

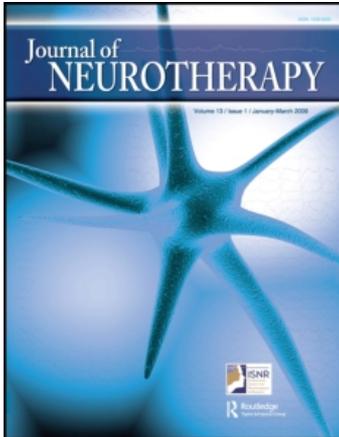
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Are the Effects of rTMS in Parkinson's Disease Clinically Relevant?

Floor Thomassen, MSc
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ABSTRACT. *Introduction.* Earlier studies have shown that brain stimulation by means of repetitive Transcranial Magnetic Stimulation (rTMS) over the primary motor cortex can decrease the motor impairments in Parkinson's disease (PD). The present study focused on the clinical relevance of rTMS in the treatment of PD.

Method. Thirteen PD patients received a minimum of 10 sessions of 2,000 pulses 5 Hz rTMS over the hand and leg area over the primary motor cortex, with a stimulation intensity of 120% of the motor threshold. In our analysis an effect could be considered as clinically relevant if the quality of life (QoL) improved with 30% or more.

Results. Paired-sample *t*-tests revealed a significant improvement of Unified Parkinson's Disease Rating Scale score, walking speed, and mood. A minority of the patients (38%) who underwent rTMS showed an improvement in QoL of greater than 30%. The improvements on QoL correlated significantly to scores of motor improvements on the Unified Parkinson's Disease Rating Scale but not to improvements in mood as assessed by the Geriatric Depression Scale. The use of rTMS did not demonstrate any effects on tremor, freezing of gait, and activities of daily life, and rTMS had no effect on the stage of disease. It mainly improved rigidity, finger and hand movements, and leg agility.

Conclusion. This study shows that although there can be significant group effects of rTMS on PD symptoms, these significant effects do not automatically imply that these are clinically relevant. Therefore we advise that future studies in the field of neuromodulation (rTMS, neurofeedback, etc.) also focus more on the clinical relevance of the treatment under investigation rather than only report "significant group differences."

KEYWORDS. Clinical relevance, neuromodulation, Parkinson's disease, quality of life, repetitive Transcranial Magnetic Stimulation, rTMS

INTRODUCTION

Parkinson's disease (PD) is a progressive neurological disease, characterized by a degeneration of dopaminergic neurons in

the substantia nigra, a structure of the basal ganglia. It manifests mainly in impaired motor functions, such as bradykinesia, rigidity, and tremor. This can have a substantial impact on the activities of daily life, mood,

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and quality of life (Kuopio, Marttila, Helenius, Toivonen, & Rinne, 2001; Magerkurth, Schnitzer, & Braune, 2005).

The main treatment modality for PD is medication, which mostly consists of the precursor L-dopa (Barbeau, 1969). A more invasive treatment is Deep Brain Stimulation (DBS). In a 6-month study of patients with severe motor complications of PD, neurostimulation of the subthalamic nucleus, as compared with medication alone, caused greater improvements from baseline to 6 months in motor function and quality of life (Deuschl et al., 2006). Although DBS is associated with these improvements, it is an invasive procedure with side effects like potential device-related complications or cognitive decline, speech difficulty, and depression (Rodriguez-Oroz et al., 2005).

Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive brain stimulation technique. Many studies have shown that magnetic brain stimulation of the primary motor cortex can improve the motor impairments in PD (Fregni, Simon, Wu, & Pascual-Leone, 2005; Hamada, Ugawa, & Tsuji, 2008; Khedr, Farweez, & Islam, 2003; Khedr, Rothwell, Shawky, Ahmed, & Hamdy, 2006; Lomarev et al., 2006). In a systematic review and meta-analysis, Fregni et al. (2005) pooled the data of eight controlled trials in which the effect of rTMS on motor function in PD was evaluated. They found a significant but modest effect size for rTMS treatment in PD (Cohen's $d=0.6$). The placebo conditions yielded a small—nonsignificant—effect size (Cohen's $d=0.1$). Despite the positive pooled effect size, there is large variability in results where some studies failed to find any effects of rTMS (Boylan, Pullman, Lisanby, Spicknall, & Sackeim, 2001; Okabe, Ugawa, & Kanazawa, 2003). The study with the largest effect size is by Khedr et al. (2003), where rTMS was applied at 5 Hz over the motor cortex (hand and leg area 2,000 pulses 10 days). This resulted in an improvement on the Unified Parkinson's Disease Rating Scale (UPDRS) score, walking speed, and a self-assessment scale, which lasted for at least 1 month. Similar results were obtained by Lomarev et al. (2006) and Khedr et al.

