

Transcranial magnetic stimulation in the treatment of motor and neuropsychiatric symptoms of Parkinson's disease: a literature review

Transkranijinės magnetinės stimuliacijos panaudojimas gydant motorinius ir neuropsichiatrinius Parkinsono ligos simptomus: literatūros apžvalga

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SUMMARY

Introduction. Parkinson's disease is primarily a motor disorder, but oftentimes causes neuropsychiatric symptoms to emerge. Patients have an increased risk of mood disorders, cognitive impairment and dementia, as well as impaired sleep and psychosis. Because the effectiveness of treatment with medications is reduced with prolonged use, supplemental treatment options are required. As a result, transcranial magnetic stimulation has emerged as a potential non-invasive treatment option due to its facilitatory or depressive effects on cortical and subcortical activity.

Aim. To assess the newest scientific literature on the efficacy of transcranial magnetic stimulation in treating motor and neuropsychiatric symptoms of Parkinson's disease.

Methodology. Literature search was performed using the "Pubmed" database. The following keywords and their combinations were used: "Parkinson's disease", "motor symptoms", "non-motor symptoms", "depression", "anxiety", "cognitive impairment", "dementia", "TMS", "treatment". 56 full-text publications written in the English language were reviewed. The time period selected was 2014-2024. Descriptive analysis was performed for the literature review.

Results. Transcranial magnetic stimulation has been shown to improve both motor and neuropsychiatric symptoms in Parkinson's disease patients. The most robust evidence is for treating motor symptoms by targeting either the primary motor cortex, or in conjunction with the prefrontal cortex using a high frequency protocol, the latter protocol also contributing to improvements in mood. Additionally, improvements in mood and less so cognitive impairment were observed after targeting the dorsolateral prefrontal cortex. The therapeutic effect is transient and dependent on the amount and frequency of sessions, and needs to be maintained with supplemental use.

Conclusions. Parkinson's disease is a complex disorder which may cause both motor and neuropsychiatric symptoms, requiring a multimodal approach for its treatment. One treatment modality of emerging interest is transcranial magnetic stimulation, which is promising for improvement of motor, mood and cognitive symptoms.

Keywords: Transcranial magnetic stimulation, Parkinson's disease treatment

SANTRAUKA

Įvadas. Parkinsono liga - motorinis sutrikimas, tačiau dažnai sukelia ir neuropsichiatrinius simptomus. Pacientai turi didesnę nuotaikos, kognityvinių, miego sutrikimų, demencijos bei psichozės riziką. Kadangi vaistų veiksmingumas gydant šią ligą mažėja po ilgalaikio jų vartojimo, svarbus papildomas gydymas. To pasekoje daug dėmesio skirta neinvazinei transkranijinei magnetinei stimuliacijai dėl jos efekto slopinant arba skatinant smegenų žievės ir požievio jaudrumą. **Tikslas.** Apžvelgti naujausią literatūrą, aprašančią transkranijinės magnetinės stimuliacijos veiksmingumą gydant motorinius ir neuropsichiatrinius simptomus sergant Parkinsono liga.

Metodai. Literatūros apžvalga atlikta naudojant duomenų bazę „PubMed“. Buvo naudoti šie raktažodžiai ir jų kombinacijos: „Parkinson's disease“, „motor symptoms“, „non-motor symptoms“, „depression“, „anxiety“, „cognitive impairment“, „dementia“, „TMS“, „treatment“. Apžvelgtos 56 visatekstės publikacijos anglų kalba, spausdintos 2014-2024 metais. Literatūros apžvalgai naudota aprašomoji analizė.

Rezultatai. Transkranijinė magnetinė stimuliacija buvo veiksminga palengvinant tiek motorinius, tiek neuropsichiatrinius Parkinsono ligos simptomus. Stipriausi įrodymai gydant motorinius simptomus buvo stimuliuojant arba pirminę motorinę žievę, arba kartu stimuliuojant priešaktinę žievę naudojant aukšto dažnio protokolą, kuris stimuliuojant abi smegenų sritis taip pat prisidėjo prie nuotaikos pagerėjimo. Tuo tarpu užpakalinės šoninės priešaktinės žievės stimuliavimas prisidėjo prie nuotaikos ir kiek mažiau kognityvinių sutrikimų gerinimo. Vis dėlto terapinis efektas praeinantis ir priklausomas nuo sesijų kiekio bei dažnio, o papildomos sesijos reikalingos efektui išlaikyti.

