Clinical applications of transcranial magnetic stimulation in patients with movement disorders

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Transcranial magnetic stimulation (TMS) is a method of non-invasive brain stimulation that affects the cerebral cortex but not 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. Repeated stimulation (eg, 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. In this Review, we describe the theoretical background to TMS techniques and discuss the uses of TMS as a potential diagnostic tool in movement disorders. The difficulties in bringing the technique into regular clinical diagnostic practice will be discussed and the evidence for the potential of repetitive TMS as a therapeutic tool in patients with movement disorders will be reviewed.

TMS and rTMS: a brief technical overview
Transcranial magnetic stimulation (TMS) is a safe and non-invasive method of stimulating cortical neurons. A magnetic field generator sends a current with a peak amplitude of about 8000 A, that lasts about 1 ms, through an induction coil placed on the scalp. The 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 (figure 1).

Several TMS applications have been developed to investigate the physiology of the motor system. These range from simple concepts that are used in clinical practice (eg, assessment of central motor conduction time [CMCT]) to complex examples that include pairs of TMS stimuli or paired TMS and peripheral stimuli, which can be used to assess the excitability of corticospinal neurons, interneurons, and connected structures (panel 1). These more complex applications have been used extensively to help understand the pathophysiology of movement disorders.1-3

In addition to these tests of specific neural pathways, TMS has been used to investigate mechanisms of synaptic plasticity in the cerebral cortex. There has been much experimental work in animals and in brain slices from animals to investigate the mechanisms of synaptic plasticity by different applications of electrical stimulation delivered through microelectrodes.4 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, is by theta burst stimulation: a pattern of stimulation based on the firing arrangement that occurs in hippocampal neurons in cats and 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 electroencephalogram terminology).4 The introduction of transcranial magnetic

Figure 1: Neuronal activation by TMS
The electrical current in the coil and the current induced in the brain by the magnetic field flow is in the same plane (tangential to the skull-brain surface). The black spots in the inset shows the optimum site of neuronal activation (ie, 90° angle between axons and the electrical field in the brain).
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) could be a therapeutic tool in the specialty of movement disorders, in particular by creating long-lasting (plastic) changes in the excitability of synapses within the motor system as a way to modulate symptoms.

There are 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 (ie, LTP-like effect) that can last out 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 is usually given intermittently (eg, 200 pulses, every 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 (ie, a LTD-like effect) 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 modelled 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 LTD-like or LTD-like changes, although has had limited use in therapeutic studies so far. The effects of rTMS are called LTD-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, and electrical stimulation prior to rTMS9 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 s for 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. Second, some 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. Third, participants with epilepsy or implantable electronic devices, such as pacemakers or deep brain stimulators, might show activation of GABAB (inhibitory) interneurons that synapse onto pyramidal cells. Infl uenced by activity in cholinergic pathways.

Silent period
A period of electromyography suppression caused by TMS in an actively contracting muscle that is caused by activity in GABA<sub>B</sub> (inhibitory) interneurons that synapse onto pyramidal cells.

**Paired pulses of TMS**

**Short interval intracortical inhibition**
Suppression of a test motor-evoked potential (MEP) by a subthreshold conditioning stimulus 10–15 ms earlier. This might show activation of GABA<sub>B</sub> (inhibitory) interneurons that synapse onto pyramidal cells.

**Intracortical facilitation**

**Long intracortical inhibition**
Suppression of a test MEP by a suprathreshold conditioning stimulus 100–200 ms earlier. This might show activation of GABA<sub>B</sub> (inhibitory) interneurons that synapse onto pyramidal cells.

**Interhemispheric inhibition**
Suppression of a test MEP by a suprathreshold conditioning stimulus applied 10–40 ms earlier over the contralateral motor cortex.

**Combining single pulse of TMS and peripheral electrical nerve stimulation**
**Short afferent inhibition**
Suppression of a test MEP by an electrical stimulus to the median nerve at the wrist. Influenced by activity in cholinergic pathways.
are typically excluded from studies with rTMS.\textsuperscript{1} However, some investigators have, with appropriate safety measures, used TMS in patients with deep brain stimulators.\textsuperscript{12,13} Last, 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 flat) 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.\textsuperscript{14} 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.\textsuperscript{14}

Diagnostic applications of TMS in movement disorders

Several TMS applications have been used to investigate the pathophysiology of movement disorders, and these could have potential diagnostic application for such conditions. The most commonly applied techniques are motor thresholds, input-output curves, short intracortical inhibition, intracortical facilitation, interhemispheric 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. Panel 1 shows these 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.\textsuperscript{15} We focus instead in this section on the potential clinical diagnostic applications of TMS.

