Journal of
Alzheimer's Disease & Parkinsonism

Pallanti S et al., Alzheimers Disease & Parkinsonism 2015, 5:2
DOI: 10.4172/2161-0460.1000191

Review article Open Access

Transcranial Magnetic Stimulation Treatment for Motor Symptoms in Parkinson's Disease: A Review of Two Decades of Studies

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Rec date: Apr 13, 2015, **Acc date:** June 29, 2015, **Pub date:** July 06, 2015

Abstract

In the last two decades, repetitive Transcranial Magnetic Stimulation (rTMS) has been increasingly employed in Parkinson's disease (PD) to enhance and restore motor function. Different cortical regions have been investigated as treatment targets (i.e. primary motor cortex, dorsolateral prefrontal cortex and supplementary motor area) and stimulation parameters (frequency, intensity, number of pulses) showed high heterogeneity between studies. Herein we review 40 studies, both open-label and randomized controlled trials: mixed results have been yielded regarding the effectiveness of rTMS treatment for motor symptoms in PD, due to the high variability of employed protocols, sham procedures and target regions. Although overall results seem to support the notion of potential beneficial effects of rTMS in PD, further research is needed to identify the optimal treatment parameters and to evaluate the potential conjunct use of rTMS in patients with deep brain stimulation (DBS) implants.

Keywords: Parkinson's disease; Transcranial magnetic stimulation; Treatment; Motor function

Introduction

Parkinson's disease (PD) is a chronic degenerative disorder of the central nervous system, primarily affecting motor function. Motor symptoms derive from the loss of dopaminergic neurons in the substantia nigra [1], while later in the progression of the disease, cognitive, behavioral and psychiatric symptoms may arise, particularly dementia and depression [2].

Current pharmacological treatments aim at symptoms management: in the last 30 years, levodopa (L-DOPA) has been the most widely used treatment for motor symptoms and still represents the most effective drug for PD [3]. Nevertheless, as the disease progresses, L-DOPA efficacy diminishes, leading to fluctuations in drug response ("on-off" periods). This requires a dose increasing, which usually leads to major side effects such as levodopa-induced dyskinesias (LIDs) [4]. Also, pharmacological agents seem to be effective in the short-term but cannot stop the dopaminergic degeneration and, consequently, the disease progression. Therefore, non-pharmacological approaches with potential disease-modifying effects have been developed: surgical procedures, such as deep brain stimulation (DBS), are currently widely employed, yet their use is restricted to a few selected patients due to their invasive features [5]. On the other hand, repetitive Transcranial Magnetic Stimulation (rTMS) has been investigated as a non-invasive candidate treatment for PD, particularly for motor symptoms. Two decades of studies have provided mixed results regarding rTMS efficacy in PD, probably due to the variability among protocols parameters and treatment targets. Herein we will review the most employed rTMS treatment protocols for motor symptoms in PD, summarizing results obtained from 40 studies, both open-label and randomized controlled trials (RCTs), focusing on different target areas. We will also briefly discuss the potential use of rTMS in patients with DBS implants.

Cortical And Functional Alterations in Parkinson's Disease

Several cortical and subcortical dysfunctions have been identified in PD. The disease is generally attributed to disruptions in the nigrostriatal dopamine system: these are also responsible of a global effect on brain organization at a cortical level [6]. One of the major evidences is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to a consequent depletion of dopamine in the striatum and is responsible of impaired synaptic plasticity [7]. The impairment in neuroplasticity, particularly in long-term depression (LTD) and long-term potentiation (LTP) induction, seems to be related to symptoms onset [7,8].

Corticospinal excitability has been investigated in PD through the employ of TMS protocols (e.g. paired-associative stimulation – PAS), focusing on motor-evoked potentials (MEPs) responses, which are thought to reflect LTD-like or LTP-like phenomena [9]. Cortical plasticity seems to be impaired since the early stages of disease [10] and dopaminergic agents, such as L-DOPA, may not suffice to restore plasticity [11]. Multiple corticospinal pathway alterations were found in PD: an excessive excitability, concomitant to or resulting from reduced inhibition, was found at 'rest', while defective activation or inadequate modulation was found during production of a voluntary output [12]. Motor cortical facilitation appears to be increased while inhibition is decreased in PD: increased cortical facilitation, which may be a compensatory mechanism, partly accounts for the decreased inhibition, but there is also impairment in synaptic inhibition in PD [13]. Diminished central silent period (CSP) and short-interval intracortical inhibition (SICI) were reported, while an enhanced size of MEPs has been illustrated [12].

