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Therapeutic effect of repetitive transcranial magnetic stimulation on motor function in Parkinson's disease patients

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Cortical excitability of the primary motor cortex is altered in patients with Parkinson's disease (PD). Therefore, modulation of cortical excitability by high frequency repetitive transcranial magnetic stimulation (rTMS) of the motor cortex might result in beneficial effects on motor functions in PD. The present study aims to evaluate the effect of rTMS of the motor cortex on motor functions in patients with PD. Thirty-six unmedicated PD patients were included consecutively in this study. The patients were assigned in a randomized pattern to one of two groups, one group receiving real-rTMS (suprathreshold 5-Hz, 2000 pulses once a day for 10 consecutive days) and the second group receiving sham-rTMS using closed envelopes. Total motor section of Unified Parkinson's Disease Rating Scale (UPDRS), walking speed, and self-assessment scale were performed for each patient before rTMS and after the first, fifth, 10th sessions, and then after 1 month. Evaluation of these measures was performed blindly without knowing the type of rTMS. ANOVA for repeated measurements revealed a significant time effect for the total motor UPDRS, walking speed and self-assessment scale during the course of the study in the group of patients receiving real-rTMS ($P = 0.0001$, 0.001, and 0.002), while no significant changes were observed in the group receiving sham-rTMS except in self-assessment scale ($P = 0.019$). A 10-day course of real-rTMS resulted in statistically significant long-term improvement of the motor functions in comparison with the sham-rTMS. The rTMS could have a therapeutic role of for PD patients.

Introduction

The primary pathology of Parkinson's disease (PD) is located in basal ganglia (Albin *et al*., 1989; DeLong, 1990). However transcranial magnetic stimulation (TMS) studies have demonstrated altered excitability of the motor cortex in PD. Studies using electrical and magnetic stimulation techniques have shown that the corticomotoneurone connection is normal in PD (Dick *et al*., 1984). This means that bradykinesia is not primarily the result of any deficit in the final output pathways of the motor areas of the cortex. Most authors reported that the motor cortex of patients with PD has the same threshold for stimulation as in healthy subjects (Priori *et al*., 1994; Ridding *et al*., 1995). However, when the patients are tested at rest, the slope of the input–output relationship between stimulus intensity and response size is steeper than normal. Perhaps as a result of this, voluntary contraction facilitates responsed less than for normal subjects (Valls-Sole *et al*., 1994). Although this could be the result of a primary basal ganglia deficit, it seems probable that it could also be an attempt to compensate for the slow recruitment of commands to move by making it easier to recruit activity from a resting state (Berardelli *et al*., 2001). There are also changes in the excitability of cortical inhibitory circuits. A suprathreshold stimulus given whilst the subject makes a tonic voluntary contraction evokes a muscle twitch followed by a post-excitatory silent period (SP). The disappearance of voluntary activity during the period of silence is thought to be because of activation of the cortical GABAergic inhibitory systems that suppress motor cortical output for 100–200 ms (Fuhr *et al*., 1991). The silent period is shorter in bradykinesia patients (Cantello *et al*., 1991; Priori *et al*., 1994) and is normalized by treatment with L-dopa (Priori *et al*., 1994). Cortical inhibition can also be tested in subjects at rest using the double-pulse paradigm of Kujirai and colleagues (Kujirai *et al*., 1993). Again, in patients the amount of inhibition is smaller than normal (Ridding *et al*., 1995). With long interstimulus intervals and larger conditioning and test stimuli, a different type of abnormality is found. This suggests that patients with PD have

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reduced facilitation during voluntary muscle activation. It may be that these effects on inhibition and excitation reflexes reduced facilitatory input to the cortical excitatory and inhibitory circuits from basal ganglia. Both could affect the speed of recruitment of cortical motor output in bradykinesia (Berardelli *et al*., 2001). Repetitive transcranial magnetic stimulation is able to modulate the corticospinal excitability and the effects appear to last beyond the duration of the rTMS itself (Maeda *et al*., 2000). Mally and Stone (1999) found beneficial results of rTMS trails in PD but they did not use a control group. Siebner *et al*. (1999, 2000 found that real but not sham, rTMS was associated with beneficial effect on motor functions. However, Ghabra *et al*. (1999) and Tergau *et al*. (1999) failed to find any beneficial effect. Because the paucity and variability of data on this topic, the aim of the present study was to study the cumulative and lasting effects of rTMS of the motor cortex on motor functions in a group of unmedicated patients with PD.