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. Although any differences in motor system physiology between, for example, patients with dystonia and patients with Parkinson’s disease (PD) might be interesting for the researcher, these are unlikely to be important in a clinical setting. However, a simple test that can, for example, 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. There are, however, data of potential clinical diagnostic interest and these are briefly summarised below.

Differentiation of parkinsonian 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]).

Kuhn and colleagues\textsuperscript{16} 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 flatter 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\textsuperscript{17} 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.\textsuperscript{12} 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.

Eusebio and colleagues\textsuperscript{18} 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.\textsuperscript{19} Eusebio and colleagues found 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.19,20 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.

TMS has also been used to investigate aspects of motor system physiology in patients with PD caused by mutations in PARK2. The main finding that is of clinical diagnostic interest is that a delay in CMCT was seen in patients with mutations in PARK2, in contrast to normal CMCT in patients with idiopathic PD.21,22

Psychogenic versus organic dystonia

A perennial problem, particularly seen in specialist movement disorder clinics, is distinguishing between movement disorders with a psychogenic or an organic cause. Electrophysiological tests can be of help, particularly in patients with tremors or jerks.22 Patients who present with a fixed abnormal posture, usually of the foot and commonly associated with severe pain, are an area of persistent difficulties.23 Although debate continues with regard to the exact nature of this condition,25 tests that differentiate such abnormal posturing from postures seen because of other conditions would be clinically useful (eg, primary and secondary degenerative dystonia). Dystonia is characterised by involuntary muscle spasms that lead to an abnormal posture of the affected body part. There are many causes and many clinical phenotypes, which range from focal dystonia to severe generalised dystonia.

Espay and colleagues27 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. 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.26 This might be a further factor that was not taken into account in the study by Espay and colleagues.

Summary and future potential

In summary, the TMS measures used so far give little to the clinician in terms of diagnostic tools for patients with movement disorders, which is in line with a consensus statement from the International Federation of Clinical Neurophysiology on the diagnostic usefulness of TMS techniques.27 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 potential clinical interest for TMS. A common finding is that the 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, TMS techniques could be used to identify unaffected carriers. This hypothesis is based, in part, on work in 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 do unaffected carriers.28 On the basis of these 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.

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.29 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.29 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, therefore, might benefit from a potential protective treatment) 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.30 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

Of all the movement disorders, PD has received the 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 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) or the dorsolateral prefrontal cortex (DLPFC) 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 (which indicated dopamine release) 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 (as well as the well-recognised large placebo response to therapeutic interventions in PD) emphasises the need for adequate sham control conditions in rTMS therapeutic studies.

As indicated, there is evidence, at least in animal models of PD, that levodopa-induced dyskinesia might represent abnormal plasticity in the motor system. In light of this, some studies with rTMS have specifically looked at the potential application of brain stimulation in PD patients with dyskinesia (as discussed below).

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. The results were inconsistent, and subsequent research focused on the possibility of using rTMS to induce effects that could outlast the stimulation. Results from a small number of single-session, proof-of-principle studies are shown in table 1. 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 almost all 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 shown, 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 affect 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 a
single 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 (table 2). 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.\(^\text{13}\) 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,\(^\text{16}\) but were gradually lost.\(^\text{22}\) 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;\(^\text{23,24}\) 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 different 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 effects of rTMS are on functional outcome in PD is unclear, nor is there consensus about which symptoms are most likely to respond to rTMS.