Lastly, neuroimaging studies showed a decreased activity in the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC) [14] and primary motor cortex (M1): the latter was found to be hypoactive in early PD and hyperactive in the advanced stages of the disease [15,16].

Rtms Rationale in Parkinson's Disease

There is very little basic knowledge about the mechanisms of action of rTMS in PD, in fact remarkably different protocols have been employed: both low- and high-frequency stimulation have been investigated, as well as focal or circular coils and both motor and frontal/prefrontal targets. Since rTMS is capable to reach a 2-cm depth, subcortical structures such as the basal ganglia, cannot be directly modulated by the stimulating coil but may be modulated through functional connections with cortical areas (network effect) [17]. For instance, a series of studies showed functional changes within the basal ganglia after high-frequency rTMS over the left M1 or left DLPFC, which determined a focal release of endogenous dopamine [18-20]. This led to the development of protocols targeting three main cortical areas: the M1, SMA and DLPFC, characterized by a pathological increase or decrease in excitability during various stages of PD. Other cortical regions have been targeted (i.e. vertex, dorsal premotor cortex (PMd), occipital cortex), yet the number of studies on these targets is very limited and results have been generally inconsistent.

rTMS treatment in PD generally aims at improving motor symptoms, such as LIDs, bradykinesias and freezing of gait (FOG), though some studies also focused on non-motor symptoms, including depression and apathy [21], speech and voice [22,23] and cognitive functions [24].

An increase in cortical excitability and facilitatory effects on M1 are broadly documented after high-frequency stimulation [25,26]; by contrast, low-frequency stimulation is known to decrease cortical excitability [27]. Nevertheless, it is difficult to establish univocally the exact effects of low- or high-frequency protocols, since it is likely that the effects depend on the state of activity of the brain at the time of stimulation [28].

rTMS Studies in PD

In the last two decades a growing number of studies investigated the role of rTMS in the treatment of PD: herein we review 40 studies [29-68], whether randomized or open-label, summarizing results obtained by stimulation targeting different cortical regions. We decided to include only studies focusing on motor symptoms, therefore studies employing neuropsychological testing, mood rating scales, voice and speech rating scales and cortical excitability or neurotransmitter levels measures were excluded. Most studies focused on three regions: M1, SMA and DLPFC [29-63] [Table 1-3], while fewer targeted other areas [36, 61,64-68][Table 4]. Nine studies [32-34,39,45,52,54,55,63] tested the effects of only one rTMS session, while the remaining administered a higher number of sessions, ranging from 2 to 20. Most studies, especially those targeting M1, SMA and DLPFC, administered high-frequency stimulation (24 of 40 studies) [29-34,37-38,40-44,49-51,53-55,57-58,60-62], while low-frequency stimulation was employed primarily in studies targeting other regions. The intensity of stimulation ranged from 20% of motor threshold to 120%. Sample sizes were generally under 30 subjects, except for five studies [36,40,57,58,64]. In regard to outcome measures, the Unified Parkinson's Disease Rating Scale – Section III (UPDRS-III) was the most employed measure (33 of 40 studies) [32-34,36-44,47-51,53-68], yet some studies employed other motor function measures such as movement and reaction time [29,30,35], Grooved Pegboard test for fine movement [31], pointing, pronation supination, Purdue Pegboard Test [45], movement frequency [46] and gait kinematics [52].

