in millivolts in the left motor cortex in G1 has significantly decreased (from 2.13 ± 0.97 to 1.4 ± 0.38) with a variation of -35%, while, the activation threshold in the left motor cortex in G2 decreased to a lesser extent (from 2.40 ± 1.58 to 1.98 ± 1.21) varying by -19%. In the figure 5 the difference between the results of G1 and G2 is clearly visible. The black line represents the G1 the blue line the G2. The solid line represents the PRE immobilization the dotted line the POST immobilization.

RC LH

	5%	10%	15%	20%	25%	**Average**	±	**%**
G1PRE	1,168511	1,944878	2,746835	3,110596	3,06703	**2,139554**	0,971042	
G1POST	1,017198	1,391586	1,500705	1,639377	1,786621	**1,40191**	0,384711	**-35%**
VIBRPRE	0,824963	1,688494	2,768821	3,413977	3,991648	**2,408305**	1,583342	
VIBRPOST	0,745631	1,366648	2,015415	2,619951	3,185187	**1,965409**	1,219778	**-19%**

Figure 3: *Data in millivolts regarding RC LH.*

RC RH

	5%	10%	15%	20%	25%	Average	±	%
G1PRE	0,762866	1,406087	1,890516	1,929199	2,193592	**1,478229**	0,715363	
G1POST	0,904894	1,769436	2,242703	2,526964	2,757148	**1,831021**	0,926127	**+23%**
VIBRPRE	0,747637	1,347435	2,525756	3,409005	3,741063	**2,24435**	1,496713	
VIBRPOST	1,074759	1,461438	2,20934	3,315294	3,360892	**2,217825**	1,143066	**+0%**

Figure 4: *Data in millivolts concerning RC RH.*

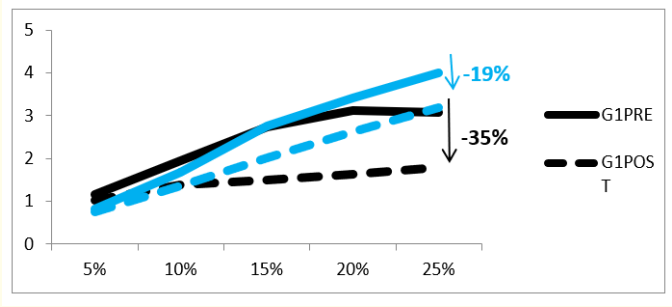

Figure 5: *The RC of the left motor cortex where the difference between the results of G1 and G2 is clearly visible.*

Cortical excitability in the right cortex in G1 and G2: By studying the excitability of the right motor cortex there is a substantial difference between the results obtained by studying G1 and G2. Analyzing the following data (Figure 6), it is possible to note how the activation threshold expressed in millivolts in the right motor cortex in G1 is significantly increased (from 1.47 ± 0.71 to 1.83 ± 0.92) with a variation of +23%, while, the activation threshold in the right motor cortex in G2 remained almost unchanged (from 2.25 ± 1.49 to 2.21 ± 1.14) with a variation of +0%. The black line represents the G1 the blue line the G2. The solid line represents the PRE immobilization the dotted line the POST immobilization.

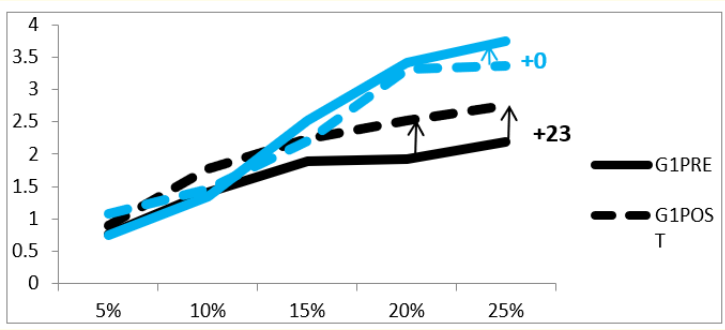

Figure 6: *The RC of the right motor cortex.*

Interhemispheric inhibition LtoR and **RtoL:** The difference between the results detected by interhemispheric inhibition in G1 and G2, presumably, is the most significant data of the present research because it shows the effectiveness and importance of a vibration protocol in the stabilization of callosal trans activity.

