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Repetitive deep transcranial magnetic stimulation for motor symptoms in Parkinson's disease: A feasibility study☆

Oren S. Cohen[a,b,*], Yael Orlev[a], Gilad Yahalom[a,b], Revital Amiaz[b,c], Zeev Nitsan[d], Lilach Ephraty[a], Amihai Rigbi[e], Chen Shabat[a], Abraham Zangen[f], Sharon Hassin-Baer[a,b]

[a] Parkinson Disease and Movement Disorders Institute, Sagol Neuroscience Center and Department of Neurology, Chaim Sheba Medical Center, Tel-Hashomer, Israel
[b] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[c] Department of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer, Israel
[d] Barzilai Medical Center, Ashkelon, Israel
[e] Department of Behavioral Sciences Kinneret Academic College on the Sea of Galilee, Israel
[f] Department of Life Sciences, Ben-Gurion University, Beer-Sheba, Israel

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ABSTRACT

Objectives: Repetitive transcranial magnetic stimulation (rTMS), using standard coils, provided modest symptomatic benefits in patients with Parkinson's disease (PD). In our previous exploratory studies, using the newly developed Hesed coil (providing deeper rTMS; rDTMS) high frequency (HF), excitatory rDTMS over the primary motor cortex (M1), did not achieve sufficient beneficial effect for PD symptoms, while low frequency (LF) inhibitory stimulation, was mildly beneficial.

To further investigate the optimal rDTMS stimulation parameters for PD patients, and to assess whether there is an added value for dual stimulation, consisting of HF rDTMS over the prefrontal cortex (PFC) along with LF M1 rDTMS. The rational for the selection of the current stimulation parameters and sites lies on the previous studies that demonstrated an inhibitory effect of 1 Hz rTMS on the increased cortical activity in PD as well as dopamine release by PFC stimulation.

Patients and methods: An open comparative active study of one month duration (12 sessions) of LF rDTMS over M1 alone ($n = 9$) or combined with HF PFC rDTMS (M1-PFC, $n = 10$). Outcome measures included the total and motor Unified Parkinson's Disease Rating Scale scores (T-UPDRS and M-UPDRS) and other variables, were collected at baseline and on days 30 and 60.

Results: For the M1 + PFC group, T-UPDRS score improved from baseline to day 30, by 15% (median: 52 points, decreased to 44, $p = 0.02$, effect size: 0.51) and M-UPDRS score improved by 24% (median: 37 points decreased to 28, $p = 0.04$, effect size: 0.47). The corresponding results for the M1 group were insignificant. Additionally, the between groups comparison, was insignificant.

Conclusion: rDTMS, consisting of M1 excitation with PFC inhibition improved PD motor symptoms but was not significantly superior to M1 rDTMS alone. rDTMS stimulation protocols for M1 should be further evaluated in larger scale controlled studies.

1. Introduction

Patients with Parkinson's disease (PD) may remain functional with a reasonable quality of life for several years, thanks to effective pharmacological options; on the long run though, medical therapy commonly fails, and additional therapeutic interventions are required in order to preserve independent motion and function. Deep brain stimulation (DBS) using electrodes implanted into deep brain nuclei is an effective method of treatment for patients with advanced PD, but is limited to a subset of patients due to its invasive nature, surgical complications and occasional side effects [1].

Transcranial magnetic stimulation (TMS) is a non-invasive technique for brain stimulation based on electro-magnetic induction that spreads along local neural networks to distant cortical and subcortical regions and may induce lasting effects on cortical excitability [2]. Several clinical studies of repetitive TMS (rTMS)

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* Corresponding author at: Department of Neurology, Chaim Sheba Medical Center and the Sagol Center for Neuroscience, Tel-Hashomer 52621, Israel.
E-mail address: oren.cohen@sheba.health.gov.il (O.S. Cohen).

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for PD have been published, some of which reported moderate improvement of motor symptoms [3,4]. Both high frequency (HF) and low frequency (LF) stimulation of the primary motor cortex (M1) have been shown to be effective in PD [5]. A few studies reported significant improvement in motor tasks [6,7] or rigidity [8] following rTMS in PD. However, a lack of clinical efficacy has been reported in controlled trials using repeated sessions of LF rTMS of M1 [9,10]. Regarding HF rTMS of M1, subsequent studies supported the "therapeutic" value of HF rTMS of M1 in PD, showing global improvement of UPDRS part III motor scores, especially of movement speed or gait velocity, following the focal stimulation of hand representation [8,11–13] or the bilateral stimulation of a larger M1 area [14,15]. Stimulation of prefrontal targets was previously attempted for PD patients: LF (0.5 Hz) stimulation of dorsolateral prefrontal cortex (PFC) was initially found to improve motor performance [16]; however this was not confirmed in subsequent studies and it was suggested that the motor benefit was secondary to antidepressant and cognitive effects [17].

