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

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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].

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

					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	.0ă			

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.

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.

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

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

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