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Review Article

Transcranial Magnetic Stimulation in Patients with Movement Disorders: A Review of Observational Study

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Abstract

Transcranial magnetic stimulation is a painless non-invasive brain stimulation technique used in cortical function in healthy individuals, inter alia and the pathophysiology of movement disorders [1]. It has been using for the treatment of a large variety of neurological and psychiatric diseases. In this study, we describe the mechanism of TMS techniques and discuss the clinical uses of TMS as a potential diagnostic tool in movement disorders. We also illustrate the basic rationale on which the therapeutic use of transcranial magnetic stimulation is based in a patients with movement disorders.

Keywords: Transcranial Magnetic Stimulation (TMS); Coil; Pulses

Introduction

Transcranial magnetic stimulation (TMS) is a painless non-invasive brain stimulation that affects the cerebral cortex but excluded deep structures [2]. Movement disorders patients, the application of TMS has been to investigate the excitability of connections with the motor areas of the cortex and this revealed information on pathophysiology and inter-individual variability in the responses has resulted in difficulties in translating this method into a clinically applicable diagnostic use [2]. Cantello and colleagues reported that repeated stimulation by 1 Hz for 25 minutes can result in long-term plasticity in the motor system; this led to increased in therapeutic applications. TMS uses magnetic field generator sends a current with peak amplitude of about 6000A to 8000A, that lasts about 1ms, through an induction coil placed on the scalp. Experimental evidence revealed the current creates a magnetic field that is perpendicular to the coil and this passes through the skull and induces an eddy current within the brain, parallel to the coil. However, sufficient intensity of stimulation must be used base on therapeutic use and the coil is held over the motor cortex, then descended downwardly and produced in the corticospinal pathway, and evidence by activation of muscles via recorded by surface electromyography [3]. Several studies also stated that TMS applications have been developed to investigate the physiology of the motor system from simple concepts that are used in clinical practice to complex sample. TMS research evidence revealed the clinical understanding of the pathophysiology of movement disorders and tests of specific neural pathways. Other Studies revealed that TMS has been used to investigate mechanisms of synaptic plasticity in the cerebral cortex. Research from animals investigates the mechanisms of synaptic plasticity by different applications of electrical stimulation delivered through microelectrodes [4]. There are two types of post-synaptic and this include the long-term potentiation (LTP) and long-term depression (LTD). Animal stimulation consistently produce LTP with high frequency stimulation, that typically given in an intermittent way of 100 pulses at 100 Hz every 12s for fifteen trials, and longer periods of lower frequency stimulation are applied to produce LTD with 2 - 5 Hz pulses given continuously for 15 - 25 minutes). The therapeutic way of inducing LTP in animal

studies is by theta burst stimulation with a stimulation pattern based on the firing arrangement that occurs in hippocampus neurons in rats, particularly when exploring novel environments [5]. The principle mode is high-frequency of 60 - 100 bursts of 3 - 4 pulses repeated at about 8-10 Hz. Transcranial magnetic stimulators reproduce the stimulation mode seen used in LTP and LDP studies in animals has opened the possibility of investigating the same mechanisms in the brains of conscious human beings [4].

Repetitive transcranial magnetic stimulation (rTMS)

The therapeutic tool in the specialty of movement disorders by creating long-lasting changes in the excitability of synapses within the motor system to modulate symptoms. There are differences between the type of stimulation that is used in animal studies and rTMS given to human beings. Firstly, study from Chen and colleagues, 2008 stated that the combination of high frequency and high-intensity stimulation used in animal studies can lead to seizures in human beings. Neuroimaging scientist consensus study agreed the safety guidelines set limits on the stimulation parameters to be used In human beings which stipulated that 5 Hz stimulation can induce an increase in cortical excitability that can outlast the stimulation by a few minutes and frequencies greater than 1 Hz are traditionally thought to induce LTP-like effects in human beings [6].

