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Article

Effects of Excitatory Repetitive Transcranial Magnetic Stimulation of the P3 Point in Chronic Stroke Patients – Case reports

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Abstract: Objective: to evaluate the effects of excitatory repetitive transcranial magnetic stimulation (rTMS) of the international 10-20 system P3 point (intraparietal sulcus region) 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). Methods: three patients (C1: 49.83/2.75, C2: 53.17/3.83, C3: 63.33/3.08 years-old at stroke/ years post-stroke, respectively) received two weeks (five days/ week) of rTMS at 10 Hz of P3. A patient was treated in similar conditions with a sham coil (S1: 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). Results: we found increased scores for LL in motor function subsection for C1 and C3 and in sensory function for C2 by A2 that remained at A3. We also found an increased score for UL motor function for C2 and C3, but the score decreased by A3 for C2. C3 score for UL range of motion increased by A3 compared to A1 and A2. Conclusion: In a variable way, P3 excitatory rTMS increased FMA scores in different upper and lower limb subsections of our three treated patients.

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

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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], though the variety of results of TMS with this population requires further studies. 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 aphasia or motor impairments due to brain lesion [5,19], and they found similar or more consistent results compared to those obtained by inhibitory stimulation. These studies suggest the possibility that the utility of

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the excitatory rTMS on the post-stroke brain could be 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 P3 point in the international 10-20 system correspond to the intraparietal sulcus, a very gyrified region [21] in the human brain that have been receiving increasing attention from the scientific community due to its relevance in sensorimotor integration and in several aspects of motor coordination, such as motor planning [22,23,24], reaching and gripping/grasping [25,26], and online correction [26]. According to Herwig et al. [27], the P3 stimulation may achieve the intraparietal sulcus or surrounding regions in the Brodmann areas 7 (BA 7) and 40 (BA 40).

It was found that BA 40's activation intensity is greater in people with long-term motor training [28]. In addition, its earlier activation in the post-stroke acute phase was correlated with better motor recovery [29]. Both BA 40 and BA 7 have already been related to sequential finger movements [30,31]. Their activation grows from unimanual to bimanual movements and from symmetrical to asymmetrical bimanual movements [32] and they are involved in extracting task-relevant information when different inputs are available [33]. Left BA 7 was also correlated to reaching and grasping in unimanual tasks [34].

As a tertiary cortex, this region is connected to many other [22,35], and therefore its stimulation could lead to a broader effect on motor function. However, this region 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 intraparietal sulcus and its surrounding regions [36,37]. Excitatory magnetic stimulation of this spared region could provide information about the effect of positive stimulation of a spared area on originally connected injured areas within the same hemisphere. Particularly, the excitatory stimulation of the P3 point could have positive effects on the motor and sensory functions, based on the findings already described associated with the stimulated region.

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 [38]. 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 tangentially on the scalp with the handle directed upward and posteriorly at a 45° to the frontal plane, nearly parallel to the central sulcus. 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 [39]. 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 mainly refers to the intraparietal sulcus in the left-hemisphere [27], where the anterior intraparietal area is located. Figure 1 shows the P3 positioning and the stimulated areas according to Herwig et al. [27], illustrating the proportionality for each one of them. We delivered 40 trains of 50 pulses each at 10 Hz and 90% RMT of each individual patient with 25 seconds interval, totalling 2000 pulses in a 20 minutes session, for two weeks (five days/ week). The 10 Hz frequency was chosen according to international TMS guidelines, which advise that the 10 Hz frequency must be preferably chosen relative to 20 Hz, 15 Hz and 5 Hz, and the other parameters are in accordance with the safety ranges for high-frequency rTMS [41]. Blood pressure was evaluated before, immediately after and five minutes after each rTMS session. The coil was positioned tangentially on the scalp with the handle pointing posteriorly to the base of the neck at 30° relative to the transverse plane. This position follows the positioning described by Koch et al. [42] to better achieve the anterior intraparietal area. 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 sham coil was unattached to the stimulator, while the active coil was kept near the sham coil to provide the sham auditive stimulation.