In a meta-analysis [18] the authors concluded that rTMS can exert a significant, albeit modest, positive effect on the motor function of patients with PD; however practical guidelines could not be drawn due to heterogeneity in techniques and methodologies. It should be noted that in these previous studies standard TMS coils (round or figure-of eight shaped) were used, which, when using up to 120% of motor threshold, can reach 1–2 cm in depth [19] but cannot offer effective direct stimulation of deeper brain structures as the intensity of stimulation needed is usually intolerable. The Hesed Coil (H-coil) is a relatively new development of TMS, designed to maximize summation of induced fields around a target, and minimize non-tangential coil elements close to that area [20,21]. The Hesed coil allows safe (sub-convulsive) stimulation of 3–4 cm in depth. The increased depth induced by the H-coil comes at the expense of the capability to focus the stimulation however it allows wider volumes of stimulation and therefore a direct and effective stimulation of deeper and larger brain areas. It was suggested that the effects of the H-coil to induce repetitive deep TMS (rDTMS) spread from the directly targeted brain region along neural connections using cortical and subcortical targets as "entry ports" [22,23] thus stimulating deeper brain areas that could potentially induce more pronounceable therapeutic effects in patients with PD.

It is believed that increased excitability of cortico-striatal pathways and decreased intracortical inhibition may play a role in the pathophysiology of the motor deficit in PD [22,24]. The specific effect of rTMS on cortical excitability may depend on the frequency, intensity, duration and inter-train intervals. High-frequency (5–20 Hz, HF) stimulation has been shown to increase cortical excitability while low-frequency ($\leq$1 Hz, LF) rTMS presumably decreases it [25]. In addition, the PFC is closely connected by neuronal networks and circuit with the basal ganglia and therefore most rTMS studies have targeted the primary motor cortex (M1) and/or the PFC.

In our previous exploratory rDTMS studies, using the H-coil, high frequency, excitatory rDTMS over M1 did not provide beneficial effects on PD symptoms, while low frequency, inhibitory M1 stimulation, was mildly beneficial [26]. In view of these suboptimal results the aim of the present study was to further investigate the optimal rDTMS stimulation parameters for PD patients, as well as assessing whether there is an added value for dual stimulation, consisting of HF rDTMS over the PFC along with LF stimulation of M1. The rational for the selection of the current stimulation parameters and sites lies on previous neuroimaging [27] and electrophysiological studies [28–30] that demonstrated an inhibitory effect of 1 Hz rTMS on the increased cortical excitability that has been previously documented in PD and the consequent assumption that 1 Hz rTMS can neutralizes this hyperexcitability causing "pseudo-normalization". The rational for additional PFC stimulation is based on animal rTMS studies that indicate that prefrontal projections modulate dopamine release in the striatum [31], possibly through activation of the substantia nigra [32] and that HF rTMS can cause a shift toward production of dopaminergic neurons [33]. In addition, in humans with PD, HF rTMS of prefrontal areas has been associated with improved motor and psychiatric symptoms with increased striatal dopamine release [34,35].

2. Methods

Patients diagnosed as idiopathic PD according to the UK Brain Bank Criteria [36], and followed up at the PD and Movement Disorders clinic at Sheba Medical Center, were included in this open-label comparative group pilot study if they were 40 years or older, had a Hoehn and Yahr stage of II–IV, and were on stable anti-Parkinsonian therapy for at least one month. Exclusion criteria included a history of seizures, frequent headaches, head injury or neurosurgical intervention, significant hearing loss, dementia (Mini mental state examination (MMSE) score >25 [37] or treatment with neuroleptics; likewise patients with metallic particles in the head, implanted cardiac pacemaker or neurostimulators were excluded.

The study was approved by the institutional review board (IRB) and all participants signed an informed consent form prior to inclusion.

Patients were asked and examined prior to inclusion for presence of clinically noticeable asymmetrical motor signs, at which point right and left body scores were calculated using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) to confirm asymmetry. The hemisphere contralateral to the predominantly affected body side (predominant side, PS) was chosen to be at the focus of stimulation.

