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Review

Therapeutic applications of repetitive transcranial magnetic stimulation (rTMS) in movement disorders: A review

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is emerging as a valuable adjunctive therapeutic modality in movement disorders. It is a non-invasive technique of repeated stimulation of the cerebral cortex by a train of magnetic pulses. The therapeutic effect of rTMS was first noted in depression. Later several researchers have investigated the role of rTMS in various movement disorders, notably Parkinson's disease, dystonia, Tourette's syndrome etc. The rTMS protocols used in these studies vary widely, lacks uniformity and often the results are not consistent. The optimal rTMS parameters for each disorder are yet to be established. This review discusses the current knowledge on the therapeutic applications of rTMS in various movement disorders.

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1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique of repeated stimulation of the cerebral cortex by a train of magnetic pulses. Transcranial magnetic stimulation was first introduced in late 1980's [1] and rTMS was introduced in 1989. Since then a large number of studies have involved rTMS as an investigational tool as well as a potential treatment for a variety of neurological and psychiatric disorders. Early studies on healthy volunteers demonstrated that rTMS to the primary motor cortex (M1) can modulate the cortical excitability, thereby producing changes in several physiological parameters [2]. These changes are seen in motor threshold (MT), motor evoked potential (MEP), silent period (SP), intracortical facilitation (ICF), intracortical inhibition (ICI) and cortical plasticity. The definitions of these terminologies are given in Table 1. These changes have implications in the treatment of movement disorders. Stimulating the cerebral cortex at frequencies $\leq$1 Hz is referred to as low-frequency rTMS, whereas stimulation at frequencies $>$1 Hz is referred to as high-frequency rTMS [3]. This distinction is based on the different physiological effects and the risks associated with high and low frequency stimulations [3]. High frequency stimulation induces an increase in cortical excitability and low frequency stimulation causes a decrease in cortical excitability [4,5]. However this is not true in all the circumstances as it depends on the site of stimulation. Theta burst stimulation (TBS) is a type of rTMS introduced by Huang. In TBS high frequency repetitive stimulation is used for modulating the cerebral cortical function. The different modalities of TBS include intermittent TBS (iTBS) and continuous TBS (cTBS). The pattern consists of three pulses delivered at 50 Hz every 200 ms, simulating a theta like-rhythm. In iTBS, 10 bursts are grouped and repeated every 10 s, for a total duration of 191.84 s resulting in 20 trains with 600 pulses. In cTBS 40 s train of 50 Hz burst repeated at 5 Hz (200 bursts) are delivered without interruption for a total duration of 40.04 s resulting in 600 pulses [6]. This review discusses the applications of rTMS in various movement disorders.

1.1. Physiological basis of rTMS

The primary motor cortex (M1) (Brodmann area 4) consists of pyramidal or Betz cells in layer V that give rise to numerous excitatory corticospinal projections. These projections control the hand movements by virtue of fast conducting fibers. Most of these fibers are oriented perpendicularly to the brain surface while some run parallel to brain surface. Direct electrical stimulation of exposed brain in animal studies demonstrates direct, D waves which are the earliest descending volley. Synaptic activation of corticospinal projections gives rise to indirect, I waves. Removal of the gray matter abolishes I waves but not the D waves. TMS stimulates the

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Table 1
Terminology [139,140].

Terminology	Definition
Motor evoked potential (MEP)	An EMG potential obtained after stimulating the motor cortex
Motor threshold (MT)	Lowest stimulator intensity that elicits an MEP of >50 μV in amplitude in muscles at rest or 200 μV in active muscles in at least 5 out of 10 consecutive stimulus
Silent period (SP)	A period of EMG suppression induced by single pulse TMS during voluntary contraction of the muscle
Intracortical facilitation (ICF)	An increase in the test MEP amplitude following conditioning stimulus at interstimulus intervals of 8–30 ms using paired stimulus
Intracortical inhibition (ICI)	A decrease in the test MEP amplitude following conditioning stimulus at interstimulus intervals of 1–6 ms using paired stimulus

corticospinal fibers indirectly producing the I waves [7]. These I waves occurs as continuing cycles appearing at regular intervals suggesting a synchronizing mechanism. rTMS by stimulating the motor cortex induces a change in cortical plasticity. Cortical plasticity refers to the functional reorganization of the inter neuron connections, representation patterns and neuronal properties. rTMS can either cause excitation or inhibition of the cerebral cortex and thereby modulate cortical plasticity. Modulation of cortical plasticity may have beneficial or detrimental effects and depends upon the site of stimulation and the rTMS protocol used. The exact mechanisms by which rTMS modulates the cortical excitability beyond the duration of rTMS are not clear. Inhibition of the GABAergic pathways produces cortical excitation [8]. The changes in synaptic plasticity brought by rTMS are explained by long term potentiation (LTP) and long term depression (LTD) [9]. LTP is induced by high frequency stimulation and LTD by low frequency stimulation. The cellular basis of LTP is mediated by the post-synaptic N-methyl-D-aspartate (NMDA) receptor which has an intrinsic calcium channel. Activation of this NMDA receptor leads to calcium flux into the post-synaptic neuron with induction of LTP [10]. Calcium then activates downstream enzymatic pathways and changes in pre- and post-synaptic neurons. This increases the synaptic strength. It also induces the expression of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on the post-synaptic neuron which increases the cells sensitivity to glutamate [11].

The persistent or long lasting effect of rTMS (late-LTP or L-LTP) is thought to be exerted by gene induction and protein synthesis. The effects may last hours, days or even weeks [11]. Gene expression has resulted in increased synthesis of c-fos mRNA in the paraventricular nucleus of the thalamus [12], parietal cortex [13], BDNF mRNA in the hippocampus and parietal cortex [14].

LTD on the other hand is characterized by depression of the synaptic transmission. It is induced by low frequency stimulation over long periods. It is dependent on the activation of NMDA receptors but the resultant calcium influx is slow and small. This leads to internalization of AMPA receptors with consequent reduced sensitivity of the post-synaptic neuron to glutamate [11].

rTMS has also been found to modulate the brain monoamines and neurotransmitters. rTMS reduces dopamine in frontal cortex and increased levels in the striatum [15]. Serotonin was increased in hippocampus [15] and there was reduced release of arginine vasopressin from the hypothalamus [16]. rTMS also exerts its effect by modulation of the brain receptors. The antidepressant effect is due to the upregulation of beta adrenergic receptors [17] and reductions of $5HT_2$ receptors in the frontal cortex in animal behavioral models of depression. Increased $5HT_{1A}$ receptors in frontal and cingulate cortex and NMDA receptors expression in the hypothalamus has also been found in animal models [18].

1.2. rTMS protocols

There are several rTMS protocols depending on the various stimulation parameters as described earlier. It can be classified into simple rTMS and patterned rTMS protocols [19]. Simple rTMS protocols have an identical interstimulus interval (ISI) between the different pulses. It can be low frequency or high frequency protocol. Patterned protocols have different ISIs. This include theta burst stimulation (continuous or intermittent TBS), paired pulse stimulation (PPS) and quadripulse stimulation (QPS). The effects of TBS on the primary motor cortex have been found to be similar with conventional rTMS [20]. There are several advantages of TBS over rTMS. The duration of TBS is shorter, uses low intensity, less heating of the coil and more tolerable to children.

