

Use of non-invasive stimulation in movement disorders: a critical review

O uso da estimulação não-invasiva em distúrbios do movimento: uma revisão crítica

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ABSTRACT

Background: Noninvasive stimulation has been widely used in the past 30 years to study and treat a large number of neurological diseases, including movement disorders. **Objective:** In this critical review, we illustrate the rationale for use of these techniques in movement disorders and summarize the best medical evidence based on the main clinical trials performed to date. **Methods:** A nationally representative group of experts performed a comprehensive review of the literature in order to analyze the key clinical decision-making factors driving

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transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in movement disorders. Classes of evidence and recommendations were described for each disease. **Results:** Despite unavoidable heterogeneities and low effect size, TMS is likely to be effective for treating motor symptoms and depression in Parkinson's disease (PD). The efficacy in other movement disorders is unclear. TMS is possibly effective for focal hand dystonia, essential tremor and cerebellar ataxia. Additionally, it is likely to be ineffective in reducing tics in Tourette syndrome. Lastly, tDCS is likely to be effective in improving gait in PD. **Conclusions:** There is encouraging evidence for the use of noninvasive stimulation on a subset of symptoms in selected movement disorders, although the means to optimize protocols for improving positive outcomes in routine clinical practice remain undetermined. Similarly, the best stimulation paradigms and responder profile need to be investigated in large clinical trials with established therapeutic and assessment paradigms that could also allow genuine long-term benefits to be determined.

Keywords: Parkinson's Disease; Movement Disorders; Transcranial Direct Current Stimulation; Transcranial Magnetic Stimulation.

RESUMO

Introdução: A estimulação não-invasiva tem sido amplamente utilizada nos últimos 30 anos no estudo e no tratamento de um grande número de doenças neurológicas, incluindo distúrbios do movimento. **Objetivos:** Nesta revisão crítica, discutimos o embasamento científico do uso da estimulação não-invasiva em distúrbios do movimento e as evidências científicas dos principais ensaios clínicos realizados. **Métodos:** Um grupo de especialistas realizou uma revisão crítica abrangente da literatura a fim de analisar as principais aplicações da estimulação magnética transcraniana (EMT) e da estimulação transcraniana por corrente contínua (ETCC) em distúrbios do movimento. As classes de evidência e de recomendação foram descritas para cada doença. **Resultados:** Apesar da grande variabilidade da metodologia e baixo efeito clínico, a EMT é provavelmente eficaz para o tratamento dos sintomas motores e da depressão na doença de Parkinson. A eficácia em outros distúrbios do movimento ainda é incerta. A EMT é possivelmente eficaz para o tratamento da distonia focal da mão, do tremor essencial e da ataxia cerebelar. No entanto, é provavelmente ineficaz na redução dos tiques na síndrome de Tourette. Finalmente, a ETCC é provavelmente eficaz na melhora da marcha na doença de Parkinson. **Conclusões:** As evidências até o momento sugerem que a estimulação não-invasiva pode ser benéfica para o alívio de alguns sintomas em determinados distúrbios do movimento como a doença de Parkinson, o tremor essencial, a distonia e a ataxia. Os protocolos de aplicação e paradigmas de estimulação ainda precisam ser investigados em ensaios clínicos maiores, assim como os seus efeitos a longo prazo.

Palavras-chave: Doença de Parkinson; Distúrbios do Movimento; Estimulação Transcraniana por Corrente Direta; Estimulação Magnética Transcraniana.

INTRODUCTION

Noninvasive stimulation is increasingly used to study brain function in movement disorders, to explore therapeutic options in orphan diseases (such ataxia) and as adjuvant therapy in conditions such as dystonia and Parkinson's disease (PD)¹. Two main techniques are available for human noninvasive brain stimulation: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). These neuromodulatory techniques are applied over selected cortical areas to modulate specific electrical activity in cortical-subcortical networks that are supposedly related to a given set of symptoms¹.