Therapeutic trials of levodopa-induced dyskinesia

Three small studies have specifically investigated the effect of rTMS protocols on the severity of levodopa-induced dyskinesia. Koch and colleagues\(^\text{44}\) 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 the

<table>
<thead>
<tr>
<th>Target</th>
<th>Design</th>
<th>rTMS protocol</th>
<th>Participants; Hoehn and Yahr scale score(^a)</th>
<th>Disease duration (years; standard deviation)</th>
<th>Outcome measures</th>
<th>Effects immediately after the end of rTMS</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Lefaucheur and co-workers(^a)</td>
<td>Left M1 (hand area)</td>
<td>Several cross-over, double-blinded protocols with patients off drugs; compared with sham and levodopa protocols</td>
<td>10 Hz (facilitation): TNP=2000, 80% RMT; 0.5 Hz (inhibition): TNP=2000, 80% RMT</td>
<td>N=12 (no tremor); 3-4 (0-2)</td>
<td>Motor UPDRS; finger tapping; dexterity Purdue Pegboard test; 7 metre walking task</td>
<td>~15% improvement in total UPDRS after both real rTMS protocols (65% after levodopa, no change after sham)</td>
<td>Tested once (20 min after the end of rTMS)</td>
</tr>
<tr>
<td>Sommer and co-workers(^a)</td>
<td>M1† (hand area on the most affected side)</td>
<td>Cross-over, double-blinded protocol with patients on drugs; compared with sham</td>
<td>1 Hz (excitatory), paired pulse: 90% AMT (first), 120% (second); TNP=900, RMT interval: 3 and 10 ms; 1 Hz (inhibition): TNP=900, 1200% RMT</td>
<td>N=11, 5.5 (15§)</td>
<td>Finger-tapping task</td>
<td>~10% improvement in tapping rate after all active protocols.</td>
<td>Not present after 30 min</td>
</tr>
<tr>
<td>Boylan and co-workers(^a)</td>
<td>SMA† (bilateral on the midline)</td>
<td>Cross-over, single-blinded protocol with patients off drugs; compared with sham</td>
<td>10 Hz (facilitation): TNP=2000, 110% RMT (but not in all participants)</td>
<td>N=8, 2-3</td>
<td>Reaction and movement time; spiral drawing; timed tasks; motor UPDRS</td>
<td>Deteriorations seen in spiral drawing and movement times after real rTMS. No effect on UPDRS (no changes after sham in any test).</td>
<td>Tended to persist after 1 week</td>
</tr>
<tr>
<td>Siebner and co-workers(^a)</td>
<td>M1† (hand area on the most affected side)</td>
<td>Cross-over, single-blinded protocol with patients off drugs; compared with sham</td>
<td>5 Hz (facilitation): TNP=2000, 90% RMT</td>
<td>N=10 (40% tremor); 1-2b (subscore)</td>
<td>Motor UPDRS</td>
<td>~30% improvement in UPDRS (no considerable change after sham).</td>
<td>Tested once (1 h after the end of rTMS)</td>
</tr>
<tr>
<td>Siebner and co-workers(^a)</td>
<td>M1† (hand area on the most affected side)</td>
<td>Cross-over, single-blinded protocol with patients off drugs; compared with sham</td>
<td>5 Hz (facilitation): TNP=2000, 90% RMT</td>
<td>N=12; not recorded (mean motor UPDRS=28)</td>
<td>Speed of ballistic movement; accuracy of ballistic movement</td>
<td>Improvement in movement speed (mean 13%). No deterioration in accuracy.</td>
<td>Tested only immediately after rTMS</td>
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\(^a\)Data are mean Hoehn and Yahr scale score (standard deviation). \(\text{rTMS}\) delivered with a focal figure-of-eight coil. \(\text{rTMS}\) consists of pairs of stimuli given at a standard interstimulus intervals; pairs repeat at a 1 Hz frequency. Disease severity measured with the Columbia University rating scale score. \(\text{AMT}=\)active motor threshold. \(\text{M1}=\)primary motor cortex. \(\text{RMT}=\)resting motor threshold. \(\text{rTMS}=\)repetitive transcranial magnetic stimulation. \(\text{SMA}=\)supplementary motor area. \(\text{TNP}=\)total number of pulses. \(\text{UPDRS}=\)unified Parkinson’s disease rating scale.

Table 1: Details of single-session studies into the use of rTMS in Parkinson’s disease.
stimulation protocol at 15 min post-stimulation). No effect was seen after sham stimulation. Dyskinesia worsened after stimulation with 5 Hz.

