Article

Effects of Excitatory Transcranial Magnetic Stimulation of the Anterior Intraparietal Area in Chronic Stroke Patients

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Abstract: 1) Objective: to evaluate the effects of excitatory transcranial magnetic stimulation of the anterior intraparietal area in chronic patients with a frontal lesion and parietal sparing due to stroke on the impaired upper (UL) and lower limb (LL) as measured by Fugl-Meyer Assessment (FMA). 2) Methods: three patients (P1: 49.83/2.75, P2: 53.17/3.83, P3:63.33/3.08 years-old at stroke/years post-stroke, respectively) received two weeks (five days/ week) of rTMS at 10 Hz of the left anterior intraparietal area (AIP). A patient was treated in similar conditions with a sham coil (56.58/4.33) No complimentary therapy was delivered during the study. Patients were evaluated before, after- and two-months post-treatment (A1, A2 and A3, respectively). 3) Results: We found increased scores for lower limb in motor function subsection for P1 and P3 and in sensory function for P2 by A2 that remained at A3. We also found an increased score for upper limb motor function for P2 and P3, but the score decreased by A3 for P2. P3 score for upper limb ROM increased by A3 compared to A1 and A2. 4) Conclusion: AIP excitatory rTMS increased the FMA scores for lower and upper limb function, showing a broader effect when compared to M1 stimulation.

Keywords: anterior intraparietal area; stroke; rTMS; Fugl-Meyer Assessment; fast frequency TMS; motricity; sensibility; chronic patients

1. Introduction

TMS is a widely studied tool for the treatment of post-stroke patients. Several studies have obtained promising results for treating depression [1,2], aphasia [3-6] and pain [7-10], as well as for improving motor function [2,11-14]. Such studies are generally based upon the interhemispheric imbalance model [15], which states that the injury of one hemisphere increases the activation of the contralateral hemisphere, which, in turn, exerts a greater inhibition over the injured hemisphere [15-17]. Most of these studies have applied the inhibitory repetitive transcranial magnetic stimulation (rTMS) to the intact hemisphere and excitatory rTMS to the injured hemisphere [3,13,15,]. Excitatory stimulation, however, does not only present opposite results from inhibitory stimulation. Its results tend to be broader and more intense, whereas inhibitory stimulation, tends to generate changes in a smaller number of cortical centers with a lower intensity [17,18]. Some researchers have applied the excitatory stimulation on the usually inhibited unlesioned hemisphere in patients with depression or aphasia [5,19], and they found similar or more consistent results compared to those obtained by inhibitory stimulation. These studies seem to indicate that the utility of the excitatory TMS on the post-stroke brain is not restricted to the model of inter-hemispheric imbalance.

Studies evaluating the effects of rTMS on motor function have typically used the primary motor cortex as the stimulation site [7,8,11-14,20]. These studies have obtained good results with acute [13] and chronic patients [7,11,14,20]. However, direct application to the primary motor cortex may restrict the excitatory rTMS effects to the stimulated neurons since the main output of the primary cortex is directed to the muscles and not to other areas of the brain, thus reducing the effectiveness of excitatory stimulation.

The anterior intraparietal area is an area closely linked to the elaboration of movements and their correction on the occurrence of an unexpected perturbation [21-24]. As a tertiary cortex region, the anterior intraparietal area is connected to many other regions [21,25], and its stimulation could lead to a broader effect on motor function. However, the anterior intraparietal area is also usually damaged in more extensive strokes involving the middle cerebral artery. A stroke that spared the lower trunk or the parietal branch of the middle cerebral artery would preserve the anterior intraparietal area [26,27]. Magnetic stimulation of the spared intraparietal area could provide information about the effect of stimulation of a spared area on originally connected injured areas within the same hemisphere. Particularly, the excitatory stimulation of the anterior intraparietal area could cause either no effect on the affected limb, either affect only the upper extremity or even affect both lower and upper extremities. Thus, this study aimed to investigate the effects on motor and sensory functions of the impaired lower limb and upper limb produced by the excitatory magnetic stimulation of the spared anterior intraparietal area in chronic stroke patients.

2. Materials and Methods

Ethics Statement

The project was approved by the Université du Québec à Montréal, Canada. Ethical approval was obtained from the UNICEUB Research Ethics Committee (CEP-UNICEUB), Brasília, Brazil – report nº 2.044.460/17.

