THE IMPACT OF LEFT PREFRONTAL REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON DEPRESSION IN PARKINSON'S DISEASE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

(Full length article)

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Abbreviations: ADL = Activities of Daily Living (Schwab and England Scale); BDI = Beck Depression Inventory; DLPFC = dorsolateral prefrontal cortex, ESS = Epworth Sleepiness Scale; HYS = modified Hoehn Yahr Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MICD= minimally important clinical difference; MMSE = Mini-Mental State Examination; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation, TUG = Timed up and go test; UPDRS = Unified Parkinson’s Disease Rating Scale; VAS = Visual Analogue Scale

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Abstract

Based on several open-label and case studies, repetitive transcranial magnetic stimulation (rTMS) seems to have an antidepressive effect on patients with Parkinson’s disease (PD). However, this hypothesis requires further confirmation.

We conducted a randomized, double-blind placebo-controlled study to evaluate the effect of rTMS over the left dorsolateral prefrontal cortex (DLPFC) on depression and various motor and non-motor features of PD.

Twenty-two PD patients with mild or moderate depressive episodes were assigned into two groups, one receiving real-rTMS (90% of resting motor threshold, 5 Hz, 600 pulses-a-day for 10 days) over the left DLPFC, and another group receiving sham-rTMS. An investigator blinded to the treatment performed three video-taped examinations on each patient: before stimulation (baseline), 1 day (short-term) and 30 days after treatment-session ended (long-term effect). MMSE, UPDRS, Hoehn-Yahr, Epworth Sleepiness, Visual Analogue and Montgomery-Asberg Depression Rating Scales (MADRS), Beck Depression Inventory (BDI), and Trail making and Stroop tests were applied.

In the actively treated group, not only depression rating scales showed significant improvement 30 days after treatment ended (BDI by 44.4% and MADRS by 26.1%), but also the accuracy of Stroop test (by 16%). We could also demonstrate an insignificant improvement in UPDRS-III by 7.5 points (31.9%, p=0.06). In the sham-treated group none of the examined tests and scales improved significantly after sham stimulation.

Our study demonstrated the beneficial effect of the left DLPFC rTMS on depression in PD lasting at least 30 days after treatment. However, this result should be confirmed in patients with severe depression by further clinical trials.
Introduction

Affective problems are one of the most important non-motor features of idiopathic Parkinson’s disease (PD). Among those, depression is the most common form affecting approximately 40-70% of the patients. Depression may not just interfere with the motor symptoms of PD, but it can also cause immense personal suffering, and decreased quality of life with increased disability and caregiver burden.

The diagnosis of depression in patients with PD may be difficult because of overlapping symptoms of the two disorders; its prevalence may be underestimated consequently. Non-depressed PD patients may show typical features of depression: Psychomotor retardation, bradykinesia, reduced mimic movements, sleep disturbances, difficulties in mental concentration and fatigue may also be part of the neurological deficits solely caused by PD. Therefore, the diagnosis of depression in patients with PD is based on subjectively experienced symptoms including reduced emotional reactivity, feelings of emptiness and hopelessness, and inability to experience pleasure.

The profile of depressive symptoms in PD also differs from that of uni- or bipolar depression. Various studies have confirmed that the pattern of dysphoric sadness without feelings of guilt or self-reproach, and lower suicide rate are typical for PD. These differences suggest that depression associated with PD might represent a specific form of depression distinct from unipolar depression.

Despite the severe adverse consequences of depression in PD, there is little hard evidence to guide clinical treatment. Although some newer dopamine agonists also have antidepressive effect; the use of tricyclic or non-tricyclic antidepressants is frequently required. However, the side-effects of these agents may also worsen some preexisting non-motor problems in PD, e.g. sexual dysfunction.
Therefore, a distinct, non-invasive and well-tolerable antidepressive method is needed for treating depression in PD. Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is an FDA approved technique improving drug-resistant major depression\textsuperscript{7,8}. Based on its favorable side-effect profile and tolerability\textsuperscript{9}, DLPFC rTMS seems to be a useful tool in treating concurrent depression with PD. However, there are contradictory data available on the efficacy in this special depression entity probably due to the different study design, the limited number of patients enrolled and the different methodologies used during stimulation (e.g., type of coils; site, intensity and frequency of stimulation; and number of pulses applied)\textsuperscript{10-13}.

As far as the authors are aware, there is only a sole double-blind trial available investigating the antidepressive effect of rTMS on depression in PD\textsuperscript{14}; therefore, we aimed to perform a parallel group, randomized, double-blind study on this topic.