During TMS administration, a short-lasting magnetic field is created in the coil, which induces a relatively focal electrical field in the subjacent cortex (Figure 1). This electrical field can cause depolarization or hyperpolarization of the voltage-gated ion-channels in the cell membranes, which leads to modifications in neuronal activation thresholds². The TMS technique has distinct variables, such as stimulus amplitude, pulse waveform, pulse duration and the diameter and shape of the coil³. The interaction of TMS pulse and brain tissue is complex, depending on cortical morphology, tissue conductivity, design of the TMS coil and the current running through it. In general, low (≤ 1 Hz) or high (≥ 5 Hz) frequency rTMS is used to, respectively, decrease or increase cortical

brain excitability³. Repetitive TMS (rTMS) refers to the application of trains of repeated magnetic pulses delivered to the scalp. Repetitive stimuli can lead to a build-up of effects that might enhance the therapeutic benefits gained from a single application through reduction of the action potential threshold, response enhancement and neuroplasticity due to generation of multiple action potential³. In order to produce cumulative effects, besides rTMS trains, several sessions are usually needed, which in most cases are given daily for 5, 10 or more days^{1,4}. An alternative use of rTMS has been developed, modelled on theta burst stimulation (TBS) in animals, a technique that comprises short, repeated bursts of TMS pulse at 50 Hz. This is a potentially useful option in movement disorder treatment, and it is discussed later in this paper³. TMS is now FDA-approved, as a treatment for patients with depression (unipolar or bipolar), migraine and obsessive-compulsive disorder.

Transcranial direct current stimulation (tDCS) modulates spontaneous neuronal activity through an electrical current applied through a pair of electrodes placed on the scalp. tDCS does not facilitate massive synchronized discharge of action potentials, as TMS does, but it induces polarity-specific changes of resting membrane potential⁵. Cortical excitability is diminished through cathodal stimulation (neuronal hyperpolarization), whilst anodal stimulation increases excitability by means of depolarizing neurons. Although tDCS has been

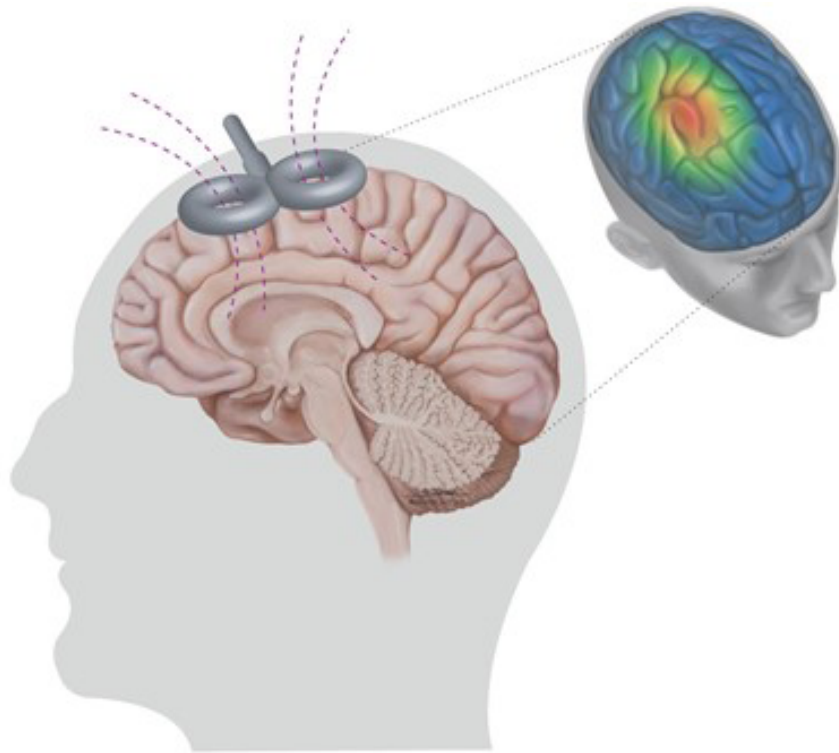


Figure 1. Brain activation by means of transcranial magnetic stimulation. The magnetic field in the transcranial magnetic stimulation coil (left) and the schematic representation of the electrical current induced in the brain (right).

studied less in relation to movement disorders, this review will highlight the most relevant studies that have applied these techniques in clinical trials.