rTMS studies targeting M1

25 studies [29-53] [Table 1] focused on M1 as target area: 4 of these [36, 41, 43, 53] also provided multiple targets stimulation. Most studies (17 of 25) [29-34,37-38,40-44,49-51,53] employed high-frequency stimulation, while the number of pulses and the number of sessions were characterized by high heterogeneity, ranging from 75 to 3000 pulses per session and from 1 to 20 sessions. The first study performed in PD patients [29] reported an improvement of movement time and reaction time following high-frequency rTMS over M1: most later studies (19 of 25) [29-30,33-35,37-42,44-46,48-53] also found improvements on motor performance after rTMS treatment. One of these studies [53] employed a deep TMS (dTMS) protocol with an H-coil to stimulate motor and prefrontal cortices: the authors found a significant UPDRS-III improvement after treatment. The remaining 6 studies [31,32,36,43,45,47] found no significant improvements after rTMS treatment: Ghabra et al. [31] found no significant effect of high-frequency rTMS on fine movement in 11 PD patients. Tergau et al. [32] found no significant effect on both UPDRS-III and reaction time following both low- and high-frequency stimulation. Okabe et al. [36] found no significant differences between M1, occipital or sham stimulation in a sample of 85 subjects, since UPDRS total and motor scores improved to same extent in all groups. Rektorova et al. [43] found no improvements in freezing of gait after low-frequency stimulation both over M1 and DLPFC. Rothkegel et al. [45] found no clinically relevant difference after one session of both conventional low- and high-frequency rTMS and theta-burst stimulation: none of the protocols excelled placebo stimulation. Lastly, Filipovic et al. [47] found no significant differences in motor function after 4 sessions of low-frequency rTMS.

Study	N of patients	Stimulation parameters	N of pulses / session	N of sessions	Outcome measure
Pascual-Leone et al., [29]	6	5 Hz – 10% RMT	n.a.	3	Movement time; reaction time
Siebner et al., [30]	12	5 Hz – 90% RMT	750	2	Movement time
Ghabra et al., [31]	11	5 Hz – 90% RMT	n.a.	2	Grooved Pegboard test (Fine movement)
Tergau et al., [32]	7	1/ 5/ 10/ 20 Hz – 90% MT	500	1	UPDRS-III;

					reaction time
Siebner et al., [33]	10	5 Hz – 90% RMT	2250	1	UPDRS-III
De Groot et al., [34]	9	5 Hz – 90% RMT	2250	1	UPDRS-III; movement time
Sommer et al., [35]	11	1 Hz – 120% RMT	900	3	Movement time
Okabe et al., [36]	85	0.2 Hz – 110% AMT	100	8	UPDRS-III
Khedr et al., [37]	19	5 Hz – 120% MT	2000	10	UPDRS-III
Bornke et al., [38]	12	10 Hz – 90% RMT	1000	2	UPDRS-III
Lefaucher et al.,[39]	12	0.5 / 10 Hz – 80% RMT	600 / 2000	1	UPDRS-III
Khedr et al., [40]	35	10 / 25 Hz – 100% RMT	3000	6	UPDRS-III
Lomarev et al., [41]	18	25 Hz – 100% RMT	1200	8	UPDRS-III
Khedr et al., [42]	20	25 Hz – 100% RMT	3000	6	UPDRS-III
Rektorova et al., [43]	6	10 Hz – 90% RMT	1350	5	UPDRS-III; FOG
Kim et al., [44]	9	5 Hz – 90% RMT	75	2	UPDRS-III
Rothkegel et al., 2009	22	0.5 / 10 Hz – 80% RMT	600 / 2000	1	Pointing; pronation supination; Purdue Pegboard Test
Gruner et al., [46]	15	1 Hz – 90% RMT	1800	4	Movement frequency
Filipovic et al., [47]	10	1 Hz – 90% RMT	1800	4	UPDRS-III
Kodama et al., [48]	1	0.9 Hz – 110% AMT	200 – 600	20	UPDRS-III
González-García et al., [49]	10	25 Hz- 80% RMT	200	15	UPDRS-III
Benninger et al.,[50]	13	50 Hz – 80% AMT	600	8	UPDRS-III
Maruo et al., [51]	21	10 Hz – 100% RMT	1000	3	UPDRS-III
Von Papen et al., [52]	10	1 Hz – 80% RMT	900	1	Gait kinematics
Spagnolo et al., [53]	27	10 Hz – 90% RMT	1680	12	UPDRS-III

