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

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Introduction

- Cortical excitability of the primary motor cortex is altered in patients with Parkinson’s disease (PD). Therefore, modulation of cortical excitability by high frequency rTMS of the motor cortex might result in beneficial effects on motor functions in PD.

Aim of the work

- 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

- 36 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.

- No patients with magnetic devices or any other implanted device or patients with a history of seizure were encountered.
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 not significant differences between both groups (Table 1).

All patients submitted to the following assessments.

- Unified Parkinson’s Disease Rating Scale

- 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.

- Self-assessment scale

- 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

- Resting motor threshold of abductor digiti minimi (ADM) muscle was determined using a single TMS pulse.

- 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 maximum output.
In each session 1000 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.

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.

**Results**

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 significant differences between groups in any rating scales.
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.
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-Shacharet 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).
In the present study, we had the opportunity to measure the serum dopamine concentration before and after six sessions of 25 Hz rTMS over motor cortex in 20 of the patients that we reported previously.

We could therefore correlate the results with patients' clinical scores at the same time points.

- We selected patients who had been receiving no or irregular dopaminergic medication to avoid any interaction of rTMS effects with that of medication history. Patients under regular treatment were excluded. None of the patients had received antiparkinsonism medication for at least 1 week before the start of the study.

- All patients had moderate to severe symptoms (Hoehn & Yahr stage III–V 1967) of PD.

- None of the patients had rTMS before. All patients provided fully informed consent. The local Ethical Committee had approved the experimental protocol.
Assessment of Patients

All patients were assessed with the following: Unified Parkinson’s Disease Rating Scale (UPDRS): motor function was investigated according to the motor section of UPDRS, which contains 14 items. Enzyme immunoassay for the quantitative determination of dopamine in plasma.

Sample collection and storage:

Two EDTA plasma samples are collected for each patient for the assay. The first sample was taken before the first session of rTMS and the second sample was taken 1 to 2 hours after the last session.

There was significant improvement in UPDRS and increases in serum dopamine after six rTMS sessions (paired t-test, P 0.001 and 0.01 respectively).
Figure 1 shows that there were significant negative linear correlations (nonparametric Spearman’s correlation) between individual patient’s UPDRS and serum dopamine level before ($r = 0.502, P = 0.02$).

Figure 1 shows that there were significant negative linear correlations (nonparametric Spearman’s correlation) between individual patient’s UPDRS and serum dopamine level after six sessions ($r = 0.508, P = 0.09$).
Here, we show that this improvement was paralleled by an increase in plasma levels of dopamine and that these levels correlated with clinical status before and after treatment. Although we only measured dopamine in plasma, it seems likely that the changes we observed reflected changes in cerebral dopamine levels.

This is because a number of previous reports have shown that a single session of rTMS over frontal and central areas of cortex can increase dopamine release in the striatum both in humans.

The mechanism is unknown but could involve either a pre-synaptic action from corticostriate terminals activated by the TMS pulses onto dopaminergic inputs to striatum, or a more complex route involving input from cortex to the brainstem dopamine neurons.

Such effects, however, would only lead to transitory increases in dopamine levels. If repeated sessions of rTMS lead to longer lasting changes in dopamine, such as might be responsible for the long lasting clinical effects seen in the present patients, then different mechanisms must be involved.
We can only speculate on how this might occur. It is known, for example, that a single session of rTMS can influence levels of brain-derived neurotrophic factor (BDNF) in human and rat brain, and that BDNF can prevent or recover damage to dopamine neurons due to environmental or chemical toxins. A related neurotrophic factor, growth derived neurotrophic factor (GDNF), can increase growth of dopaminergic neurons in the brain.

Thus, it is possible that repeated sessions of rTMS could improve growth and enhance activity of dopaminergic neurons in the brains of PD patients via actions on intermediary factors. If so then this could lead to enhanced dopamine function and improve clinical status for long periods after finishing rTMS treatment.

Conclusion,

- The results provide preliminary in vivo evidence of cumulative rTMS effects on dopaminergic neurotransmission in PD patients.

- Further studies are needed on a large number of patients to corroborate our results, and to define whether they relate directly to long-term effects on dopaminergic function in the brains of patients with PD.
Thanks a lot for your attention