Methods

Subjects

Twenty two patients with idiopathic PD (11 male, age 68.5±7.9 year) were enrolled. All of them fulfilled the UK Brain Bank criteria for PD and criteria of Diagnostic and Statistical Manual of Mental Disorders 4\textsuperscript{th} revision (DSM-IV) for depression. Categorization of patients to mild and moderate depression was based on the appropriate criteria of DSM-IV by one of our investigators not participating in the treatment and the evaluation-process to ensure blindness of study. Depressive symptoms were observable in both ON and OFF states; patients with clear-cut OFF period-related depression were not included. Each subject gave written informed consent according the Regional Ethical Board of University of Pecs. Exclusion criteria for participation were the following: antidepressant usage within 2 months of the study protocol, presence of any implanted cardiac pacemaker or deep brain stimulator, coincidence of any serious medical condition (e.g. heart failure) which could interfere with the study protocol,
of epilepsy, and presence of dementia either measured by Mini-Mental State Examination (MMSE)\textsuperscript{15} or diagnosed by fulfilling the criteria of DSM-IV for dementia.

**Study procedure**

The patients were randomly assigned to either an actively treated group (n=12) or a sham-treated group (n=10, Table 1). Besides age and gender, type of PD (e.g. tremor-dominant or rigid-akinetic), the applied dopamine-agonist dosage (expressed in levodopa equivalent dosage\textsuperscript{16}) and severity of depression (mild or moderate) were taken into consideration during randomization.

rTMS was performed over the left DLPFC with a Magstim rapid stimulator (Magstim, Whitland, UK) using a 70 mm figure-of-eight coil. The site of stimulation was 5 cm anterior in the parasagittal plane from the point of the optimal stimulation of right hand muscles (primary motor area) as described by Pascual-Leone and Hallett\textsuperscript{17}. The coil was held tangentially to the skull with the handle pointing occipital and parallel to the midline. Six hundred impulses a day were applied using an intensity of 90\% of resting motor threshold (RMT) with 5 Hz frequency (12 trains of 10 seconds with 20 seconds intertrain interval) for 10 days. Sham-rTMS was carried out in the same site with the same stimulation parameters, but the coil was held perpendicularly.

An investigator blinded to the treatment performed three video-taped examinations on each patient: **baseline** (before stimulation), **short-term** (one day after the stimulation session ended, on day 11) and **long-term assessments** (30 days after stimulation ended, day 41). To improve reliability of measurements, the same investigator (EB) evaluated all patients. During the examination period, the medication of all subjects was kept constant. For neuropsychological analyses, MMSE\textsuperscript{15, 18}, Beck Depression Inventory (BDI)\textsuperscript{19, 20} and Montgomery-Asberg Depression Rating Scale (MADRS)\textsuperscript{21, 22}, Stroop\textsuperscript{22} and Trail-making tests\textsuperscript{22} were obtained. Unified Parkinson’s Disease Rating Scale (UPDRS), modified Hoehn-Yahr Scale (HYS), timed up and go test (TUG)\textsuperscript{23}, Schwab and England Activity of Daily Living Scale (ADL)\textsuperscript{24}, Visual Analogue
(VAS)$^{25}$ and Epworth Sleepiness Scales (ESS)$^{26}$ were measured to assess various motor and non-motor features of PD.

At the end of study, we asked the patients and the examiner taking the tests whether active stimulation was applied. Effectiveness of blinding was measured by the number of patients at whom either the patient or the examiner expected an active stimulation. Treatment responsiveness was also calculated by the number of patients experienced a clinically relevant (at least 2 points) improvement on MADRS 30 days after treatment ended$^{27}$.

**Statistical analysis**
Statistical evaluation was done by using the SPSS software package (version 17, SPSS Inc.). Because none of the obtained data followed the normal distribution, non-parametric Mann-Whitney, Wilcoxon’s and Friedman tests were performed. The level of statistical significance was set at 0.05.

**Results**

There were no significant differences between the baseline characteristics of actively- and sham-treated groups. (Table 1 and 2). All of the enrolled patients finished the study protocol. No side-effects occurred in the treated group except for a mild transient headache (n=2), which required neither the interruption of the study nor any medical treatment. The effectiveness of blinding was acceptable. (Table 2.)