In a follow-up paper, 44 these investigators reported 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 62 assessed the effect of high-frequency (10 Hz) stimulation of the DLPFC or motor cortex, given as daily sessions for 5 days, on gait and bradykinesia in patients with PD. 62 The intervention did not show any benefit and the study was terminated early.

However, in a separate report, 62 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**

**Rationale for the use of rTMS**

Electrophysiological assessment of patients with dystonia (typically primary dystonia) has detected widespread abnormalities of inhibitory motor circuits in the brain, brainstem, and spinal cord. 67 Functional imaging has also shown increases in blood flow or.

<table>
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<tr>
<th>Studies to excite the M1 bilaterally</th>
<th>Participants</th>
<th>Mean Hoehn and Yahr scale score; mean UPDRS (standard deviation)</th>
<th>Disease duration (years; standard deviation)</th>
<th>rTMS target</th>
<th>rTMS protocol</th>
<th>Design</th>
<th>Outcome measures</th>
<th>Effects immediately after the end of the rTMS period</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Khedr and co-workers 56</td>
<td>N = 36</td>
<td>2–3, 27 (8)</td>
<td>3 (2)</td>
<td>Leg and hand in succession</td>
<td>5 Hz (facilitation)*: TNP = 1000 × 4 (leg and hand areas), 120% hand RMT, compared with sham</td>
<td>Double blinded, placebo controlled; once daily for 10 days, no drugs</td>
<td>motor UPDRS; 25 metre walking, self-assessment (0, 1, 5, 10, and 40 days from rTMS onset)</td>
<td>~50% gain in mUPDRS; ~25% gain in walking speed; no gains seen after sham, except for self-assessment tools (real: 35%, sham: 10%)</td>
<td>Present when retested 1 month after the end of rTMS</td>
</tr>
<tr>
<td>Khedr and co-workers†</td>
<td>N = 55</td>
<td>(per group)</td>
<td>(per group)</td>
<td>Leg and hand, hand and leg and hand</td>
<td>25 Hz (1000 pulses × 4) 10 Hz (1000 pulses × 4)</td>
<td>Double blinded, placebo controlled, once daily for 8 days, no drugs</td>
<td>motor UPDRS; 25 metre walking, self-assessment; timed motor tasks (0, 0.6, and 35 days from rTMS onset)</td>
<td>~26% gain in mUPDRS in all groups; improvement was delayed in the sham group (12–16 weeks); compared with the actual one (4–8 weeks). Self-assessments tended to be better after real rTMS only at week 16.</td>
<td>Some gain lost when retested 1 month after the end of rTMS</td>
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<tr>
<th>Studies to inhibit the M1 bilaterally</th>
<th>Participants</th>
<th>Mean Hoehn and Yahr scale score; mean UPDRS (standard deviation)</th>
<th>Disease duration (years; standard deviation)</th>
<th>rTMS target</th>
<th>rTMS protocol</th>
<th>Design</th>
<th>Outcome measures</th>
<th>Effects immediately after the end of the rTMS period</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Okabe and co-workers 48</td>
<td>N = 85</td>
<td>2–3, ~24 (14)</td>
<td>9 (5)</td>
<td>Hand area</td>
<td>0.2 Hz (probably inhibition)*: TNP = 50 × 2 (hands), 110% hand AMT, compared with placebo tRMS and sham</td>
<td>Double blinded, placebo controlled, once weekly for 8 weeks, on drugs</td>
<td>UPDRS; timed motor tasks; HRSD; self-assessment (0, 1, 4, 8, 12, and 16 weeks from rTMS onset)</td>
<td>~26% gain in mUPDRS in all groups; improvement was delayed in the sham group (20% in walking); G2: ~50% gain in UPDRS; G3: ~15% gain mainly in mUPDRS G4: No major gains</td>
<td>Gains not present when retested at week 12</td>
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<tr>
<th>Studies to excite non-motor cortical targets</th>
<th>Participants</th>
<th>Mean Hoehn and Yahr scale score; mean UPDRS (standard deviation)</th>
<th>Disease duration (years; standard deviation)</th>
<th>rTMS target</th>
<th>rTMS protocol</th>
<th>Design</th>
<th>Outcome measures</th>
<th>Effects immediately after the end of the rTMS period</th>
<th>Duration</th>
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<tr>
<td>Del Olmo and co-workers 59</td>
<td>N = 13</td>
<td>2–3</td>
<td>8 (5)</td>
<td>DLPC (most affected brain side)</td>
<td>10 Hz (facilitation): TNP = 450, 90% hand RMT, compared with sham</td>
<td>Double blinded, placebo controlled, once daily for 10 days, on drugs</td>
<td>7 metre walking, timed motor tasks (0, 1–10, and 12 days from rTMS onset)</td>
<td>No differences between real and sham rTMS.</td>
<td></td>
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<tr>
<th>Studies to excite multiple cortical targets</th>
<th>Participants</th>
<th>Mean Hoehn and Yahr scale score; mean UPDRS (standard deviation)</th>
<th>Disease duration (years; standard deviation)</th>
<th>rTMS target</th>
<th>rTMS protocol</th>
<th>Design</th>
<th>Outcome measures</th>
<th>Effects immediately after the end of the rTMS period</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Lomarev and co-workers 60</td>
<td>N = 16</td>
<td>2–3, ~35 (8)</td>
<td>14 (7)</td>
<td>Hand M1 and DLPC bilaterally</td>
<td>25 Hz (facilitation)*: TNP = 300 × 4, (hand areas and DLPC), 100% hand RMT, compared with sham</td>
<td>Double blinded, placebo controlled, twice weekly for 4 weeks, on drugs</td>
<td>10 metre walking, timed motor tasks; UPDRS (0, 5, and 12 weeks from rTMS onset)</td>
<td>Gradual gains up to ~18% (gait) or 36% (upper limb) assessed both on and off drugs; no clear gains in UPDRS; no effects in the sham group.</td>
<td>Present when retested 1 month after the end of rTMS</td>
</tr>
</tbody>
</table>