The use of several protocols for treating the same disorder suggests that an ideal rTMS protocol is yet to emerge. The various rTMS protocols used in different rTMS studies are presented in Tables 3–9.

Table 2
Cortical excitability changes in various movement disorders.

Study	Changes in cortical excitability
(A) Parkinson's disease	
Dick et al., 1984 [109]	No change in MT
Cantello et al., 1991 [110]	↓ MT, short SP
Valls-Solé et al., 1994 [111]	↓ MT, short SP, ↑ MEP size
Priori et al., 1994 [112]	No change in MT, short SP
Ellaway et al., 1995 [113]	↑ MT
Strafella et al., 2000; Pierantozzi et al., 2001; Bares et al., 2003. [114–116]	↓ SICI
Sailer A et al., 2003 [117]	↓ LAI, ↓ SAI on more affected side in medicated patients
Spagnolo F et al., 2013 [118]	↓ MT, short SP
(B) Levodopa induced dyskinesia (LID)	
Morgante F et al., 2006 [119]	↑ CSP
Barbin L et al., 2013 [120]	↓ SICI
(C) Huntington's disease	
Meyer et al., 1992 [121]	↑ Motor threshold, CMCT, ↓ MEP amplitude
Tegenthoff et al., 1996 [97]	↑ CSP
Abbruzzese et al., 1997 [122]	Decreased ICI
Modugno et al., 2001 [123]	Normal MEP latency, MEP size, ↑ CSP
Nardone et al., 2007 [124]	Normal MT, CMCT, SP, ↓ ICF
Schippling et al., 2009 [125]	↑ MT, MEP recruitment – more gradual; ↑ SAI threshold
(D) Tic disorders	
Ziemann U et al., 1997 [126]	Normal MT, ↓ CSP and SICI
Moll GH et al., 2001 [127]	↓ CSP and SICI
Orth M et al., 2008 [128]	Normal MT, ↓ SICI
Orth M et al., 2009 [129]	↑ MT and ICF, ↓ SAI
Heise KF et al., 2010 [130]	Short SICI
(E) Dystonia	
Ridding et al., 1995 [131]	Reduced cortical inhibition
Rona et al., 1997 [132]	Normal MT, short SP
Chen et al., 1997 [133]	Reduced inhibition and ↓ SP on symptomatic side
Filipović SR et al., 1997 [134]	↓ SP
(F) Essential tremor	
Romeo S et al., 1998 [135]	Normal cortical excitability and CSP
Shukla G et al., 2003 [136]	Normal CSP
Pinto AD et al., 2003 [137]	Normal cortical excitability
(G) Corticobasal degeneration	
Pal PK et al., 2008 [101]	↑ MT (both RMT and AMT), ↓ ISP, absent pplHI

Abbreviations: CMCT – central motor conduction time, CSP – cortical silent period, ICF – intracortical facilitation, ISP – ipsilateral silent period, iTBS – intermittent theta burst stimulation, LAI – long latency inhibition, MEP – motor evoked potential, MT – Motor threshold, pplHI – paired pulse interhemispheric inhibition, SAI – sensory afferent inhibition, SICI – short intracortical inhibition, SP – silent period, ↑ – increased, ↓ – decreased.

Table 3
Therapeutic uses of rTMS in motor symptoms of PD.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
High frequency stimulation						
Pascual et al., 1994 [29]	6 PD and 10 controls	Effect on choice reaction time movement time and error rate	Prospective case control study	5 Hz rTMS over MC in a single session	Improves motor performance	No adverse events noted
Siebner et al., 1999 [41]	12 unmedicated PD	Effect on bradykinesia	Sham controlled study	Real-rTMS applied to M1 contralaterally to the more severely affected limb and frontal sham-rTMS was applied 3 cm anteriorly to Fz in a random order on 2 separate days. Stimulus intensity 10% below MT	Significant decrease in total movement time	No adverse events noted
Khedr et al., 2003 [39]	55 PD	Effect on motor performance	Prospective case control study	6 consecutive daily sessions (3000 stimuli each) of 25 Hz rTMS of M1 and occipital stimulation	Improved UPDRS score, walking and self assessment scale	No adverse events noted
Lomarev et al., 2006 [37]	18 PD	To assess safety and efficacy of rTMS	Double blind placebo controlled study	8 rTMS sessions of 25 Hz rTMS of M1 over 4 weeks, 300 pulses each over right and left MC, DLPFC	Cumulative benefit of improving gait and upper limb bradykinesia	No adverse events noted
Hamada M et al., 2009 [34]	98 PD	To assess the effect of rTMS on motor symptoms	Double blind multicentre sham controlled parallel study	5 Hz rTMS,110% MT, train of 50 pulses over SMA one session per week for 8 weeks	Improves bradykinesia in PD patients	No adverse events noted
Benninger et al., 2012 [36]	26 PD	To study safety and efficacy of 50-Hz rTMS in PD	Randomized, double blind, sham-controlled study	2 groups − 13 received 50 Hz real rTMS and 13 received sham stimulation over MC for 2 weeks in 8 sessions	Short lived improvement in on state ADL (UPDRS-II) with no improvement in motor symptoms	No adverse events noted
Randhawa BK et al., 2013 [43]	10 PD	To assess the effect of rTMS on SMA on handwriting	Randomized blind real and sham crossover study	1200 pulses of rTMS at 110% of MT at 5 Hz over SMA	Increased vertical size of handwriting and diminished axial pressure	No adverse events noted
Mak MK et al., 2013 [32]	22 PD	To study corticomotor excitability and improvement in walking	Randomized blinded controlled trial	Of 22 patients, 11 each were randomly allocated to control and experimental group. Experimental group received 5 Hz rTMS over leg area of MC for 6 min for 12 sessions over 4 weeks for experimental group and control group received sham stimulation	Improvement in fast walking speed in experimental group	No adverse events noted
Benninger DH et al., 2009 [35]	10 PD	To determine safety of 50 Hz rTMS	Randomized prospective study	50 Hz rTMS on primary motor cortex (M1) using 60% RMT and 0.5 s train duration and then increased to 90% intensity and train duration increased in steps to 2 s	No improvement in UPDRS, Grooved Pegboard Test,	No adverse effects
Rothkegel et al., 2009 [51]	22 PD	To determine the suitable rTMS protocol in PD patients	Pseudo-randomized two protocol rTMS and sham study	5 different rTMS protocols on 5 consecutive days in a pseudo-randomized and counterbalanced order. The protocols tested were 2 conventional rTMS protocols (0.5 and 10 Hz) with cTBS and iTBS and a sham condition. The site of stimulation being M1	Neither of the protocols differed from placebo	No adverse effects
Low frequency stimulation						
Arias et al., 2010 [28]	18 PD	To study the efficacy of low frequency rTMS on motor symptoms in PD	Randomized double-blind placebo-controlled trial design	1 Hz rTMS 90% MT, over 10 days on vertex with each session consisting of 2 trains of 50 stimuli each. 9 patients received real and 9 received sham rTMS	Total UPDRS and motor part improved	No adverse events noted
Kimura H et al., 2011 [45]	12 PD	To study safety and efficacy rTMS on motor symptoms of PD	Crossover placebo controlled study	0.2 Hz rTMS of 4-week sham rTMS followed by 4-week real rTMS. Real rTMS using 0.2 Hz over motor and SMA. Sham rTMS was applied with the coil placed vertically at 5% anterior from Fz according to the 10–20 system.	Improvement in UPDRS scores after real rTMS	No adverse events noted
Okabe S et al., 2003 [138]	85 PD	To study efficacy of low frequency rTMS in PD	Sham controlled study	3 groups of PD: Group 1 and 2 received 100 stimulus of 0.2 Hz at 1.1 times of MT once a week for 8 weeks over motor cortex and occipital respectively and group 3 sham electrical stimulation	No significant difference in UPDRS and HDRS	No adverse events noted
Filipović SR et al., 2010 [50]	10 PD	Effect of 1 Hz rTMS on motor functions in PD	Placebo controlled study	1800 stimuli at 1 Hz rate delivered over the motor cortex for four consecutive days on two separate occasions. On one of these real rTMS was used and on the other sham rTMS (placebo) was used	No improvement in UPDRS III and also in Motor Scale subscores for axial symptoms, rigidity, bradykinesia	No adverse effects