Subjects

Participants were selected from a comprehensive analysis of the medical records of patients seen at Dr Henrique Santillo Rehabilitation and Readaptation Center – CRER's outpatient clinic from January to October 2017 in Goiânia, Brazil. To be included in the study, patients had to have a diagnosis of a first-ever left-hemisphere stroke due to the involvement of the middle cerebral artery two to five years prior to the study. The parietal lobe had to have been spared by the stroke. Analysis of the lesion extension and parietal sparing was based on imaging examinations by the patient's neurologist and the research team. Patients had to be between 40 and 70 years old and consistently right-handed prior to stroke according to the Edinburgh Inventory [28]. In addition, neurodegenerative diseases, moderate to severe musculoskeletal disorders previous to stroke, psychiatric disorders, uncorrected or stroke-related visual impairments, diabetes mellitus, and any contraindications for TMS procedures, were considered as exclusion factors. Eligible participants agreed to participate in the study by signing the informed consent form. A personal companion was present at the presentation of the research and the signing of the informed consent form.

Evaluations

Patients were evaluated with the Fugl-Meyer Assessment (FMA) before the treatment (A1). An occupational therapist evaluated the upper extremity and a physical therapist evaluated the lower extremity. These assessments were repeated at the end of the treatment (A2) and two months after A2 (A3). Evaluations were administered by the same professionals, in the morning in the same room.

rTMS

To determine each participant's resting motor threshold (RMT), the coil was positioned with the handle at a 45° angle to the anterior-posterior axis. Single TMS pulses were applied to the participant's left M1 on the C3 point of the international 10-20 system. RMT was defined as the lowest level of machine output that elicited three twitches in the first dorsal interosseous of six consecutive TMS pulses [29]. Repetitive TMS was performed with a Neurosoft stimulator with a 76-mm figure-of-eight coil on the P3 point of international 10/20 system, which refers to Brodmann's area 40 in the

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left-hemisphere [30], where the anterior intraparietal area is located. We delivered 40 trains of 50 pulses each at 10 Hz and 90% RMT of each individual patient with 25 seconds interval, totalizing 2000 pulses in a 20 minutes session, for two weeks (five days/ week). These parameters are in accordance with the safety ranges for high-frequency rTMS [31]. Blood pressure was evaluated before, immediately after and five minutes after each rTMS session. The coil was positioned 45º reward to the frontal plane. Participants lay down their side on a stretcher during stimulation with head supported for comfort and better positioning of the coil. The sham patient was equally positioned, but the coil was unattached to the stimulator. No complementary therapy was delivered in this period for none of the four patients.

3. Results

Medical records of patients resulted in the pre-selection of seven patients, four of whom agreed to participate. One patient was randomly chosen to receive sham treatment. Patient 1 (P1 – woman) was 49. years-old and 2.75 years post-stroke. Patients 2 and 3 (P2 and P3 – men) were 53 and 63 years-old, with 3.83 and 3.08 years post-stroke, respectively. The patient who received the sham treatment (S1 – man) was 56 years-old and 4.33 years post-stroke. The Fugl-Meyer Assessment (FMA) scores are found in Table 1.

Table 1. Fugl-Meyer Assessment subsections scores.

			P1			**P2**			**P3**			**S1**	
		max	*A1*	*A2*	*A3*	*A1*	*A2*	*A3*	*A1*	*A2*	*A3*	*A1*	*A2*
LL-FMA	motor function	**34**	27	33	34	29	28	30	17	21	21	18	19
	sensory function	**12**	10	10	12	6	12	12	9	10	10	10	11
	ROM	**20**	20	20	20	20	20	18	18	18	18	16	16
	joint pain	**20**	10	12	14	20	20	20	20	20	20	19	20
UL-FMA	motor function	**66**	66	66	66	13	18	16	4	8	8	2	2
	sensory function	**12**	12	12	12	12	12	12	6	6	6	6	6
	ROM	**24**	24	24	24	24	24	24	18	18	24	13	13
	joint pain	**24**	23	23	22	20	20	20	18	18	20	20	20

P1, P2, P3: treated patients; S1: sham treated patient; max: subsection maximum score; A1: pre-treatment evaluation; A2: post-treatment evaluation; A3: two-months follow-up evaluation; LL-FMA: lower limb Fugl-Meyer Assessment; UL: upper limb Fugl-Meyer Assessment; ROM: range of motion.

Patient P1 increased six points on the FMA lower limb motor function subsection after rTMS treatment, and this increase was still present two months after the end of the treatment when the score reached the maximum value. She gained two points on the pain subsection by A2 and reached the maximum value by A3, and she also gained two points on the sensory function subsection by A3. She was the only patient to present some idiopathic chronic pain after stroke. Instead patient reported some difficulty in performing activities of daily living with the right hand, FMA was unable to find any impairment in motor function subsection, since she reached the highest score at baseline. Patient minimally decreased the upper limb pain score by A3, indicating an increase in hand pain level. Patient P2 increased his score on the FMA lower limb sensory function subsection by six points, reaching the maximum score for this subsection, and this increase remained by A3. Motor function and range of motion subsections minimally fluctuated by A2 and A3. He gained five points by A2 on the upper limb motor function subsection, but this gain was lost by A3. No changes were observed on the other subsections. Patient P3 presented the lowest scores for lower extremity motor function subsection at baseline, and he increased its score by four points by A2. This gain remained by A3. He also gained a single point for the sensory function by A2 that remained by A3. His score on the upper extremity motor subsection was also the lowest in the group, indicating severe hemiparesis. By the end of the treatment, he regained the ability to hold an object with the hand and release it when solicited, granting an additional four points by A2. This ability was still present by A3. The range of motion subsection presented a discrete increase by A2 that reached six points compared to A1 by A3 and increase two points on the pain subsection by A3. These gains correspond to the hand and wrist. Score variations by subsection for lower limb and upper limb can be found in Figure 1 and Figure 2, respectively. Patient S1 only presented a single point fluctuation in lower limb sensory function and pain subsections and no changes in upper limb subsections by A2, therefore he did not participate in A3.

