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CASE REPORT

LONG-TERM EFFECT OF LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER THE UNAFFECTED POSTERIOR PARIETAL CORTEX IN PATIENTS WITH UNILATERAL SPATIAL NEGLECT*

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Objective: **To explore long-term effects on unilateral spatial neglect of low-frequency repetitive transcranial magnetic stimulation (rTMS) over the unaffected posterior parietal cortex.**
Design: **Uncontrolled pilot study.**
Subjects: **Two chronic-phase patients with left-sided unilateral spatial neglect from cerebral infarction.**
Methods: **Six rTMS sessions were undertaken for 2 weeks. Each session included 900 stimuli applied over P5 at an intensity of 95% motor thresholds and a frequency of 0.9 Hz. The Behavioural Inattention Test, either the Mini-Mental State Examination or the Revised Hasegawa Dementia Scale, Brunnstrom Recovery Stage, and Barthel Index were evaluated at 2-week intervals until 6 weeks after rTMS sessions. Single-photon emission computed tomography was performed 2 weeks before and after rTMS.**
Results: **Behavioural Inattention Test scores improved remarkably, especially from 2 to 4 weeks after rTMS sessions. At 6 weeks, Behavioural Inattention Test scores still remained above pre-rTMS levels. Other clinical evaluations as well as single-photon emission computed tomography showed no significant change during the study.**
Conclusion: **In this small pilot study, low-frequency rTMS over the unaffected posterior parietal cortex decreased unilateral spatial neglect for at least 6 weeks.**

Key words: stroke, repetitive transcranial magnetic stimulation, unilateral spatial neglect, Behavioural Inattention Test.

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS), a new therapy that affects cortical excitability in a manner depending on stimulation frequency, has been applied to many disorders in psychiatry and neurology. Because low-frequency rTMS reduces excitability in directly stimulated sites as well as in other functionally connected areas (1), stimulation at such frequencies might be expected to improve unilateral spatial neglect (USN) according to the attention-shifting model (2) by correcting the relative hyperactivity of the unaffected hemisphere. In previous studies rTMS was applied over the parietal lobe, the lesion site known to be responsible for USN in healthy subjects (3, 4) and in patients with stroke (4–6). Brighina et al. (5) reported that left USN in 3 patients with stroke was ameliorated by 7 sessions of 1 Hz subthreshold rTMS over the left posterior parietal cortex (P5). Although they found improvement to be limited until 2 weeks after the rTMS sessions, duration of effect to exceed 2 weeks remained unclear. In addition, they reported changes in USN in terms of 3 visuospatial tasks, but without using standardized instruments such as the Behavioural Inattention Test (BIT) or other cognitive functions.

In this study we explored the long-term effects of low-frequency rTMS over the left posterior parietal cortex in 2 chronic-phase stroke patients with left USN, using well-accepted clinical evaluations including the BIT.

METHODS

Patients

We obtained ethics committee approval at our university hospital for the protocol prior to the study. The 2 patients examined, both right-handed, gave their informed consent for the procedures. Both had right-sided brain damage from cardiogenic brain embolism about 6 months before rTMS (clinical and demographic details are given in Table I). At the beginning of the rTMS study, both patients had severe left hemiparesis and left USN, which was confirmed by the BIT. Left homonymous hemianopsia was demonstrable by ophthalmological examination only in patient B. During the study both patients also underwent physical and occupational therapy 5 times a week without special adaptations or treatment for USN. Both took the same medications.