(*continued on next page*)

Table 3 (*continued*)

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Combination frequency stimulation						
Lefaucheur et al., 2004 [38]	12 PD	Effect on motor performance	4 intervention prospective study using both real and sham rTMS	L-dopa intake, 600 stimuli of 0.5 Hz over 20 min applied over left PMC, 20 trains of 2000 stimuli of 10 Hz rTMS, 10 Hz sham rTMS	High frequency reduced rigidity and bradykinesia and low frequency reduced bradykinesia and improved walking	No adverse events noted
Shirota Y et al., 2013 [46]	106 PD	To study the effect of rTMS on SMA	Randomized, double-blind, sham-controlled, multicenter study with a parallel design	3 groups:36 received low-frequency (1-Hz) rTMS, 34 high-frequency (10-Hz) rTMS, and 36 sham stimulation. Weekly intervention for 8 times	Group which received 1 Hz showed improvement in UPDRS-III after 20 weeks, only transient improvement in other two groups	No adverse events noted

Abbreviations: ADL – activities of daily living, DLPFC – dorsolateral prefrontal cortex, MC – motor cortex, MT – motor threshold, PD – Parkinson's disease, PMC – premotor cortex, rTMS – repetitive transcranial magnetic stimulation, SMA – supplementary motor area, HDRS – Hamilton Depression Rating Scale, UPDRS – Unified Parkinson Disease Rating Scale.

1.3. Rationale of using rTMS in movement disorders

rTMS has been shown to modulate the motor cortical excitability and depending on the stimulation parameters it can either excite or inhibit the brain. These parameters include the intensity, frequency, number, duration of stimulation and the number of sessions delivered. Studies involving TMS in movement disorders have shown changes in the cortical excitability. The cortex may be either hyperexcitable or hypoexcitable. In hyperexcitable states MT, silent period (SP), short intracortical inhibition (SICI) are reduced and intracortical facilitation (ICF) is increased, whereas in hypoexcitable states MT, SP, SICI are increased and ICF is reduced. Various studies have shown that high frequency stimulation increases cortical excitation [21,22] and low frequency stimulation inhibits cortical excitability [3,23]. The effect on corticospinal excitability following rTMS persists for seconds to minutes and sometimes hours. The corticospinal excitability is measured in terms of the size or amplitude of the motor evoked potential (MEP) and the motor threshold. This evidence forms the basis of using low-frequency rTMS to treat disorders with cortical hyperexcitability and high frequency rTMS in conditions with low cortical excitability (Table 2). Primary motor cortex (M1) is linked with other ipsilateral and contralateral motor regions, parietal cortex, cerebellum and sensory afferents. rTMS over primary motor cortex (M1) influences PMC, SMA, thalamus and cerebellum with its connections. These influences include projections from M1 in the ipsilateral and contralateral hemispheres. The interactions of M1 with other structures may be classified as excitatory or inhibitory, however there is overlap to some extent. The output represents a net effect of several specific interactions [24]. In view of this complex interaction, various studies have used PMC, SMA and cerebellum as the site of stimulation with different effects. Cerebellar stimulation induces long lasting changes in the cerebello-thalamo-cortical circuit and also the limbic areas as shown in many studies. Cerebellar rTMS modulates motor control, cognitive functions, emotion and mood.

2. Therapeutic applications in movement disorders

2.1. Parkinson disease (PD)

PD is a chronic degenerative disorder of the brain characterized by degeneration of the dopaminergic neurons in substantia nigra pars compacta (SNPc) leading to a hypokinetic rigid state. The disease is characterized by tremor, rigidity, bradykinesia and postural instability [25].

2.2. Motor symptoms of PD

PD is the most studied movement disorder with regard to TMS especially in treating the motor symptoms [26]. Initially, drugs like levodopa or dopaminergic agonists are able to control these symptoms, but with the progression of the disease these drugs become less effective. Abnormalities in cortico-basal ganglia-thalamo-cortical circuit are responsible for the symptoms of PD. As PD is due to abnormal neuronal activity within the basal ganglia and cortical regions, including the primary motor cortex (MC), premotor cortex (PMC)/supplementary motor cortex (SMA), several studies have used rTMS to improve brain function in PD.

Depending on the target, cortical stimulation has been shown to improve motor performance or other symptoms associated with PD, such as depression [27]. rTMS has shown promising results in improving gait and other motor symptoms providing a therapeutic alternative. Significant clinical effects have been obtained in PD patients by stimulating different cortical regions with rTMS at