Išvados. Parkinsono liga – kompleksinis sutrikimas, sukeliantis tiek motorinius, tiek neuropsichiatrinius simptomus, kurių palengvinimui reikalingas daugiaveiksnis gydymas. Vienas iš pasirinkimų – transkranijinė magnetinė stimuliacija, kurios potencialiam efektui tirti gydant motorinius, nuotaikos bei kognityvinius simptomus sergant Parkinsono liga skiriama vis daugiau dėmesio.

Raktažodžiai: Transkranijinė magnetinė stimuliacija, Parkinsono ligos gydymas

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a method of safe and non-invasive brain stimulation via electromagnetic induction, which works in modulating cortical and subcortical activity and their resulting effects by discharging an electrical current into a TMS coil, producing a brief perpendicular magnetic pulse to a certain depth from the surface of the scalp, which leads to axonal depolarization [1–3].

Three basic types of TMS exist: single pulse (sTMS), discharging a single pulse every few seconds; paired-pulse (ppTMS), discharging two paired pulses with either identical or different intensities every few milliseconds; and repetitive TMS (rTMS), delivering a combination of more than two pulses every interval of less or equal to two seconds [3].

An increasing amount of data has shown TMS to be promising in both the diagnosis and treatment of various adult neurological and psychiatric conditions, with rTMS being the predominant type used in their treatment, due to its effects on neuronal plasticity and potentiating synaptic transmission in treated patients, currently is approved for treatment of obsessive-compulsive disorder, smoking cessation and major depressive disorder, with a response rate of 40-60% in the latter [2, 4, 5].

The most common complications reported have included headaches (6.9%) and discomfort at the stimulation site (2.7%), the most common serious complication of this treatment method being seizures, with a risk of around 0.01% per session, however, the risk increases substantially in patients with epilepsy, increasing to about 3% per session [6, 7].

An important topic of emerging research is TMS use as an adjunctive treatment in Parkinson's disease (PD), a progressive neurodegenerative disorder mostly presenting later in life that is caused by the accumulation of alpha-synuclein (Lewy bodies) in the neuronal bodies of various parts of the brain, predominantly substantia nigra, causing its degeneration and leading to a loss of dopamine in the basal ganglia, which control muscle tone and movement [3, 8].

The disease affects 0.1–0.2% of the population, with prevalence increasing to 1% in people above 60 years of age [8]. A core feature of the disease is parkinsonism, a group of disorders characterized by movement problems, including bradykinesia, rigidity, and tremor [9]. However, non-motor manifestations are also characteristic of the disease, affecting up to 99.7% of patients and can be either somatic, such as pain, gastrointestinal and olfactory dysfunction, urinary incontinence and orthostatic hypotension, or neuropsychiatric, such as cognitive impairment, sleep, mood disorders, dementia and psychosis. [10–12].

Currently, no specific laboratory or imaging tests exist to confirm the diagnosis of PD, and the disease is diagnosed clinically, by looking for characteristic symptoms and excluding other causes of Parkinsonism, such as medications, essential tremor, progressive supranuclear palsy, Lewy body dementia, multisystem atrophy, hydrocephalus or subcortical stroke [8].

Treatment of motor symptoms usually consists of dopamine replacement therapy using either levodopa, combined with carbidopa or benserazide, which are most effective at

providing symptom relief, or dopamine agonists, which have lesser efficacy but also fewer side effects; other medications based on symptoms, such as apomorphine or anticholinergics, and physiotherapy playing an important supplemental role [8, 9, 12–14]. Treatment of non-motor symptoms mirrors their treatment in the general population, but may be affected by adverse reactions from both motor and non-motor symptom management – for example – dopaminergic, anticholinergic medications, amantadine may contribute to psychosis, dopamine agonists may cause impulse control disorders, benzodiazepines may worsen cognitive function. In addition, there is a lack of evidence in terms of treatment of certain neuropsychiatric symptoms, such as anxiety or mild cognitive impairment [9].