The patients were randomized to one of two treatment protocols: one group received rDTMS over M1 alone and the other was stimulated over M1 and sequentially over the PFC. The treatment outline of both protocols consisted of a one-month period in which patients had 12 rDTMS sessions (3 times a week). rDTMS was administered as an add-on treatment to the patient's regular medication schedule and the stimulation was provided in the "on medication" state except for the first treatment, in which the patients were assessed before and after a single rDTMS treatment in the "off medication" state. rDTMS was carried out with a high-speed magnetic stimulator (Magstim, UK) connected to the H2 version of the Hesed coil [19,38]. In order to ascertain the accurate location and intensity of the stimulation, the motor threshold (MT) (defined as the lowest stimulation intensity able to produce motor-evoked potentials of the right abductor pollicis-brevis in 50% of the trials delivered) was initially determined in each treatment session. Spatial coordinates were recorded, using markings on a cloth cap placed on the subject's head, to ensure placement reproducibility in consequent sessions. For the dual stimulation group, following M1 stimulation the helmet was moved toward the midline and lowered 5.5 cm anterior to the motor spot (above the glabellar line) for PFC stimulation. The PFC target was defined according to previous TMS studies in depression, and MRI studies confirm that such placement targets the PFC. The coil is placed toward the midline as M1 stimulation of the hand might require some tilt for targeting the optimal spot of hand activation at minimal threshold, while no tilt of the helmet is required for the PFC stimulation.

The stimulation parameters are presented in Table 1.

The effects of the 1 month rDTMS treatment were assessed before the first rDTMS treatment (baseline day) and after treatment period termination (day 30) as well as following an additional month (day 60), always in the "on medication" state. The efficacy of treatment was assessed regarding motor symptoms while non-motor measures were used for safety monitoring. The primary and

Table 1
Repetitive deep transcranial magnetic stimulation protocol: stimulation parameters.

Brain area stimulated	Number of patients	Frequency (Hz)	Intensity (% of motor threshold)	Number of Trains	Train duration (seconds)	Inter-train interval (seconds)
M1 + PFC	**10**	1	110	900	1	0.5
		10	100	40	2	20
M1	**9**	1	110	900	1	0.5

M1 + PFC: sequential stimulation of low frequency over the primary motor cortex and then high frequency over the prefrontal cortex; M1: low frequency stimulation over the primary motor cortex alone. M1: primary motor cortex, PFC: prefrontal cortex.
The values in bold are clinically significant.

secondary outcome measures were the change in the total UPDRS (T-UPDRS) and motor UPDRS (M-UPDRS) scores [39] from baseline to day 30, respectively. Additional outcome measures consisted of the changes in UPDRS scores from baseline to day 60, including the predominant side (PS) lateralized M-UPDRS sub-scores (M-UPDRS-PS. Additionally the changes from baseline of other motor tasks including the nine hole pegboard (NHP) test (both hands), 10 s (digitalized) finger and foot tapping (both sides) and the 3-meter 'Timed Up & Go' (TUG) test were assessed. Non-motor outcomes, used for adverse event monitoring, included the Beck Depression Inventory (BDI) [40], digit forward and backward tests and word fluency (both phonemic and semantic) tests [41].

Additionally the effect of a single rDTMS stimulation session was evaluated on the first day of treatment, before and after rDTMS in the "off medication" state and the primary outcome measure of the single stimulation assessment was the change in M-UPDRS score rated before and after treatment; additional measures were the NHP test, finger and foot tapping and the TUG test.

Raters and patients were blinded to treatment arm.

2.1. Statistical analysis

Due to the small number of participants in each group, the statistical analysis was based on a non-parametric approach. Wilcoxon signed-rank test was used for within group comparisons; Mann–Whitney test was used for between groups comparison. Effect size (ES) calculation was based on *z*-to-*r* equation [42] and was interpreted as "small", "medium" and "large" according to the guidelines mentioned in Field [42]. Analyses were performed with the use of IBM-SPSS 20.

