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

Opeyemi Oluwasanmi Adeloye, Oyeneyin Babatunde David and Olukoju Idowu

University of Medical Science Teaching Hospital, Ondo, Nigeria

Abstracts:

Transcranial magnetic stimulation is a painless non-invasive brain stimulation technique that used in cortical function in healthy individuals and inter alia, the pathophysiology of movement disorders. Many years, its use has evolved from primarily research purposes to treatment of a large variety of neurological and psychiatric diseases. In this article, we describe the theoretical background to TMS techniques and discuss the uses of TMS as a potential diagnostic tool in movement disorders. We also illustrate the basic principles on which the therapeutic use of transcranial magnetic stimulation is based and review the clinical trials that have been performed in patients with movement disorders.

Introduction:

Transcranial magnetic stimulation (TMS) is a painless non-invasive brain stimulation that affects the cerebral cortex but excluded deep structures. In patients with movement disorders the most common application of TMS has been to test the excitability of connections within and among motor areas of the cortex, which has provided useful information on pathophysiology; however, inter-individual variability in the responses has resulted in difficulties in translating this method into a clinically applicable diagnostic use. Cantello and colleagues reported that repeated stimulation (e.g., 1 Hz for 20 min) can result in long-term plastic changes in the motor system, which has led to increased interest in possible therapeutic applications. Transcranial magnetic stimulation (TMS) uses magnetic field generator sends a current with peak amplitude of about 8000A that lasts about 1ms, through an induction coil placed on the scalp. Experimental studies revealed that current creates a magnetic field that is perpendicular to the coil; this passes through the skull and induces an eddy current within the brain, parallel to the coil. If a sufficient intensity of stimulation is used, and the coil is held over the motor cortex, then descending volleys can be produced in the corticospinal pathway, and the resulting activation of muscles can be recorded by surface electromyography. 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. Complex applications have been used extensively to help understand the pathophysiology of movement disorders and tests of specific neural pathways. Studies revealed that TMS has been used to investigate mechanisms of synaptic plasticity in the cerebral cortex. Research from animals and in brain slices from animals to investigate the mechanisms of synaptic plasticity by different applications of electrical stimulation delivered through microelectrodes. These studies have identified two main types of post-synaptic, long-term plasticity: long-term potentiation (LTP) and long-term depression (LTD). The types of stimulation that most consistently produce LTP in animal studies are high frequency stimulation, which are typically given in an intermittent way (eg, 100 pulses at 100 Hz every 10 s for ten trials), whereas longer periods of lower frequency stimulation are applied to produce LTD (eg, 1–5 Hz ppulses given continuously for 20–30 min). Effective way of inducing LTP in animal studies, is by theta burst stimulation: a pattern of stimulation based on the firing arrangement that occurs in hippocampal neurons in rats, particularly when exploring novel environments. The basic pattern is high-frequency (50–100 Hz) bursts of 3–4 pulses repeated at about 4–7 Hz (the theta frequency in electro encephalogram

Terminology transcranial magnetic stimulators that can reproduce the stimulation patterns 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.

Repetitive transcranial magnetic stimulation (rTMS)

This could be a 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. Many differences between the type of stimulation that is used in animal studies and rTMS given to human beings. First, the combination of high frequency and high-

intensity stimulation that are used in animal studies can lead to seizures in human beings and, in view of this, internationally agreed safety guidelines set limits on the stimulation parameters used. In human beings, 5 Hz stimulation can induce an increase in cortical excitability that can outlast the stimulation by a few minutes; thus, frequencies greater than 1 Hz are traditionally thought to induce LTP-like effects in human beings.

High-frequency stimulation Impact

This is usually given intermittently (eg, 200 pulses, break for 1 min, a further 200 pulses, and so on, up to the maximum permitted limit); this pattern might be important with regard to the effects produced. A standard protocol to decrease cortical excitability uses 1 Hz stimulation, usually given in a continuous train of about 900–1800 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.