Material and methods

Thirty-six patients diagnosed as PD were included consecutively in this study. They attended the Department of Neurology (Assiut University Hospital, Assiut, Egypt), during the period from January 2001 through March 2002 and were asked to participate in this study. All patients fulfilled the UK Parkinson's disease Brain Bank Criteria for idiopathic PD (Hughes *et al*., 1992). No patients with magnetic devices or any other implanted device or patients with a history of seizure were encountered. Twenty-three patients were males and 13 were females. All patients receive no antiparkinsonism medication for at least 1 month before the start of the study (16 were newly diagnosed and 20 patients were under irregular treatment). The mean age (SD) was 57.65 ± 8.7 years and the mean duration of illness was 3.26 ± 2.8 years. Body bradykinesia was a prominent feature in all patients (three patients were akinetic), while rigidity was observed in 30 patients, and tremors in 24 patients. Postural instability was manifested in 12 patients, and asymmetrical onset was recorded in 26 patients with no significant differences between both groups (Table 1). All patients had mild to moderate severity of symptoms (stages II and III, Hoehn and Yahr, 1967). All patients provided fully informed consent. The local Ethical Committee approved the experimental protocol.

All patients submitted to the following assessments.

Unified Parkinson's Disease Rating Scale

Motor functions were investigated according to the motor section of Unified Parkinson's Disease Rating Scale (UPDRS), which is a rating tool to follow the longitudinal course of the disease. The motor section of the scale contains 14 items (speech, facial expression, tremor at rest, action tremor, rigidity, finger taps, hand movements, hand pronation-supination, leg agility, rising from a chair, posture, gait, postural stability, and body bradykinesia), each ranked from 0 (normal), 1 (mildly impaired), 2 (moderately impaired), 3 (severely impaired) to 4 (can barely perform the task).

Table 1 Demographic and clinical data of the studied groups

	Total numbers ($n = 36$)	Group 1 ($n = 19$)	Group 2 ($n = 17$)	
		Real-rTMS	Sham-rTMS	*P*-value
Age (years)	57.6 ± 8.9	57.8 ± 9.2	57.5 ± 8.4	NS
Mean ± SD (range)	(36–75)	(36–70)	(40–75)	
Sex				
Male/female	24/12	14/5	10/7	NS
Duration of illness (years)	3.45 ± 2.3	3.05 ± 2.1	3.6 ± 2.4	NS
Clinical Features (number, %)				NS
Bradykinesia	36 (100%)	19 (100%)	14 (82.4%)	
Rigidity	34 (94.4%)	19 (100%)	15 (88.2%)	
Tremors	28 (77.8%)	13 (86.4%)	15 (88.2%)	
Postural instability	15 (41.7%)	9 (47.4%)	6 (35.3%)	
Asymmetric onset	29 (80.6%)	15 (78.9%)	14 (82.4%)	
Total motor section of UPDRS (mean ± SD)	26.76 ± 8.3	29.5 ± 9.3	24.18 ± 7.82	NS
Walking speed (mean ± SD)	81.75 ± 54.2	83.83 ± 52.2	79.88 ± 60.6	NS
Self-assessment score (mean ± SD) (seconds)		20.1 ± 3.45	19.8 ± 3.64	NS

Walking speed

The patients were requested to rise from a chair, walk, but not run, as fast as possible for a distance of 25 m, turn around, walk back, and sit down again. This procedure was repeated three times. The time (seconds) to complete the task (walking time) in the three trials was measured separately and then averaged.