3. Results

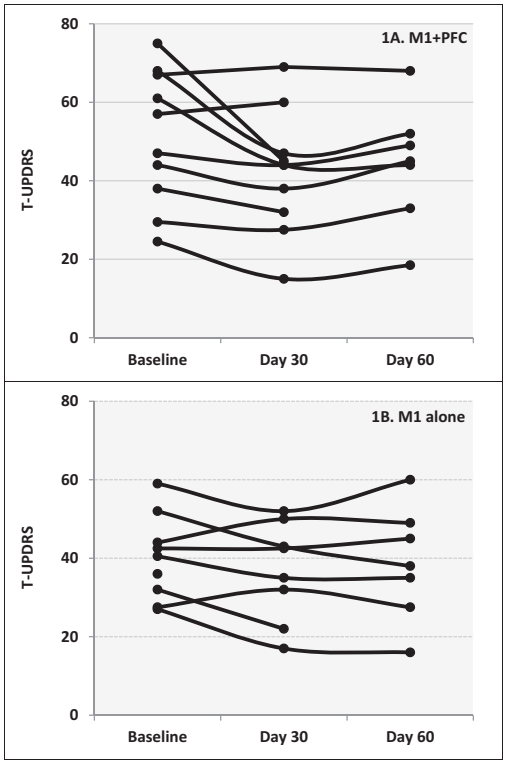
Nineteen PD patients were recruited and randomized for this study (Table 2) and treated by the H-coil: Ten patients received LF stimulation over M1 followed by HF stimulation over PFC (the M1-PFC stimulation group). Of these patients, in six the right side of the brain was stimulated and four patients were stimulated on the left side. Nine patients received stimulation over M1 alone (5 to the right side and 4 to the left side). The two patient groups were comparable for age, PD duration and disease severity scores (Table 2; $p > 0.1$).

The changes in outcome measures following the 1 month rDTMS treatment are presented in Table 3. Significant changes were found on day 30 versus baseline for the M1 + PFC group regarding T-UPDRS score (15% decrement, $z = -2.3$; $p = 0.02$; ES = 0.51) and M-UPDRS score (24% decrement, $z = -2.1$; $p = 0.04$; ES = 0.47) (Table 3). Fig. 1 presents the T-UPDRS decrement for each subject within each group. It appears from this figure that most patients in M1 + PFC group (1A) manifested a decrementing trend from baseline to day 30, compared to the patients in the M1 group (1B). The T-UPDRS medians collapsed over the patients were 52 (Baseline) and 44 (Day 30) in the M1 + PFC group; 41 (Baseline) and 39 (Day 30)

Table 2
Baseline characteristics of the study participants.

Variable	M1 + PFC group	M1 group	*p* Value
No. of patients	10	9	
Gender (M/F)	7/3	7/2	0.70
Age, years (M ± SD)	60.9 ± 12.2	68.8 ± 7.8	0.11
PD duration, years (M ± SD)	7.8 ± 6.5	5.1 ± 4.3	0.35
T-UPDRS score at baseline (MD, IQR)	52 (36–67)	41 (30–48)	0.13
M-UPDRS score at baseline (MD, IQR)	37 (26–43)	26 (23–29)	0.07
Baseline Hoehn and Yahr stage (Mode)	2	2	0.82
LEDD, mg (*M* ± SD)	416.3 ± 265.3	534.5 ± 426.3	0.73

M = male, F = female, M1 = primary motor cortex, PFC = prefrontal cortex, T-UPDRS = Total Unified Parkinson's Disease Rating scale score, M-UPDRS = Motor Unified Parkinson's Disease Rating scale score, LEDD = Levodopa equivalent daily dose, mg = milligrams, *M* = mean, MD = median, SD = standard deviation, IQR = Interquartile range; Mode = the score that occurred most frequently for this variable.



M1=primary motor cortex

PFC=prefrontal cortex

T-UPDRS= Unified Parkinson's Disease Rating scale, total score.

Fig. 1. Total UPDRS scores at baseline and after 30 and 60 days of treatment for the M1 + PFC group (1A) and for the M1 group (1B). M1, primary motor cortex; PFC, prefrontal cortex; T-UPDRS, Unified Parkinson's Disease Rating scale, total score.

Table 3
The effect of rDTMS at baseline and after 30 and 60 days of treatment for the M1 + PFC group and for the M1 alone group.

	M1+PFC rDTMS group					M1 rDTMS group				
	Baseline	Day 30	*p*	Day 60	*p*	Baseline	Day 30	*p*	Day 60	*P*
T-UPDRS	52	44	**0.02***	45	0.50	41	39	0.09	37	0.18
M-UPDRS	37	28	**0.04***	33	0.26	26	24	0.24	24	0.83
M-UPDRS-PS	18	14	0.12	15.5	0.17	9	9	0.07	9	0.49
NHP-PS (seconds)	32	26	0.07	28	0.96	32	28	0.05	30	0.26
TUG (seconds)	8	8	0.65	8	0.20	7	8	0.59	8.44	0.67
Finger tapping-PS	48	48	0.10	46	0.41	50	56	0.72	47	0.62
Foot tapping-PS	33	33	0.10	29	0.74	33	32	0.51	33	0.44

M1 = primary motor cortex, PFC = prefrontal cortex, T-UPDRS = Total Unified Parkinson's Disease Rating scale score, M-UPDRS = Motor Unified Parkinson's Disease Rating scale score, PS = predominant side, M-UPDRS-PS = the lateralized M-UPDRS score for the predominantly affected side, NHP = Nine hole pegboard, TUG = timed up and go test.
The values in bold are clinically significant.
* Statistically significant.