Procedures

Patients were seated in a comfortable chair in a quiet room with their arms fully supported. The rTMS sessions were carried out on Monday, Wednesday, and Friday for 2 weeks (total, 6 sessions) with biphasic pulses given by a magnetic stimulator (Magstim Rapid System 1000/50,

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Table I. *Clinical and demographic details of 2 patients with stroke with unilateral spatial neglect. The days given within parenthesis are based on the stroke onset which is set to 0*

	Patient A	Patient B
Age, Sex	59 years, male	61 years, female
Stroke type	Cardiogenic brain embolism (right ICA)	Cardiogenic brain embolism (right MCA)
Damaged lesions	Right frontotemporal lesion	Right temporoparietal lesion Left MCA-PCA "watershed" lesion (old, asymptomatic)
Surgical treatments	Internal-external decompression (Day 1), cranioplasty (Day 31)	Internal-external decompression (Day 1), cranioplasty (Day 32)
Co-morbidity	Atrial fibrillation	Atrial fibrillation, hypertension, hyperlipidaemia
First rTMS session	Day 186	Day 175
Clinical evaluations	BIT-C 68, BIT-B 24, HDS-R 21, BRS I/I/I, BI 35	BIT-C 35, BIT-B 7, MMSE 23, BRS I/I/II, BI 40, left homonymous hemianopsia

ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; BIT-C = conventional subtests of the Behavioural Inattention Test; BIT-B = behavioural subtests of the Behavioural Inattention Test; HDS-R = Revised Hasegawa Dementia Scale; MMSE = Mini-Mental State Examination; BRS = Brunnstrom Recovery Stage proximal upper extremity/distal upper extremity/lower extremity; BI = Barthel Index.

Magstim, Wales, UK) via a standard figure-8-shaped coil. The outer diameter of each half-coil was 10 cm. Each session consisted of 900 stimuli at a frequency of 0.9 Hz and an intensity of 95% of the motor threshold obtained at the first session. The motor threshold was defined as the intensity at which motor evoked potentials (MEPs) from the right abductor pollicis brevis (APB) muscle larger than 0.05 mV were evoked in at least 5 of 10 trials with the patient at rest. Stimuli were applied over P5, designated according to the international 10/20 Systems. For monitoring of safety, the electroencephalogram (EEG) from C4 with reference to the right earlobe and MEPs from the left APB were recorded during each session.

Evaluations

We used the Japanese edition of the BIT, in which the conventional (BIT-C) and the behavioural (BIT-B) subtests had cut-off scores of 131/146 and 68/81, respectively. Other clinical evaluation instruments used included either the Mini-Mental State Examination (MMSE) or the Revised Hasegawa Dementia Scale (HDS-R); Brunnstrom Recovery Stage (BRS); and the Barthel Index (BI). These clinical evaluations were carried out at 6 time points: 2 weeks before (time 1), the day before the first rTMS session (time 2), the next day (time 3), 2 weeks after (time 4), 4 weeks after (time 5) and 6 weeks after the last rTMS sessions (time 6). Single-photon emission computed tomography (SPECT, ^{123}I-Iomazenil) was performed at times 1 and 4.

RESULTS

Both patients completed the rTMS sessions without adverse symptoms and did not show either epileptiform afterdischarges in the EEG or MEPs from the left APB. BIT scores are shown in Fig. 1. Their BIT scores improved significantly after the rTMS sessions, with peak scores at time 4 in patient A (BIT-C 100, BIT-B 38) and at time 5 in patient B (BIT-C 83, BIT-B 35). In addition, at time 6 BIT scores remained higher than those before the rTMS sessions for both patients.

Other clinical evaluations showed no changes in Brunnström Recovery Stage (BRS) or slight change in global cognitive functions (1 point in patient A, 2 points in patient B) during the study. Although BI scores did not change, activities of daily living (ADL) related to USN improved after rTMS sessions in both patients, the best ADL were noted at time 4 in patient A and at time 5 in patient B. For example, difficulty in directing a wheelchair and in transfers between bed and wheelchair decreased. SPECT showed no significant change in cerebral blood flows in either patients between the 2 time points examined.

DISCUSSION

Our results in both patients showed that 0.9 Hz rTMS over the unaffected posterior parietal cortex improved USN according to the BIT. Peak BIT scores were noted at 2 weeks or more after the sessions, and those at 6 weeks still remained better than those at baseline. No significant change in other clinical evaluations was noted during the study.