Analyzing the following data (Figure 7-9), it can be seen that in IHI L to R the ratio between conditioning coil and test increases by + 35% in G1, that is, it means that the inhibition that the left cortex sends to the right cortex decreases by this percentage, while, always with reference to the data concerning the IHI LtoR it remains unchanged in G2 (modification around 0%). Similar data can also be found in IHI RtoL, in fact, in G1 we find a -26% change in the ratio between conditioning coil and coil test, this means that the inhibition that the right cortex sends to the left cortex increases, while, in G2 we again record a change close to 0%, this data confirms again how the vibration acts effectively on the transcallosal interaction.

IHI LtoR

	cond/test	%
G1PRE	0,493933359	
G1POST	0,670399875	**+35%**
VIBRPRE	0,441051301	
VIBRPOST	0,454667366	**0%**

IHI RtoL

	cond/test	%
G1PRE	0,638398491	
G1POST	0,472813772	**-26%**
VIBRPRE	0,402857074	
VIBRPOST	0,416600703	**0%**

Figure 7: *Data in millivolts concerning IHI: LtoR (left table) and RtoL (right table).*

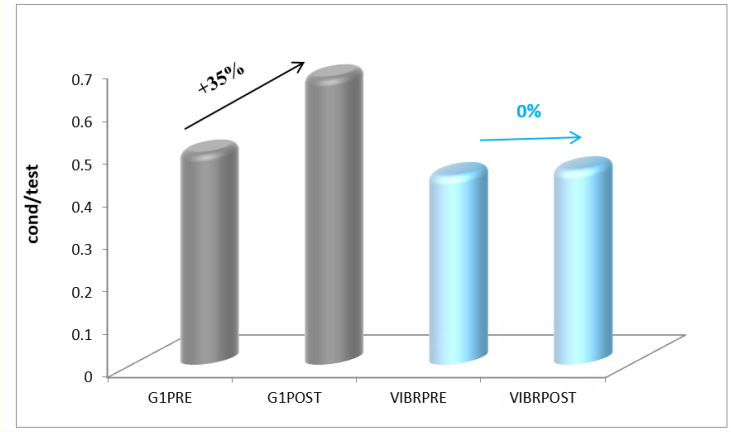

Figure 8: *IHI LtoR.*

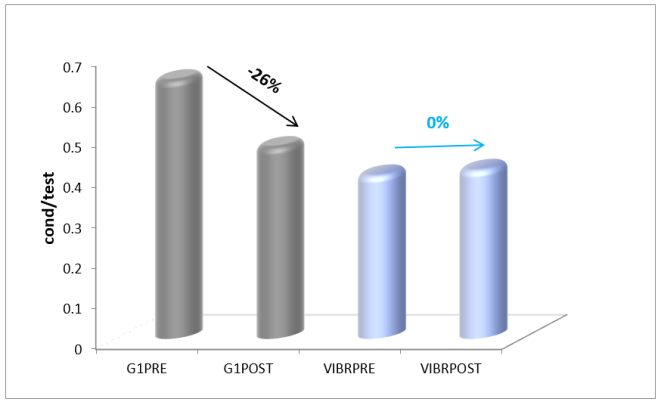

Figure 9: *IHI RtoL.*

Discussion

About effects of immobilization, TMS in the motor cortex has been used to study plasticity changes in cortical excitability associated with immobilization [13,16-19].

Although these studies have produced conflicting results, a likely result has been that even short-term inactivity is able to induce a reduction in cortical excitability in the area of the motor cortex relative to limited muscle [13,19], probably due to a depression induced by local synapses [13].

This is the first study to show that transcallosal interaction can be modulated with short-term hand inactivity. Recent work has shown that the activity of the transcallosal and corticospinal pathways are regulated by populations of similar interneurons [20,21].