Table 4
The effects of a single rDTMS treatment in each treatment group.

	M1+PFC rDTMS group			M1 rDTMS group		
	Pre stimulation(median)	Post stimulation(median)	*p*	Pre stimulation(median)	Poststimulation(median)	*p*
M-UPDRS	39	31	**0.04***	29	25	0.11
M-UPDRS-PS	19	17	0.11	11	10	0.23
TUG (seconds)	9	9	0.37	8	8	0.59
NHP-PS (seconds)	34	35	0.11	32	29	0.59
Finger tapping (PS)	48	52	0.14	43	49	0.64
Foot tapping (PS)	27	26	0.44	31	26	0.37

M1 = primary motor cortex, PFC = prefrontal cortex, M-UPDRS = Motor Unified Parkinson's Disease Rating scale, PS = predominant side, M-UPDRS-PS = the lateralized M-UPDRS score for the predominantly affected side, NHP = Nine hole pegboard.
The value in bold is clinically significant.
* Statistically significant.

in the M1 group. A significant difference between baseline and Day 30 was found in the M1 + PFC group only ($z = -2.3$, $p = 0.02$). None of the other motor outcome measures changed significantly. By day 60 the changes were no longer significant. The BDI score decreased by 61% on day 60 (baseline median score = 6.5; day 60 = 2.5; $z = -2.12$; $p = 0.03$, ES = 0.53) for the M1 + PFC group. No significant correlations were found between BDI differences and T-UPDRS or M-UPDRS differences, either in the whole sample or in each group separately. Cognitive measures did not change (data not shown).

For the M1 group no significant changes were observed in any of the variables in either time point. Between groups comparisons, at each time point, using the Mann–Whitney *U* test, yielded insignificant differences for all of the measures above.

Patient assessment following a single rDTMS session demonstrated a significant decrease of 21% ($z = -2.01$; $p = 0.04$; ES = 0.45) in the M-UPDRS score for the M1 + PFC group but not for the M1 group (Table 4). Changes in all other collected measures following the single session were insignificant for either group and so were the differences between the groups.

3.1. Safety

The treatment was well tolerated. Adverse events were mild and transient and included: head discomfort during stimulation ($n = 9$), transient fatigue ($n = 3$), and rare mild visual transient hallucinations ($n = 1$). Patients did not notice any worsening of their hearing and audiograms were unchanged.

4. Discussion

The current open-label pilot rDTMS study, examined the efficacy of two rDTMS protocols as a treatment for the motor symptoms of PD. LF-inhibitory stimulation over M1 with sequential HF-excitatory stimulation over PFC induced motor improvement, while LF-inhibitory stimulation over M1 alone did not induce a significant change; yet the dual stimulation was not significantly superior to rDTMS of M1 alone.

The beneficial effect of the dual stimulation may result from a synergistic effect of M1 and PFC stimulation. The possible beneficial effect of stimulation over M1 is probably due to the inhibitory effect of 1 Hz rDTMS on increased cortical excitability that has been previously documented in PD both by neuroimaging [27] and electrophysiological studies [28–30]. Cortical excitability studies in PD revealed an excessive corticospinal output resulting from reduced intracortical inhibition [43]. It is plausible that 1 Hz rDTMS induces cortical inhibition that neutralizes this hyperexcitability causing "pseudo-normalization".

The basic hypothesis of this study was therefore that in PD, M1 stimulation may be enhanced by sequential stimulation of the PFC. This assumption is based on animal rTMS studies that indicated that prefrontal projections modulate dopamine release in the striatum [31], possibly through activation of the substantia nigra [32] and that HF rTMS can cause a shift toward production of dopaminergic neurons [33]. In addition, in humans with PD, HF rTMS of prefrontal areas has been associated with improved motor and psychiatric symptoms and in healthy controls with increased striatal dopamine release [34]. Positron emission tomography (PET) studies in PD patients and in controls have shown that HF rTMS applied at 10 Hz over M1 or the dorsolateral PFC induced a focal release of endogenous dopamine within the ipsilateral dorsal striatum, probably by activating corticostriatal projections [35]. Both the striatum and subthalamic nucleus receive major excitatory glutamatergic inputs from various cortical areas, mainly PFC, M1 and supplementary motor area. Depending on parameters of stimulation, these glutamatergic projections can either increase or decrease dopamine release in the striatum, via activation of GABAergic striatonigral pathways. A potential beneficial effect of the dual stimulation may therefore result from both increased excitability of neuronal circuits connecting the PFC to the basal

ganglia as well as by normalization of the hyperexcitability of M1 in advanced PD patients.