Table 4
Therapeutic uses of rTMS in non-motor symptoms of PD.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Low frequency stimulation						
Potrebić et al., 2001 [64]	8 PD patients fulfilling DSM IV criteria for depression (5) and dysthymia (3)	Effect of rTMS in PD with depression as measured by HDRS	Prospective real rTMS study	0.5 Hz rTMS with 80% MT and B/L 4 site stimulation (prefrontal, frontal, parietal and occipital areas) for 10 consecutive days	Significant fall in Hamilton Depression Rating Scale (HDRS)	Safe to use
Furukawa et al., 2009 [25]	6 PD	Effect on cognitive dysfunction	Prospective rTMS study in PD patients	0.2 Hz rTMS of frontal region (Fz) at 1.2 times MT 100 stimuli per session and its effect on Trail Making Test part B (TMT-B), WCST, Wechsler Adult Intelligence Scale Revised (WAIS-R), self-rating depression scale (SDS), Functional Independence Measure (FIM) was evaluated	Improvement in TMT-B, Wisconsin card sorting test (WCST), SDS score and 20 m walk time	No adverse effects
Brusa et al., 2009 [63]	8 PD	Effect of 1 Hz rTMS in PD patients with bladder disturbances	Prospective real rTMS study in PD patients with lower urinary tract (LUT) dysfunction	1 Hz rTMS 65% of MT and 900 stimuli daily for 5 consecutive days over 2 weeks delivered at about 1 cm ahead of Cz. Urodynamic parameters (volume, pressure and flow variables) were evaluated	Increased bladder capacity and the first sensation of filling phase. Reduction of International Prostate Symptom Score (IPSS)	No adverse effects
High frequency stimulation						
Boggio et al., 2005 [60]	25 PD	To study the effect of rTMS on cognitive function in PD with concurrent depression	Randomized prospective comparison study of rTMS versus fluoxetine. Neuropsychological battery was assessed at baseline and after 2 and 8 weeks after rTMS	25 PD patients randomly divided into 2 groups – group I received active rTMS (15 Hz 110% MT and 10 daily sessions of left DLPFC plus placebo) and group II received sham rTMS and fluoxetine 20 mg/d	Improvement of Stroop, Hooper and Wisconsin test performances in both groups	No adverse effects
Dias et al., 2006 [55]	30 PD	Effect of rTMS on vocal function in PD	Real and sham rTMS using two rTMS parameters	15 Hz rTMS (110% of MT 3000 pulses per session) of DLPFC and 5 Hz (90% of MT and 2250 pulses) of M1 (mouth area)	DLPFC stimulation lead to mood amelioration and subjective improvement of the V-RQOL and M1 stimulation lead to improvement of the fundamental frequency and voice intensity	No adverse effects
Srovnalova et al., 2011 [57]	10 PD	Effect of rTMS on cognitive processing	Randomized pilot crossover study using real and sham rTMS	1 active and 1 sham session of 25 Hz on day 1 and 3 sequentially over B/L IFG	Improvement in all Stroop test subtests (word, color, color-word)	No adverse effects
Benninger et al., 2011 [33]	26 PD	Safety and efficacy of rTMS	Randomized, double-blind, sham-controlled study	13 received iTBS – 50 Hz burst of 3 pulses 8 session over 2 weeks on MC and DLPFC and 13 received sham stimulation	Beneficial effects on mood but no effect on gait, UPDRS score and bradykinesia	No adverse effects noted
Murdoch et al., 2012 [53]	10 PD	Effect of rTMS on articulatory dysfunction in PD	Real rTMS versus sham placebo rTMS	5 Hz rTMS applied to 10 active stimulation and 10 sham stimulation for 10 min/day (3000 pulses), for 10 days	Improved speech intelligibility, communication efficiency ratio, maximum velocity of tongue movements and distance of tongue movements at 2 and 12 months post-stimulation	No adverse effects noted
Eliasova I et al., 2013 [56]	12 PD and 21 healthy controls	Effects of high-frequency rTMS on motor aspects of speech	Randomized case control study	Two sessions of 10 Hz rTMS applied over the primary orofacial sensorimotor area (SM1) and the left DLPFC	Stimulation of SM1 resulted in improvement in voice quality and intensity and an increase in speech rate and tongue movements	No adverse effects

Abbreviations: B/L – bilateral, DLPFC – dorsolateral prefrontal cortex, FIM – Functional Independence Measure, HDRS – Hamilton Depression Rating Scale, IFG – inferior frontal gyrus, MC – motor cortex, MT – motor threshold, PD – Parkinson's disease, PMC – premotor cortex, rTMS – repetitive transcranial magnetic stimulation, SDS – self-rating depression scale, SRTT – Serial Reaction Time Task, SMA – supplementary motor area, TMT-B – Trail Making Test part B, UPDRS – Unified Parkinson's Disease Rating Scale, WAIS-R – Wechsler Adult Intelligence Scale Revised, WCST – Wisconsin card sorting test.

Table 5
Therapeutic use of rTMS in levodopa induced dyskinesias.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Low frequency stimulation						
Brusa et al., 2006 [67]	10 advanced PD with LID	Effect on peak dose dyskinesia	Combined sequential real and sham rTMS	90% MT and 900 pulses of 1 Hz rTMS for 15 min over B/L SMA	Transient reduction of dyskinesias	No adverse effects
Filipović et al., 2009 [70]	10 PD with prominent dyskinesias	Effect on peak dose dyskinesia	Placebo-controlled, single-blinded, crossover study	1 Hz rTMS 1800 pulses delivered over MC for 4 consecutive days twice – once by real rTMS and next by sham rTMS	Reduction of clinically assessed dyskinesia scores and also subjective improvement was seen	No adverse effects
Kodama et al., 2011 [68]	1 patient	Effect of rTMS in painful off period dystonia – LID	Case report	0.9 Hz rTMS over contralateral MC and SMA	Stimulation of MC reduced the painful dystonia and walking disturbances	No adverse effects
High frequency stimulation						
Koch G et al., 2009 [69]	10 PD with peak dose dyskinesia	To investigate whether modulation of cerebellothalamocortical circuits may result in modification of LID	Placebo controlled single blind study	Single session cTBS – 3 pulse bursts of 50 Hz with 80% MT over lateral cerebellum followed 1 week later by sham stimulation	↓ SICI and ↑ LICI with reduction of LID. 2 week course of B/L cerebellar cTBS reduced LID for 4 weeks	No adverse effects

Abbreviations: B/L – bilateral, cTBS – continuous theta burst stimulation, DLPFC – dorsolateral prefrontal cortex, LICI – long interval intracortical inhibition, LID – levodopa induced dyskinesia, MC – motor cortex, MT – motor threshold, PD – Parkinson's disease, PMC – premotor cortex, rTMS – repetitive transcranial magnetic stimulation, SICI – short intracortical inhibition, SMA – supplementary motor area, SP – silent period, ↑ – increased, ↓ – decreased.

Table 6
Therapeutic use of rTMS in tic disorders.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Chae JH et al., 2004 [82]	8 TS	To assess improvement in tic score	Single session, single blinded, placebo controlled, crossover	rTMS at 110% of MT over left MC (twice) or left PFC (twice) using either 1 Hz or 15 Hz over 5 days	No significant improvement in YGTSS, YBOCS and CGI score	No adverse effect
Mantovani et al., 2006 [74]	10 patients (5 with OCD, 3 with TS, 2 with OCD and TS)	Effect of low frequency rTMS on OCD in TS	Prospective cohort study	1 Hz rTMS 100% of MT delivered over SMA with 1200 stimuli per day for 10 daily sessions	Improves tics and reductions were seen in the YBOCS, YGTSS, CGI, HARS, HDRS, SAD, BDI, SCL-90, and SASS.	No adverse effects
Mantovani et al., 2007 [80]	2 TS	To assess improvement in tic score	Prospective unblinded study	1 Hz with 100% MT and 1200 pulses, 5 times a week for 2 weeks	Improvement noted in YGTSS	No adverse effects noted
Kwon et al., 2011 [78]	10 TS	Efficacy of rTMS in children with TS	Open label cohort study	1 Hz rTMS 100% of MT delivered over SMA with 1200 stimuli per day for 10 daily sessions	Significant reductions were seen in the Yale Global Tourette's Syndrome Severity Scale (YGTSS) and Clinical Global Impression (CGI) and reduction of tics	No adverse effects and worsening of symptoms
Le et al., 2013 [75]	25 Tourette Syndrome (TS)	Effect on various tic severity scales	Prospective real rTMS study in children with TS	1 Hz rTMS of 110% MT delivered over B/L SMA for 20 daily sessions	Significant reductions on the Yale Global Tic Severity Scale, Clinical Global Impression Scale, Swanson, Nolan and Pelham Rating Scale, version IV for attention-deficit hyperactivity disorder, Children's Depression Inventory, Spence Children's Anxiety Scale and a novel Attention Test	No adverse effects