Why use noninvasive stimulation in movement disorders?

Despite the fact that the basal ganglia, the core of movement disorder pathophysiology, cannot be reached directly by tDCS or TMS, stimulation over an appropriate cortical region that is part of the basal ganglia circuitry could influence activity within these loops and potentially produce clinical benefit⁴. Thus, the therapeutic background mechanisms for the use of these techniques have both local properties (over well-established cortical areas associated with movement disorders) and remote properties. For example, stimulation of the supplementary motor area (SMA) has been associated with improvement of freezing of gait (FoG) in PD⁵. Because the SMA is a pivotal area for gait initiation and is activated less in PD with FoG than in PD without FoG, its direct stimulation makes sense and has been specifically studied⁷.

The distant, indirect effects of stimulation have been recently studied using noninvasive and invasive techniques (deep brain stimulation, DBS) in movement disorders. For example, parkinsonian patients respond better to subthalamic nucleus (STN) DBS when the stimulation site is functionally connected to the SMA (mainly dorsal STN projections)⁸, while

tics in patients with Tourette syndrome (TS) are better controlled when thalamic stimulation is more densely connected with the cingulate and frontal middle gyrus⁹. TMS of the human primary motor cortex (M1) induces release of dopamine in the ipsilateral putamen, as detected by [11C]raclopride PET¹⁰. Additionally, magnetic stimulation of the pre-SMA significantly affects intrinsic connectivity between the pre-SMA and the striatum observed in functional MRI paradigms¹¹. Besides metabolic and functional influences on basal ganglia, motor TMS suppresses pathological beta frequency oscillations in the STN in PD patients¹². Taken together, the local and remote effects of cortical stimulation would be able to reset abnormal activity in one or more nodes of the altered distributed network and ultimately improve the symptoms of the underlying movement disorder. In the following sections, we analyze the main clinical studies on this matter to date.

METHODS

A nationally representative group of experts performed a comprehensive analysis of the literature in order to develop a critical review on key clinical decision-making factors driving noninvasive modulation in movement disorders.

The methodological quality of the trials reviewed was classified in accordance with the PEDro scale, which includes ten criteria (internal validity with eight criteria and statistical analysis with two criteria; [Supplementary File 1](#))¹³. Classes

of evidence and recommendations were described in accordance with the American Academy of Neurology's classification for rating therapeutic studies, whenever possible (Supplementary File 2 and 3)¹⁴. Furthermore, the aim of the present review was to analyze the relevance and applicability of the evidence to the targeted patient group and the likelihood of a clinical impact through the intervention.

Studies were identified by searching electronic databases and scanning the reference lists of articles. Only articles in English were included, through systematically searching the Medline, Embase and Google Scholar databases. The last search was run on July 19, 2020. The reference and citation lists of relevant studies were manually screened for potential eligible articles. We searched for the terms "Parkinson's disease", "dystonia", "tremor", "ataxia" and "Tourette syndrome", in combination with terms describing the type of stimulation (TMS and tDCS). We included published reports of clinical trials that examined the clinical effects after neuromodulation interventions (classes I, II, III and IV of evidence). For the sake of conciseness, we did not include studies already present in or preceding the meta-analysis and systematic reviews that we reviewed.