Our failure to demonstrate a statistical difference between the groups and evidently a superiority of the combined M1 + PFC stimulation may stem from the following: First, the sample size tested was insufficient to detect statistically significant differences between the groups. Other possible explanations include a higher baseline score in the M1 + PFC group that may result in greater room for improvement, compared to the M1 only group and the fact that M1 stimulation tended to induce some beneficial effect (although not statistically significant) perhaps due to the reduction of hyperexcitability in this area. Finally, it is possible that adding PFC stimulation using these parameters is indeed not beneficial. A recent study [44] indicated that at low intensity of rDTMS over M1 at a frequency of 10 Hz, combined with 10 Hz stimulation over the PFC was effective for PD motor symptoms, supporting the possibility that stimulation intensity plays a critical role in the clinical outcome of PD patients [45,46].

Our study has several limitations. The first one is the lack of a sham stimulation group. PD patients are known to have higher placebo response [47] and it has been shown that sham TMS can induce dopamine transmission in PD patients [48], Therefore, the positive treatment results in the dual stimulation group can be attributed, at least partially, to a placebo effect. A second limitation is the differences between the groups as the patients in the M1 group were slightly older, had a lower baseline M-UPDRS score and were taking more Levodopa. Although except for the M-UPDRS the other variables were not statistically different one cannot rule out that they had some effect on the treatment efficacy. Another limitation is that in those patients treated by Levodopa the treatment was given when the patient was on-medication while in one study [49] it was shown that rTMS affected intracortical inhibition (ICI) only in unmedicated patients and whether patients are in a medicated or an unmedicated appear to be critical for rTMS effects in PD patients. Finally there is the possibility that the order of stimulation could affect clinical outcomes. The reason for starting with M1 stimulation was to reduce the risk for seizures induced by TMS since low frequency stimulation can reduces cortical excitability and maybe partially effective in treatment of epilepsy.

In conclusion, the current study could not trace superiority of dual stimulation (PFC + M1) over M1 stimulation alone in the treatment of symptoms of PD. However, a significant reduction in total and motor UPDRS scores was achieved in the dual stimulation group. Further establishment of the benefit of this rDTMS protocol for PD symptoms should be accomplished by larger-scale double-blinded sham-controlled studies.

Conflict of interest

Dr. Cohen declares that he has no conflict of interest.
Mrs. Orlev declares that she has no conflict of interest.
Dr. Yahalom declares that he has no conflict of interest.
Dr. Amiaz declares that she has no conflict of interest.
Dr. Nitsan declares that he has no conflict of interest.
Dr. Ephraty declares that she has no conflict of interest.
Mrs. Shabat declares that she has no conflict of interest.
Dr. Rigbi declares that she has no conflict of interest.
Professor Zangen is a consultant and has financial interest in Brainsway LTD.
Dr. Hassin-Baer declares that she has no conflict of interest.