Self-assessment scale

Each patient was requested to evaluate the following nine parameters in a questionnaire (similar to the protocol used by Tergau *et al*. (1999): total body mobility, hand agility, walking, arising from chair, tremors, mood, concentration, sleep and dreaming. Each of these nine items was scored from 1 (best), 2 (no change) and 3 (worst), and the patients were asked to judge the past 24 h.

Patients were assigned in a randomized pattern to one of the two groups, a group which received real-rTMS and one which received sham-rTMS by using closed envelops.

Repetitive transcranial magnetic stimulation

During the session, the patients were seated comfortably in a reclining chair, rTMS was delivered through a figure-eight coil (the outer diameter of each wing is 9 cm, the maximum field strength = 1.5 tesla) attached to a MagLite stimulator (Dantec Medical, Skovelund, Denmark) set to Keypoint recording equipment (Dantec Medical). The motor evoked potential (MEP) threshold in the resting abductor digiti minimi (ADM) muscle was determined using a single TMS pulse. An electromyogram was recorded from ADM in the primary motor area located by moving the coil until maximal amplitude motor evoked potentials were produced. Once the optimal position was located, the motor threshold was determined. Motor threshold of the hand was determined by delivering single TMS over the optimal position and by reducing the stimulus intensity in steps of 1% stimulator output. The resting motor threshold was defined as the lowest TMS intensity capable of eliciting a small MEP (usually 50 μV) while the investigated muscle was at rest. The optimal extensor digitorum brevis (EDB) motor representation were also determined by the same procedure.

Real-rTMS was applied with the center of the coil placed over the optimal position for lower limbs (EDB) for the first 1000 pulses and then the coil was moved over the optimal position for the hand (right then left hemispheres), 500 pulses were applied for each hemisphere. Stimulus intensity was always set to 120% of motor threshold for the hand only because lower limb motor threshold is high and out of safety guidelines for rTMS. We used a figure-eight coil with a large diameter. It allows for focal stimulation and good penetration into the depth of the interhemispheric fissure for activation of the leg (Dvorak *et al*., 1991). In each session 1000×2 pulses of 5 Hz were continuously delivered, each with the handle of the coil pointing occipitally. The sham rTMS was applied in the same conditions with the coil elevated and angled away from the head to reproduce the subjective sensation of rTMS but to avoid induction of current in the brain. During rTMS, all patients wore earplugs in order to protect the ears from the acoustic artifact associated with the discharge of the stimulation coil. Sessions were administered once per day for 10 consecutive days, follow-up of the patients was done using the same previous scales 1 h after the first, fifth, and 10th session, and after 1 month from the last session.

Evaluation of these measures was performed blindly without knowing the type of rTMS.

Data analysis

Before, after the first, fifth, 10th rTMS, and after 1 month from the last session, disability was assessed using the motor section of UPDRS, walking speed, and self-assessment scales for each group. At the base line assessment (i.e. before 5 Hz rTMS), the mean values of different disability scales (UPDRS, walking speed, and self-assessment scale) between both groups were compared using Student's *t*-test for independent samples. Mean ± SD values were used to represent data. The level of significance was set at $P < 0.05$. The correlation coefficient was calculated for UPDRS and age, duration of illness, walking speed, and self-assessment scale.

ANOVA for repeated measurements analysis for variance was used for statistical analysis. Conditional on a significant ANOVA, a *post hoc t*-test for paired sample was performed. ANOVA with the stimulation condition as the main factor was used to compare the differential effect of the rTMS conditions (real-rTMS versus sham-rTMS) on changes of disability (i.e. changes in UPDRS, walking speed, and self-assessment).