(2006), who applied high frequency TMS (10 or 25 Hz) over the left and right primary motor cortex. Lomarev et al. also stimulated the dorsolateral prefrontal cortex in addition to the primary motor cortex. Málly, Farkasb, Tóthfalusic, and Stoned (2004) studied long-term effects of repeated TMS in PD and found that the rTMS + medication group remained stable over the time course of 3 years, whereas there was deterioration in the medication only group on the Hoehn and Yahr (1967) scale. It has to be noted that this study employed a circular coil and relatively low stimulation intensities.

The results of the aforementioned studies and meta-analysis suggest rTMS could be a beneficial and a safe treatment in PD. Although most studies found statistical effects, the question remains whether these effects can also be regarded as clinically relevant. In a field study we investigated the effect of 10 sessions of 5 Hz rTMS, with a focus on the clinical relevance of the effects. A treatment can be considered as clinically relevant if quality of life (QoL) improves. QoL is measured by a questionnaire that considers a variety of domains on which PD can have a negative influence, namely, mobility, activities of daily live (ADL), emotional well-being, stigmatization, social support, cognition, communication, and physical difficulties. A decrease of the negative influence of PD on these domains will cause an improvement of QoL. Based on a study of Deuschl et al. (2006) and Zahodne et al. (2009) in which a mean improvement of 24 to 38% and 14 to 38%, respectively, in QoL were reached after DBS, in the present study a responder is defined as an improvement of at least 30% on a QoL scale. This is the primary outcome measure of this study. Other clinical measures such as the UPDRS, mood, and walking speed are also investigated to further objectify the effects of rTMS in PD.

METHODS

Participants

Thirteen patients (age = 65.7 ± 10.1 years) with a diagnosis of PD participated in this

field study on a treatment-as-usual basis. All patients were referred via the Dutch Association for Parkinson's disease. Exclusion criteria were cochlear implants, metal parts in the body, pacemaker, history of seizures (epilepsy), and history of brain surgery. Furthermore, before treatment commenced all participants underwent a Quantitative EEG, which was screened for abnormalities and paroxysmal EEG. The duration of disease varied from 3 months to 11 years ($M = 5.7 \pm 3.6$ years). The main symptoms were bradykinesia and rigidity. Four patients experienced tremors. Severity varied from unilateral plus axial involvement (Stage 1.5 Hoehn & Yahr) to severe disability (Stage 4 Hoehn & Yahr). Twelve patients were on antiparkinsonism medication, and 1 patient did not receive medication. Medication dosages were kept constant for the duration of the study.

Assessments

PD symptoms and severity were assessed by the motor section of UPDRS and the modified Hoehn and Yahr (1967). Gait and walking speed were investigated according to the Freezing of Gait Questionnaire and a walking test, in which the patients were requested to walk a fixed distance (20 m) as fast as possible, turn around, and walk back again. Furthermore the Nottingham Extended ADL Index, Parkinson's disease QoL questionnaire (PDQ-39), and Geriatric Depression Scale (GDS) were administered.

All measurements took place on medication prior to and after treatment. To more closely assess time effects, the motor section of UPDRS was also administered at Session 5. The walking test was administered every treatment session. The walking test was assessed only when the initial performance was slower than a normal walking speed (which is considered as a walking time above 25 s) to prevent floor-effects.

Treatment

Treatment consisted of 10 sessions rTMS, administered three to four times a week

using a Magstim SuperRapid stimulator (Magstim Company, Spring Gardens, UK). A figure-of-eight coil was used (Magstim Air Cooled Coil, 70 mm diameter), and rTMS was continuously applied at 5 Hz over the hand area (500 pulses left hemisphere, 500 pulses right hemisphere) and the lower limbs area (1,000 pulses) of the primary motor cortex. Stimulus intensity was 120% of the motor threshold (MT). MT was defined as the lowest stimulation intensity necessary to produce thenar muscle activity (as indicated by thenar EMG exceeding $50 \mu\text{V}$) with a single pulse delivered over the motor cortex for at least 50% of the stimulations. For every session the MT was determined for both the left and the right hemisphere. The highest MT from either left or right hand area was used to stimulate the primary motor cortex for the lower limbs.