Table 1: rTMS studies in PD: M1 as target area. rTMS, repetitive Transcranial Magnetic Stimulation; PD, Parkinson's Disease; M1, Primary Motor Cortex; Hz, Hertz; MT, Motor Threshold; AMT, Active Motor Threshold; UPDRS (III), Unified Parkinson's Disease Rating Scale (Section III); FOG, Freezing of Gait.

rTMS studies targeting SMA

rTMS treatment has been administered over the SMA by 6 studies [54-59] (Table 2): two employed high-frequency stimulation [54,57], two employed low-frequency [56,59] and the remaining two employed both high- and low-frequency stimulation [55,58]. The number of pulses was between 900 and 1800 pulses/session and the treatment duration involved more than one session except for two studies [54,55]. SMA trials yielded mixed results: the first study on this target area [54] reported a worsening in complex movements after one session of high-frequency rTMS, while all the other five found some degree of improvement. Koch et al. [55] reported that low-frequency stimulation markedly reduced dyskinesias, while high-frequency stimulation determined a slight, but not significant increase in dyskinetic behavior. A transient reduction in dyskinesias was also observed after one session of low-frequency rTMS, without further beneficial effects with repeated sessions [56], while a decrease in LID lasting for 24 hours after 10 sessions of low-frequency rTMS, yet without a change in motor performance was observed by Sayin et al. [59]. Modest improvements in motor symptoms were also reported by Hamada et al. [57]. One randomized, double-blind, sham-controlled, multicenter study with a parallel design [58] provided Class 1 evidence for the effectiveness of 1 Hz rTMS over the SMA for motor symptoms in PD: low-frequency stimulation was compared to both high-frequency and sham stimulation and the effects were monitored for up to 20 weeks: at this time, results showed 6.84-point improvement of the UPDRS part III in the 1-Hz group, while sham stimulation and 10-Hz rTMS improved motor symptoms transiently, but their effects disappeared during the observation period.

Study	N of patients	Stimulation parameters	N of pulses / session	N of sessions	Outcome measure

Boylan et al., [54]	10	10 Hz – 96% MT	2000	1	UPDRS-III
Koch et al., [55]	8	1 / 5 Hz – 90 / 110% RMT	900	1	UPDRS-III
Brusa et al., [56]	10	1 Hz – 90% RMT	900	5	UPDRS-III
Hamada et al., [57]	99	5 Hz – 110% RMT	1000	8	UPDRS-III
Shirota et al., [58]	106	1/ 10 Hz – 110% RMT	1000	8	UPDRS-III
Sayin et al., [59]	17	1 Hz – 90% RMT	1800	10	UPDRS-III; AIMS

Table 2: rTMS studies in PD: SMA as target area. rTMS, repetitive Transcranial Magnetic Stimulation; PD, Parkinson's Disease; SMA, Supplementary Motor Area; Hz, Hertz; RMT, resting motor threshold; MT, Motor Threshold; UPDRS (III), Unified Parkinson's Disease Rating Scale (Section III); AIMS, Abnormal Involuntary Movement Scale.

rTMS studies targeting DLPFC

7 studies [41,43,53, 60-63] employed rTMS over the DLPFC and four [41,43,53,61] provided multiple targets stimulations. All studies except one [63] employed high-frequency stimulation, UPDRS-III as outcome measure and more than one session of rTMS. Only two of the multiple targets studies found some degree of improvement after rTMS treatment: cumulative benefits due to the stimulation of both M1 and DLPFC in each session (300 pulses for each of 4 target areas: left and right M1, left and right DLPFC) were found [41], as well as UPDRS-III improvements after dTMS stimulation with a double target protocol (840 pulses on M1 and 840 pulses on PFC) [53]. The remaining studies [43,60-63] failed to find any improvements in motor function after rTMS treatment.