RESULTS

Parkinson's disease

Noninvasive stimulation has been studied in PD for almost three decades, and this has resulted in a much larger amount of clinical exploration than in relation to the other diseases discussed in this review. In PD, our search revealed 85 trials using TMS and 37 using tDCS. Given that many recent meta-analyses and systematic reviews are available, only recent non-included trials were selected for individual review, totaling nine studies (Table 1). PEDro scores ranged from 5 to 9 (mean = 8.0 ± 1.4), with six high-quality studies (PEDro 8 or 9).

Transcranial magnetic stimulation

The motor effects of rTMS have been subjected to several meta-analyses. The most recent of these included 28 randomized controlled or crossover trials up to July 2019, with 25 trials evaluating motor symptoms in a total of 787 patients¹⁵. Only five rTMS studies were published subsequently, and these are discussed individually. All forms of rTMS stimulation were found to ameliorate motor symptoms in a statistically significant manner, even within subgroup analyses. Using UPDRS-III as a standard motor outcome, a quantitative analysis was possible. This showed distinct effect magnitudes, measured using the standard mean difference (SMD). Per stimulation site, the primary motor cortex (M1) had the highest SMD compared with placebo, with 2.22; followed by the dorsal lateral prefrontal cortex (DLPFC) with 1.42; and the SMA and a combination of M1 + DLPFC, both with reported

SMD of 1.27¹⁵. High-frequency rTMS was more effective than low-frequency rTMS. The improvement was greater under off-medication conditions (SMD 2.98) than under on-medication conditions (SMD 1.51)¹⁵. This is mostly in agreement with a previous 2018 meta-analysis on 23 trials, in which significant motor benefit from high-frequency M1 and SMA stimulation was reported, with greater effect from the former, while non-motor effects were demonstrated using low-frequency rTMS or stimulation over the DLPFC¹⁶.

Recent trials are in agreement about the motor efficacy of the technique, as measured by means of UPDRS-III, including two positive trials with 20 Hz rTMS on M1¹⁷, one with 10 Hz on the SMA¹⁸, and two comparative trials. The first of these comparative trials showed longer-lasting efficacy of 20 Hz rTMS on M1, compared with 1 Hz¹⁹, while the other showed improvement with 5 Hz only on the pre-SMA, compared with M1²⁰.

Dysphagia was evaluated through a single trial, which showed class II evidence of limited improvement after high-frequency rTMS sessions (consisting of 10 daily sessions targeting M1, followed by monthly booster sessions). The improvement of dysphagia was correlated with overall motor improvement²¹. Cerebellum rTMS has been tested as a target for motor improvement in PD, but with disappointing results. Single-session cerebellar 1 Hz rTMS in 20 patients resulted in minor improvement of upper-limb mobility, but worsening of fine motor movements²².

Regarding non-motor symptoms, the most recent meta-analysis with rTMS, on depression in the setting of PD, included eight trials comprising a total of 331 patients¹⁵. Like non-PD depression patients, left DLPFC stimulation was found to be effective for the improvement of depression scores (SMD 1.64), which was consistent with a previous meta-analysis²³. Lastly, a recent meta-analysis found that rTMS on the M1 or PFC did not have any significant effect on cognition²⁴, while minor cognitive improvement was observed in a later study using 20 Hz rTMS on bilateral M1, in PD patients with dementia¹⁷. No study on TMS and PD has described any serious side effects.

Interpretation

High-frequency rTMS stimulation over M1 is currently the most supported form of rTMS for motor symptoms in PD and is likely to be effective. Other sites and parameters have shown smaller margins of effect so far. High-frequency rTMS DLPFC has already been approved by the FDA for treating major depression in non-PD patients and is likely to be effective for depression in PD patients, thus mirroring what has been established for non-PD patients in this setting.

Theta burst stimulation

Three studies used cerebellar continuous TBS (cTBS) for levodopa-induced dyskinesias, among a total of 39 patients,

Table 1. Characteristics of recent Parkinson's disease studies.

