

Effect of repetitive transcranial magnetic stimulation on unilateral visuospatial neglect in stroke patients

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Background: Visuospatial neglect (VSN) is a debilitating, attentional disorder that affects approximately 40–81% of patients after stroke. It interferes with the rehabilitative process and is associated with poor functional outcome. **Objective:** The aim of this study was to assess the influence of repetitive transcranial magnetic stimulation on unilateral visuospatial neglect in stroke patients. **Patients and Methods:** Thirty ischemic stroke patients from both sexes represented the sample of the study. Their age ranged from 45 to 65 years. The patients were assigned into two equal groups; control group (G1) and study group (G2). The control group treated with a designed physical therapy program and the study group treated with the same program in addition to low frequency repetitive transcranial magnetic stimulation (rTMS) over the posterior parietal cortex (PPC). The treatment was conducted three times per week, for two weeks. Line bisection and Bell cancellation tests were used to assess visuospatial neglect. Barthel index was used to assess functional activities pre and post treatment. **Results:** There was a significant improvement in scores of Line bisection and Bell cancellation tests in both groups with more favorable effect in G2 ($p < 0.05$) and a significant improvement in scores of Barthel index scale in both groups however the difference between the two groups was not significant ($p > 0.05$). **Conclusion:** Repetitive transcranial magnetic stimulation over contralesional posterior parietal cortex added to the designed physiotherapy program has a positive effect in improving visuospatial neglect in post-stroke patients.

Key Words: Repetitive transcranial magnetic stimulation, visuospatial neglect, stroke, Barthel index, Line cancellation test, Bells cancellation test.

Introduction

Visuospatial neglect (VSN) is a multicomponent syndrome in which patients fail to report, respond, or orient to information presented on the contralesional space [1]. Approximately 40–81% of patients after stroke demonstrate unilateral spatial neglect in the acute phase, and this symptom is sustained in approximately one-third of these patients [2].

It occurs with lesions in either hemisphere, but it is more severe and enduring after right hemisphere stroke [3]. It interferes with the rehabilitative process and is associated with a poor functional outcome [4].

Visual scanning, central cueing, prism adaptation, sensory stimulation, and dopaminergic and noradrenergic drugs are all used to treat VSN. However, these treatments are inadequate in terms of inducing complete

recovery in most stroke patients [5]. Therefore, more effective interventions are required to facilitate recovery.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain-stimulation procedure. It has a positive effect on emotional, cognitive, sensory and motor functions in patients with neuropsychiatric diseases. It can modify neuronal activity through plastic changes in motor cortical networks, including long term potentiation (LTP), modulation of neurotransmitters or gene induction[6].

Aim of the work

The aim of the present study was to assess the influence of repetitive transcranial magnetic stimulation on unilateral

visuospatial neglect in stroke patients.

Subjects, Instrumentations and Methods

Subjects:

Thirty ischemic stroke represented the sample of the study. The diagnosis was confirmed by MRI and/or CT scan. The patients were selected from the Outpatient Clinic of Kasr El Aini, Teaching Hospital, Cairo University and from the Out-Patient Clinic, Faculty of Physical Therapy, Cairo University. It was proved that all patients have unilateral visuospatial neglect confirmed by line bisection and bells cancellation tests.

Inclusion criteria:

Patients' age ranged from 45 to 65 years and duration of illness ranged from two weeks to three months.

Exclusion criteria:

Patients with implanted metallic devices, visual, auditory,

vestibular deficits or cognitive impairments, history of seizure, previous strokes or other neurological disorders were excluded.

Unilateral visuospatial neglect was assessed by Line bisection and Bell cancellation tests pre and post treatment for all patients. In Line bisection test; six of 20 lines of various lengths are arranged at the center, left, and right of a 21.5 cm × 28 cm sheet of A4 paper. The test is performed by placing the test sheet at the front and center of each patient. The patient was instructed to use the pencil provided to indicate the midpoint of each line. Scores are determined by measuring the distance between the actual midpoint of each line and the midpoint indicated by the patient, adding these values, and then dividing the sum by the number of lines. [7].