Given these challenges as well as the limited efficacy of standard treatment, which provides effective symptom relief for only 3–6 years on average while causing uncomfortable side effects, it's extremely important to look for supplemental treatment options where possible to improve the patient's quality of life and extend the symptom-free period [8, 12].

This article will assess the newest scientific literature on the efficacy of transcranial magnetic stimulation in the treatment of motor and neuropsychiatric symptoms of Parkinson's disease.

METHODS

Literature search was performed using the "Pubmed" database. The following keywords and their combinations were used: "Parkinson's disease", "motor symptoms", "non-motor symptoms", "depression", "anxiety", "cognitive impairment", "dementia", "TMS", "treatment". 56 publications written in the English language were reviewed. The time period selected was 2014-2024. Descriptive analysis was performed for the literature review.

PD TREATMENT AND TMS

As PD is primarily a movement disorder, motor manifestations are a fundamental part of its progression, with resting tremor often marking its onset, and the other cardinal symptoms being bradykinesia, rigidity and postural instability [8,12]. Current treatment modalities for motor symptoms include dopamine replacement therapy in the early stages of disease, usually using levodopa in combination with carbidopa or benserazide, the latter preventing conversion of levodopa to dopamine in peripheral tissues, with dopamine agonists also being frequently used to stabilize the on-off periods that are experienced after prolonged use of the aforementioned treatment [12, 14]. Additionally, monoamine oxidase B inhibitor, such as selegiline or a catechol-O-methyl transferase inhibitor may be added to increase the half-life of levodopa, thus increasing the time it may remain in the central nervous system [12]. For up to 40% of patients who suffer the levodopa-induced side effect of dyskinesia (LID), or have a pronounced tremor, amantadine has been shown to be a useful option, additionally providing relief for most motor symptoms [12, 15]. For late-stage patients who don't respond to medications, invasive deep brain stimulation is available to stabilize the balance of excitatory and inhibitory signals, usually to either the subthalamic nucleus (STN) or globus pallidus [8, 16].

However, in addition to being expensive and laborious, as well as requiring strict selection criteria, this treatment usually only helps with tremor and rigidity, generally doesn't improve and may even cause or worsen neuropsychiatric symptoms, such as thought, mood and anxiety disorders, apathy, hypomania, and the patients continue to suffer from speech and swallowing impairments [16–18]. That is why some studies have emerged using TMS to stimulate cortical regions, with rTMS being the most appropriate protocol due to its longer-lasting effects in changing the amplitude of motor evoked potentials (MEP, which are used as a measure of cortical excitability) - either potentiating or depressing it [19, 20]. As a rule of thumb, high-frequency (HF) rTMS should increase cortical excitability, while low-frequency (LF) rTMS should decrease it [20]. Similarly, theta burst stimulation (TBS) is another frequently used rTMS protocol, which uses a theta stimulation pattern in either a continuous (inhibitory cTBS) or intermittent (facilitatory iTBS) manner to influence cortical excitability [21]. Although the mechanisms through which TMS produces its therapeutic effects are not clear, several studies using TMS as a diagnostic tool have identified that there is increased inhibition in patients suffering from PD, suggesting a reduced cortical excitability, while other studies identify hyperexcitability along with reduced plasticity [16, 21]. Marked reduction of short-interval intracortical inhibition (SICI, which is used to assess inhibition in the motor cortex) and cortical silent period (CSP, which should be reduced by increased inhibition) as well as ipsilateral CSP duration have been reported, in contrast to reduced intracortical facilitation (ICF) in other studies – these results may suggest polymorphic neurophysiological changes in PD [22, 23]. Various corticomotor excitability changes may lead to differing symptoms in PD patients, such as reduced corticomotor inhibition in patients suffering from freezing of gait [24]. Meanwhile, patients with cognitive impairments are shown to have higher SICI, with greatest inhibition in Parkinson's disease dementia, and progressively reducing ICF the more cognitive impairment progressed [25]. Furthermore, higher SICI correlated with worse Unified Parkinson's Disease Rating Scale (UPDRS) scores, while stronger ICF correlates with needing less dopaminergic medication [26].