Abbreviations: CGI – Clinical Global Impression, FIM – Functional Independence Measure, HDRS – Hamilton Depression Rating Scale, MC – motor cortex, MT – motor threshold, OCD – obsessive compulsive disorder, PMC – premotor cortex, rTMS – repetitive transcranial magnetic stimulation, SAD, SASS, SDS – self-rating depression scale, SMA – supplementary motor area, TS – Tourette's syndrome, YBOCS – Yale Brown obsessive compulsive disorder scale, YGTSS – the Yale Global Tourette's Syndrome Severity Scale.

Table 7
Therapeutic use of rTMS in dystonia.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Siebner et al., 1999 [88]	16 focal hand dystonia	To evaluate the effectiveness of low frequency rTMS in writers cramp	Single session, single blinded, placebo controlled, crossover	1 Hz rTMS with 90% MT and 1200 pulses over M1 area	Reduction in pen pressure and number of stroke inversions and self reported improvement	No adverse effects
Lefaucher et al., 2004 [85]	3 generalized dystonia patients	Effect on painful axial spasms	Pilot study in 3 patients	1 Hz rTMS of premotor cortex (PMC)	Reduced the painful spasms	No adverse effects
Murase et al., 2005 [87]	9 writer's cramp and 7 controls	Effect on writer's cramp	Prospective cohort study	0.2 Hz rTMS over PMC, SMA and MC. Silent period and handwriting assessment was done before and after rTMS to each of 3 areas	Improves handwriting in writers cramp on stimulation of PMC only	No adverse effects
Allam et al., 2007 [86]	1 patient of primary cervical dystonia	Effect of rTMS in primary segmental dystonia	Case report	1 Hz rTMS with 90% MT and 1200 stimuli per day for 5 daily sessions over PMC	A reduction of 50% in the neck subset of the Burke, Fahn and Marsden torsion dystonia scale (BFM) was observed	No adverse effects

Abbreviations: CHBF – cerebellar hemisphere blood flow, MC – motor cortex, MT – motor threshold, PET – positron emission tomography, PMC – premotor cortex, rTMS – repetitive transcranial magnetic stimulation, SMA – supplementary motor area.

Table 8
Therapeutic use of rTMS in essential tremor.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Gironell et al., 2002 [90]	10 ET	Effect of rTMS of cerebellum in ET	Double-blind, crossover, placebo-sham controlled design	1 Hz active rTMS with 100% of MT spread over 1 week session each of 30 trains of 10 s duration over cerebellum followed by sham stimulation	Tremor improvement as evidenced by a significant reduction in scores on the clinical rating scale and accelerometric values 5 min post-active rTMS	No adverse effects
Avanzino et al., 2009 [93]	15 ET and 11 controls	Effect of low frequency rTMS in changing the timing properties and motor behavior in patients of ET	Prospective cohort study	1 Hz rTMS of ipsilateral lateral cerebellum	Patients of ET had longer touch duration (TD) and a lower inter tapping interval (ITI) which was normalized. Coefficient of variation of ITI was also restored to normal values	No adverse effects
Hellriegel et al., 2012 [92]	10 ET and 10 controls	Effect on ET	Prospective placebo controlled study	cTBS of left MC (hand area) at 80% (real cTBS) and 30% (control cTBS) of active MT in two separate sessions one week apart	A subclinical reduction in tremor was observed as measured with accelerometry	No adverse effects
Popa et al., 2013 [91]	11 ET and 11 controls	Efficacy of 1 week of rTMS on tremors and cerebello-thalamo-cortical circuit dysfunction	Open label trial	1 Hz rTMS applied to B/L posterior cerebellum	Significantly improved total and specific (tremor, drawing, functional disability) scores, and reduced tremor amplitude. The effects persisted for 3 weeks post-rTMS	No adverse effects

Abbreviations: B/L – bilateral, cTBS – continuous theta burst stimulation, ET – essential tremor, MT – motor threshold, rTMS – repetitive transcranial magnetic stimulation.

Table 9
Therapeutic use of rTMS in other neurodegenerative disorders.

Author	No. of patients	Aims	Type of study	Methodology	Result	Safety
Shimizu et al., 1999 [107]	4 SCA	Therapeutic efficacy of rTMS in SCA	Case series	rTMS of 100% MT daily for 21 days over B/L cerebellar hemispheres	Number of feasible steps in tandem gait test increased, blood flow of the cerebellar hemisphere, putamen and pons were significantly increased	No adverse effects
Brusa et al., 2005 [98]	4 HD patients	Effect of rTMS on chorea in HD	Pilot study	5 Hz rTMS delivered at 110% MT and 18 trains of 50 stimuli over SMA of both hemispheres	Improvement of choreic symptoms in HD patients	No adverse effects
Ihara et al., 2005 [106]	SCA	Effect on disease severity and changes in CSF of SCA patients	Prospective cohort study	rTMS of SCA patients	Reduction of AFR in CSF, decline in ataxia severity and increased CHBF	No adverse effects
Santens et al., 2009 [95]	Small group of PSP patients	Effect of rTMS in PSP	Pilot study	5 Hz high frequency rTMS of MC	Improved axial symptoms in PSP patients	No adverse effects

Abbreviations: AFR – ascorbate free radical, B/L – bilateral, CHBF – cerebellar hemisphere blood flow, CSF – cerebrospinal fluid, HD – Huntington's disease, MC – motor cortex, MT – motor threshold, PMC – premotor cortex, PSP – progressive supranuclear palsy, rTMS – repetitive transcranial magnetic stimulation, SCA – spinocerebellar ataxia, SMA – supplementary motor area, ↑ – increased, ↓ – decreased.

inhibitory (low) or excitatory (high) frequency. High-frequency (5 Hz) rTMS is capable of modulating cortical activity and has been reported to have significant benefit to general motor function in PD [28]. Patients with PD on medications have shown improvement in psychomotor speed performance using low frequency rTMS. The improvement is seen mostly in the off medication state [29]. Studies in patients with PD have disclosed that a single session of rTMS can improve some or all of the motor symptoms for 30–60 min and repeated sessions can lead to effects that can last for at least 1 month [30]. rTMS applied at 5-Hz frequency over the leg area of the motor cortex showed improvement in walking [31,32].