Author, year	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Khedr et al., 2020	Double-blind sham-controlled randomized trial	33 PD with dementia	20 Hz rTMS (2000 pulses) in 15 sessions, at 90% RMT with figure-of-eight.	Bilateral M1, hand area	Significant improvement in UPDRS III (22% improvement at three-month follow-up: 61 ± 16.4 vs 48.4 ± 14); minor but significant improvement in cognitive tests (MoCA 16.33 ± 4.23 vs 17.50 ± 3.93 ; MMSE 19.82 ± 2.71 vs 20.73 ± 3.17).	9	Class II
Hanoglu et al., 2020	Randomized controlled trial	16 PD (pre-SMA and M1)	5 Hz rTMS (2000 pulses) in 10 sessions with circular coil.	Bilateral pre-SMA or bilateral M1	Significant UPDRS improvement (41%) only in pre-SMA group. (23.75 ± 7.57 vs 14.00 ± 5.47 , one week after the end of stimulation).	5	Class IV
Hill et al., 2020	Double-blind sham-controlled, crossover (washout 1 week)	14 PD	iTBS (2 s TBS trains every 10 s for 600 pulses) with figure-of-eight at 80% AMT, in one session.	Left DLPFC	No difference in cognitive tests or mood.	7	Class III
Workman et al., 2020	Double-blind sham-controlled, crossover (washout of five days)	7 PD	2 or 4 mA tDCS, in single session.	Unilateral or bilateral cerebellar	Significant improvement ($p = 0.03$) in Berg balance score in bilateral 4 mA group, versus no gait improvement in sham group. Four out of seven patients were considered responders due to their improvement in Berg Balance Score after one session. No longer follow-up was done.	8	Class II
Khedr et al., 2019	Double-blind sham-controlled randomized trial	33 PD with dysphagia	20 Hz rTMS (2000 pulses each side), in 10 sessions, at 90% RMT with figure-of-eight; five monthly follow-up sessions.	Bilateral M1, hand area	Significant improvement in UPDRS III (26%) after three months of follow-up (61.9 ± 13.2 vs 45.8 ± 13.1 ; $p = 0.0001$), and in dysphagia scores; and reduction of swallowing time for solids, seen through videofluoroscopy.	9	Class II
Sanna et al., 2019	Double-blind sham-controlled, crossover (washout of one week)	11 PD with dyskinesias	cTBS (600 pulses) at 80% AMT, with circular coil, in single session.	Cerebellum	Decrease in dyskinesias and serum BDNF in active group.	8	Class II
Khedr et al., 2019b	Double-blind sham-controlled randomized trial	52 PD (26 each group)	20 Hz rTMS (at 90% RMT) or 1 Hz rTMS (at 100% RMT), with figure-of-eight; 2000 pulses.	Bilateral M1	Improvement in UPDRS (24%) in both groups, compared with baseline, but longer-lasting in 20 Hz group (45.27 ± 20.01 vs 34.54 ± 13.02 ; one-month follow-up).	8	Class II
Trung et al., 2019	Single-blind sham-controlled randomized trial	28 PD with MCI (14 active and 14 sham)	iTBS (2 s TBS trains every 10 s for 600 pulses) with figure-of-eight at 80% AMT, in six sessions.	Left DLPFC	No difference in cognition between groups. In-group analysis showed improvement in attention, both in sham and in active group. Improvement in visuospatial function was only observed after active stimulation.	6	Class III
Mi et al., 2019	Double-blind sham-controlled randomized trial	30 PD with FoG (20 active and 10 sham)	10 Hz rTMS (1000 pulses) with figure-of-eight at 90% RMT, in 10 sessions.	SMA	MDS-UPDRS III changed by -3.00 (95% CI -4.92 to -1.08), -5.20 (95% CI -7.12 to -3.28), -6.69 (95% CI -8.73 to -4.66) and -5.79 points (95% CI -7.86 to -3.71), from baseline (T0) to T1, T2, T3 and T4 respectively. FoG-Q changed by -1.60 (95% CI -2.37 to -0.83) and -2.13 points (95% CI -2.97 to -1.29), from baseline to T2 and T4, respectively. Gait cadence and duration of turn for sitting also improved in the active group over four weeks of follow-up.	9	Class II