High-frequency stimulation impact

The uses of intermittently such as 200 pulses break for 1 min, a further 200 pulses, upwardly, up to the maximum permitted limit. This mode might be important with a standard protocol to decrease cortical excitability uses 1 Hz stimulation, usually given in a continuous train of about 800 - 1600 pulses. An alternative use of rTMS has been developed that was modeled on theta burst stimulation in animals; the technique comprises short, repeating bursts of TMS pulse at 50 Hz. This seems to be a much quicker method to induce LTP-like or LTD-like changes, although has had limited use in therapeutic studies so far [6].

Literature Review on Effectiveness of rTMS

This also known as LTP-like or LTD-like, It stimulate indirectly for the effect of the stimulation at the level of the synapse in human beings instead of the effect by changes in mode (e.g. size of the motor evoked potential induced by a TMS shock of a particular intensity or changes in functional imaging parameters [1]. Many evidence claimed the effects between rTMS and LTP and rTMS and LTD which induced in animal studies. Example include, the effects of rTMS in humans beings can be modulated by NMDA antagonists, GABA antagonists, and electrical stimulation prior to rTMS in similar ways to LTP and LTD in animal studies [1]. The effects of some mode of rTMS can be modulated by muscle contraction during and shortly after the stimulation. This is applicable in the design of clinical studies such as asking the patient to move immediately after stimulation may change the effect of rTMS. Clinical understanding of therapeutic rTMS studies shows technical structure: Firstly, the intensity of rTMS is related to the resting motor threshold (RMT), the minimum intensity of stimulation to the motor cortex evoke a response in the target muscle. Therefore, investigators might describe their stimulation application as "15 min of 1 Hz of rTMS given at 90% RMT" [1]. This means that TMS pulses were given continuously once per 15 min at an intensity of 90% of the RMT. Higher frequencies of stimulation, the total number of pulses divided into trains that separated by intertrain intervals of lengths. Secondly, studies used repeated sessions of rTMS in healthy individuals have shown that repeated sessions of rTMS of daily use can lead to a build-up of effects that enhance therapeutic benefits from a single application [7]. Thirdly, participants with epilepsy and pacemakers or deep brain stimulators are contraindicated with rTMS. However, research evidence stated the safety measures used TMS in patients with deep brain stimulators. Lastly, different investigators used placebo method of stimulation in therapeutic studies. Two major method identified: either a sham coil and makes a sound that discharge of a real TMS coil; or a real TMS coil that is held on the edge on the scalp and that discharge certain energy into the brain. TMS given at high intensities with > 90% RMT induces a sensation on the scalp, which is not replicated by current placebo coil methods, thus leading to a potential problem with unmasking of participants. A coil that incorporates an electrical stimulator that produces scalp sensation but does not stimulate the brain has been developed to improve the similarity between real and sham rTMS [8].

Diagnostic applications of TMS in movement disorders

Established findings of TMS applications has been used to investigate the pathophysiology of movement disorder and have potential diagnostic application for other conditions. There are different application method and techniques which include the motor thresholds, input-output curves, short intracortical inhibition, intracortical facilitation, inter hemispheric inhibition, and silent pe-

riod. Chen and colleagues investigated the response of the motor system to single sessions of repetitive TMS to assess the sensitivity of the motor system to plastic changes, rather than look for any therapeutic effect of this stimulation. Also, Cantello., *et al.* study revealed the techniques and the information with regard to the state of the motor system that they can each provide. Cantello stated further that the most important potential diagnostic application of TMS can be to useful to distinguish patients who have similar symptoms and different underlying causes of their movement disorder, for example, patients with Parkinson's disease (PD) and dystonia. Andrew in 2013 reported the important in a clinical setting and importance between patients with PD and progressive supranuclear palsy (PSP) in a clinical settings. A Research concerns was particularly in movement disorder and whether TMS might help to distinguish between movement disorders with organic or psychogenic causes. In contrast, the studies of clinically relevant concerns were investigated and the data are frequently not sufficient specificity and sensitivity to lead to the application of the tests in a clinically diagnostic way in individual patients.

Differentiation of parkinsonism conditions

A common research clinical findings expatiate difficulty in differentiating patients with different parkinsonian conditions. The differentiation between PD and atypical parkinsonism can be clinically difficult, particularly in the early stages; this has important ramifications for the patient in terms of treatment and prognosis. A further clinical conundrum, although the importance to the patient is the challenges of differentiate the different causes of atypical parkinsonism whether is PSP, multiple system atrophy [MSA], and corticobasal degeneration [CBD]).