The optimal rTMS parameter to obtain a beneficial effect is still not known. Higher frequency may be more effective. High frequency rTMS (50 Hz) was found to be safe with marginal improvement in UPDRS II. A prolongation of the cortical SP was observed in these patients following rTMS [33]. The relation between prolongation of silent period and improvement in UPDRS is difficult to explain.

High frequency rTMS over SMA significantly improves bradykinesia in PD patients supporting the hypothesis that neuronal activity of SMA is profoundly associated with hypokinetic symptoms in PD [34]. Studies have also used 50 Hz rTMS and were found to be safe and well tolerated but caution is advised for patients with paroxysmal EEG activity [35]. In a randomized, double blind, sham-controlled study, use of 50-Hz rTMS of the motor cortices in 8 sessions over 2 weeks produced a short-lived "on"-state improvement in activities of daily living (UPDRS II) without any adverse events [36]. SMA is a potential stimulation site for PD treatment; application of 5 Hz rTMS leads to improvement in motor symptoms [34]. Compared to 10 Hz occipital stimulation, 25 Hz rTMS over motor areas had more improvement in UPDRS score. The effect was observed to be cumulative and long lasting that was maintained for 1 month [30]. In a double-blind placebo-controlled study the effects of 25 Hz rTMS on bilateral MC and dorsolateral prefrontal cortex (DLPFC) on gait and bradykinesia in patients PD was assessed. rTMS sessions had a cumulative benefit in improving gait, as well as reducing upper limb bradykinesia in PD patients that correlates with increased MEP amplitude evoked by left MC rTMS [37]. High-frequency rTMS over MC has been shown to decrease rigidity and bradykinesia in the upper limb contralateral to the stimulation, while low-frequency rTMS reduces upper limb rigidity bilaterally and improves walking. Thus 10 Hz rTMS increases intracortical facilitation, while 0.5 Hz rTMS restores intracortical inhibition. These results support MC as the possible target for rTMS in PD [38]. Similar improvement in motor symptoms as assessed by UPDRS score was seen in other studies also [39,40]. The therapeutic effect of rTMS on motor symptoms in PD patients may be due to the inhibition of dopaminergic systems. Improvement in bradykinesia and UPDRS score has been demonstrated in other studies also by stimulating MC with 5 Hz rTMS [41,42]. In another study, stimulation of SMA using 5 Hz rTMS increased vertical size of handwriting and diminished axial pressure suggesting improvement in fine motor tasks [43]. 25 Hz rTMS over bilateral motor hand area (M1) improves bradykinesia which was substantiated by the fMRI findings of increased caudate activity during complex taping test [44].

Studies involving low frequency stimulation have also shown improvement in UPDRS score [45,46]. This therapeutic response is likely to be due to the changes in brain monoamine levels induced by rTMS [47]. SMA is important in motor planning and preparatory processes, since SMA stimulation has no effect on movements in their later stages when planning is already complete, but may disrupt movements in their early stages, when preparation for later stages is still in progress [48].

A meta-analysis of several randomized controlled trials using high frequency rTMS to treat motor symptoms of PD was found to be beneficial and low frequency had no effect [49]. However these studies differ from each other in cortical targets of stimulation, stimulation protocols used, sample size, UPDRS score prior to rTMS, duration of the disease, various pharmacological agents. All these factors make it extremely difficult to formulate an ideal stimulation protocol. In general M1 is the most frequently used cortical target in PD, clinical efficacy is also observed on stimulation of SMA. However there are other studies also that have not shown any benefit after rTMS [50]. Filipović et al. using low frequency stimulation did not show any improvement either in the total motor score or subscores for axial symptoms, rigidity, bradykinesia and tremor. Intermittent TBS (iTBS) of M1 and PFC has not shown any improvement in gait, bradykinesia and other motor symptoms of PD [33]. However iTBS is safe and without any adverse effects. The effect of low frequency rTMS on motor symptoms is not clear. Studies have not shown any significant improvement in bradykinesia, rigidity and gait abnormality [28,50]. Other studies using high frequency rTMS did not improve UPDRS score [35] and motor performance (pointing movement, pronation–supination, walking) [51]. In summary, the efficacy of rTMS in PD patients is still not clear and a consensus on the most effective rTMS protocol is yet to emerge. This calls for multicenter trials to address the issue. The details of the above studies are summarized in Table 3.

2.3. Non-motor symptoms of PD

Non-motor symptoms are frequently seen in patients of PD. These include delusions, depression, visual disturbances, diplopia, bowel and bladder disturbances, daytime sleepiness, vivid dreams, parasomnias, loss of smell and taste, orthostatic dizziness etc. Non-motor symptoms cause significant morbidity [52].

Studies have shown beneficial effect of rTMS on vocal function in PD. High-frequency rTMS (5 Hz) was evaluated as a therapeutic tool for the treatment of articulatory dysfunction in PD. Speech intelligibility, communication efficiency ratio, maximum velocity of tongue movements and distance of tongue movements improved after repeated rTMS [53]. However another study did not find any improvement in articulatory abnormality after rTMS probably because the patients had no or minimal dysarthria [54]. Stimulation of the left dorsolateral prefrontal cortex (DLPFC) with 15 Hz rTMS has shown mood amelioration and subjective improvement of the voice-related quality of life (V-RQOL) and stimulation of M1 area using 5 Hz resulted in significant improvement of the fundamental frequency and voice intensity [55]. Eliasova et al. studied the effects of high-frequency (10 Hz) rTMS applied over the primary orofacial sensorimotor area (SM1) and the left DLPFC on motor aspects of voiced speech in PD resulted in measurable improvement in voice quality and intensity and an increase in speech rate and tongue movements [56].

With progression of the disease, PD patients develop cognitive decline. In PD patients, Sequential application of high frequency rTMS over both the left and right inferior frontal gyri (IFG) increased the speed of cognitive processing in both the congruent and incongruent conditions of the Stroop test [57]. Improvement in neuropsychological functions (trail making test, Wisconsin card sorting test) and self-rating depression scale (SDS) has been observed with 0.2 Hz rTMS [25]. Alleviation of mood and cognitive disorders was observed when rTMS is applied to the DLPFC [58]. In another study a single session of high-frequency rTMS applied over the left dorsal PMC and left DLPFC was well tolerated and safe but did not show any effect on cognitive scale and motor symptoms [59]. This shows that rTMS can affect the functional recovery of the fronto-striatal circuit. Comparison of fluoxetine versus 15 Hz rTMS

of the left DLPFC revealed significant improvement of Stroop (colored words and interference card) and Hooper and Wisconsin (perseverative errors) test performances after both treatments [60]. The results show that rTMS can improve some aspects of cognition in PD patients similar to that of fluoxetine. The mechanisms for this cognitive improvement are not clear. Abnormalities in the dorsolateral prefrontal circuit and the associated caudate nucleus are thought to underlie the executive dysfunction [61]. rTMS improves the executive functioning as demonstrated by the neuropsychological tests.