The effectiveness of rTMS

This also called LTP-like or LTD-like because it is not possible to record directly the effect of the stimulation at the level of the synapse in human beings; rather, the effect is inferred by changes in parameters such as the size of the motor evoked potential induced by a TMS shock of a particular intensity, or changes in functional imaging parameters. However, there are clear similarities between the effects of rTMS and LTP and rTMS and LTD that are induced in animal studies. For example, 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. The effects of some forms of rTMS can be modulated by muscle contraction during and shortly after the stimulation. This event is important in the design of therapeutic studies (eg, asking the patient to move immediately after stimulation might abolish or change the effect of rTMS). To understand the design of therapeutic rTMS studies, a few technical points need to be highlighted. First, the intensity used to deliver rTMS is commonly related to the resting motor threshold (RMT) the minimum intensity of stimulation to the motor cortex that is needed to evoke a response in the target muscle. Therefore, in a typical study, investigators might describe their stimulation application as "20

min of 1 Hz of rTMS given at 90% RMT". This means that TMS pulses were given continuously once per 20 min at an intensity of 90% of the RMT. With higher frequencies of stimulation, the total number of pulses is usually divided into trains, which are separated by intertrain intervals of various lengths. Secondly, therapeutic studies used repeated sessions of rTMS Studies in healthy individuals have shown that repeated sessions of rTMS (eg, daily sessions) can lead to a build-up of effects that might enhance any therapeutic benefits gained from a single application. Thirdly, participants with epilepsy or implantable electronic devices, such as pacemakers or deep brain stimulators are typically excluded from studies with rTMS. However, some investigators have, with appropriate safety measures used TMS in patients with deep brain stimulators. Lastly, a number of investigators have used some form of placebo stimulation in therapeutic studies. Two main methods are used: either a sham coil that looks similar and makes a sound that is similar to the discharge of a real TMS coil; or a real TMS coil that is held on the edge on the scalp (rather than fl at) and that does not discharge substantial amounts of magnetic energy into the brain. TMS given at high intensities (>90% RMT) induces a considerable 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.

Diagnostic Applications of TMS in movement Disorders

Established findings of TMS applications have been used to investigate the pathophysiology of movement disorder and have potential diagnostic application for other conditions. The most commonly applied techniques are motor thresholds, input-output curves, short intracortical inhibition, intracortical facilitation, inter hemispheric inhibition, and silent period. In addition, some investigators have examined 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. Cantello study revealed the techniques and the information with regard to the state of the motor system that they can each provide.

The insights that TMS techniques have given into the pathophysiology of movement disorders have been reviewed elsewhere. The most important potential diagnostic application of TMS would be to help

distinguish patients who might have similar symptoms but in fact have different underlying causes of their movement disorder, for example, patients with Parkinson's disease (PD) and dystonia might be interesting for the researcher, these are unlikely to be important in a clinical setting. However, a simple test enable the distinction between patients with PD and those with progressive supranuclear palsy (PSP) would be of clinical interest. A common related concern, particularly in specialist movement disorder clinics, is whether tests that incorporate TMS might help to distinguish between movement disorders with organic or psychogenic causes. Unfortunately, the studies in which these clinically relevant concerns were investigated are, in general, scarce and, in those that are available, the data are frequently not of 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 clinical conundrum is how to distinguish 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 difficulty, although perhaps of less importance to the patient, is the problem of distinguishing the different causes of atypical parkinsonism (eg, PSP, multiple system atrophy [MSA], and corticobasal degeneration [CBD]).