Observational analysis and results in motor disorder (A review of different studies)

Kuhn and colleagues investigated the response to a range of TMS protocols in 13 patients with MSA, 18 with PSP, 13 with CBD, and 15 with PD. Clear differences were found among the groups: patients with PSP and MSA had diagrammatical stare input-output curves than other groups; patients with CBD had higher resting thresholds and lager input-output curves than did other groups; the silent period was short; and transcallosal inhibition was low in patients with CBD. By contrast, patients with PSP or MSA had prolonged silent periods. Wolters and colleagues found abnormalities of transcallosal inhibition in patients with CBD or PSP that were not seen in patients with MSA or PD. Intracortical inhibition was abnormal in all groups of patients assessed by Kuhn and colleagues, similar to previous findings in patients with PD and atypical parkinsonism changes. Despite these major group differences, there was overlap among test results on all of these measures in patients with different diagnoses, even though these patients were typical clinical cases and not early patients with few symptoms where the clinician would require other help in diagnosis from any potential TMS test. Kuhn., *et al.* [10] study data are of interest pathophysiologically and the results suggest that the solution to the main clinical problem distinguishing between PD and atypical Parkinsonism by the application of TMS. Eusebio and colleagues investigated 2013 diagnosis of MSA with TMS techniques and focused on the possible implication of the corticospinal tract in MSA, as shown by the results of previous clinical and pathological studies. The triple stimulation test (TST) was used and more sensitive measure of corticospinal conduction than CMCT. Eusebio and colleagues in 2014 stated further that the results of the TST were more commonly abnormal in patients with MSA than in those with PSP or PD. In a well-managed patients there was clear overlap among different groups, with several patients with MSA having normal TST results, whereas no patients with PD or PSP had an abnormal TST result. None of these studies in patients with atypical parkinsonian conditions has confirmed the eventual diagnosis with autopsy; this would clearly be a complex and time-consuming study to undertake. The clinical diagnosis of patients with atypical parkinsonian conditions, particularly CBD and PSP but also in patients with a typical clinical phenotype, is difficult and frequently incorrect. Thus, the usefulness of these techniques is again called into question, and perhaps would only be answered by an, admittedly difficult, study of a series of TMS (and perhaps other) techniques delivered repeatedly to patients with parkinsonism that varies from early symptoms to late disease, followed by autopsy confirmation of the underlying diagnosis. Espay and colleagues used several electrophysiological techniques, including TMS, to test a group of patients with psychogenic dystonia, to compare them with patients with organic dystonia. TMS measures of intracortical inhibition, intracortical facilitation, and silent period were abnormal in patients with either psychogenic or organic dystonia. The results of this study raise several questions with regard to the pathophysiology of psychogenic dystonia; however, from a clinical standpoint, these results indicate that TMS tests are not yet suitable to aid the diagnosis of these patients. Dystonia is characterised by involuntary muscle spasms

that lead to an abnormal posture of the affected body part. Clinical phenotypes, which range from focal dystonia to severe generalised dystonia. Patients with psychogenic dystonia might have underlying personality disorders or other psychiatric disturbances. In this regard, there is a correlation between a personality dimension that is related to negative emotion and anxiety and intracortical inhibition in a sample from the general population. TMS measures used so far give little to the clinician in terms of diagnostic tools for patients with movement disorders. The TST could potentially be of benefit to diagnose patients with MSA but whether the test can correctly identify patients with the early symptoms of MSA is unknown. The success of this test is perhaps unlikely because TST is a measure where abnormalities correlate with severity of clinical symptoms. If confirmed in a larger series of patients, the TST could be a useful screening tool in patients with prolonged CMCT and with mutations in PARK2, particularly because such mutations are a relatively common cause of young-onset PD. There are other areas of for TMS.