Table 2: Details of multiple-session studies into the use of rTMS in Parkinson's disease

* rTMS delivered with a focal figure-of-eight coil. † Patients were randomised in one of four groups (G1–G4). ‡ rTMS delivered with a less focal round coil. AMT = active motor threshold, DLPC = dorsolateral prefrontal cortex, G = group, HRSD = Hamilton rating scale for depression, M1 = primary motor cortex, RMT = resting motor threshold, rTMS = repetitive transcranial magnetic stimulation, TNP = total number of pulses. UPDRS = unified Parkinson's disease rating scale.

glucose metabolism in various brain areas, including the prefrontal, cerebellar, insular, parietal, and SMA areas. Some of these abnormalities were only present during movement. As a result, rTMS has been postulated as a potential candidate to reduce this abnormal cortical excitability and, potentially, have an effect on symptoms. Although this rationale was behind most of the rTMS studies in dystonia, developments in understanding the pathophysiology of dystonia have shown that dystonia could have its pathological basis in the enhanced ability of the brain to undergo plastic change. From a clinical point of view, dystonia occurs after intense practise of complex movements in both human beings and animals. Dystonia is triggered or worsened by injury that increases LTD in the cortex that corresponds to the injured limb. From an experimental point of view, dystonia is associated with an excessive response to several plasticity-inducing protocols (eg, paired associative stimulation, transcranial direct current stimulation, and rTMS). These data support the hypothesis that in dystonia there is an increased tendency to form associations between inputs and outputs, which could lead to abnormal unwanted connections and subsequent impairment of motor control. Dystonia is, therefore, a candidate for the therapeutic use of rTMS.

Therapeutic studies of rTMS

So far, four studies have assessed the effects of rTMS in patients with dystonia (table 3): 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. Murase and colleagues administered daily sessions of inhibitory rTMS over the premotor cortex for 5 consecutive days in three patients with severe generalised secondary dystonia. All patients were severely disabled and had painful axial spasms in addition to the dystonia. Two patients had a reduction in the severity of the dystonia, as graded on the Burke-Fahn-Marsden scale (reduction of about 20 points in both patients), whereas one patient had no improvement. There was no change in the disability score for any of the patients. The number of painful spasms per day decreased after treatment (from >20 per day to two per day in one patient), and the severity of pain during each spasm also decreased after treatment in two of three patients. In a single case report, Allam and colleagues described a 37-year-old man with focal segmental dystonia that affected the neck and right arm who was treated with an identical regimen to that used by Lefaucheur and colleagues. 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 arm dystonia.