Observational Studies in Motor Disorder

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. Substantial differences were found among the groups: patients with PSP and MSA had steeper input-output curves than other groups; patients with CBD had higher resting thresholds and fatter 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. Despite these substantial 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 those early patients with few symptoms where the clinician would be most likely to require other help in diagnosis from any potential TMS test. Therefore, although these data are of interest pathophysiologically, the results suggest that the solution to the main clinical problem distinguishing between PD and atypical Parkinsonism would not be assisted by the application of available TMS techniques. Another study from Eusebio and colleagues looked more specifically at the 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. They used a triple stimulation test (TST), a much more sensitive measure of corticospinal conduction than CMCT. Eusebio and colleagues stated further that the results of the TST were more commonly abnormal in patients with MSA than in those with PSP or PD. However, even in these well-characterised 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 diffi cult, 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 confi rmation 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 studyraise 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 generally follow a common overarching design: a set of measures (cognitive task, motor or visual excitability or any other correlate of neural activity) is compared with or without the impact of TMS-induced interference effects applied to a given cortical area. Considering the reversible nature of rTMS effects on the TMS targeted region and its associated network, the same set 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. Let us consider that 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 applied over the right Intraparietal Sulcus (IPS) on the posterior parietal human cortex. There exist 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

Other Potential Clinical uses

TMS techniques could be used to identify unaffected carriers. Common finding stated genes that cause dystonia have low penetrance; therefore, there are unaffected gene carriers within affected families. For those genes that are already known, such unaffected carriers can easily be identified and given appropriate genetic counselling. However, in families where the genetic cause is not known. Another hypothesis from patients with dystonia caused by mutations in TOR1A, where unaffected carriers seem to have similar abnormalities on some TMS measures (eg, intracortical inhibition and silent period) as does unaffected carriers. So far from this data, 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 shows that patients with dystonia caused by mutations in TOR1A have an excessive response to rTMS, and the response lasts substantially longer than that in healthy controls. Unaffected gene carriers who are of an age (>30 years) when they are unlikely ever to show symptoms have a completely different response to rTMS; rather, they show almost no change with stimulation. This difference, if it is present from birth, would potentially enable the identification of the dystonic syndrome in childhood before any symptoms have developed, and potentially allow differentiation of those patients with TOR1A who are most likely to develop dystonia and those who are unlikely ever 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. 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 substantial increase (normalisation) in intracortical inhibition was 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 one of the movement disorders and most attention with regard to rTMS therapeutic studies. The physiological data for the use of rTMS in patients with PD are reviewed, followed by the clinical therapeutic and observational evidence for use of rTMS to treat motor and non-motor symptoms of PD. Physiological evidence for rTMS The pathological process that underlies PD causes widespread dysfunction of the brain and that particularly affects processing in the cortico basal ganglial loops. Most experimental and clinical interest has focused on motor symptoms of PD, although a considerable proportion of disability in PD is due to non-motor symptoms such as depression. The treatment of depression in patients with PD and rTMS has been reviewed elsewhere. Functional imaging studies have, in general, identified hypometabolism within the supplementary motor area (SMA) and the prefrontal cortex during movement in patients with PD and that are thought to be caused by the primary dysfunction in the basal ganglia. Therapy for PD (eg, levodopa) can, to a certain extent, reverse such changes in both human beings and animals. Therefore, excitatory rTMS might have a similar effect, which might be translated into an improvement in clinical (motor) symptoms. rTMS is also capable of inducing dopamine release from the basal ganglia: in healthy individuals, application of 10 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. 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. Evidence of human Model of PD, that levodopa-induced dyskinesia might represent abnormal plasticity in the motor system; some studies 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 (5 Hz), low-intensity rTMS protocol delivered once over the M1, with the aim to increase excitability.45–47 The results were inconsistent, and subsequent research focused on the possibility of using rTMS to induce effects that could outlast the stimulation. There was considerable variation in the inclusion criteria, stimulation protocols, outcome measures, and overall study design. In most cases, the hand motor area of the M1 contralateral to the most affected body side was chosen as the target, and excitatory and inhibitory rTMS were applied. After all applications of real rTMS, a 10–30% improvement was shown in most studies for outcome measures, with no effects after sham stimulation. In most cases, the duration of these effects was not tested, but this was probably less than 30 min. In some cases, 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 shown48, there was little correlation between the electrophysiological and behavioural changes seen. Results from two studies showed that patients with PD needed to be on medication for rTMS to aff ect their cortices in the way expected from studies in healthy individuals. This is important for the design of future therapeutic studies and might re-emphasise the fact that the induction of plasticity in animal studies is aided by dopamine receptor activation. Therapeutic trials of motor symptoms: multiple-session studies despite the inconsistency of the single-session results, the transient clinical gains seen in some studies after asingle session of rTMS have encouraged long-term treatment studies in patients with PD. The idea is that if delivered for long enough and frequently enough, the effects of rTMS could build-up and gradually restore the abnormal cortical excitability or corticocortical connectivity, or both, that results from the underlying pathological process in PD. As with