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References

[1] A.P. Duker, A.J. Espay, Surgical treatment of Parkinson disease: past present, and future, Neurol. Clin. 31 (3) (2013) 799–808.
[2] A. Pascual-Leone, J. Grafman, L.G. Cohen, B.J. Roth, M. Hallett, Transcranial magnetic stimulation. A new tool for the study of the higher cognitive functions in humans, in: Grafman, Boller (Eds.), Handbook of Neuropsychology, Elsevier, Amsterdam, 1996, pp. 267–290.
[3] J. Mally, T.W. Stone, Improvement in Parkinsonian symptoms after repetitive transcranial magnetic stimulation, J. Neurol. Sci. 162 (1999) 179–184.
[4] M.P. Lomarev, S. Kanchana, W. Bara-Jimenez, M. Iyer, E.M. Wassermann, M. Hallett, Placebo-controlled study of rTMS for the treatment of Parkinson's disease, Mov. Disord. 21 (2006) 325–331.
[5] J.P. Lefaucheur, N. André-Obadia, A. Antal, et al., Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS), Clin. Neurophysiol. 125 (11) (2014) 2150–2206.
[6] M. Sommer, T. Kamm, F. Tergau, G. Ulm, W. Paulus, Repetitive paired-pulse transcranial magnetic stimulation affects corticospinal excitability and finger tapping in Parkinson's disease, Clin. Neurophysiol. 113 (2002) 944–950.
[7] U. Gruner, C. Eggers, M. Ameli, A.S. Sarfeld, G.R. Fink, D.A. Nowak, 1 Hz rTMS preconditioned by tDCS over the primary motor cortex in Parkinson's disease: effects on bradykinesia of arm and hand, J. Neural. Transm. 117 (2010) 207–216.
[8] J.P. Lefaucheur, X. Drouot, F. Von Raison, I. Menard-Lefaucheur, P. Cesaro, J.P. Nguyen, Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease, Clin. Neurophysiol. 115 (2004) 2530–2541.
[9] P. Arias, J. Vivas, K.L. Grieve, J. Cudeiro, Controlled trial on the effect of 10 days low frequency repetitive transcranial magnetic stimulation (rTMS) on motor signs in Parkinson's disease, Mov. Disord. 25 (2010) 1830–1838.
[10] S.R. Filipovicí, J.C. Rothwell, K. Bhatia, Low-frequency repetitive transcranial magnetic stimulation and off-phase motor symptoms in Parkinson's disease, J. Neurol. Sci. 291 (2010) 1–4.
[11] H.R. Siebner, C. Mentschel, C. Auer, B. Conrad, Repetitive transcranial magnetic stimulation has a beneficial effect on bradykinesia in Parkinson's disease, Neuroreport 10 (1999) 589–594.
[12] C.H. Bornke, T. Schulte, H. Przuntek, T. Muller, Clinical effects of repetitive transcranial magnetic stimulation versus acute levodopa challenge in Parkinson's disease, J. Neural. Transm. 68 (2004) 61–67.
[13] J.Y. Kim, E.J. Chung, W.Y. Lee, et al., Therapeutic effect of repetitive transcranial magnetic stimulation in Parkinson's disease: analysis of (11C) raclopride PET study, Mov. Disord. 23 (2008) 207–211.
[14] N. Gonzalez-Garcıa, J.L. Armony, J. Soto, D. Trejo, M.A. Alegria, R. Drucker-Colin, Effects of rTMS on Parkinson's disease: a longitudinal fMRI study, J. Neurol. 258 (2011) 1268–1280.
[15] E.M. Khedr, J.C. Rothwell, O.A. Shawky, M.A. Ahmed, N. Foly, A. Hamdy, Dopamine levels after repetitive transcranial magnetic stimulation of motor cortex in patients with Parkinson's disease: preliminary results, Mov. Disord. 22 (2007) 1046–1050.
[16] N. Dragasevic, A. Potrebic, A. Damjanovic, et al., Therapeutic efficacy of bilateral prefrontal slow repetitive transcranial magnetic stimulation in depressed patients with Parkinson's disease: an open study, Mov. Disord. 17 (3) (2002) 528–532.
[17] F. Fregni, C.M. Santos, M.L. Myczkowski, et al., Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 75 (2004) 1171–1174.
[18] F. Fregni, D.K. Simon, A. Wu, A. Pascual-Leone, Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature, J. Neurol. Neurosurg. Psychiatry 76 (2005) 1614–1623.
[19] Y. Roth, A. Amir, Y. Levkovitz, A. Zangen, Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils, J. Clin. Neurophysiol. 24 (2007) 31–38.
[20] Y. Roth, A. Zangen, M. Hallett, A coil design for transcranial magnetic stimulation of deep brain regions, J. Clin. Neurophysiol. 19 (2002) 361–370.
[21] A. Zangen, Y. Roth, B. Voller, M. Hallett, Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil, Clin. Neurophysiol. 116 (2005) 775–779.
[22] A. Priori, A. Berardelli, M. Inghilleri, N. Accornero, M. Manfredi, Motor cortical inhibition and the dopaminergic system, Brain 117 (1994) 317–323.
[23] G.S. Pell, Y. Roth, A. Zangen, Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms, Prog. Neurobiol. 93 (2011) 59–98.
[24] M.C. Ridding, R. Inzelberg, J.C. Rothwell, Changes in excitability of motor cortical circuitry in patients with Parkinson's disease, Ann. Neurol. 37 (1995) 181–188.
[25] R. Chen, J. Classen, C. Gerloff, et al., Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation, Neurology 48 (1997) 1398–1403.
[26] O.S. Cohen, S. Hassin-Baer, R. Amiaz, et al., Repetitive transcranial magnetic stimulation using the H-coil for Parkinson's disease, Mov. Disord. 25 (suppl. 2) (2010) S293–S294.
[27] B. Haslinger, P. Erhard, N. Kampfe, et al., Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa, Brain 124 (2001) 558–570.