Regarding The Bell cancellation test 35 target stimuli (bell figures) were mixed with 280 other distractors (familiar figures such as houses, horses ...) presented on an A4 sheet of white paper. The stimuli are pseudo-randomly organized in seven columns containing five bells each. These columns are positioned in the sheet of paper as follows: three on the left side, one in the middle and three on the right side of the page. The patient was asked to circle with a pencil all the bells found without losing time. The maximum score is 35. An omission of 6 or more bells on the right or left half of the page indicates unilateral spatial neglect (USN) [8].

Barthel Index was used to measure the patient's functional activities (ADL). It consists of 10 items. The items of the index are weighted according to a scheme

developed by the authors of the Barthel index. The values assigned to each item are based on time and amount of actual physical assistance required if a patient is unable to perform the activity. [9].

The patients were assigned into two equal groups of fifteen patients each; G1 control group treated by a designed physiotherapy program for "25-30" min. the program consisted of visual scanning exercises, stretching exercises, facilitation for weak muscles, strengthening exercise, postural control and balance, functional training and gait training. G2 the study group were treated low frequency rTMS followed by the same designed physiotherapy program. The treatment was conducted three sessions per week, day after day for successive two weeks.

Stimulation technique: repetitive TMS was delivered to the scalp over the posterior parietal cortex (PPC) of the contra-lesion side using a *Magstim rapid²* machine (Magstim Company, Whitland, UK) connected with a figure-eight shaped coil. Each patient had six sessions over two weeks. The coil was held tangentially to the patient's scalp and oriented at about 45° with the axes. Position of the coil was adjusted to find the optimal scalp position (approximates to the sites of p3 or p4 of the international 10-20 system) and the location of stimulation was marked to maintain consistency among sessions. The session comprised of four trains of 300 stimuli each

delivered at one Hz with 90% of resting motor threshold. The train duration was five minutes with one minute intertrain interval for a total of 20 minutes stimulation period and 1200 pulses in each session.[14]

Statistical analysis

The obtained data were collected and statistically analyzed using the arithmetic mean and standard deviation (SD). Wilcoxon test was used for comparison within each group. Mann-Whitney U-test was used for comparison between groups. P-value was used to indicate the level of significance (P<0.05 was considered significant).[13]

RESULTS

There was no statistical significant difference ($P>0.05$) between both groups regarding baseline characteristics including age, Body mass index and pretreatment scores of Line bisection, Bell cancellation tests and Barthel index as shown in Table (1, 2).

Comparison of all variables pre and post treatment within each group revealed a significant difference in both groups ($P<0.05$) (table 3).

Also, Post-treatment comparison of all variables between both groups showed that a statistically significant decrease in Line bisection test score in study group compared to that of the control group ($P=0.01$). There was a statistically significant increase in Bell cancellation tests score in study group compared to control group ($P=0.016$). There was no significant difference between the two groups in barthel index score ($P>0.05$) (table 4).

Table 1. Age and body mass index (BMI) in both groups.

Variant	Control group (G1) Mean±SD	Studygroup (G2) Mean±SD	P-value
Age (Year)	56.20 ±6.30	57.53 ±3.35	0.476
BMI (Kg/m ²)	26.50 ±2.71	27.33 ±3.65	0.490

Table 2. Comparison mean values of Line bisection , Bell cancellation tests and Barthel index scores pretreatment in both groups.

Variant	Pre treatment		
	(G1) Mean±SD	(G2) Mean±SD	P-value
Line bisection test score	7.47 ±2.10	8.67 ±1.67	0.125
Bells cancellation test score	22.93 ±3.19	24.53 ±3.06	0.119
Barthel index score	76.00 ±9.67	75.67 ±6.23	0.596

Table 3. Comparison of mean values of Line bisection , Bell cancellation tests and Barthel index scores pre and post treatment in each group.

Variant	G1		P-value	G2		P-value
	Pre treatment (Mean±SD)	Post treatment (Mean±SD)		Pre treatment (Mean±SD)	Post treatment (Mean±SD)	
Line bisection test score	7.47 ±2.10	4.27 ±1.75	0.001*	8.67 ±1.67	2.87 ±0.99	0.0001*
Bells cancellation test score	22.93 ±3.19	27.73 ±3.05	0.001*	24.53 ±3.06	30.53 ±1.50	0.0001*
Barthel index score	76.00 ±9.67	83.33 ±8.16	0.0001*	75.67 ±6.23	83.33 ±6.72	0.0001*

*significant P < 0.05

Table 4. Comparison of mean values of Line bisection , Bell cancellation tests and Barthel index scores post treatment in both groups.