the single-session studies, a range of targets and stimulation protocols have been tested. The most common target is the M1, and in most instances the hand and leg areas have been stimulated bilaterally during the same session. In one study, M1 stimulation was combined with DLPFC stimulation. Despite the methodological differences, 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 15% to an impressive 50% for some of the outcome measures. On some occasions, improvements were shown to last for up to 1 month after the end of the stimulation regimen, but were gradually lost. However, results have not been uniform, and some stimulation 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. However, what the eff ects of rTMS are on functional outcome in PD is not unclear, nor is there consensus about which symptoms are most likely to respond to rTMS. Finally, whether rTMS will off er further benefit to that available from PD medications is questionable. Therapeutic trials of levodopa-induced dyskinesia Three small studies have specifically investigated the effect of rTMS protocols on the severity of levodopainduced 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 (66% reduction in dyskinesia scale, as judged by reviewers of video footage who were unaware of thstimulation protocol at 15 minpost-stimulation). No 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 did not have a cumulative effect, either from video rating or from

patient diaries of dyskinesia occurrence and severity. Rektorova and colleagues assessed the effect of highfrequency (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 did not show any benefit and the study was terminated early. However, in a separate report, these investigators detailed the effect of DLPFC stimulation on dyskinesia in four patients: all reported a subjective improvement indyskinesia 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. Dystonia may be focal, involving just one region such as the head, neck or face. The pathophysiology of dystonia can be cateqorized in inherited (ie automosomal dominant, recessive,x-linked or mitochodral) Acquired (i.e vascular,iatrogenic, neoplastic, traumatic or psychologenic and idiopathic (sporadic or familiar) (Aibanese et al.,2013) four 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. A sham condition was used in both studies. After one session of rTMS over the motor cortex. Allam and colleagues described 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. 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 therapeutic use of rTMS in a few small studies with a wide range of stimulation parameters. Results from three studies that included a 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 diff erent 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.

Chorea

The use of rTMS in chorea has been reported in the use of rTMS in chorea has been reported in two studies: one small study in patients with Huntington's disease and one single-case report of a patient with post-stroke hemichorea. Brusa and colleagues applied either 5 Hz, 1 Hz, or

sham rTMS over the SMA on 3 consecutive days to four patients with Huntington's disease. Videos were taken at baseline and at different time points after stimulation (15, 30, 45, and 60 min), and were assessed by raters, who were unaware of the stimulation type or timing of the video. A substantial 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 (mean of 13 points at baseline; mean of 6 points at 15 min), whereas 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 a cross-over 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. No difference between sham and real stimulation was seen at 60 min. The intensity used for the stimulation (100% of stimulator output) was high; therefore, whether participants might have been able to tell the difference between real and sham stimulation is debatable. In addition, 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.

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 min after stimulation. In another study, where premotor stimulation was given once per day for 2 days, there was a cumulative beneficial eff ect 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 (ie, drinking and brushing hair), which were sustained for about 1 week. The use of rTMS (17 Hz over the DLPFC in daily sessions for 5 days) in a patient with depression and tardive dyskinesia has been reported.88 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 fi nal rTMS session.