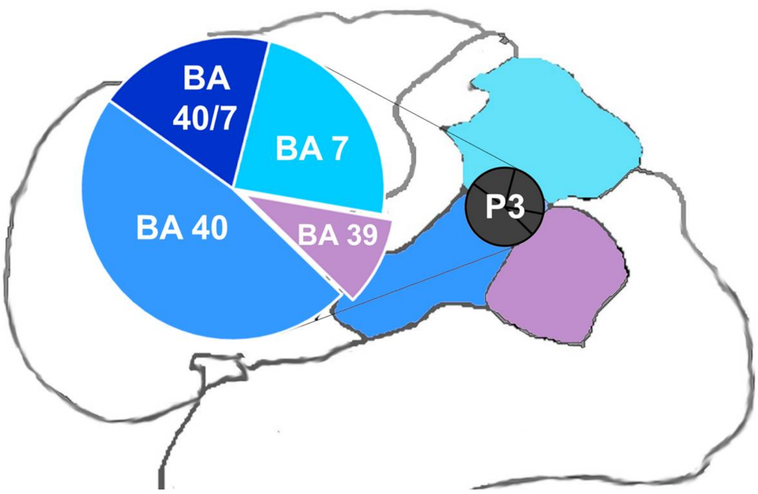

Figure 1. Possible stimulated areas by the international 10-20 system P3 point. The main figure illustrates the P3 positioning in the brain. The highlighted graphic illustrates the probability associated with each Brodmann area according to Herwig et al. [27]. BA 40 = Brodmann area 40 close to the intraparietal sulcus; BA 7 = Brodmann area 7 close to the intraparietal sulcus; BA 40/7 = intraparietal sulcus; BA 39 = Brodmann area 39 close to Brodmann area 40.

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 (C1 – woman)

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was 49. years-old and 2.75 years post-stroke. Patients 2 and 3 (C2 and C3 – 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. Figure 2 shows the spared intraparietal sulcus and the lesioned M1 of each participant. The images were performed as part of the medical monitoring of each patient and outside the institution where this study took place, therefore without the purpose of serving as the basis for scientific research. The Fugl-Meyer Assessment (FMA) scores are found in Table 1.

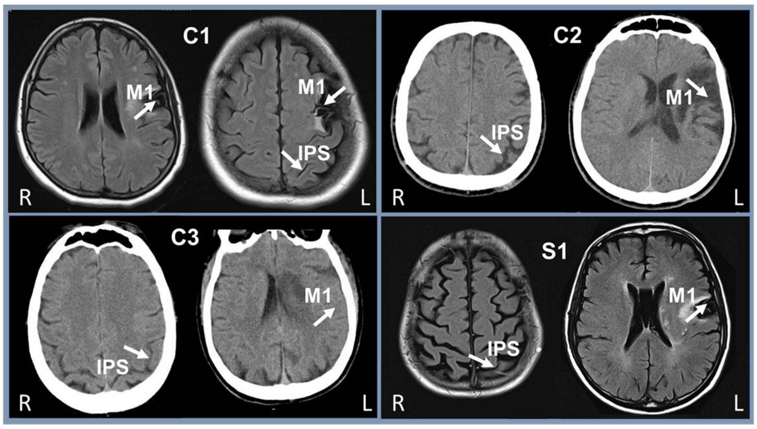

Figure 2. Computed tomography (patients C2 and C3) and magnetic resonance image (patients C1 and S1) showing the spared intraparietal sulcus and the affected primary motor cortex. IPS = intraparietal sulcus; M1 = primary motor cortex; C1-3 = treated patients; S1 = sham patient. L = left side of the brain; R – right side of the brain.

Table 1. Fugl-Meyer Assessment subsections scores.

			C1			C2			C3			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	18
	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

C1, C2, C3: 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 C1 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. Although the patient reported some difficulty in performing activities of daily living (ADLs) with the right hand, FMA was unable to find any impairment in motor function subsection, since she reached the highest score

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at baseline. Patient minimally decreased the upper limb pain score by A3, indicating an increase in hand pain level.

Patient C2 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 in the other subsections.

Patient C3 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.

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.

Score variations by subsection for lower limb and upper limb can be found in Figure 3 and Figure 4, respectively.