TMS study models designs and paradigms in physiological and pathological studies

TMS studies investigated by Robertson., *et al.* 2003 follow a model design and stipulated a set of measures for cognitive task, motor or visual excitability and is compared without/with the impact of TMS-induced interference effects applied to a given cortical area. We are considering the physiological rationale of reversible nature of rTMS effects on the TMS targeted region and its associated network and the same mode of measures performed at baseline, under TMS before or after stimulation, and after recovery may be statistically compared in classical pre-post and recovery (A-B-A configuration) designs. The same population of participants becomes its own reference population, so that potential bias related to between participant variability when comparing to independent control groups is limited or null. However, intra-individual, test-retest variability is essential to consider and needs further study. Three main types of TMS studies are used to determine causal relationships between targeted cortical areas and cognitive tasks or measurable physiological signals (Robertson., *et al*. 2003). A demonstrative example of a TMS study using the three modalities, on-line, off-line and chronometric. The mode to consider by the goal is to study the cerebral areas causally involved in a detection and localization task in which the target is presented in the left or right visual field unilaterally or bilaterally. TMS coil is has been applied over the right Intraparietal Sulcus (IPS) on the posterior parietal human cortex. Exist evidence identified three possible study designs. In the on-line study, high-frequency pulses are delivered on the area at each trial, in a continuous way in the period. Preceding and following target presentation. In the off-line study. Participants' performance is assessed on a significant number of trials in the same task immediately before and after TMS. In the chronometric study single pulses or short trains of rTMS are delivered to a given brain area at distinct time intervals [7].

Other potential clinical uses

TMS techniques genetically used to identify unaffected carriers and genetics finding stated genes that cause dystonia have low penetrance and there are unaffected gene carriers within affected families. the genes that are already known in unaffected carriers easily identified and given appropriate genetic counseling. There are some families where the genetic cause is idiopathic. What answer can we provide for these? Observational studies so far, it is possible that individuals who are at risk in families with genetic dystonia could be screened with TMS techniques, and the unaffected carriers identified. Many studies show that patients with dystonia caused by mutations in TOR1A shows excessive response to rTMS, and the response lasts longer than that in healthy controls. Although, Another hypothesis from patients with dystonia caused by mutations in TOR1A, where unaffected carriers seem to have similar abnormalities on some TMS measures (e.g. intracortical inhibition and silent period) as does unaffected carriers. Unaffected gene carriers who are of an age less than 28 years. are unlikely to show symptoms have a completely different response to rTMS; rather, they show almost no change with stimulation [7]. This difference, it is possible to be present from birth and potentially able for identification of the dystonic syndrome in childhood before any symptoms have developed, and potentially allow differentiation of those patients with TOR1A who likely to develop dystonia and those unlikely to develop symptoms. Research in animal models of PD show differences in the response to repetitive electrical stimulation among animals that develop dyskinesia in response to levodopa and those that do not. If such differences are also seen in human beings with PD, it might be possible to use TMS techniques to stratify patients into high-risk or low-risk of developing levodopa-induced dyskinesia before treatment is started, which could be used to help guide treatment choices. Finally, TMS might also help

the diagnostic categorisation of patients with attention-deficit hyperactivity disorder (ADHD), commonly seen in patients with Tourette's syndrome [7]. Being homozygous for a particular polymorphism in SLC6A3 is associated with a risk of ADHD and poor behavioural response to methylphenidate. In one study of changes in intracortical inhibition after a single dose of methylphenidate, a clear increase in intracortical inhibition seen only in children with ADHD who were heterozygous for the SLC6A3 polymorphism, with no response seen in the children who were homozygous. This shows how a simple TMS measure could be used to help categorise patients with ADHD and possibly predict their response to medication.