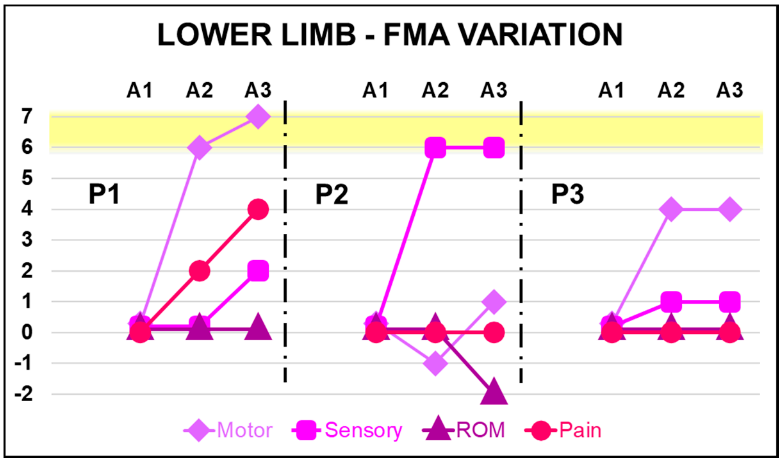

Figure 1. Score variation for lower limb FMA subsections. Yellow region indicates minimal clinically important difference according to Pandian et al. [32].

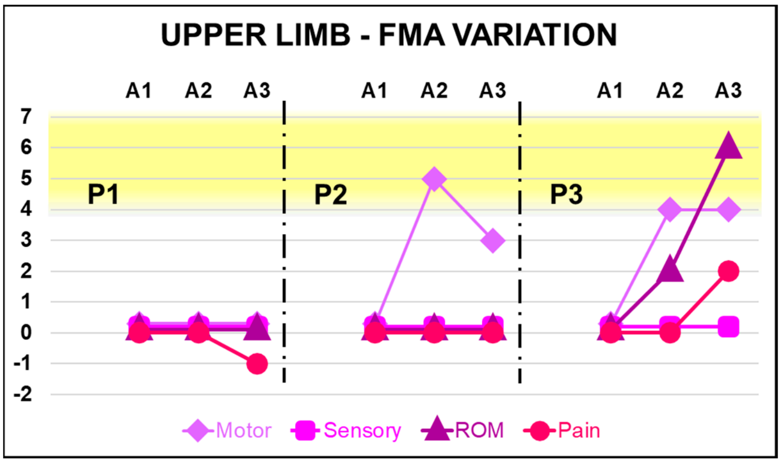

Figure 2. Score variation for upper limb FMA subsections. Yellow region indicates clinically important differences according to Page & Fulk [37].

4. Discussion

This study aimed to investigate the effects on motor and sensory functions of the impaired lower limb and upper limb produced by the excitatory magnetic stimulation of the spared anterior intraparietal area in chronic stroke patients. We found an increase in motor function, sensory function, and pain level scores for the affected lower and upper extremities of chronic stroke patients, suggesting that rTMS of the spared anterior intraparietal area may yield wide-ranging benefits.

Lower extremity

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Both patients 1 and 3 had an improvement of their lower extremity motor function score as assessed by the FMA. Patient 1 increased her score six points by A2 and gained one more point by A7, reaching the maximal score on this FMA subsection. Pandian et al. [32] found that a six-point change on the motor function subsection in chronic stroke patients is clinically important, therefore her score was clinically significantly changed between baseline and post-treatment evaluations. She also presented a progressive increase on the sensory subsection and a reduction of pain. For Patient 3 the improvement of his motor function score did not reach the minimal clinically important difference indicated by Pandian et al. [32], and this improvement was accompanied by a slight increase in sensory function. Although these variation values were low, they mirror the motor and sensory gains observe in patient 1.