[28] F. Maeda, J.P. Keenan, J.M. Tormos, H. Topka, A. Pascual-Leone, Modulation of cortical excitability by repetitive transcranial magnetic stimulation, Clin. Neurophysiol. 111 (2000) 800–805.
[29] S. Romeo, F. Gilio, F. Pedace, et al., Changes in the cortical silent period after repetitive magnetic stimulation of cortical motor areas, Exp. Brain Res. 135 (2000) 504–510.
[30] J. Chu, Impaired presynaptic inhibition in the motor cortex in Parkinson's disease, Neurology 72 (2009) 842–849.
[31] S. Murase, J. Grenhoff, G. Chouvet, F.G. Gonon, T.H. Svensson, Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo, Neurosci. Lett. 157 (2009) 53–56.
[32] M. Karreman, B. Moghaddam, The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area, J. Neurochem. 66 (1996) 589–698.
[33] O. Arias-Carrión, S. Hernández-López, O. Ibañez-Sandoval, J. Bargas, A. Hernández-Cruz, R. Drucker-Colín, Neuronal precursors within the adult rat subventricular zone differentiate into dopaminergic neurons after substantia nigra lesion and chromaffin cell transplant, J. Neurosci. Res. 84 (2006) 1425–1437.
[34] A.P. Strafella, T. Paus, J. Barrett, A. Dagher, Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus, J. Neurosci. 21 (2001) 157.
[35] A. Strafella, J.H. Ko, J. Grant, M. Fraraccio, O. Monchi, Corticostriatal functional interactions in Parkinson's disease: a rTMS/[^{11}C]raclopride PET study, Eur. J. Neurosci. 22 (2005) 2946–2952.
[36] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (1992) 181–184.
[37] M.F. Folstein, S.E. Folstein, P.R. McHugh, Mini-mental state. A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198.
[38] Y. Levkovitz, Y. Roth, E. Eran, Y. Yoram, A. Sheer, A. Zangen, Deep transcranial magnetic stimulation – a randomized controlled safety and cognitive study, Clin. Neurophysiol. 118 (2007) 2730–2744.
[39] S. Fahn, R.L. Elton, UPDRS program members, Unified Parkinson's disease rating scale, in: S. Fahn, C.D. Marsden, M. Goldstein, D.B. Calne (Eds.), Recent Developments in Parkinson's Disease, Macmillan Healthcare Information, Florham Park, NJ, 1987, pp. 153–163, 293–304.
[40] A.T. Beck, C.H. Ward, M. Mendelson, J. Mock, J. Erbaugh, An inventory for measuring depression, Arch. Gen. Psychiatry 4 (1961) 561–571.
[41] M. Lezak, Neuropsychological Assessment, 3rd ed., Oxford University Press, New York, 1995.
[42] A. Field, Discovering Statistics using SPSS, Sage, London, 2009, pp. 550.
[43] B.U. Kleine, P. Praamstra, D.F. Stegeman, M.J. Zwarts, Impaired motor cortical inhibition in Parkinson's disease: motor unit response to transcranial magnetic stimulation, Exp. Brain Res. 138 (2001) 477–483.
[44] F. Spagnolo, M.A. Volonté, M. Fichera, R. Chieffo, E. Houdayer, M. Bianco, L. Leocani, Excitatory deep repetitive transcranial magnetic stimulation with H-coil as add-on treatment of motor symptoms in Parkinson's disease: an open label, pilot study, Brain Stimul. 7 (2) (2014) 297–300.
[45] H. Rothkegel, M. Sommer, W. Paulus, Breaks during 5 Hz rTMS are essential for facilitatory after effects, Clin. Neurophysiol. 121 (3) (2010) 426–430.
[46] G. Todd, S.C. Flavel, M.C. Ridding, Low-intensity repetitive transcranial magnetic stimulation decreases motor cortical excitability in humans, J. Appl. Physiol. 101 (2) (2006) 500–505.
[47] F. Fregni, P.S. Boggio, F. Bermpohl, F. Maia, S.P. Rigonatti, E.R. Barbosa, A. Pascual-Leone, Immediate placebo effect in Parkinson's disease – is the subjective relief accompanied by objective improvement? Eur. Neurol. 56 (4) (2006) 222–229.
[48] A.P. Strafella, J.H. Ko, O. Monchi, Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation, Neuroimage 31 (4) (2006) 1666–1672.
[49] B. Fierro, F. Brighina, M. D'Amelio, et al., Motor intracortical inhibition in PD: L-DOPA modulation of high-frequency rTMS effects, Exp. Brain Res. 184 (4) (2008) 521–528.