Therapeutic applications of rTMS in patients with movement disorders

Parkinson's disease is a neurological movement disorders and clinical attention on rTMS therapeutic studies is widely accepted as part of the management. The therapeutics application of rTMS in patients with PD are reviewed, followed by observational evidence for use of rTMS to treat motor and non-motor symptoms of PD. Physiological evidence for rTMS and the pathological process that underlies PD causes widespread dysfunction of the brain and that particularly affects processing in the cortico basal ganglial loops. Experimental evidence has focused more on motor symptoms of PD [10], although a few percentage of disability in PD is due to non-motor symptoms such as depression. Depression management with TMS has been discussed in another study. Functional imaging studies identified hypometabolism within the supplementary motor area (SMA) and the prefrontal cortex during movement in patients with PD and caused by the primary dysfunction in the basal ganglia. Management for PD with medication such as levodopa reverse many changes in both human beings and animals trials. rTMS excitatory has a similar effect translated into an improvement in clinical (motor) symptoms (Cuhn., *et al.* 2007). rTMS has capability of inducing dopamine release from the basal ganglia in healthy individuals, the application of 15 Hz of rTMS over the motor cortex (M1)36 or the dorsolateral prefrontal cortex (DLPFC)37 induced ipsilateral dopamine release from the putamen and caudate, respectively, as measured by raclopride binding [11]. A similar effect has been shown in patients with PD after stimulation of the motor cortex. In one of these studies, decreased raclopride binding was seen bilaterally, despite rTMS stimulation being given to only one motor cortex. One interpretation of this finding is that it shows a placebo effect of stimulation; an alternative interpretation is that the actual effects of rTMS are different in patients with PD compared with healthy individuals. Bilateral decreases in raclopride binding have also been shown in patients with PD who received sham rTMS. The possible placebo effect of rTMS emphasizes the need for adequate sham control conditions in rTMS therapeutic studies [10]. Evidence of human Model of PD, that levodopa-induced dyskinesia represent abnormal plasticity in the motor system. Many literatures with rTMS have specifically looked at the potential application of brain stimulation in PD patients with dyskinesia. Therapeutic trials of motor symptoms: single-session studies. Early studies of the potential therapeutic application of rTMS in PD investigated changes in parkinsonian motor symptoms during a high-frequency of 5 Hz with low-intensity rTMS protocol delivered once over the M1, with the aim to increase excitability. The results were inconsistent, and subsequent research focused on the possibility of using rTMS to induce effects that could outlast the stimulation [7]. We only have little method in the inclusion criteria, stimulation protocols, outcome measures, and overall study design. In most study, the hand motor area (M1) contralateral to the affected body side was chosen as the target, and excitatory and inhibitory rTMS were applied. After all applications of real rTMS, a 10 - 30% improvements was shown in most studies with outcome measures, with no effects after sham stimulation. In another case study, the duration of these effects was not tested, but this was probably 25 min or lesser. In another investigation, measures of corticospinal excitability were used: the effects of rTMS on corticospinal excitability were generally weak or absent, depending on whether the patients were studied on or off medication, although some degree of normalisation in the activity of inhibitory cortical circuits was shown and electrophysiological and behavioural changes seen in the studied conducted by Magistris and his colleaques in 1998. Results from all the studies shows that patients with PD needed to be on medication for rTMS to affect their cortices in the way expected from studies in healthy individuals. This is important for the design of future therapeutic studies and standard for induction of plasticity in animal studies is aided by dopamine receptor activation [10]. motor symptoms clinical trial: multiple-session studies inconsistency of the single-session results, the transient clinical gains seen in some studies after a single session of rTMS have encouraged long-term treatment studies in patients with PD. The

basic effects of rTMS build-up and gradually restore the abnormal cortical excitability or corticocortical connectivity, or both, that results from the underlying pathological process in PD. In a single-session studies, a range of targets and stimulation protocols have been tested and validate as standard by America Neuroimaging Scientist Association. The common target is the M1 and in most instances the hand and leg areas have been stimulated bilaterally during the same session. In one clinical study, M1 stimulation was combined with DLPFC stimulation [10]. There are methodological differences such as excitatory (high-frequency) rTMS can improve upper-limb bradykinesia, gait speed, and the score in the motor section of the unified Parkinson's disease rating scale (UPDRS); these improvements range from 10% to an impressive 40% for some of the outcome measures. In rare occasions, improvements were shown to last for up to 1 month after the end of the stimulation regimen, but were gradually lost. eventually, results have not been same, and some stimulation standard and regimen protocols have shown no benefit after rTMS. The choice of stimulation parameters was frequently based on safety concerns rather than on objective measures of excitability. For example, the hand and the leg motor area were stimulated with the same intensity; however, higher stimulation intensities are usually necessary for the pulse to reach the leg motor area, which is deep in the wall of the central sulcus. rTMS might have remote as well as focal consequential effects, and thus it is highly probable that the response of a cortical area to a standard rTMS train of pulses might be diff erent if preceded by another rTMS train given to a functionally relevant area; this results in difficulty in predicting the consequences of sequential arm area stimulation followed by leg area stimulation. The effects on clinician-based measures of function can be generally seen after rTMS in patients with PD [10].