PD patients also have impaired time processing in the off state. Application of high frequency (5 Hz) over the right DLPFC leads to significant improvement in time processing as evidenced by improvement in the time reproduction task [62].

5 Hz rTMS over the parietal cortex improved sleep fragmentation ($P = 0.0002$) and sleep efficiency ($P = 0.0002$) and reduced the average duration of nocturnal awakenings.

Patients with PD may present with lower involuntary detrusor overactivity. A 2-week course of low frequency 1 Hz rTMS temporarily improved the urinary symptoms by increasing bladder capacity and the first sensation of filling phase. The effect lasted for up to 2 weeks after the end of the stimulation [63].

PD is also associated with depression in a significant number of patients [64]. Several open studies have shown that both high frequency and low frequency may have antidepressant action [15]. Low frequency 0.5 Hz rTMS was shown to improve the Hamilton Depression Rating Scale with the effect persisting for 2 weeks [64]. Dorsolateral prefrontal cortex (DLPFC) is the target for rTMS in depression [4] and rTMS is a relatively safe and painless method associated with antidepressant action in PD patients [60]. The antidepressant action of rTMS and its maintenance for two weeks offers a choice to use this method in subacute depression until the full effect of medication is reached. 5 Hz rTMS over the left DLPFC improved depression in PD that lasted for 30 days in a double blind placebo controlled study [65]. However these handful studies lack uniformity in patient selection and site of stimulation. Sample size in most of these studies is small to come to any conclusion. DLPFC appears to be the appropriate site for most of the non-motor symptoms.

2.4. Levodopa induced dyskinesias (LID)

Long-term therapy with levodopa and dopamine agonists in PD patients often leads to the development of fluctuations in motor response known as LID. It is more often seen in advanced PD patients. Presently LIDs are managed by strategies that involve either delaying the introduction of levodopa therapy, use of amantadine, deep brain stimulation (DBS) or continuous dopaminergic stimulation using injectable drugs. Glutamate overactivity causes development of dyskinesias [66]. The role of striato-thalamo-cortical motor circuits has been implicated in its pathogenesis with overactivation of cortical motor and premotor areas in LID [67]. rTMS has been recently evaluated as a possible therapeutic tool in LID. Studies have shown that low-frequency rTMS over the MC and SMA can reduce LID in PD. 1 Hz rTMS over these areas was able to induce a transient reduction in the severity of LID, confirming that an over-activity of these areas plays an important role in the pathophysiology of LID [67]. In a case report of a patient with painful off-period dystonia involving unilateral lower limb, 0.9 Hz rTMS over primary motor area significantly reduced the painful dystonia and walking disturbances [68]. The prolongation of the cortical SP is the likely explanation for the improvement in Unified Parkinson's Disease Rating Scale (UPDRS)-motor score.

Procedures such as deep brain stimulation in LID have shown metabolic changes in the cerebellum and a 2 week course of bilateral cerebellar rTMS induced persistent reduction of peak-dose LID for up to four weeks [69]. They observed that cerebellar cTBS reduced SICI and increased LICI, implying cortical reorganization that is associated with reduction of LID. This study emphasizes the role of cerebello-thalamo-cortical pathways in LID and the anti-dyskinetic effect of cerebellar cTBS. Peak dose dyskinesias respond much better to rTMS. Repetitive 1 Hz stimulation of motor cortex showed small but significant reduction in dyskinesia severity lasting for 3 days. No adverse effects on motor function and PD symptoms were noted [70]. Single session of 1 Hz rTMS decreases the excitability of SMA with transient reduction of dyskinesias in LID [67]. However, repeated sessions of stimulation failed to enhance and/or prolong the beneficial effects [71]. There was no significant improvement when the frequency was increased to 5 Hz. These studies show that MC, SMA and cerebellum are the potential therapeutic sites for treatment of LID and can help in reducing the dose of levodopa.

2.5. Tic disorder

Tourette's syndrome (TS) is a chronic neuropsychiatric disorder of childhood onset that is characterized by multiple motor and phonic tics [72]. Many children improve by they reach adolescence. However, some adults with TS continue to experience severe symptoms and significant disability. The exact cause is not known, however abnormalities in the basal ganglia-thalamo-cortical circuit have been hypothesized to have an important role in the pathophysiology of involuntary tics. There may be a deficient inhibitory control through this circuit. Brain imaging has shown altered corpus callosum (CC) morphology in these patients [73]. They combined TMS with diffusion tensor imaging (DTI) to study the interhemispheric connections between the left and right motor hand areas. The left to right interhemispheric inhibition (IHI) was weaker than right to left IHI in TS patients. The combined TMS–DTI study showed an abnormal functional interhemispheric connectivity and altered structure–function relationship in the motor CC in TS. Evidence suggests that MC, PMC and SMA are hyperexcitable in these patients. Hence rTMS targeting the SMA can reduce tic severity [74]. Majority of the studies have stimulated the SMA with positive results. The other areas stimulated in TS are the MC and PMC. It has been found that 1 Hz rTMS to the SMA can improve clinical symptoms in children with TS for at least six months [75]. A statistically significant reductions in various tic severity scales was observed. Theta burst stimulation (TBS) has been used in children with TS by stimulating the left M1 area [76,77]. TBS was found to be safe and well tolerated in children. rTMS over the SMA has positive effects on ameliorating tics. rTMS over the SMA to children with TS results in a significant clinical improvement possibly by normalization of both the hemisphere hyperexcitability [78]. In patients with TS the above-threshold short intracortical inhibition (SICI) recruitment and sensory afferent inhibition (SAI), a paradigm to examine sensory motor integration is reduced. This leads to reduced excitability of cortical inhibition that contributes to the difficulty that patients have in suppressing tics. Reduced SAI indicates intracortical inhibition is not only limited to the motor cortex but also involves circuits linking sensory input and motor output [72]. The extent of involvement of these neuronal circuits determines the phenotype of Tourette spectrum disorders. rTMS is now considered as one of the emerging therapies for TS [79]. Low frequency rTMS applied to the SMA leads to significant increase in MT which is stable for next 3 months. There is normalization of the overactive motor cortical regions and restoration of hemispheric symmetry in motor threshold [80]. Stimulation of left PMC alone or left PMC followed by right PMC did not show any significant improvement in tics [81]. This suggests that an appropriate rTMS

protocols need to be used in order to explore its potential for the treatment of tics. rTMS with frequencies of 1 Hz and 15 Hz has been used in adults with TS [82]. There was no worsening of tics or other involuntary movements and it was safe. Some studies did not find any significant improvement in symptoms with rTMS [83]. In conclusion use of low frequency rTMS over SMA may reduce motor and vocal tics in TS patients.