Study	N of patients	Stimulation parameters	N of pulses / session	N of sessions	Outcome measure
Lomarev et al., [41]	18	25 Hz – 100% RMT	1200	8	UPDRS-III
del Olmo et al., [60]	13	10 Hz – 90% RMT	450	10	UPDRS-III
Rektorova et al., [43]	6	10 Hz – 90% RMT	1350	5	UPDRS-III; FOG
Sedlackova et al., [69]	10	10 Hz – 100% RMT	1350	3	UPDRS-III
Pal et al., [62]	22	5 Hz – 90% RMT	600	10	UPDRS-III
Nardone et al., [63]	4	1 Hz – below AMT	1800	1	UPDRS-III
Spagnolo et al., [53]	27	10 Hz – 100% RMT	1680	12	UPDRS-III

Table 3: rTMS studies in PD: DLPFC as target area. rTMS, repetitive Transcranial Magnetic Stimulation; PD, Parkinson's Disease; DLPFC, Dorsolateral Prefrontal Cortex; Hz, Hertz; RMT, resting motor threshold; UPDRS (III/IV), Unified Parkinson's Disease Rating Scale (Section III/IV); FOG, Freezing of Gait.

rTMS studies targeting other cortical regions

7 studies [36,61,64-68] focused on rTMS stimulation over other cortical regions apart from M1, SMA and DLPFC, although two studies [36,61] provided multiple targets stimulation including M1 and DLPFC. Only one study [61] employed high-frequency stimulation and was among the multiple targets studies. All studies except for the abovementioned one [61] delivered a low number of pulses, ranging from 30 to 100, although in repeated sessions. Three studies [64-65,68] targeted the vertex of the skull: the first 2 studies [64-65], conducted by the same authors, reported significant improvements in motor symptoms as suggested by the decrease in UPDRS scores, while the latter [68] found no differences between real and sham stimulation groups and suggested the lack of therapeutic value of this stimulation protocol, which should have been abandoned. Other three studies [36, 61, 67] focused on the occipital cortex as target area and no improvements were found. Sedlackova et al. [61] targeted the occipital cortex as control stimulation site and delivered high-frequency rTMS stimulation on DLPFC and dorsal Premotor Cortex (PMd): results showed no significant effect for both areas on all outcome measures. Lastly, two studies [66,67] targeted frontal regions, both with low-frequency stimulation and a low number of pulses: Shimamoto et al. [66] found showed a significant decrease of the UPDRS scores after 2 months, and a significant increase in ADL scores. Ikeguchi et al. [67] found that frontal rTMS significantly improved motor performances including ADL and motor scores in UPDRS, while occipital rTMS showed no any significant effects on clinical tests: compared to occipital rTMS, frontal rTMS significantly improved ADL of UPDRS.

Study	N of patients	Target area	Stimulation parameters	N of pulses/ session	N of sessions	Outcome measure
Mally & Stone, [64]	49	Vertex	1 Hz – 30-60% MO	30 x 2	10	UPDRS
Mally & Stone, [65]	10	Vertex	1 Hz – 20% MT	30	20	UPDRS; GRCT
Shimamoto et al., [66]	18	Frontal	0.2 Hz – 700 V	60	8	UPDRS-III
Ikeguchi et al., [67]	12	Frontal; occipital cortex	0.2 Hz – 70% MO	60	6	UPDRS-III ADL
Okabe et al., [36]	85	Occipital cortex	0.2 Hz – 110% RMT	100	8	UPDRS-III
Sedlackova et al., [61]	10	PMd; occipital cortex	10 Hz – 100% RMT	1350	3	UPDRS-III
Arias et al., [68]	18	Vertex	1 Hz – 90% RMT	100	10	UPDRS-III

Table 4: rTMS studies in PD: Other target areas. rTMS, repetitive Transcranial Magnetic Stimulation; PD, Parkinson's Disease; PMd, dorsal Premotor Cortex; PFC, Prefrontal Cortex; Hz, Hertz; MO, maximum output; UPDRS (III), Unified Parkinson's Disease Rating Scale (Section III); GRCT, graded rating clinical test; ADL, Activities of Daily Living.