Variant	Post treatment		
	(G1) Mean±SD	(G2) Mean±SD	P-value
Line bisection test score	4.27 ±1.75	2.87 ±0.99	0.010*
Bells cancellation test score	27.73 ±3.05	30.53 ±1.50	0.016*
Barthel index score	83.33 ±8.16	83.33 ±6.72	1.00

*significant P < 0.05

DISCUSSION

The present study was conducted to investigate the influence of repetitive Transcranial Magnetic Stimulation on visuospatial neglect in stroke patients. Thirty patients participated in this study. They were randomly assigned into two equal groups' study and control groups. All the patients were evaluated before and after treatment by using Line bisection test, bells cancellation test, clock drawing test and Barthel Index scale.

The results of the present study showed significant improvement in the score of Bells cancellation test in both control and study groups with more significant improvement in the study group (GII). The higher significant improvement in (GII) may be attributed to the physiological effect of repetitive

transcranial magnetic stimulation. Low frequency (1Hz) rTMS on posterior parietal cortex PPC of the contrlesional side induces transient parietal impairment. It inhibits the pathological overactivation of the contralesional hemisphere. Post-stroke hyperactivity of the intact hemisphere was thought to lead to excessive inhibition of the damaged hemisphere, thus exacerbating attentional deficits. If hyperactivity of the intact hemisphere was reduced by rTMS, this could relieve inter-hemispheric inhibition, and thus disinhibit the damaged hemisphere, and potentially restore some function this agree with [23].

Three mechanisms have been proposed that may potentially account for recovery from unilateral

visuospatial neglect in stroke patients: perilesional reconstitution, laterality-shift, and disinhibition[24]. It can be hypothesized that low frequency rTMS on the contralesional hemisphere induces recruitment of the homotopic cortex of the contralateral hemisphere needed for attention processing and release the damaged hemisphere from the excessive inhibition previously exerted by the intact hemisphere [17].

It was reported that the presence of a nonlateralized deficit in spatial working memory affects the performance of neglect patients on cancellation tests [18]. Repetitive TMS was found to improve spatial working memory. It may potentially speed up the processes of information storage, manipulation, and updating of working memory. TMS actually has a hemodynamic effect on remote, interconnected, frontal

regions that play a crucial role in the spatial WM. It facilitates the frontoparietal network that mediates attentional allocation to visual locations and facilitates visual processing [19].

The results of the present study proved that there was significant improvement in the score of line bisection test in both groups with more significant improvement in the study group (GII). The higher significant improvement in (GII) may be attributed to the physiological effect of repetitive transcranial magnetic stimulation on enhancing the patterns of eye fixation during line bisection. It was reported that biased line bisection are due to damage to the temporo-parietal junction [20]. Repetitive TMS was found to activate the temporoparietal junction (TPJ) that is specifically involved in visual perception of items thus may improve performance in line bisection test,

this agree with **Song et al., 2009**
and Lim et al., 2010.[21,25]

To understand the mechanism of contralesional non-invasive brain stimulation on spatial neglect; **Fu et al.,(2017)** studied the application of Continuous theta-burst stimulations (cTBS) on the left posterior parietal cortex in patients with visuospatial neglect after right brain stroke. Resting-state fMRI were employed to assess resting-state functional connectivity (RSFC) changes in the attention network. They reported that visuospatial neglect (VSN) is associated with injuries in the inferior parietal lobule, superior temporal gyrus, subcortical nuclei, and ventral frontal cortex. Specifically, VSN is thought to involve damage to the dorsal attention network (DAN) and ventral attention network (VAN) located in these

frontal and temporoparietal cortices.[17]

During spatial orientation, the superior parietal lobule is thought to shift the spatial attention to relevant events, while intraparietal sulcus and the inferior parietal lobule is responsible for maintaining such attention. On the other hand, TPJ mainly participates in the coordination of attention for internal representations and external sensory stimuli. The left and right DANs, respectively, control selective spatial attention and responses to the stimulus in the contralateral space, dynamically directing attention according to previous experiences and current goals. The VAN is reported to be mainly responsible for detecting and redirecting attention from the environment to unexpected and behaviorally relevant events. In this framework, the right TPJ in the

VAN may act as a circuit breaker that interrupts ongoing activity in the DAN and shifts attention to novel information of interest. Interference with the TPJ is considered to be a primary cause of VSN.[17]