MOTOR SYMPTOMS

The majority of studies evaluating rTMS use in treating PD have used an 8-coil TMS coil, which is able to target a cortical area focally, to apply to either the primary motor cortex (M1), the prefrontal cortex (PFC), or the supplementary motor cortex (SMC), although the effect sizes were modest [27]. However, emerging research has increasingly focused on treatment using rTMS protocols, often with an H-Coil (which is able to target deeper brain regions at the expense of focality) to target both hemispheres of usually either the PFC, M1, both, or SMC, at the same time, as the motor manifestations of PD are typically bilateral [3, 27, 28]. A meta-analysis using Bayesian network has found that targeting both bilateral M1 and PFC using high-frequency (5–20 Hz) rTMS was the most effective intervention in improving Unified Parkinson's Disease Rating Scale part III scores, with a mean difference of 7.60 points [28]. The rationale behind targeting both M1 and PFC is to

simultaneously induce improvements in motor and cognitive function [21]. In addition, High-frequency stimulation of only M1 bilaterally using an 8-coil has long been established to show improvements in motor function in PD patients, such as UPDRS scores, walking speed and key tapping, with an effect being greater at 25 Hz than 10 Hz frequency [3]. Furthermore, HF rTMS (20 Hz) using an 8-coil over M1 bilaterally has been demonstrated to improve dysphagia, a swallowing dysfunction symptomatic in up to 54.5% of PD patients, which was measured by UPDRS, Activities of Daily Living (ADL) and Arabic-Dysphagia Handicap Index (A-DHI) as well as Video-fluoroscopy – there were significant improvements in all items over the sham group that lasted for 3 months after the sessions [29].

Meanwhile, in patients with dysarthria, the stimulation of the primary sensorimotor areas has been shown to lead to an increased speech rate and tongue movements as well as improvement in voice quality and intensity [30].

Gait disturbance, as characterized by slow speed, short steps and reduced walking ability, are one of the most debilitating symptoms of PD, and can lead to functional decline and falls: it has been shown that when paired with physical therapy, both 1 Hz and 25 Hz rTMS over M1 bilaterally is effective in enhancing improvements in walking speed and complex walking tasks, with the improvement correlating with increased CSP and SICI [31]. Similarly, a meta-analysis found that for freezing of gait, as measured by FOG-Q, walking time, TUG and UPDRS, frequencies of 1 Hz to 25 Hz all appear to show substantial efficacy, 25 Hz group having a statistically insignificant yet better effect size than the others, and stimulation of M1, SMC or M1 and DLPFC together all appearing to be similarly efficacious stimulation sites, with stimulation of DLPFC alone showing no positive effect for these scores [32]. In addition, the positive effects of stimulating M1 on bradykinesia and rigidity seem to be present even after a single rTMS session, with repeated daily sessions for 10 days showing improvements that last for a month, supplemental monthly sessions counteracting the decay of TMS benefits [21]. However, pairing low-frequency (1 Hz or less) stimulation over M1 or M1 and dorsal premotor cortex combined doesn't seem to show significant improvement, although studies exist showing LF rTMS benefits in treating motor symptoms by stimulating only M1 [28, 33, 34]. Additionally, The dorsal premotor cortex doesn't seem to show benefits even when higher-frequency (>1 Hz) rTMS is applied, possibly because this area is not as affected by neurodegeneration of substantia nigra due to having less vital input from the basal ganglia [21]. However, low-frequency stimulation has been shown to be effective in treating motor symptoms when stimulating SMC, though several physiological studies suggest that LF rTMS less than 0.9 Hz does not induce changes in cortical excitability [3, 35–37]. In general, abnormal SMC activity has been associated with bradykinesia and dyskinesia, basal ganglia to SMC motor pathways involved in voluntary movement control showing greatest deficits in individuals suffering from PD [21]. Evidence exists showing both the benefits of single-session applications to SMC without long-term effects, and lasting benefits of repeated sessions for 24 hours to 20 weeks after

application [21, 38].