<table>
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<tr>
<th>Clinical details</th>
<th>rTMS target</th>
<th>Design</th>
<th>rTMS protocol</th>
<th>Outcome measures</th>
<th>Effects</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Allam and co-workers</td>
<td>One patient with segmental dystonia</td>
<td>Dominant M1*</td>
<td>Unblinded, once daily for 5 days, no sham</td>
<td>1 Hz (inhibition): TNP=1200, 90% RMT</td>
<td>BFM scale (neck section)</td>
<td>~50% improvement in neck section of BFM. No improvement in other aspects of dystonia (eg, right hand)</td>
</tr>
<tr>
<td>Lefaucheur and co-workers</td>
<td>Three patients with secondary generalised dystonia, including painful axial spasms</td>
<td>Dominant M1*</td>
<td>Unblinded, once daily for 5 days, no sham</td>
<td>1 Hz (inhibition): TNP=1200, 90% RMT</td>
<td>BFM scale, number, and severity of painful axial spasms (self-carer report)</td>
<td>~20-point improvement in BFM (movement scale) in 2 of 3 patients. No change in BFM disability scale. Marked reduction in number and severity of axial spasms.</td>
</tr>
<tr>
<td>Murase and co-workers</td>
<td>Eight patients with focal hand dystonia</td>
<td>Dominant M1, PM and SMA*</td>
<td>Single session, single blinded, placebo controlled, cross-over, compared with sham rTMS</td>
<td>0.2 Hz (inhibition): TNP=1250, 85% RMT, 100% AMT (M1, PM), 100% AMT (SMA)</td>
<td>Self-assessment of computerised writing test (pen pressure, tracking error)</td>
<td>Considerable reduction in pen pressure and tracking error after PM stimulation. 78% of patients reported improvement after PM stimulation.</td>
</tr>
<tr>
<td>Siebner and co-workers</td>
<td>16 patients with focal hand dystonia</td>
<td>Dominant M1*</td>
<td>Single session, single blinded, placebo controlled, cross over (10 of 16 patients); compared with sham rTMS</td>
<td>1 Hz (inhibition): TNP=1200, 90% RMT</td>
<td>Self-assessment of computerised writing test (pen pressure, tracking error)</td>
<td>Considerable reduction in pen pressure and number of stroke inversions. Self-report of improvement in 6 of 16 patients.</td>
</tr>
</tbody>
</table>

* = rTMS delivered with a focal figure-of-eight coil. BFM = Burke-Fahn-Marsden dystonia rating scale. M1 = primary motor cortex. PM = premotor cortex. RMT = resting motor threshold. rTMS = repetitive transcranial magnetic stimulation. SMA = supplementary motor area. TNP = total number of pulses.

Table 3: Therapy studies with rTMS as a potential treatment for 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 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 (table 4).

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 different parameters (table 4), 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 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, a beneficial effect of an inhibitory theta burst rTMS protocol was seen on the abnormal movements (as rated by a video rater who was unaware of the protocol), that lasted for about 24 h after stimulation. Similar effects were not seen with a session of sham rTMS.

Other disorders

rTMS has been used to treat other movement disorders, typically in small proof-of-principle studies.