PD: Parkinson's disease; rTMS: repetitive transcranial magnetic stimulation; iTBS: intermittent theta-burst stimulation; tDCS: transcranial direct current stimulation; cTBS: continuous theta-burst stimulation; RMT: resting motor threshold; AMT: active motor threshold; MCI: mild cognitive impairment; UPDRS-III: Unified Parkinson's Disease Rating Scale-III; FoG-Q: freezing of gait questionnaire; SMA: supplementary motor area; M1: primary motor cortex.

who all showed improvement in dyskinesias after either a single or five sessions²². However, cerebellar cTBS did not show any significant effect on tremor²². cTBS over M1 had no significant motor effect although when applied over the SMA, a mild yet significant motor improvement after a single session was detected²⁵. Intermittent TBS (iTBS) over the premotor cortex (PMC) resulted in no improvement in motor or mood scores²⁶. For cognition, single and multiple-session iTBS over the DLPFC failed to elicit any improvement²⁷. No study on TBS and PD has described any serious side effects.

Interpretation

Cerebellar cTBS is likely to be effective for controlling levodopa-induced dyskinesias, but there is currently insufficient evidence to support the use of TBS to treat any other motor or non-motor symptoms or signs.

Transcranial direct current stimulation

The most recent systematic review for tDCS and motor symptoms included 29 sham-controlled trials up to July 2019 with a total of 550 patients. Despite the number of studies, the study designs were highly heterogeneous. Both anodal and cathodal stimulation over M1, DLPFC and SMA showed inconsistent and contradictory results, with the sole exception of few distinct multitarget approaches with positive findings for locomotion²⁸. A more restricted systematic review analyzed only upper-limb outcomes from 10 studies. The results showed UPDRS improvement after unilateral or bilateral M1 tDCS, especially for bradykinesia. However, these results did not allow the authors to recommend any specific protocol, due to the diverse paradigms found in the studies²⁹.

The effect of tDCS on gait was specifically evaluated through a meta-analysis involving 18 sham-controlled trials with a total of 325 PD patients. The results showed that there was an overall positive but small effect size³⁰. Again, the diversity of trial designs limited the interpretation, with single or multiple stimulation targets among PMC, M1, PFC or SMA varying in each trial. However, the positive effect size was homogeneous throughout the studies, and the individual effect size variability was low. Six studies that assessed long-term effects failed to show significance³⁰. A recent crossover trial with anodal tDCS over the cerebellum reported improvement in dyskinesia during the active phase, with no other detectable motor improvement²².

Interpretation

Current tDCS application for PD is significantly hampered by significant heterogeneity in the population characteristics, PD stages, stimulation parameters, trial designs and outcome measurements. Thus, deriving a consensus on any set of stimulation procedures is extremely difficult. No recommendation is currently possible for motor symptoms other than gait, for which the method is likely to be effective

but with a limited effect size (its use as an add-on therapy is discussed below).

Dystonia

Dystonia is a syndrome characterized primarily by excessive muscle contractions leading to abnormal postures and involuntary twisting movements³¹. As it represents a heterogeneous group of disorders, in this review we will focus on isolated dystonia, given that certain pathophysiological mechanisms have been consistently identified and may have implications for widening the therapeutic strategies, such as noninvasive stimulation³¹.

Three general abnormalities appear to underlie network pathophysiology: loss of inhibition at different levels of the central nervous system leading to overflow phenomena, altered sensory integration and maladaptive synapse plasticity³².