Following cTBS of the intact posterior parietal cortex in patients with unilateral VSN, reduced intra-hemispheric VAN connectivity was observed, while no RSFC changes between the bilateral DANs were detectable. The reduction in intra-hemispheric VAN RSFC may improve the functional correlation between VAN structures with other brain regions outside of VAN, leading to a relative decrease in RSFC within different VAN structures. Alternatively, it may suggest that the attention network can be modulated by changing activity of the left posterior parietal cortex. Or it might be associated with local

inhibition of the left posterior parietal cortex and its nearby structures by cTBS. Local inhibition of the left posterior parietal cortex may potentially increase cortical excitability of the homologous cortices in the contralateral right hemisphere, including TPJ and STS. [17]

The results of the present study proved that there was significant improvement in the score of clock drawing test in both groups with no significant difference between them. This improvement may be attributed to the physiological effect of exercise on brain. It increases the cerebral tissue oxygenation, blood flow velocity and cerebral metabolism and homeostasis which in turn improve the speed of information processing, motor learning, implicit memory and executive function. This result agreed with **McAuley et al., (2004)**, **Kluding et al., (2007)**,

Barbara et al., (2009) and Rand et al., (2010)[26,27,28,29]. Improvement in cognitive flexibility was proportional to the degree of exercise [42].

Exercises produce vascular changes, including an increase in oxygen saturation, promote angiogenesis, and increase cerebral blood flow (CBF) in areas related to cognitive function [30]. They increase the activity of antioxidant enzymes thus decrease oxidative stress and/or neuroinflammation. It enhances also availability of dopamine (DA) in projections to the dorsal and/or ventral striatum and enhances expression of neurotrophic factors BDNF and GDNF, which could promote plasticity for learning and memory [31]. Regular exercises trigger plasticity-related changes in the central nervous system, including synaptogenesis, enhance

glucose utilization, angiogenesis, and neurogenesis. They also increase social networks and improve psychological well-being factors thus all stimulates cognitive performance of clock drawing test [32].

The physiologic effects of functional improvements in clock drawing test and executive function following physical therapy program have primarily focused on three hypotheses. The first hypothesis suggests that exercise produces vascular changes, including an increase in oxygen saturation, promotes angiogenesis, and increases cerebral blood flow (CBF) in areas related to cognitive function[33]. The second hypothesis proposes that changes in neurotransmitters after exercise may be responsible for the behavioral changes in cognition [34]. Finally, the most prominent

hypothesis demonstrate an increase in neurotrophic factors as a result of exercise. Neurotrophins such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor, and nerve growth factor are endogenous proteins that have been described as factors that regulate the proliferation and differentiation of cells in the developing central nervous System [35].

Our results showed improvements Barthel's index score in both groups but there were no significant difference between both groups indicating that the improvement in ADL functions was attributed to physiotherapy program and that rTMS doesn't induce additional effect on ADL functions. The improvement in ADL functions may be attributed to the effect of

physical therapy program on aerobic power, muscle strength and endurance, flexibility, and body composition that have important implications for maintaining physical independence and reducing the severity of comorbidities in persons with stroke [36]. **Morey and coworkers 1998** examined the relationship between physical fitness and physical independence in 161 older men and women (mean age 72.5 yr) and concluded that exercise training to enhance physical function needed to include a combination of strength, cardiorespiratory endurance, and flexibility[37]. **Ferketich and coworkers 1998** developed a fitness training program for older women (60–75 yr) and found that strength and endurance

training was important for improving physical independence[39]. **Cress et al. 1999** developed a fitness training program for older adults (70 yr) and noted that improvements in maximal oxygen consumption and muscle strength resulted in greater gains in physical functioning and physical independence[38].

It increases the patients' awareness of their hemiplegic field, and promote patients to respond with repetitive movements when primed, leading to a better interhemispheric symmetry that would reduce unilateral neglect over their contralesional field, and improve hemiplegic arm motor performance[40].

Unilateral neglect is a multifactorial syndrome that

has two common manifestations. The first is spatial representation, which is the ability to form a whole representation of space, and usually extinction is said to co-exist when patients respond accurately to unilateral stimulation of the contralesional side, but consistently ignore bilateral simultaneous stimulation.[41]. The second aspect of neglect is motor exploration, whereby patients conduct visual searches or oculomotor scanning with a covert bias to the ipsilesional side.