Discussion

Overall, there is growing evidence of potential beneficial effects of rTMS treatment for motor symptoms in PD: of the 40 studies reviewed, only 12 [31,32,36,43,45,47,54,60,61-63,68] did not find any improvement and one of these reported a symptoms worsening after stimulation [54]. Nevertheless, the magnitude of effects varied significantly across studies, probably due to the heterogeneity between stimulation protocols (in terms of frequency, intensity, duration) and targeted regions. Moreover, many studies were not sham-controlled and for sham-controlled studies, different methods of sham stimulation have been used: tilted [33,37,54,56,60,62], sham [39,47,63] and inactive coils [50,66,68] have been used, as well as occipital stimulation [40,49,61], coil back surface [41] and realistic sham [51,57,58]. A very recent review [69] examined 20 RCTs of rTMS treatment for motor dysfunction in PD to evaluate the efficacy of treatment and identify protocols factors that moderate the effects of treatment. The authors reported a significant medium effect size (standardized mean difference – SMD = 0.46) favoring active rTMS over sham treatment in the reduction of motor symptoms in PD. Moreover, the most efficacious treatment protocols appeared to be high-frequency stimulation over M1 and low-frequency stimulation over other frontal regions. The effect sizes for high-frequency rTMS over M1 (SMD = 0.77) and for low-frequency stimulation over frontal areas (SMD = 0.50) were the highest and significant, while the those obtained for low-frequency stimulation over M1 (SMD =0.28) and high-frequency over frontal regions (SMD = 0.23) were not significant. Also, in terms of moderating factors, the number of pulses per session and the number of pulses across sessions appeared to be significant predictors of rTMS effects: a greater number of pulses per session or across sessions was associated with larger treatment effects. These results updated the previous reviews [70,71], which also reported significant, albeit modest, positive effects of rTMS treatment on motor symptoms in PD. Further research regarding the efficacy of rTMS treatment on motor symptoms in PD is definitely needed: the clarification of optimal stimulation parameters (intensity, frequency, number of pulses) and target area is compelling. Long-term effects of rTMS treatment also need to be clarified to establish the optimal treatment duration (number of sessions): the immediate effects after one or a couple of consecutive sessions, albeit significant, might be short-lived, while a higher number of sessions requires careful monitoring for the likelihood of an increase of adverse effects after multiple sessions. Also, future studies should focus on the response to rTMS treatment depending on the stage of illness to identify individualized stimulation parameters for early and advanced stages of PD, targeting the prevailing symptoms, either motor or cognitive.

Regarding rTMS safety, a recent review [72] examined 1137 patients with PD who underwent rTMS treatment: only 51 adverse events were attributed to rTMS treatment and were mainly scalp pain, mild transient headache, transient tinnitus, nausea and transient increase in pre-existing back pain. All adverse events attributed to rTMS were minor and no studies reported the need for medical care in response an event: given the low rate of occurrence and the transient nature of the events, the authors concluded that rTMS does not carry significant risk of adverse events in the PD population. Moreover, TMS has also been used in patients with DBS implants: of 15 studies [73-87], only three [73,75,76] employed rTMS, while all the other employed single pulse TMS paradigms. No adverse events were reported in all 122 patients, so that preliminary evidence suggests that rTMS do not carry significant risk in this population [72]. Nevertheless, some recent contributions suggest to avoid rTMS administration in DBS implanted patients, due to the risk of electrical tissue injury [88,89]. An intriguing perspective may be the rethinking of TMS and DBS as complementary strategies instead of alternative procedures: as an investigational tool, TMS may help in evaluating cortical excitability before and after DBS. For example, TMS studies have shown subthalamic nucleus (STN) DBS ability to modulate cortical excitability, restoring intracortical inhibition [85,86], while basal ganglia DBS seem to mimic the effects of pharmacological dopaminergic therapy on PD patients cortical activity, probably recovering the modulation of thalamo-cortical motor pathway [87]. TMS and functional imaging might also be used to optimize the delivery of STN-DBS to improve specific functions such as speech production and general motor abilities [77]. Ultimately, the conjunct use of TMS and DBS might provide useful insights regarding the physiological mechanisms underlying the disorder and DBS mechanism of actions and, therefore, TMS employ in the selection of suitable candidates for DBS treatment might be promising.

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