The current treatment of dystonia includes selected drugs for specific cases, such as dopa-responsive dystonia, botulinum toxin injections for focal dystonia and surgery, notably DBS. However, new insights into the pathophysiology of dystonia and positive results from invasive neuromodulation trials have shown that this disorder should be seen as a consequence of network malfunction. In dystonia, there is an increased tendency to form aberrant input and output connections, potentially leading to abnormal improper connectivity and ultimately impairment of motor control¹. As such, dystonia could be potentially responsive to noninvasive neuromodulation strategies.

Here, we selected studies on adults with three forms of focal dystonia: hand dystonia, cranio-cervical dystonia (CCD) and blepharospasm.

Hand dystonia

Fifteen clinical trials have evaluated the effects of noninvasive stimulation for hand dystonia. These trials consisted of a total of 176 patients with different clinical presentations: writer's cramp (96), musician's dystonia (70), focal hand dystonia (9) and dystonic tremor (1). These studies were heterogeneous with regard to methodology, neuromodulation technique and parameters and outcome measurements. Their main findings are summarized in Table 2. In terms of methodological quality, PEDro scores ranged from 3 to 8 (6.5 ± 1.5). Three studies had scores < 6 and were considered to be low quality³³⁻³⁵. For the remaining ten studies, seven were classified as moderate and five as high quality with PEDro scores of 6/7 and 8 respectively³⁶⁻⁴⁰. In fact, most of the trials presented class III or IV evidence and had an exploratory approach to the technique and its clinical outcome.

Most studies have targeted the motor cortex (PMC in six; M1 in five; SMA in one). Regarding the neuromodulation technique, seven studies applied rTMS (four single-blinded, one double-blinded, two open), seven used tDCS (all

double-blinded), and one used cTBS (one single-blinded). The majority of these studies were performed in a single session and had short follow-up periods.

Overall, a limited number of studies reported clinical improvement, especially with short-term evaluation. An open-label study of rTMS on M1 showed that this method can reinforce deficient intracortical inhibition and may temporarily improve handwriting³⁴. These results were reinforced by two other single-blinded trials^{41,42} and one double-blinded trial⁴³, in which rTMS of the PMC led to temporary improvement in handwriting. Another target with good response was SI, which induced improvement in writer's cramp, measured by a 20 min writer's task⁴⁴.

Regarding tDCS, only one double-blinded cathodic stimulation reported a good outcome, with an improvement in the effectiveness of rehabilitation in task-specific (musician's) dystonia³⁸. A current of 2 mA was used, applied to the SMA bilaterally during the first 20 min of a 1 hour sensorimotor rehabilitation program over 10 sessions. In this trial, neuro-modulation caused an increase in the effectiveness of rehabilitation of musician's dystonia.

Interpretation

The evidence presented to date does not provide a high level of recommendation for the use of noninvasive modulation in hand dystonia. So far, studies have presented heterogeneous designs and quality, although interesting positive outcomes have been reported. The most promising target seems to be the PMC. Low-frequency rTMS over the PMC is possibly effective in improving handwriting temporarily in FHD (studies with class III evidence). For other types of hand dystonia, including musician's dystonia, there is insufficient evidence to support the use of rTMS or tDCS.

Cranio-cervical dystonia (CCD)

Regarding CCD, only three clinical trials, consisting of a total of 38 patients, have evaluated the therapeutic effects of noninvasive stimulation (Table 3). PEDro scores ranged from 4 (one low-quality study) to 9 (mean, 7.25 ± 1.8), while most had scores of up to 7, which was considered high quality although still presenting class III evidence.

These studies presented heterogeneous techniques and targets: (1) two tTMS in motor cortical areas; and (2) one cTBS in the cerebellum. Koch et al.⁴⁵ performed a double-blind sham-controlled trial of five sessions per week for two weeks among 18 CD patients with cTBS of the cerebellum bilaterally. They showed that there was a small, but significant improvement in TWRTS in comparison with baseline scores, at the first evaluation after the end of stimulation period (mean 33.6 ± 4.2 versus 38.8 ± 4.1 ; $p = 0.008$). Another study showed a mild improvement through targeting dPMC and M1⁴⁶. Although a limited number of case series have

reported improvements of CCD scores through tDCS, no formal clinical trial has been performed to date.