**Neuropsychiatric tests**
Both of the examined depression rating scales verified a statistically significant improvement in the actively treated group. Comparing the short-term results to the baseline values, BDI improved from 9 points to 5 points (median, 44.4% improvement, p<0.05) whereas MADRS decreased from 11.5 points to 10 points (13.0% improvement, p<0.05). These improvements were stable or even more pronounced as far as the long-term results are
concerned (BDI remained 5 points; MADRS decreased to 8.5 points, a total improvement of 26.1% compared to baseline, \( p<0.05 \)). The number of treatment responders in the real-rTMS group was significantly higher (\( n=9, 75\% \)) than in the sham-group (\( n=2, 20\% \)). In the actively stimulated group, the accuracy of the Stroop test also improved both short- and long-term (from 78.1% to 90.6%, \( p<0.01 \)). However, results of the trail-making tests and the MMSE had not changed significantly in the actively treated group. (Table 2)

In the sham treated group, none of the examined neuropsychological variables demonstrated any significant changes from the baseline. BDI had a total improvement of 10.5%, whereas MADRS had 9.4%, which did not exceed the level of significance. (Figure 1, Table 2)

**Tests evaluating motor and non-motor features of PD**

All but one patient in the actively treated group felt subjective improvement after rTMS treatment. They reported faster movement, cognition, and better sleep. However, several objective scales (VAS, HYS, ADL and ESS) were unable to detect these subjective feelings.

In the actively treated group, the UPDRS-I and UPDRS-II improved (from 3 to 1.5 points and from 13 to 10.5 points, respectively), which lasted at least 30 days (\( p<0.05 \)). Timed up and go test also improved (from 12.5 to 11.0 seconds, median, \( p<0.05 \)). Similarly motor examination (UPDRS-III) also demonstrated a **7.5-point** improvement (from 23.5 point to 16.0 points, median); however, this change was only close to the level of significance (\( p=0.06 \)). On the other hand, HYS remained unchanged over both short- and long-term period. (Table 2)

Again, in the sham-treated group the examined tests and scales did not reveal any significant changes. (Table 2)

**Discussion**

In the present study we aimed to evaluate the antidepressive effects of rTMS over left DLPFC in a randomized, double-blind and placebo-controlled manner. Fulfilling our
expectations, we could demonstrate significant improvement in both of the applied depression rating scales, which either lasted for at least 1 month after treatment ended or even showed a further improvement. Although the total size of improvement (BDI by 44.4% and MDRS by 26.1%) was in the previously the reported range\textsuperscript{10, 11, 14, 28} only the change in MADRS exceeded the level of minimally important clinical difference (MICD, 3 points improvement vs. 2 points required for MICD\textsuperscript{27}). However, the size of improvement in BDI was only close to this limit (4 points improvement vs. 5 points required for MICD in case of BDI\textsuperscript{29}), which might be due to different factors:

1. In our study, only patients with mild or moderate depression were included. According to Hiroe et al., a change between 0-9 points on BDI “represents no or slight change, with 5 indicating a minimally important clinical difference (a smaller difference is enough when the baseline depression is mild, and a larger difference is required when the baseline depression is severe)\textsuperscript{29}.”

2. MADRS was designed to be sensitive to detect change in depression, whereas, BDI was originally designed as a screening device rather than a diagnostic tool\textsuperscript{30}. Therefore, treatment responsiveness was defined in our study as having at least 2 points improvement (the MICD value for MADRS\textsuperscript{27}) 30 days after the treatment ended.

Taking the concept of MICD into consideration, we may conclude that our study demonstrated a statistically significant, however, clinically mild improvement in PD patients with depression. The contradictory results of some previously published open-label studies on PD with depression might arise from different study designs, patient selection methods or rTMS procedures\textsuperscript{13}. Of note, the majority of previous studies had non-blinded and/or uncontrolled design, which could have raised several biases. However, the currently applied double-blind, controlled design could have minimized the placebo-effect. This has the highest importance, because the expectation of therapeutic benefit from sham-rTMS can induce striatal dopamine
release and produce considerable placebo-effect demonstrated by neuroimaging techniques\textsuperscript{32, 33}.

The majority of previously published studies applied an rTMS intensity of 110\% of motor threshold to treat depression, even if the procedure was considered as a double-blind study\textsuperscript{14}. With this setup, however, the presence or absence of muscle contractions could guide the patients and the investigators whether active or sham stimulations was applied. In order to ensure the double-blind methodology, we applied only 90\% of RMT intensity\textsuperscript{34}. Because this smaller setup finally resulted in similar antidepressive effect\textsuperscript{14}, we might assume that stimulation intensity in the range of 90\%-110\% of RMT might have similar outcome.

Besides depression, some aspects of cognition also improved after left DLPFC rTMS. Boggio et al. demonstrated that active stimulation could improve the performance time of Stroop test by 9.5\%\textsuperscript{35}, whereas in sham-stimulated group it remained unchanged. Because naming the ink color of color-words is proved to be the most cognitive demanding type of the Stroop paradigm, we chose this color-word type test for measuring some aspects of attention and executive functioning after rTMS. Interestingly, in our study the accuracy also improved in the active treatment group by 16\%. However, based on the work of Sedlackova et al., we may presume that multi-session DLPFC rTMS is required to achieve this beneficial cognitive improvement because after a single session no such effect could be detected\textsuperscript{36}.