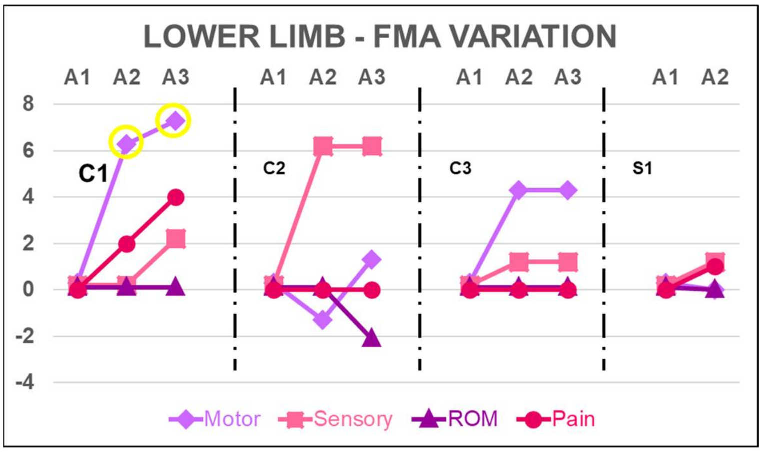

Figure 3. Score variation for lower limb FMA subsections. Yellow circles indicate minimal clinically important difference for FMA motor subsection according to Pandian et al. [43].

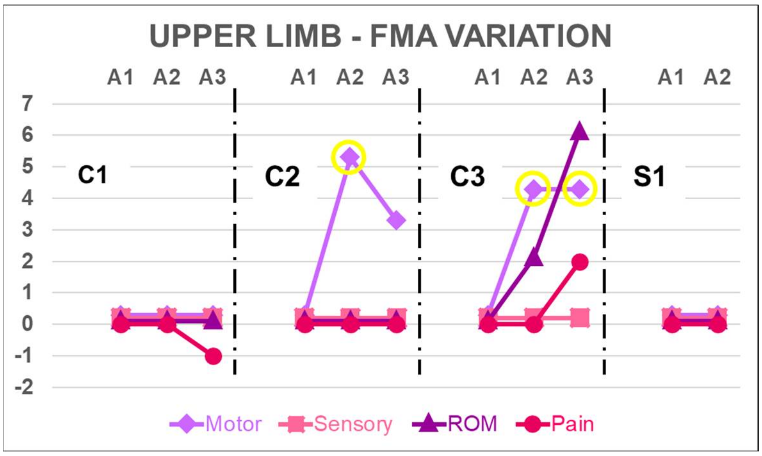

Figure 4. Score variation for upper limb FMA subsections. Yellow circles indicate clinically important difference for grasping in FMA motor subsection according to Page & Fulk [48].

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4. Discussion

This study aimed to investigate the effects of the excitatory magnetic stimulation of the P3 point on the all FMA subsections scores of the impaired lower limb and upper limb in three chronic stroke patients whose intraparietal sulcus region was spared by the middle cerebral artery stroke. We found an increase in motor function, sensory function, and pain level scores (which indicates a reduction in pain level according to FMA) for the affected lower and upper extremities, suggesting that the rTMS of this spared region could yield wide-ranging benefits.

Lower extremity

Both patients C1 and C3 had an improvement of their lower extremity motor function score as assessed by the FMA. Patient C1 increased her score six points by A2 and gained one more point by A3, reaching the maximal score on this FMA subsection. Pandian et al. [43] found that a six-point change in the motor function subsection in chronic stroke patients is clinically important, therefore her score was clinically significantly changed from baseline to post-treatment evaluations. She also presented a progressive increase on the sensory subsection and a reduction of pain. For patient C3 the improvement of his motor function score did not reach the minimal clinically important difference indicated by Pandian et al. [43], 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 C1.

Patient C2 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 [44-47]. A rehabilitation that aims to improve sensory functions tends to produce better results [45-46] since sensory integration is the base of the elaboration and structure of movement [44]. In this study, the excitatory stimulation of the P3 point increased the sensory function score of the three tread participants, reaching the subsection maximum score for patients 1 and 2. The combined gains in sensory and motor functions make a stimulation model even more beneficial to the patient since these functions are interrelated and an improvement in one area may directly make an impact on the other. Sensory and motor rehabilitation therapies could benefit from these gains obtained from stimulation in chronic stroke patient care. Our findings in these cases suggest that the excitatory rTMS of the P3 point may be beneficial to the lower limbs both for motor function and for sensory function in this stroke population.

Upper Extremity

Patient C3 presented an important gain: active palmar grasp, 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 (A3) 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 C2 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 [48], 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 C2 in A2 and patient C3 in A2 and A3 are clinically important.