Thus, a possible neurophysiological explanation for the short-term effects of "non-use" could be that the excitability of a population of interneurons that control both transcallosal fibers and corticospinal neurons is altered, thus inducing similar effects in the two neural systems. Following this hypothesis, it has been shown that the administration of an inhibitory protocol on the left motor cortex by rTMS was able to decrease the corticospinal excitability of left M1 and its transcallosal activity (IHI LtoR) [22]. In addition, a reduction in transcallosal activity (LtoR IHI) results in corticocortical stimulation associated with an increase in the corticospinal excitability of the right M1 [23,24]. Reduced inhibitory control from the left cortex to the right cortex may be helpful in facilitating unilateral movements of the left hand. All these results are in agreement with previous studies based on short-term deprivation of sensory input caused by a nervous ischemic block. In fact, acute deafferentation of the upper limb induces a focal increase in excitability of the cortex controlling the non-deafferent hand [25-27] along with improvements in spatial tactile acuity in the non-deafferent hand in healthy subjects and motor capacity in stroke patients.

With regard to motor cortex activity and proprioception, we can assume that the effect on M1 activity observed in the present work is not only attributable to a lack of voluntary movement but also to the reduction of proprioceptive information by the immobilized hand. In fact, using EEG recording, a significant reduction in the amplitude of the P45 component was observed after a short period of immobilization. P45 classically represents the processing of proprioceptive information within the motor areas [28]. These results

could suggest that the reduction in proprioceptive information processing recorded after short-term immobilization could be mainly attributable to a decrease in the flow of proprioceptive inputs from the spindle of the right arm muscle.

Presumably, the Ia input, related to the immobilized arm could be the most affected by non-use, moreover, in animal models it has been shown that this pathway has direct access to contralateral cortical sensory and motor areas [29,30]. Furthermore, it has been shown [31] that in humans M1 neurons also react to proprioceptive stimuli.

This suggests a fundamental link between proprioceptive dynamic information and M1 excitability in humans. Researchers [32,33] have also shown that vibration of the hand and forearm muscles, by activating Ia fibers, can modify the excitability of the two M1s and the trans callouse interaction between them. This finding is based on the fact that proprioceptive inputs stimulate that population of interneurons that modulate both the cortico-spinal pathway and the neurons at the base of the trancallosal pathway and for this reason there is an improvement in the activity of the right cortex in G1, perhaps caused by an excessive use of the left hand that brought greater proprioceptive inputs.

About the relevance of the present research and with the present study we have shown that with 10 hours of immobilization of the right arm there is a decrease in the excitability of the left motor cortex and a reduction in the interhemispheric inhibition LtoR, moreover, we found that the cortical excitability of the right M1 and the IHI RtoL were dependent on the use of the left hand not immobilized.

Comparing the data of G1 and G2 it was noted that the vibration protocol acted mainly on the interhemispheric connections rather than on the excitability of the contralateral cortico-spinal neurons This phenomenon is to be attributed to the different morpho-functional properties between the interneurons of the transcallosal pathway and the cortico-spinal neurons of the fifth layer of the cortex, in fact immobilization inhibits corticospinal neurons and interneurons of the transcallosal pathway both because there is an absence of movement either because proprioceptive neurons present in the somatosensory cortex (or in the M1 itself) no longer send excitatory signals due to the absence of movement. If we carry out the vibration, however, the proprioceptive neurons are activated by stimulating, consequently, the cortico-spinal neurons and the interneurons which, as already mentioned above, for different morpho-functional properties, are activated more than the cortico-spinal, consequently, the interhemispheric balance is stabilized. This means that the stimulus of the contralateral transcallosal interneurons on the ipsilateral gaba interneurons is practically equal to the basal condition, that is, with the right limb not immobilized. On this data we can say that the vibration can prevent an interhemispheric imbalance found, for example, in cases of stroke where the undamaged cortex becomes more active due to a reduced interhemispheric inhibitory action by the affected cortex and at the same time the suffering cortex is inhibited by strong inhibitions by the healthy cortex.

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