Patient 2 also showed important gains in the sensory function of the lower extremity, but there are no studies indicating a clinically important minimal difference for sensory function. Although he showed the greatest gains in sensory function among the three treated patients, motor function variation did not mimic these gains. This may be due to the variability of effects of the stimulation or more likely to the patient's specific central compromises. Since the patient started the study with 29 points out of a maximum of 34 points, a gain of five points would raise him up to the normal range without allowing him to reach the six points necessary for clinical significance. In this way, the best condition of his right lower extremity might explain the difference between him and the other patients.

Several studies have pointed the relevance of the sensory function motor performance after stroke [33-36]. A rehabilitation that aims to improve sensory functions tends to produce better results [34-35] since sensory integration is the base of the elaboration and structure of movement [33]. In this study, the excitatory stimulation of the anterior intraparietal area increased the sensory function score of the three participants, reaching the subsection maximum score for patients 1 and 2. The combined gains in sensory and motor functions make this stimulation model even more beneficial to the patient since they are interrelated and improvement in one area may directly impact the other. Sensory and motor rehabilitation therapies could benefit from these gains obtained from stimulation in chronic stroke patient care.

Upper Extremity

Patient 3 presented an important gain: active palmar grip, which he was unable to perform by A1. Hand and wrist gains account for the increase in motor function and range of motion subsections of the FMA. These gains were found at the end of the treatment and reached even greater values by the two-months evaluation when a slight increase in pain reduction was also found. Together, these changes reflected both a reduction in basal tone and a better voluntary motor control.

Patient 2 had an important gain in motor function subsection at the post-treatment evaluation, but this score reduced at the two-months evaluation.

According to Page and Hulk [37], the clinically important difference for grasping ability is 4.25 points, while for the general function of the upper extremity it is 5.25. Thus, the values achieved both by patient 2 in A2 and patient 3 in A2 and A3 are clinically important.

The anterior intraparietal area is strongly connected to the ventral premotor cortex [38-39]. Although it is hypothesized that there are direct connections between the anterior intraparietal area and the primary motor cortex, these connections still need to be described [40]. The anterior intraparietal area has been described as an important manual motor control center [41], but, to our knowledge, no study has described its role in lower extremity activity. A study has used sensory stimulation as a strategy to improve fine manual control and manual manipulation by the anterior intraparietal area in macaques [42] and it found that the anterior intraparietal area might be related to the self-image construction based on the sensorimotor information [21,43]. Here we found that the excitatory stimulation of the anterior intraparietal area improved the FMA sensory function score, suggesting that the anterior intraparietal area would facilitate the sensory input.

The major limitation of our study is the small number of patients. We evaluated 540 medical records in this study, which set this condition prevalence at just over one percent. Although this index

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may vary in different centers or countries according to the promptness of the stroke care assistance, it should still be small. Even being a relatively rare condition, it brings the possibility of studying the influence of ipsilaterally applied transcranial magnetic stimulation on a spared area closely related to the regions affected by stroke.

Precisely for this reason, the study did not aim to reduce the neuronal activity of the anterior intraparietal area, but rather to evaluate if its overactivation could, in some way, positively influence the affected areas. Studies that aimed to assess the TMS effects on depression also relied on excitatory stimulation of an uninjured area [2]; however, although depression runs with changes in cortical excitability, it is not due to direct tissue damage as seen in the stroke. Thus, the model justifies conducting the study even with few patients.

Patients 1 and 2 had a maximum score in the sensory function already in the pre-treatment evaluation. Thus, it was not possible to infer about the effect of AIP excitatory stimulation on the of the affected upper extremity sensory function based on our results. Patient 1, although had reported difficulties in performing ADLs using the affected upper extremity, obtained the highest score for the motor function already in the pre-evaluation. In this case, the Fugl-Meyer scale was not sensitive enough for this patient. No studies were found that discussed the FMA sensory function and pain absence subsections scores. Thus, there is not a parameter to proceed an integrated analysis of the different subsections of each member [44]. Although Fugl-Meyer Assessment is recommended as primary outcomes in intervention trials [45-46], lack of methods for individualized and integrated analysis of each extremity subsections reduces its effectiveness.

Our study used the international 10-20 system to determine the stimulation site. The use of a neuronavigation system and individual structural magnetic resonance imaging could add greater uniformity to the results, and the replication of the study with this apparatus might confer greater confidence regarding the effects of the anterior intraparietal area excitatory stimulation. However, the international 10-20 system ease of application and low cost with quality make this method a good tool for replication [47]. Our results were not uniform, as expected in a so reduced sample. On the one hand, this fact limited our conclusions and the possibility of further generalizations. On the other hand, this brought strength to the observed common findings, and the hypotheses that might be drawn from our observations can positively contribute to the rehabilitation research with the stroke patient.

5. Conclusions

Excitatory stimulation of the anterior intraparietal area modified the lower and upper extremity Fugl-Meyer Assessment scores in motor and sensory functions, as well as in pain reduction in chronic stroke patients.

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