The cerebellum has also been postulated to be an important target, although the results have been mixed: it has been demonstrated that cTBS applied over the lateral or bilateral cerebellum may decrease levodopa-induced dyskinesia (LID) without improving motor symptoms, while LF rTMS over the right lateral cerebellum improved gross motor movements while worsening fine motor movements [21]. As for comparative rTMS effectiveness in people using versus not using medication, cTBS and LF rTMS have been demonstrated to have the highest short-term and long-term effect on motor function when the patients are in the “off” state, while HF rTMS seems to be most effective in the “on” state [39]. On a physiological level, iTBS has been shown to restore plasticity of M1 and improve GABA-A-ergic neurotransmission, however, the clinical implications of this are unclear, although these neurophysiological effects correlate with disease severity [40]. Currently, a study evaluating iTBS effect while paired with physiotherapy is underway [41]. There is still, however, no consensus on which symptoms in PD patients are most likely to respond to TMS treatment, and the heterogeneity of protocols in studies of TMS as a treatment tool makes evaluation difficult [16].

MOOD DISORDERS

Depression and other mood disorders in Parkinson's Disease is one of the most important factors of patient's poorer quality of life, occurring in 2.7–90% of patients depending on the study, leading to poor cognitive performance, worse functional status and reduced medication adherence: depressive instead of motor symptoms being the most powerful predictor of beginning dopaminergic treatment [27, 42]. The root causes of depression in Parkinson's are still up for debate, with current theories attributing it to degeneration of monoaminergic neurotransmitter systems and fronto-cortical dysfunctions as well as neuroinflammation [42]. Current treatment consists mainly of selective serotonin reuptake inhibitors or tricyclic antidepressants, sometimes in combination with acetylcholinesterase inhibitors or MAO inhibitors [8, 42].

The earliest and most established use of rTMS has been in the treatment of medication-resistant depression using high frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex [1, 43]. DLPFC is also an important cortical target in treating PD-associated depression, and has been shown to improve its symptoms as well as general mood [21]. In a meta-analysis of 7 studies evaluating the efficacy of rTMS in treating PD-associated depression, four out of five qualitatively evaluated studies showed significant improvement in both clinician-administered Hedge's G and the self-administered Beck scores [43]. Another study found remission in 62% of depressed patients in terms of Beck and Hamilton Rating Scale for Depression (HDRS) scores using deep transcranial magnetic stimulation with an H-coil over M1 and PFC, and postulated that part of the antidepressive effect may be due to motor symptom improvement, as there were correlations between HDRS and ADL scores [34]. This is in contrast to a 2016 study that didn't find any improvement in mood symptoms of Parkinson disease over sham after 10 daily

sessions of treatment using an 8-coil over either M1 or DLPFC separately or both M1 and DLPFC, as measured by Hamilton Depression Rating Scale, but found a pronounced placebo effect in using TMS [44]. A 2020 meta-analysis found that only HF rTMS over left DLPFC had positive therapeutic effect – the effect persisted long-term, but was not more effective than oral fluoxetine, which was in contrast to some previous studies indicating that stimulation of DLPFC may be more powerful [45]. Furthermore, a 2022 study comparing the efficacy of HF rTMS, escitalopram, pramipexole and “routine treatment” (which consisted of levodopa and benserazide) showed better efficacy of both medications and TMS over “routine treatment” in treating PD-associated depression, but both medications had higher overall effect over TMS [46]. In terms of depression scores, the newest meta-analysis found that stimulating the dorsolateral prefrontal cortex had a statistically significant anti-depressive effect, with an effect size on depression scales of 0.42, however, only the self-administered Beck group score of 0.51 was significant, the effect size of Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale groups was not statistically significant, $p > 0.05$ [47]. As for anxiety, A study found HF rTMS with an 8-coil to be effective in treating both its and depression symptoms in Parkinson disease while using Visor 2 neuronavigation system to allow for precise targeting of DLPFC and the effect remained at 4 weeks follow-up [48].