Extinction caused by neglect of the left side of the body results in under or nonuse of the hemiplegic upper extremity, which decreases the general activation of the perceptual motor attentional circuits in the damaged hemisphere[40].Patients

with neglect have lower Barthel Index scores than patients without neglect, and neglect is a major predictor of functional outcome from admission to follow up in inpatients with left hemiplegic stroke [16]

The results of the present study didn't go with with the finding of **Cazzoli et al. (2012)** who reported that repeated application of continuous theta burst stimulation (cTBS) improves the spontaneous everyday behaviour and reduces disability during the activities of daily living (ADL) in patients with spatial neglect. The discrepancy between the two studies may be attributed to difference in type of stimulation. **Cazzoli et al.,(2012)** used the Catherine Bergego Scale during application of cTBS. The scale measures only the presence and severity of spatial neglect in

ADL while in the present study, we used Bathel index that measures different aspects of ADL before and after the two weeks of treatment program[15]

Conclusion

Low frequency repetitive transcranial magnetic stimulation **rTMS** over contralesional posterior parietal cortex has a positive effect in improving visuospatial neglect in post-stroke patients.

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Conflicts of interest

There are no conflicts of interest.

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تأثير التحفيز المغناطيسي المتكرر عبر الجمجمة على الإهمال البصري المكاني في المرضى الذين يعانون من السكتة الدماغية الحادة / محمد احمد زكي عراقي . أ.د. مشيرة حسن درويش ، استاذ العلاج الطبيعي لأمراض الجهاز العصبي الحركي وجراحتها كلية العلاج الطبيعي جامعة القاهرة . أ.د. محمد سليمان الطماوي أستاذ الامراض العصبية ، كلية الطب جامعة القاهرة . أ.م. د. مي بشير أستاذ مساعد بقسم الفسيولوجيا العصبية ، كلية الطب، جامعة القاهرة؛ رسالة ماجستير، العلاج الطبيعي لأمراض الجهاز العصبي الحركي وجراحتها، 2018

الخلفية: الإهمال البصري المكاني هو اضطراب الانتباه الذي يؤثر على ما يقرب من 40-81% من المرضى بعد السكتة الدماغية. وهو يتداخل مع عملية إعادة التأهيل ويرتبط بنتيجة وظيفية ضعيفة. **الهدف:** كان الهدف من هذه الدراسة تقييم تأثير التحفيز المغناطيسي عبر الجمجمة المتكرر على الإهمال البصري المكاني من جانب واحد في مرضى السكتة الدماغية. المرضى و **الطرق المتبعة في البحث :** ثلاثون مرضى السكتة الدماغية من كلا الجنسين يمثلون عينة الدراسة. وتتراوح أعمارهم بين 45 و 65 عاما. تم تقسيم المرضى إلى مجموعتين متساويتين. مجموعة الضابطة(ج2)التي عالجها برنامج العلاج الطبيعي المصمم ومجموعة الدراسة(ج1) تعاملت من قبل نفس البرنامج بالإضافة إلى التحفيز المغناطيسي المتكرر المنخفض التردد على الفترة المخية الخلفية . تم إجراء العلاج ثلاث مرات في الأسبوع، لمدة أسبوعين. تم استخدام اختبار تنصيف الخط و اختبارات إلغاء الاجراس لتقييم الإهمال البصري المكاني. وقد استخدم مؤشر بارثيل لتقييم الأنشطة الوظيفية قبل وبعد العلاج. **لنتائج:** كان هناك تحسن ذو دلالة احصائية في درجات تنصيف الخط واختبارات إلغاء الاجر اس في كلا المجموعتين مع تأثير أكثر دلالة احصائية فيوتحسن كبير في درجة مقياس مؤشر بارثل في المجموعتين مع وجود فرق غير ذو دلالة احصائية بينهم. **الاستنتاج:** التحفيز المغناطيسي المتكرر عبر الجمجمة على الفترة الخلفية للفص الجداري مضافا إلى برنامج العلاج الطبيعي المصمم له تأثير إيجابي في تحسين الإهمال البصري المكاني في مرضى ما بعد السكتة الدماغية.

الكلمات الرئيسية: التحفيز المغناطيسي المتكرر عبر الجمجمة، الإهمال البصري المكاني، السكتة الدماغية