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

<table>
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<th>Clinical details</th>
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<th>Effects</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Mantovani and co-workers</td>
<td>Two patients with TS</td>
<td>Bilateral SMA</td>
<td>Unblinded, five times a week for 2 weeks, no sham</td>
<td>1 Hz (inhibition): TNP=1200, 100% RMT</td>
<td>YGTSS 36% and 68% improvement in YGTSS for each patient, respectively</td>
<td>1–4 months</td>
</tr>
<tr>
<td>Mantovani and co-workers</td>
<td>Ten patients (5 with OCD, 3 with TS, 2 with OCD and TS)</td>
<td>Bilateral SMA</td>
<td>Unblinded, five times a week for 2 weeks, no sham</td>
<td>1 Hz (inhibition): TNP=1200, 90% RMT</td>
<td>YGTSS, YBOCS, HDRS, HARS, CGI, SCL-90, BDI, SAD, SASS 68% improvement in YGTSS, 29% improvement in YBOCS Other scales also statistically significantly improved</td>
<td>60% had improved score on CGI at 3 months</td>
</tr>
<tr>
<td>Orth and co-workers</td>
<td>Five patients with TS</td>
<td>Bilateral PM</td>
<td>Single session, single blinded, placebo controlled, cross-over; compared with sham rTMS</td>
<td>1 Hz (inhibition): TNP=1800, 80% AMT</td>
<td>YGTSS, MOVES, video assessment No considerable effect over sham on any measure</td>
<td>..</td>
</tr>
<tr>
<td>Chae and co-workers</td>
<td>Eight patients</td>
<td>Dominant PM or M1 (testing two different protocols on both targets)</td>
<td>Single session, single blinded, placebo controlled, cross-over; compared real rTMS protocols with sham</td>
<td>1 Hz (inhibition) or 15 Hz (facilitation): TNP=2400, 110% RMT</td>
<td>YGTSS, YBOCS, CGI, tic self-report scale No considerable effect over sham on any measure</td>
<td>..</td>
</tr>
<tr>
<td>Munchau and co-workers</td>
<td>16 patients (nine with TS, seven with OCD and TS)</td>
<td>Dominant PM or M1</td>
<td>Single blinded, twice daily, placebo controlled, cross-over; compared real rTMS protocols with sham</td>
<td>1 Hz (inhibition): TNP=1200, 80% RMT, 15 Hz (facilitation): TNP=1200, 90% RMT</td>
<td>YGTSS, YBOCS, MOVES, BDI No considerable effect over sham on any measure</td>
<td>..</td>
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</tbody>
</table>

* rTMS delivered with more powerful but less focal figure-of-eight coil. † rTMS delivered with a focal figure-of-eight coil. AMT=active motor threshold. BDI=Beck depression inventory. CGI=clinical global impression. HARS=Hamilton anxiety rating scale. HDRS=Hamilton depression rating scale. M1=primary motor cortex. MOVES=motor tic, obsessions and compulsions, vocal tic self evaluation scale. OCD=obsessive compulsive disorder. PM=premotor cortex. RMT=resting motor threshold. rTMS=repetitive transcranial magnetic stimulation. SAD=scale for auto-evaluation of depression. SASS=social adaptation self evaluation scale. SCL-90=symptoms check list. SMA=supplementary motor area. TNP=total number of pulses. TS=Tourette’s syndrome. YBOCS=Yale Brown obsessive compulsive disorder scale. YGTSS=Yale global tic severity scale.

Table 4: Therapy studies with rTMS as a potential treatment for tics

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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 cortex in 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 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 (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. 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.

Conclusions

We have summarised the published evidence for the use of TMS and rTMS in patients with movement disorders. An obvious 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.

Diagnostic uses of TMS

In accord with the consensus statement from the International Federation of Clinical Neurophysiology committee, the authors of this Review agree that so far there is no proven usefulness for TMS techniques in the differential diagnosis of movement disorders. This is not to overlook the huge benefit in our understanding of the underlying pathophysiology from the application of TMS techniques to patients with movement disorders, but these have not been translated into clinical applications. One recurring problem in this regard is that patients with many different movement disorders have abnormal results from TMS measures in common use (eg, short intracortical inhibition and silent period), and these abnormal results are similar in nature and severity. In addition, there is marked variability in these measures in patients with the same movement disorder and in healthy individuals. As a result, studies usually only show group effects rather than the individual patient effects necessary for clinical diagnostic tests. In addition, diagnosis of movement disorders is difficult—even with common conditions such as PD—and is particularly problematic in disorders such as PSP and CBD. The application of TMS techniques to genetically proven or pathologically proven groups of patients might be useful to reduce the clinical diagnostic uncertainty and subsequent patient variability in TMS studies. In addition, further progress is needed to develop novel TMS techniques that investigate different (or perhaps just more specific) aspects of neural circuitry.

Therapeutic uses of rTMS

What is the rationale for the use of rTMS in the treatment of movement disorders?