All patients were informed in writing and orally about the experimental nature and the potential risks of rTMS treatment, and all signed a written informed consent form.

RESULTS

The primary outcome measure of this study was the quality of life score (PDQ-39 score). Overall there was a near-significant difference in change on the PDQ-39 score ($p = .090$, $T = 1.85$, $df = 12$), showing a 16% improvement for the whole group (also see Table 1). However, given that only some people responded in a clinically meaningful way, we used a cutoff score of 30% improvement on the PDQ-39 to separate the responders from the nonresponders. Using this criterion only 38% of the participants could be classified as a responder.

Paired-sample *t*-tests for the whole group revealed a significant improvement of UPDRS score (38.3 ± 15.8 before and 33.8 ± 17.2 after treatment), walking speed (33.4 ± 4.9 s before and 29.5 ± 2.8 s after treatment), and GDS score (6.8 ± 5.3 before and 5.0 ± 4.7 after treatment); for details, see Table 1. rTMS had no significant effect on the Hoehn and Yahr stages, freezing of gait, and activities of daily life (Nottingham

TABLE 1. Paired-sample t-tests pre-post scores.

	Pre <i>M</i> (<i>SD</i>)	Post <i>M</i> (<i>SD</i>)	<i>p</i>
UPDRS	38.3 (15.8)	33.8 (17.2)	.001* ($t = 5.46, df = 7$)
Walking test	33.4 (4.9)	29.5 (2.8)	.046* ($t = 2.50, df = 6$)
Hoehn & Yahr	2.1 (0.8)	2.1 (0.8)	.337 ($t = 1.00, df = 12$)
Freezing of gait	6.4 (5.5)	6.7 (6.4)	.795 ($t = -0.27, df = 12$)
NEAI	14.6 (11.0)	14.5 (15.2)	.955 ($t = 0.06, df = 12$)
PDQ-39	47.2 (27.3)	39.5 (25.6)	.090** ($t = 1.85, df = 12$)
GDS	6.8 (5.3)	5.0 (4.7)	.015* ($t = 2.85, df = 12$)

Note. UPDRS = Unified Parkinson's Disease Rating Scale; NEAI = Nottingham Extended ADL Index; PDQ = Parkinson's disease Quality of Life questionnaire; GDS = Geriatric Depression Scale. *Significant improvement at $p < .05$; **.05 < $p < .1$ indicates a trend.

Extended ADL Index), as can be seen in Table 1.

The improvements were mainly seen on the UPDRS subscales reflecting rigidity, finger and hand movements, and leg agility. No effects on tremor were found. Figure 1 shows the UPDRS scores over time and indicates that the biggest improvement is achieved in the first five sessions. Please note that the results for the UPDRS are based on a smaller sample size due to missing values ($N = 8$).

Post hoc correlative analysis showed that there was a highly significant correlation between the difference on the PDQ and the UPDRS between pre- and posttreatment ($r = -.901, p = .002, df = 8$), but there was no correlation between the PDQ and GDS scores ($r = .354, p = .235, df = 13$). The responders improved with more than 5 points on the UPDRS and the nonresponders with less than 5 points.

Figure 2 shows the mean walking time per session. Repeated measures ANOVA revealed a significant linear time effect for walking speed (within-subject contrasts; $p < .05, F = 6.27, df = 1.6$).

DISCUSSION

This study confirms results from previous studies employing magnetic stimulation of the primary motor cortex (Fregni et al., 2005; Hamada et al., 2008; Khedr et al., 2003; Khedr et al., 2006; Lomarev et al., 2006). Ten sessions of 2,000 pulses 5 Hz rTMS over the hand and leg area of the motor cortex had beneficial effects on motor function and walking speed. Besides these effects a near-significant effect was found on QoL in the present study, showing a 16% improvement for the whole group. One of the largest

FIGURE 1. Effect of repetitive Transcranial Magnetic Stimulation (rTMS) on Unified Parkinson's Disease Rating Scale (UPDRS) score after 5 and 10 sessions (error bars are standard error of the mean [SEM]).