However, what the benefit of rTMS is on functional outcome in PD is not examine, nor is there neuroimaging scientist consensus about which symptoms are responsible for rTMS. Conclusively, rTMS will offer more benefit in the therapy for PD currently on medications is still questionable. Although, Clinical trials of levodopa-induced dyskinesia explained in Three different studies which specifically identified and investigates the effect of rTMS protocols on the severity of levodopa induced dyskinesia. Koch and colleagues found that a single session of rTMS at 1 Hz to the SMA bilaterally lowered the severity of dyskinesia for 30 min after stimulation. Therefore, 66% reduction in dyskinesia scale, as judged by reviewers of video footage who were unaware of the stimulation protocol at 15 minutes post-stimulation (Andrew., *et al*. 1998). No side effect was seen after sham stimulation. Dyskinesia worsened after stimulation with 5 Hz. In a follow-up paper, 43 a transient effect of a single session of 1 Hz stimulation over the SMA was again seen, by contrast with sham stimulation. However, daily sessions of the same stimulation for 5 days shows insignificant cumulative effect from patient diaries of dyskinesia occurrence and severity. Rektorova and colleagues assessed the effect of high frequency of 10 Hz stimulation of the DLPFC or motor cortex, given as daily sessions for 5 days, on gait and bradykinesia in patients with PD. The intervention shows insignificant benefit and the study was terminated early. Also, in another separate report, these investigators detailed the effect of DLPFC stimulation on dyskinesia in four patients: all reported a subjective improvement in dyskinesia and a non-significant reduction in the UPDRS IV (motor complications subscale) score after the 5 days of treatment. Dystonia is a movement disorder in which involuntary movement contraction cause uncontrolled twisting or abnormal postures (Cheu., *et al*, 2008). Dystonia may be focal, involving just one region such as the head, neck or face. The pathophysiology of dystonia can be categorized in inherited (i.e. autosomal dominant, recessive, x-linked or mitochondrial) Acquired (i.e. vascular, iatrogenic, neoplastic, traumatic or psychologenic and idiopathic (sporadic or familiar) (Aibanese., *et al*. 2013). Four different studies have assessed the effects of rTMS in patients with dystonia: two in patients with focal hand dystonia, one in patients with axial dystonia, and one in patients with cervical dystonia. Focal hand dystonia is difficult to treat pharmacologically or with injections of botulinum toxin, and an alternative form of treatment is clearly needed. Siebner and colleagues used inhibitory rTMS applications over the motor, premotor, and supplementary motor cortices in patients with focal hand dystonia. Sham method was used in both studies. After one session of rTMS over the motor cortex. There was a significant improvement using rTMS Allam and colleagues identified a case of 37-year-old man with segmental dystonia that affected the neck and right arm who was treated with an identical regimen. The patient had a moderate improvement in symptoms and function relating to improvement in the neck dystonia for 4 months after the stimulation; no improvement was noted in the right dystonia. Tourette's syndrome. The results of electrophysiological and imaging studies have shown cortical hyperexcitability in patients with Tourette's syndrome [10]. In electrophysiological terms, this this has been shown by a reduction

in short intracortical inhibition and afferent inhibition. Functional imaging of patients with Tourette's syndrome has detected activity in supplementary motor and limbic areas before tics. These findings have encouraged the clinical use of rTMS in a few related studies with a wide range of stimulation parameters [7]. Results from three studies that included with no sham stimulation condition reported no major effect of rTMS stimulation compared with sham stimulation. Two of these studies used low-frequency stimulation of the premotor area, with slightly different parameters, together with a rating of tic severity by clinicians and patients. Stimulation was given once a day for 2 days. The results of these two studies as well as those from Chae and colleagues of a variety of stimulation frequencies and sites, including a sham condition showed a clear placebo effect with sham stimulation, indicating that placebo responses to rTMS are important in patients with Tourette's syndrome. An uncontrolled trial and a follow-up study of rTMS given over the SMA showed impressive reductions in tic severity scales, including complete remission of tics in two patients after 2 weeks of treatment, in patients resistant to other forms of treatment. These promising results have not, as yet, led to a placebo-controlled trial [7].