Results

Thirty-six patients (19 patients received real rTMS, and 17 patients received sham rTMS) completed the 10 sessions of stimulation. However, 16 patients under real rTMS and 15 patients under sham rTMS completed the follow-up after 1 month of the last session. At the base line assessment (i.e. before 5 Hz rTMS), there were no

Table 2 Sequential assessment of UPDRS, reaction time, walking speed and self-assessment scale in both groups

Parameters	Baseline assessment	After the first session	After the fifth session	After the 10th session	Follow-up after 1 month
UPDRS					
Real-rTMS	29.5 ± 9.3	26.95 ± 7.9*	19.95 ± 7.2***	14.8 ± 7.9***	15.6 ± 6.5***
Sham-rTMS	24.5 ± 7.8	23.8 ± 7.9	24.05 ± 8.3	24.06 ± 8.0	23.7 ± 7.6
Walking speed (seconds)					
Real-rTMS	83.8 ± 52.2	82.8 ± 61.6*	73.9 ± 61.8**	70.7 ± 63.03***	71.7 ± 53.03***
Sham-rTMS	79.88 ± 60.6	77.9 ± 54.3	75.5 ± 52.3	77.7 ± 65.9	77.5 ± 53.1
Self-assessment					
Real-rTMS	20.1 ± 3.5	19.45 ± 3.4*	15.65 ± 3.7***	13.35 ± 3.8***	14.45 ± 3.5***
Sham-rTMS	19.8 ± 3.6	19.76 ± 3.6	18.88 ± 3.4*	17.65 ± 3.8**	18.56 ± 3.2*

*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$. The significant versus baseline assessment using paired t-test.

significant differences between the two groups in mean values of different disability scales (UPDRS, walking speed, and self-assessment scale) using Student's t-test for independent samples. There was a significant direct correlation between the total score of the motor section of UPDRS with age, duration of illness, self-assessment, and walking speed ($r = 0.366$; $P = 0.03$, $r = 0.406$; $P = 0.01$, $r = 0.587$; $r = 0.471$, $P = 0.004$), respectively.

Patients under real-rTMS

ANOVA for repeated measurements revealed a significant time effect on the total motor UPDRS scores, walking speed and selfassessment scores during the course of the study ($P = 0.0001$, 0.001, and 0.002, respectively). A *post hoc* t-test for paired samples demonstrated significant improvement for UPDRS score (29.5 ± 9.3 before real rTMS, 26.95 ± 7.9, 19.95 ± 7.2, 14.8 ± 7.9, and 15.6 ± 6.5 after the first, fifth, 10th sessions and after 1 month respectively, ($P < 0.05$, 0.001, 0.001, and 0.001). No significant changes were detected between the last session and after 1 month follow-up (15.6 ± 6.5) ($P = 0.679$). The same results were observed in walking speed and self-assessment scores as illustrated in Table 2. The sub-items of the self-assessment scale in the group under real rTMS, total body mobility, hand agility, walking, rising from a chair as well as mood and sleep showed significant improvement using repeated measurement analysis. There were no significant changes observed in tremors, concentration, or in dreams.

Patients under sham-rTMS

Repeated measurements of patients under sham rTMS was not associated with reduction in the total motor UPDRS scores or walking speed ($P = 0.806$ and 0.238, respectively). However, there was a significant reduction of the self-assessment score ($P = 0.019$). ANOVA demonstrated that there was a differential effect of the rTMS condition on UPDRS, walking speed, and self-assessment score ($P = 0.0001$, 0.001, and 0.003, respectively), revealing greater decrease in all scales after r-TMS as compared with the sham rTMS.

No side effects were recorded in any of the studied patients.