Sensory function

The inferior parietal lobe, as well as the intraparietal sulcus, is strongly connected to the frontal cortex [49]. Particularly, the anterior intraparietal area, which corresponds to the anterior portion of the intraparietal sulcus, is described as an important node for grasping processing [50, 51] due to its connections with parietal and frontal areas, but, to our knowledge, no study has linked the intraparietal sulcus and surrounding regions to the lower extremity motor function. Connections between the parietal cortex and the frontal cortex in a parietal-premotor network are key for sensory-motor control [22]. This network is compounded by several pathways related to reaching, grasping, body imaging, spatial processing, and diverse modalities of sensory input are linked to different portions of the intraparietal sulcus [20, 22]. Therefore, the region stimulated in our study may even be related to the self-image construction by means the sensorimotor input [22, 52]. The activation of the parietal cortex was correlated with a better sensory discrimination in chronic stroke patients [53]. Here we found that the excitatory stimulation of the P3 point area improved the lower limb FMA sensory function score for the three treated patients in different values, suggesting that the excitatory stimulation of P3 may facilitate the lower limb sensory input. Two patients obtained the maximum score for the upper limb prior the treatment and the third patient did not change his upper limb sensory function score after the treatment, therefore we cannot evaluate if the excitatory stimulation of P3 may improve it or not.

Limitations

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 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 possibility of studying, the study did not aim to reduce the neuronal activity of the intraparietal sulcus and surrounding regions, but rather to evaluate if its excitatory stimulation could, in some way, positively influence the affected areas by the stroke. Here, we did not deal with the inter-hemispheric imbalance since our intervention occurred in the same hemisphere of the lesion. We sought to evaluate, through the Fugl-Meyer Assessment, the effect of the excitatory stimulation on the affected area without stimulating it directly. This unique possibility drove us to choose the excitatory stimulation. Through the excitatory stimulation of a spared tertiary cortex strongly connected to the lesioned area, we sought to stimulate this lesioned area in a more comprehensive manner both spatially as functionally. Therefore, in our view, the possibility to influence a lesioned area through the stimulation of an ipsilateral spared area 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 C3 excitatory stimulation on the affected upper extremity sensory function based on our results. Patient C1, though had reported difficulties in performing ADLs using the affected upper extremity, obtained the highest score for the motor function in the pre-evaluation. In this case, the Fugl-Meyer scale was not sensitive enough for this patient. Studies that discussed the FMA sensory function and pain absence subsections scores were not found. Therefore, there is not a parameter to proceed an integrated analysis of the different subsections of each member [54]. While Fugl-Meyer Assessment is recommended as primary outcomes in intervention trials [55-56], lack of methods for individualized and integrated analysis of the 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 P3 excitatory stimulation. Although the P3 stimulation aims to achieve the intraparietal sulcus, three different Brodmann areas could be achieved according to

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Herwig et al. [27]. These areas have distinct connections and are engaged in different circuitries, which reduces the possibility of generalization. The delimitation of the stimulation area could provide a more consistent basis for understanding and the development of new projects. However, the international 10-20 system ease of application and low cost with quality make this method a good tool for replication [27]. The greater possibility of variation of the stimulation site associated with the international 10-20 system makes this technique more suitable for large samples. The likely variation of the stimulation site limits our conclusions and the possibility of further generalizations. Our results were not uniform, as expected in a so reduced sample, and the use of the international 10-20 system may have corroborated with this variety. Lastly, lack of the third evaluation for our sham patient reduced the impact of the scores that increased from A2 to A3. Nevertheless, the hypotheses that might be drawn from our observations with these three treated chronic stroke patients might positively contribute to the rehabilitation research with the stroke patient.

5. Conclusions

In these case reports, our findings suggest that the excitatory stimulation of the P3 might increase lower and upper extremity Fugl-Meyer Assessment scores in motor and sensory functions, as well as in pain reduction in chronic stroke patients whose intraparietal sulcus and surround regions were spared in a middle cerebral artery stroke.

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Author Contributions: "R.L.S., J.H., and V.F. conceived and designed the experiments; R.L.S, A.M.C.S., F.F.S., and S.T.I performed the experiments; R.L.S. and F.F.S. analyzed the data; R.L.S., F.F.S., and V.F. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

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