2.6. Dystonia

There is increased cortical excitability of the motor cortex and the brain stem in patients with dystonia [84]. SPECT studies of the brain have shown abnormalities in glucose metabolism and perfusion. This increased cortical excitation and facilitation can be suppressed by rTMS, thereby reducing the motor symptoms. There are only few studies of rTMS in dystonia being limited only to some case reports and small series. The motor cortex excitability can be reduced by low-frequency (1 Hz) rTMS of PMC and MC. The painful spasms (proximal and axial musculature) in severe generalized dystonia can be reduced for few days post-rTMS [85]. Low-frequency rTMS improved primary cervical dystonia in a patient by stimulating the PMC [86]. Patients with focal dystonias like writer's cramp also benefit by low frequency rTMS of the PMC. In writer's cramp rTMS prolongs the SP and improves handwriting. This improvement is noted on stimulation of the PMC but not the MC [87,88]. These studies show that PMC is the area wherein low frequency rTMS can be applied to improve dystonia, both generalized and focal.

2.7. Essential tremor (ET)

Studies have shown overactivity of the deep nuclei and cerebellar cortex in the generation of ET. Dysfunction of the cerebello-thalamo-cortical (CTC) pathways is involved in the pathogenesis [89]. Animal studies, regional blood flow and imaging studies have provided the evidence that ET is due to the abnormal overactivity of the cerebellum and its connections. Low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) of the cerebellum effectively modulates the cerebellar output and induces a transient reduction of tremors [90]. It is postulated that rTMS interferes with the oscillatory function of the cerebellar neurons and to local increase in gamma amino butyric acid (GABA). Repeated rTMS over the cerebellum significantly improves tremor scores with reduction of tremor amplitude. It also corrects the defective information processing in the CTC network. The effects can persist for 3 weeks after the last session [91]. Repeated sessions might have a cumulative and potentially long-term therapeutic effect on ET. Apart from cerebellar stimulation, M1 stimulation can also suppress ET. cTBS of the M1 area has a beneficial effect on ET as it suppresses the excitability [92]. The benefit was subclinical with no significant changes in clinical tremor rating. Patients with ET have a longer touch duration (TD) and a lower inter tapping interval (ITI) compared to normal subjects. After 1 Hz-rTMS over ipsilateral lateral cerebellum there was a reduction of TD values and normalization of ITI [93].

2.8. Progressive supranuclear palsy (PSP)

PSP is a progressive neurodegenerative disorder without any specific treatment till date. Low frequency rTMS of the cerebellum has suppressive effects known as cerebellar inhibition (CBI) [94]. This shows that Purkinje cells or the dentate-thalamo-cortical pathways are involved in PSP. This is further confirmed by the pathological findings showing severe degeneration of dentate nucleus in PSP patients. Low frequency stimulation of cerebellum might restore the balance within the circuit and can improve some of the symptoms of PSP. Also application of high frequency rTMS over the motor cortex of clinically diagnosed PSP patients results in transient improvement in the axial symptoms without any side effects [95].

2.9. Huntington's disease (HD)

HD is a genetic neurodegenerative process that is due to CAG triplet repeat mutation in the short arm of chromosome 4 that encodes the Huntingtin protein [96]. It is the elongation of triple CAG that codes for glutamine that causes intracellular aggregates of the abnormal protein leading to mitochondrial dysfunction, ATP depletion and cell death. Studies have shown altered cortical excitability with dysfunction of motor cortex–basal ganglia circuit [97]. As HD is a hyperkinetic disorder, low frequency rTMS has been used to study the effect on cortical excitability. Improvement in choreic movements has been reported by using low frequency (1 Hz) rTMS of MC [98]. rTMS has also been used to study the cortical excitability in patients with HD. rTMS of MC increased the silent period (SP) duration during voluntary contraction [99].

2.10. Other atypical parkinsonian syndromes

Patients with MSA and CBD also have abnormal motor cortical excitability. Patients with MSA have significantly large MEP amplitudes at rest, reduced intracortical inhibition (ICI) and prolonged ipsi and contralateral silent periods, whereas CBD patients have significantly increased MT, smaller response amplitudes at rest, shortened contralateral silent period, reduced transcallosal inhibition and a reduced ICI [100]. In another study patients with CBD had increased MT (both AMT and RMT), short ipsilateral silent period and absent paired pulse interhemispheric inhibition [101]. The motor cortex disinhibition is predominant in patients with MSA and CBD with more severe neuronal cell loss in the motor cortex leading to hypoexcitability of corticospinal and transcallosal pathways. There is impairment of callosal integrity in patients with CBD and PSP as evidenced by the abnormal iSP [102]. Using rTMS it was found that there is an abnormal inhibition within the motor cortex in MSA-P patients despite dopaminergic treatment [103].

2.11. Spinocerebellar degenerations (SCD)

These are group of both genetic and acquired neurodegenerative diseases that are clinically and pathologically heterogeneous and characterized by slowly progressive cerebellar ataxia. The cerebellum modulates the primary motor cortex through cerebello-thalamo-cortical connections and plays an important role in movement execution and motor control. This formed the basis for cerebellar stimulation in various studies for SCD, ET [104]. Patients with SCA have reduced cortical excitability and prolonged central motor conduction time [105]. Application of repetitive transcranial magnetic stimulation (rTMS) in patients with spinocerebellar degenerations (SCD) has shown reduction in ascorbate free radical (AFR) in cerebrospinal fluid (CSF), decline in ataxia severity and increase in cerebellar hemispheric blood flow (CHBF) [106]. In patients with SCD there is an inverse relationship between ataxia severity and CHBF, rTMS improves ataxia by decreasing oxidative stress and increasing CHBF. Cerebellar rTMS for 3 weeks has improved the time to walk, tandem gait steps and body balance. An increase in the blood flow to the cerebellar hemisphere, putamen and pons was observed that may explain its effectiveness in improving ataxic gait [107]. This might suggest that TMS over the cerebellum may be an effective therapy for patients with SCD. In patients with cerebellar symptoms due to multiple sclerosis (MS),

there was an improvement in hand dexterity tested by 5 Hz rTMS over the motor cortex [108].

2.12. Limitations of rTMS

The results of various studies exploring the effects of rTMS on cortical excitability and its usefulness in movement disorders have been inconsistent. A novel rTMS protocol encompassing the ideal stimulation parameters is yet to emerge. Further studies are required to address the issue. Another limitation is the small depth of penetration of the stimulus. The deeper structures are not affected. However if the deeper structures were to be stimulated using high intensity stimulus, it would be epileptogenic and harmful to the surface tissue [3]. Other adverse effects like headache, scalp electrode burns, histotoxicity and its effect on cognition are also reported [3]. Transient nausea has been reported as a side effect following a relatively high output of stimulator and 900 pulses at 0.9 Hz over the cerebellum [139].

Though most of the studies of rTMS in PD have shown improvement in motor and non-motor symptoms, these studies were not reproduced by the same author or by others using similar rTMS parameters. Hence it is difficult to arrive at a clear consensus on optimal rTMS protocol for PD and other movement disorders.

2.13. Conclusions

In conclusion rTMS is a safe and a potential therapeutic option in movement disorder patients. Active research in movement disorders is still taking place and has the potential to provide useful data. Based on these new research new therapeutic guidelines may be established in future. Apart from its potential clinical role, rTMS is a valuable probe of brain function that can be used to investigate the neural circuitry. This additional knowledge might help in developing new treatments that may be specifically targeted.

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