Chorea

The use of rTMS in chorea has been reported in many literatures. The clinical importance of rTMS in chorea has been reported in two studies conducted by Osaki and his colleaques: one labelled study in patients with Huntington's disease and one single-case report of a patient with post-stroke hemichorea. Brusa and colleagues applied parameter of either 1 Hz to 5 Hz, or sham rTMS over the SMA on 3 consecutive days to four patients with Huntington's disease. Recording videos were taken at baseline and at different time points after stimulation (15, 30, 45 and 60 minutes), and were assessed by raters, who were unaware of the stimulation type or timing of the video. A clear reduction was seen in the chorea subscale of the unified Huntington's disease rating scale (UHDRS) with 1 Hz stimulation at 15 min post-stimulation of mean of 13 points at baseline; mean of 6 points at 15 min, and no change was seen with sham or 5 Hz stimulation. In a single case report of a patient with hemichorea secondary to a midbrain or caudate haemorrhage, In another cross-sectional study, which included ten patients with essential tremor, a single session of 1 Hz of rTMS given over the cerebellar vermis was compared with a sham rTMS condition. Masked clinician ratings detected improvement with a standard tremor scale and accelerometry ratings of the strength of the tremor at 5 min after rTMS, but not after sham stimulation [12]. No difference between sham and real stimulation was seen at 60 minutes. The intensity used for the stimulation of full percentage of stimulator output was high; therefore, whether participants might have been able to tell the difference between real and sham stimulation is debatable. Furthermore, when stimulating over the cerebellum, it is difficult to determine whether any deeper structures will have been affected. Cortical tremor is a myoclonic condition that is frequently familial and is associated with progressive ataxia and epilepsy. Patients commonly have a postural "tremor", which is, in fact, a small amplitude repetitive myoclonus. Associated cortical discharges occur, and the disorder is classified as a form of cortical myoclonus [13]. 1 Hz of rTMS over the premotor but not the motor cortexin one patient with cortical tremor produced a substantial reduction in the spectral power of the tremor that lasted for at least 75 minutes after stimulation. In another study, where premotor stimulation was given once per day for 2 days, there was a cumulative beneficial effect on the spectral power of the tremor, although the tremor was more severe at baseline on the beginning of day two than it was on the beginning of day one. The patient also reported benefit in daily activities (i.e. drinking and brushing hair), which were sustained for about 1 week. The clinical and therapeutic benefit of rTMS of 14 Hz over the DLPFC in daily sessions for 5 days in a patient with depression and tardive dyskinesia has been reported effective. This unmasked study showed an improvement in the Simpson-Gardos clinical rating scale score for tardive dyskinesia that lasted for about 5 days after the end of the final rTMS session [14-49].

The observational view

Observational studies discussed in this review elucidate the benefit of rTMS and placebo effects after sham stimulation. Many studies have explained the mimic experience over time but there is a need to know the physiological rationale behind the mechanism. Many participants noted sensation when high stimulation intensities are used and produce more sensory stimulation of the scalp. Although, there are protocols that uses regular and burst stimulation with low stimulation intensities, and I will encourage for future trials. What are the method adopted for the therapeutic use of rTMS and clinical outcome measure? We would suggest the use of outcome measure to identify improvement and easy parameter mode for movement disorder condition.

Conclusion

We reviewed the published evidence for the use of TMS and rTMS in patients with movement disorders with observational studies. An observational question to ask at this point is where are we now in relation to the diagnostic and therapeutic applications of rTMS? The answers to this question raise important concerns for TMS researchers and might help to focus TMS research on areas with the highest potential benefit.

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