Discussion

The major finding of the present study is the lasting improvement in motor performance in PD patients under real-rTMS, whereas a randomly applied sham-rTMS induced no change in motor performance. This clinical improvement after 5 Hz rTMS over the motor area (hand and leg area) confirms a previous study reported in abstract form of Pascual-Leone *et al.* (1995). Moreover, our data is in accordance with the result of previous studies (Siebner *et al.*, 1999, 2000). Mally and Stone (1999) found beneficial results of rTMS trials (1 Hz) on motor performance of PD patients but there was no control and the clinical features of the patients were not reported in much detail (Cantello *et al.*, 2002). Others (Sommer *et al.*, 1998; Siebner *et al.*, 1999, 2000) have shown potentially beneficial effects after rTMS on some movement parameters in PD patients. Siebner *et al.* (1999) studied the effect of real and sham 5 Hz rTMS only on a small number of patients (12 patients) on two separate days. They found a significant decrease in total movement time without affecting the end point accuracy in real rTMS compared with sham rTMS. The same group subsequently (2000) reported the benefit that the same stimulus protocol exerted on the items of UPDRS assessed in 10 unmedicated PD patients. However, a study of 11 PD failed to reproduce this finding

(Ghabra *et al*., 1999). Negative results also came from the work of Tergau *et al*. (1999) that studied seven patients before and after exposition to 500 stimuli delivered at four different frequencies (1–20 Hz) in separate experimental sessions. No sham stimulation was adopted. Tergau *et al*. (1999) explained their negative findings with four possibilities; the first was that they tested motor function after but not during rTMS, the second possibility, that they tested their patients during the on-phase. The third possibility included the shortness of rTMS treatment (4 days) and the low stimulation intensity (90% of MEP threshold) used. Mally and Stone (1999) had shown that localized microelectroshock-induced TMS caused a dose-dependent improvement in certain symptoms of PD. The fourth possibility was that they used a non-focal stimulating coil and it is therefore possible that in addition to the motor cortices other brain areas were activated. TMS of the supplementary motor area disturbed rather than improved motor function in PD (Cunnington *et al*., 1996).

The improvements in the present study could be attributed largely to dopamine release. This is supported by an experimental study in which rTMS lead to increased release of dopamine in the striatum and frontal cortex (Ben-Shachar *et al*., 1997). Strafella *et al*. (2001) showed that rTMS of the prefrontal cortex induces the release of endogenous dopamine in the ipsilateral caudate nucleus as detected by positron emission tomography in healthy human subjects. The rTMS-induced release of dopamine in the caudate nucleus could be a consequence of direct stimulation of the corticostriatal axons (Rothwell, 1997). GABA is the dominant inhibitory neurotransmitter of the motor cortex. Berardelli *et al*. (1999) recorded an increase in the duration of the TMS-evoked SP during a 20-pulse train of suprathreshold rTMS in healthy volunteers as well as in PD patients. Siebner *et al*. (2000) recorded an increase in the duration of the TMS-evoked SP in PD after 15 trains of 5-Hz rTMS over the hand area. This means that 5-Hz rTMS is capable of inducing short-term change in the excitability of intracortical inhibitory circuitry in PD patients. As dopamenergic drugs result in a similar modulation of the SP, the facilitatory effect of 5-Hz rTMS on intracortical inhibition might be a candidate mechanism that mediates the beneficial effect of 5-Hz rTMS of primary motor area in PD patients.

Electroconvulsive therapy (ECT) was given to 16 non-depressed non-demented patients with advanced PD. In all the patients an antiparkinsonian effect was seen, lasting for 18 months in one patient, 3–5 months in seven patients, and a few days to 4 weeks in eight patients (Mally and Stone, 1999). After ECT the levels of homovanillic acid and neuropeptide Y in cerebrospinal fluid were significantly increased (Fall *et al*., 1995). Friedman and Gordon (1992), Aarsland *et al*. (1997), and Avila *et al*. (1997) recorded the same results. Mally and Stone (1999) stressed the well-known affinities between PD and depressive syndromes, both sharing a similar biochemical substrate, responsive to electroconvulsive therapy and TMS. However, ECT is not practical because it requires general anesthesia and has many side effects like post-ECT confusion, amnesia and others. Improvement was observed in the present study not only in motor functions but also in mood and sleep as evaluated by the self-assessment scale. The improvement observed here on the self-assessment scale in the group under sham rTMS could be explained by the placebo effect. In summary, the data of the present study support a possible therapeutic effect of real-rTMS in PD compared with sham-rTMS.

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