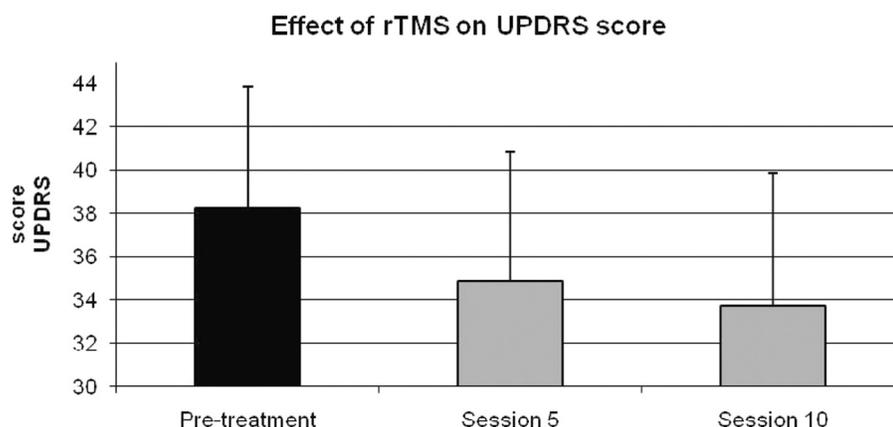
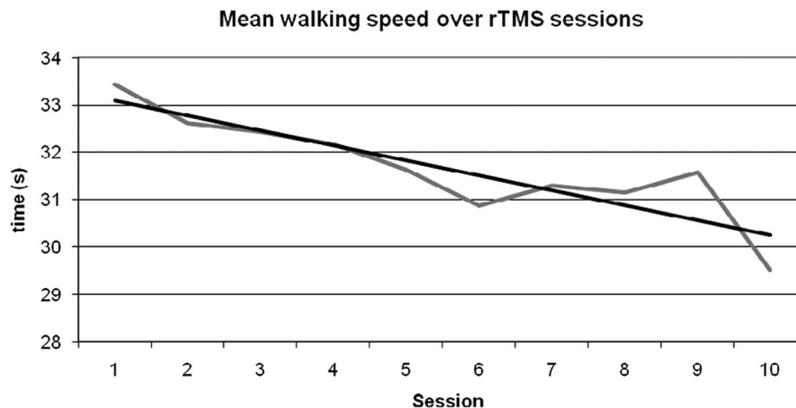


FIGURE 2. Effect of repetitive Transcranial Magnetic Stimulation (rTMS) on walking speed over sessions ($N=7$; gray line) and the trendline, which indicates a linear time effect ($p < .05$; black line). *Note.* These results are based on a smaller sample size because this test was only assessed on participants who showed impaired walking speed at the first session.



studies comparing DBS versus medication in the treatment of PD by Deuschl et al. (2006) showed that after 6 months the DBS group showed around a 25% improvement in QoL, whereas the medication group showed practically no change in QoL. The overall effects of TMS on QoL are therefore smaller than the effects of DBS on PD; however more controlled research is required to investigate this further.

The main objective of the present study was to investigate whether these improvements could also be regarded as clinically relevant. The present study reveals that a minority of the patients (38%) who underwent rTMS showed a clinically relevant improvement in QoL. This finding was confirmed by subjective reports from these responders regarding the rTMS effects on motor function. Conversely the nonresponders also subjectively indicated they did not benefit from the treatment in a clinically meaningful way. Furthermore, a strong correlation was found between QoL and motor improvement as measured on the UPDRS, showing that the QoL indeed mainly reflects improvements in motor function, and these QoL improvements are not simply related to an indirect improvement in mood (since there was no correlation to the GDS or depression scores). Tentatively it can be suggested that an improvement of 5 points or more on the UPDRS can be considered

“clinically relevant,” but more research is required to investigate that further.

rTMS did not demonstrate any effects on tremor, freezing of gait and activities of daily life. rTMS mainly improved rigidity, finger and hand movements, and leg agility. rTMS had no effect on the stage of disease. Furthermore, data tend to suggest that the biggest improvement in motor function is reached within the first 5 sessions and hence possibly 10 sessions would be sufficient for rTMS treatment in PD. Therefore, rTMS treatment is best indicated for patients with rigidity and impaired fine motor control but less for patients with mainly tremors and freezing of gait.

A weakness of this field study is the small sample size and the fact it was an open-label study and hence not placebo controlled. Furthermore, because the medication dosages were kept constant only for the duration of the rTMS treatment, no reliable follow-up has taken place. Therefore no firm conclusions can be drawn about the long-term effects.

Despite these limitations, this study shows that although there can be a significant group effect of rTMS on several PD specific scales, these significant effects do not automatically imply that these are clinically relevant. Therefore we advise that future studies in the field of neuromodulation (rTMS, neurofeedback, etc.) also focus more

on the clinical relevance of the treatment under investigation rather than report only “significant group differences.”

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