There are also inconsistent and contradictory published data available whether DLPFC rTMS might improve the motor symptoms of PD. A newer study by Epstein et al. demonstrated a significant improvement in UPDRS-III obtained during ‘off’-period; however, UPDRS-III of ‘on’ condition had only a tendency to improve after DLPFC rTMS (p=0.08)\textsuperscript{11}. Whereas Lomarev et al. showed a clear-cut therapeutic effect on the motor function\textsuperscript{37}, del Olmo et al. was unable to demonstrate any improvements after DLPFC rTMS\textsuperscript{38}. Surprisingly, we could also observe a moderate but yet insignificant (p=0.06) improvement in UPDRS-III by 7.5 points (31.9\%), which also lasted for at least 1 month after treatment ended. Possibly this difference may be partially
due to patient selection: In the randomized, controlled study of del Olmo et al., the majority of patients (7 out of 13, 53.8%) had tremor dominant features, whereas in our study this rate was only 18%.

Although according to Schulman et al., an improvement in UPDRS-III exceeding 5.2 points would represent a moderate clinical improvement in PD\textsuperscript{31}, in our study we cannot conclude such an improvement due to lack of statistical significance.

Consequently, our study confirmed that a 10-day left DLPFC rTMS had an antidepressant effect on mild or moderate depression in PD that lasted at least 30 days after stimulation ended. However, the authors are aware of some limitations of the present study. Because of the seldom availability of rTMS, we were able to perform only a single-center study instead of a multicenter one. Other problematic issue might be that only patients with clinically mild to moderate depressive episode at the time of the examination were recruited. Because rTMS is a tool that is unlikely to be available widely and at least ten days of treatment to have an effect for 30 days, its application might be restricted to those cases where ‘conventional’ antidepressive medication might have prominent side-effects (e.g. worsening in sexual dysfunction). However, further larger multicenter, randomized, placebo-controlled studies are required to test efficacy of left DLPFC rTMS on severe or drug-resistant depression and decide whether this treatment can improve parkinsonian symptoms, as well.

Acknowledgements

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13. Okabe S, Ugawa Y, Kanazawa I. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord 2003;18(4):382-388.


Legends

**Figure 1.** Comparison of baseline, short- and long-term Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI) scores. Results of the active stimulation are represented by white boxplots, whereas those of sham stimulation are demonstrated by gray diagrams. Boxplots represent the medians, and the 25th and 75th percentiles, whereas error marks demonstrate the minimum and maximum values. For definitions, please, refer to text. Significant changes are marked by "*" (p<0.05).

**Table 1.** Baseline characteristics of the patients with idiopathic Parkinson's disease randomly assigned to actively-treated and sham-treated groups. Dopamine agonist (DA) dosages are given in levodopa equivalent dosage (LED) calculated by the recommendations of Baron et al\(^{16}\). None of the baseline variables differed significantly. At the type of PD, T, R and M stand for tremor-dominant, rigid-akinetic and mixed types of PD, respectively.

**Table 2.** Results of evaluated tests are compared between the actively- and sham-treated groups. Baseline refers to the state before stimulation, short-term results were measured one day after the stimulation session ended whereas long-term assessments were made on 30 days after stimulation ended. Because none of the data followed the normal distribution, the median and the interquartile range are presented. Effectiveness of blinding was measured by the number of patients where either the patient or the examiner expected an active stimulation. A patient was considered as a treatment responder if the MADRS score improved by at least 2 points 30 days after treatment ended.
Abbreviations: ADL = Activities of Daily Living (Schwab and England Scale); BDI = Beck Depression Inventory; ESS = Epworth Sleepiness Scale; HYS = modified Hoehn Yahr Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MMSE = Mini-Mental State Examination; TUG = Timed up and go test; UPDRS = Unified Parkinson’s Disease Rating Scale; VAS = Visual Analogue Scale

Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
3. Manuscript: A. Writing of the first draft, B. Review and Critique

EP 1, 2C, 3
FN 1A, 1B, 3B
ZA 1B, 3B
EB 1C, 3B
NK 1, 2, 3

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EB. There is no financial disclosure
### Tables

#### Table 1.

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Table 2.

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<td>MADRS</td>
<td>11.5 (13.5)</td>
<td>10.0 (6.5)</td>
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<td>89.6% (8.9%)</td>
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Effectiveness of blinding

- **patient expectation**
  - 10/12 (83.3%)
  - 8/10 (80.0%)

- **examiner expectation**
  - 9/12 (75.0%)
  - 7/10 (70.0%)

Number of treatment responders

- 9/12 (75.0%)
- 2/10 (20.0%)