COGNITIVE IMPAIRMENT

Basal ganglia degeneration in PD can lead to cognitive decline, and may even result in Parkinson's Disease with Dementia (PDD), which mainly affects executive function while maintaining memory, learning and higher-level language abilities relatively intact, cognitive impairment occurring in up to 78% of PD patients [49, 50]. This is due to disruption of fronto-striatal dopamine networks as well as cholinergic deficiencies extending to frontal areas, which are associated with executive function [49,51]. However, dopaminergic therapy, especially dopamine agonists may also worsen cognitive symptoms such as executive dysfunction and attention deficits, and may even exacerbate hallucinations and delusions, which are also a relatively common finding in PDD [50]. Current treatment consists of acetylcholinesterase inhibitors, such as rivastigmine, which may worsen tremor and increase the incidence of adverse drug reactions, and removal of exacerbating agents, such as changing dopamine agonists for levodopa/carbidopa [8, 50].

TMS in PD cognitive impairment and dementia has not been extensively studied: one meta-analysis found no significant effect over sham on cognitive function when targeting either M1 or PFC [52]. However, a later pilot study using 20 Hz rTMS over M1 demonstrated it having a minor effect on cognition, specifically Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores, but not Clinical Dementia Rating Scale (CDR) and Memory and Executive Screening (MES), however, the study acknowledged that targeting other regions may be necessary [53]. For example, in a crossover study, Tower of London task improvements were observed after rTMS was used on the right

DLPFC instead of the usual left DLPFC [54]. Low-frequency rTMS over the scalp vertex of patients with PD two times per day for ten days has also been shown to significantly improve MMSE scores [51]. In contrast, iTBS in PD over two sessions failed to show an improvement in frontal executive function and memory when applied over left DLPFC [55]. However, a longer exposure of iTBS twice a day for three days with 1-2 days in between for patients with mild cognitive impairment has been shown to lead to cognitive improvements for up to one month after application, likely mediated by improvement on visuospatial abilities [56].

CONCLUSIONS

Parkinson's disease is a polymorphic neurodegenerative disease which causes both motor and non-motor symptoms in the vast majority of this patient population [11]. Non-motor symptoms can include neuropsychiatric manifestations such as mood disorders, impaired sleep, cognitive impairment, dementia and psychosis [12]. Although the neurophysiological basis of Parkinson disease symptoms is complex and yet to be fully elucidated, various rTMS protocols have shown promise in treating both motor and neuropsychiatric manifestations of this disease [21, 27]. It is well established that targeting M1 bilaterally using an 8-coil HF rTMS is one of the most effective

currently devised protocols in alleviating a wide array of motor symptoms, such as gait disturbances, dysphagia, bradykinesia and rigidity, though newer research suggests that targeting both M1 and PFC, which is often done with an H-coil, may be a similarly promising method [3, 27]. Meanwhile, the left DLPFC using HF rTMS seems to be the most appropriate target in treating PD-associated depression, although the effect is not superior to that of common medications used to treat it [45, 46]. In contrast, a singular best protocol for treating cognitive impairment and dementia in PD patients is yet to be found, though targeting DLPFC could be promising [54, 56]. In general, more sessions over a longer period of time as well as using higher frequencies of up to 25 Hz ostensibly increase the efficacy of rTMS when applied over M1 or PFC, and supplemental sessions are needed to maintain its benefits [3, 21]. Future research should focus on comparing the efficacy of HF rTMS using an 8-coil versus an H-coil (or other coils used for deep rTMS) in targeting different brain regions and their combinations, as well as whether the effect is additive to using pharmacotherapy. In addition, more research is needed to elucidate the wide array and dynamics of cortical excitability changes as well as their relationship to various symptoms during PD, and the mechanism through which rTMS achieves its therapeutic effect.

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