Functional imaging and electrophysiological studies commonly detect abnormalities of cortical excitability in patients with movement disorders that are frequently in line with predictions from disease models (eg, SMA hypometabolism in PD, abnormalities of SICI and SP in dystonia), and such patients might benefit clinically from modulation of their cortical excitability with rTMS. This argument has some appeal but is problematic. First, functional imaging and electrophysiological measures of cortical excitability are not clearly linked to clinical phenotype. Second, most movement disorders are thought to result in dysfunction of a distributed network, although perhaps triggered by basal ganglia dysfunction, and therefore changes in cortical excitability might show beneficial adaptation to the disorder, rather than a maladaptive process. In such circumstances, what the effect of modulation will be on cortical excitability in patients with movement disorders is less clear. However, if the changes in excitability are maladaptive, then rTMS might be a useful method of altering activity in these distributed networks, because its effects are known to spread from the stimulated area to connected structures. Third, the effect of rTMS applications in patients with particular movement disorders can be different to the effect in healthy individuals, and therefore it is not always sensible to extrapolate the probable effect of use of rTMS from healthy individuals to a group of patients with a particular movement disorder. There are some disorders (eg, primary dystonia and levodopa-induced dyskinesia) for which aberrant brain plasticity might have a role in the pathogenesis of the condition. Such disorders could be more appropriate to therapeutic rTMS than other disorders, in which the underlying mechanism (and therefore probable benefit of rTMS) is less clear. All these thoughts call for substantial pilot work (as has been
done to some extent for patients with PD) before therapeutic rTMS techniques are advanced into clinical trials. This pilot work should trial multiple sites and types of stimulation, and aim to assess outcome with a variety of measures, including electrophysiological, functional imaging, and clinical aspects.

**What experimental design should be used?**

Some of the studies discussed in this Review report clear placebo effects after sham stimulation, but many do not. The fact that placebo effects can occur emphasises 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. 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 beneficial magnitude that is seen with pharmacological treatments.

The logical conclusion of these findings 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 focal hand 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 of rTMS for rehabilitation after stroke has taken, with rTMS being used potentially as a method to adjust the brain into a more receptive (plastic) state, and therefore improve the response to physiotherapy. Unless there are great technical changes, rTMS will remain a hospital-based or clinic-based treatment, and will not be economically viable as 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 or with tics. 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 therapeutic use of rTMS on those conditions where rTMS might have a long-lasting disease-modifying effect, rather than purely a symptomatic one. Examples of these conditions include focal dystonia (in particular, task-specific dystonias such as musician’s dystonia), and functionally disabling levodopa-induced dyskinesia that is resistant to other treatment. 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 study, in 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 should focus 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 other 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. If a positive correlation were found, then rTMS could be used as a screening tool to help select appropriate candidates for stimulator implantation.

In conclusion, we suggest that researchers might consider the following major questions in the design of future therapeutic rTMS studies. First, does the study have a practical application if successful? For example, minimal transient improvement in arm speed in patients with PD will probably have less practical application than a successful treatment for an otherwise treatment-resistant, levodopa-induced dyskinesia. Second, is there face validity to the use of rTMS as a therapy? The theoretical basis of applying rTMS to treat movement disorders is perhaps clearer in patients with dystonia or levodopa-induced dyskinesia than in patients with other movement disorders. Third, is there merit in combining rTMS with another form of therapy? 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
task-specific dystonia). Fourth, is there good evidence on which to base the choice of stimulation site and type? If not, then this should be an essential first step before entering into clinical trials of a particular type and site of stimulation. Fifth, is there adequate placebo control? There should be a placebo-control condition, and researchers should check for systematic unmasking of participants. Lower stimulation intensities are likely to be easier to control for with a sham stimulation condition. Sixth, what is the best way to assess outcome? For future trials, we would suggest the use of a range of clinical measures that includes quality-of-life and functional outcomes.

Contributors
All authors were involved in the design, scope, and structure of this Review, and in the drafting and editing of the paper. JR had the idea to write this Review and has been involved in the planning, writing, and revision of the final version. MJE and PT did the literature search, and prepared the text and figure of the paper. JR had the idea to write this Review and has been involved in the planning, writing, and revision of the final version. MJE and PT did the literature search, and prepared the text and figure of the paper.

Conflicts of interest
We have no conflicts of interest.

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