As for duration of effect of low-frequency rTMS, additive efficacy has been suggested by study of higher numbers of stimulation sessions over several days (1). One session of rTMS induced effects lasting for 15–30 minutes in healthy subjects and for a maximum of 1 week in patients with post-traumatic stress disorder (PTSD) (1). Some studies showed that several daily stimulations with low-frequency rTMS could have affected epilepsy, auditory hallucinations and PTSD for 4–8 weeks (1). Similarly, we found that maximum effects from 6 rTMS sessions over 2 weeks were obtained after 2 weeks or more. The effects persisted in patients with chronic-phase stroke for at least 6 weeks according to the BIT. A possibility, however, existed that rTMS activating a relatively large area could have altered impairments other than USN that affected BIT scores, such as alertness, other forms of inattention, or visuoconstructional and memory deficits. In this study, however, rTMS did not appear to affect global cognitive functions based upon the MMSE or HDS-R.

A difference was noted between patients A and B in that the peak scores appeared later in patient B than in patient A, possibly because of left homonymous hemianopsia in patient B. When left USN and homonymous hemianopsia coexist in patients, more severe left-sided inattention is likely (7). Zihl (8) reported that 60% of their patients with homonymous hemianopsia had impaired visual scanning behaviour.

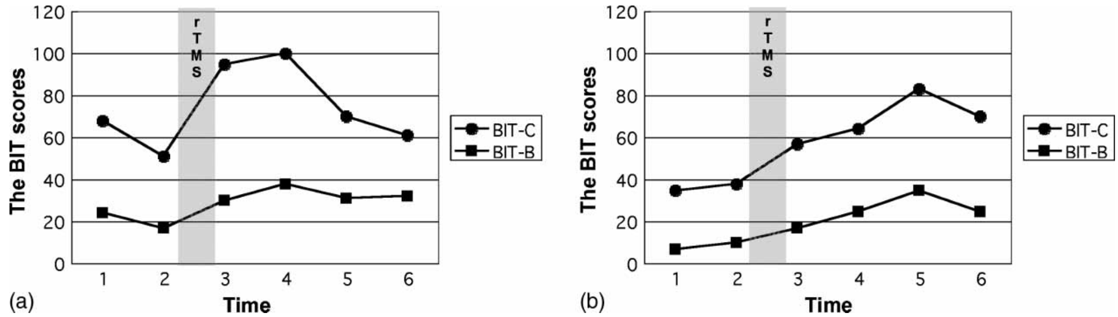

Fig. 1. The Behavioural Inattention Test (BIT) was examined at 6 time points: 2 weeks before (time 1), the day before the first rTMS session (time 2), the next day (time 3), 2 weeks after (time 4), 4 weeks after (time 5) and 6 weeks after the last rTMS sessions (time 6). The time-point marker “rTMS” corresponds to rTMS sessions. BIT-C = conventional subtests of the Behavioural Inattention Test; BIT-B = behavioural subtests of the Behavioural Inattention Test. (a) Time course of BIT scores in patient A. Peak scores for BIT-B and BIT-C were obtained at time 4. (b) Time course of BIT scores in Patient B. Peak scores for BIT-B and BIT-C were obtained at time 5.

Additional attention toward the left side induced by rTMS might have resulted from both less left USN and better visual scanning behaviour despite left homonymous hemianopsia in patient B.

In carrying out ADL, both patients required less assistance after the rTMS sessions, and their improvements appeared to be compatible with changes in the BIT scores. Because the improved ADL were related to spatial attention (9), decreased USN might well have induced the improvements. However, BI scores did not change, probably because of limited sensitivity of this index. More sensitive evaluations such as the Functional Independence Measure (FIM™) or the Catherine Berbego Scale (9) might have shown improved scores.

This investigation has obvious limitations characteristic of many pilot studies, such as the small number of subjects, no comparison with sham stimulation, and the possibility of observer bias. In the future, rTMS will need more extensive and better-controlled evaluations in USN, including determinations of optimal timing in stroke rehabilitation treatments.

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