Conclusions

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.

Observation:

Some of the studies discussed in this Review report placebo effects after sham stimulation, but many do not. The fact that placebo effects can occur emphasizes a need for a placebo condition, even in small proof-of-principle studies. The forms of placebo stimulation that are available might not effectively mimic the experience of real rTMS and, in fact, this might be a reason why some studies with a sham rTMS condition do not detect a placebo effect. Unmasking of participants is most problematic when high stimulation intensities are used, which produce more sensory stimulation of the scalp. Therefore the

systematic unmasking of participants by asking directly which sort of stimulation they believed they were receiving is an important point to check. There are protocols that use regular and burst stimulation with low stimulation intensities, and these might be easier to control for in future trials. Although it might be appropriate for small proof-of principle studies to use physician-rated outcomes (eg, UPDRS and UHDRS) as the main outcome measure, it also seems sensible to include functional outcomes and quality-of-life measures, particularly in larger clinical trials. What are the practical concerns for the therapeutic use of rTMS? The available data suggest that, even if single sessions of rTMS do have a clinical effect, this benefit is short-lived. Multiple sessions of rTMS seem to extend clinical benefit in some studies, which is paralleled by similar additive effects of multiple sessions in healthy individuals.11 In those studies where beneficial clinical effects have been reported, these tended to be mild to moderate in magnitude, and patients with PD do not achieve the benefi cial magnitude that is seen with pharmacological treatments. The logical conclusion of these fi ndings is that rTMS is most likely to have a use as an add-on or adjunctive therapy for movement disorders, alongside standard drug treatment in PD or added to a therapy programme in focalhand dystonia. In addition, it is probable that rTMS should be given in many sessions, over several days to weeks. Indeed, this is the direction that research into the use ofrTMS for rehabilitation after stroke has taken, with rTMS being used potentially as a method to adjust the brain intoa more receptive (plastic) state, and therefore improve theresponse to physiotherapy. Unless there are great technical changes, rTMS will remain a hospital-based or clinic-based treatment, and will not be economically viableas a home-based therapy. Therefore, owing to the prevalence of the conditions, rTMS is unlikely to be a viable option for the general treatment of patients with PD. In several other disorders (eg, Huntington's disease, essential tremor, and cortical myoclonus), rTMS is not proposed to affect the underlying disease process that leads to the movement disorder but is suggested to provide symptomatic relief. It is likely that such treatment will therefore need to be continued for the lifetime of the patient, although the additive effect of multiple sessions of treatment might provide days to weeks of benefit. Owing to these considerations, we suggest that it would be more appropriate to focus the study of the therapeutics of rTMS on those conditions where rTMS might have a long-lasting disease-modifying effect, rather than purely a symptomatic one. Both conditions have a pathophysiology that is postulated to relate to abnormal brain plasticity, and therefore rTMS might potentially modify the underlying pathological process. In addition, the studying a masked way, of the effectiveness of rTMS as an adjunctive therapy in patients who are functionally disabled by movement disorders resistant to other forms of treatment might be appropriate. This study shouldfocus on functional and quality-of-life outcomes, and include assessments of cost and patient satisfaction compared with standard therapy. rTMS might also have potential as an assessment test for responsiveness to cortical stimulation before the implantation of cortical stimulation devices. Such devices are a potential new surgical treatment for patients with PD and othe movement disorders, and it might be of interest to look for any correlations between response to rTMS and the clinical response to subsequent implantation of the stimulator.

The evidence so far shows that rTMS, in general, seems to have mild to moderate clinical effects, but these could be enhanced by adding rTMS to another therapy (eg, rTMS combined with a retraining programme for Reference task-specifi c dystonia). Lower stimulation intensities are likely to be easier to control for with a sham stimulation condition. For future trials, we would suggest the use of a range of clinical measures that includes quality-of-life and functional outcomes.

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