Only one double-blinded, sham control study (class III evidence) with noninvasive stimulation has been conducted in relation to blepharospasm⁴⁷. The intervention applied was rTMS to the anterior cingulate cortex, and this led to significant improvements of all clinical outcomes at the end of the active stimulations and at 1 h afterwards.

Interpretation

There is insufficient evidence to support or refute the effectiveness of noninvasive stimulation in CCD and blepharospasm, mainly because the samples of patients studied so far have been small, and the overall quality of these studies has been low. Even so, the studies performed have explored targets (such as the cerebellum and the motor cortex) that can be potentially effective for CCD, and larger studies are warranted.

Essential tremor

Nine studies analyzed the effects of noninvasive stimulation among essential tremor (ET) patients⁴⁸⁻⁵⁶. Table 4 displays the characteristics of these studies. There was great variability among them regarding methodological quality. The population was fairly homogeneous, since all the studies included ET patients ($n = 119$), and five studies also included healthy controls ($n = 61$).

Only one study provided class II evidence; three studies provided class IV, and the remaining five provided class III evidence. PEDro scores ranged from 6 to 10 (7.4 ± 1.5). Only one study satisfied all the PEDro score criteria⁴⁸, and six studies scored 6 to 7^{49-53,56}. Therefore, we considered that the majority of these studies were of moderate/high quality.

Six studies targeted the cerebellum ($n = 80$ ET patients + 33 healthy controls)^{48,49,51,52,54,56}, and three targeted the motor cortex ($n = 33$ ET + 28 healthy controls)^{50,53,55}. Only one study used cathodal tDCS⁵², while the remainder used rTMS: in five, the frequency chosen was 1 Hz, and three used cTBS. The number of sessions in rTMS studies ranged from 1 to 15 (mean = 3.7; SD = 4.8), but five of the eight studies only had one session^{48-50,53,54}. In the only tDCS study, the patients received 10 sessions⁵².

The length of the follow-up was quite variable, ranging from ≤ 1 hour after the end of stimulation (five studies) to different numbers of weeks after completion of the study protocol (four studies), with a maximum follow-up of 12 weeks⁵⁵. Obviously, this lack of uniformity limits the potential for accurate comparison of the data. In the longest follow-up, the improvement in tremor after 15 sessions of 1 Hz rTMS continued to be present until after eight weeks, but not after twelve weeks⁵⁵. Three studies showed clinical improvements through validated tremor scales after noninvasive stimulation, over periods ranging from 5 min to 12

Table 2. Characteristics of studies investigating focal dystonia.

Author, year	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Siebner et al., 1999	Open-label	16 WC, 11 HC	1 Hz rTMS at 90% RMT, in one session.	M1	rTMS can reinforce deficient intracortical inhibition and may improve handwriting temporarily.	3	Class IV
Siebner et al., 2003	Sham controlled	7 FHD (5 WC; 1 non-task specific FHD; 1 DT), 7 HC	1 Hz rTMS at 90% RMT in one session.	dPMC	No clinical improvement.	4	Class III
Murase et al., 2005	Single-blinded, sham controlled	9 WC, 7 HC	0.2 Hz rTMS at 85% RMT, in one session.	M1, PMC, SMA	Inhibition of the PMC can provide a therapeutic target for WC, as it improved handwriting after the session. However, no sustained improvement was evaluated.	7	Class III
Borich et al., 2009	Single-blinded, partial crossover with sham stimulation	6 FHD (3 WC, 3 MD with additional symptoms during writing), 9 HC	1 Hz rTMS at 90% RMT, in five sessions.	PMC	Inhibition of the PMC can provide a therapeutic target for WC, as it improved handwriting for 10 days.	6	Class III
Havrankova et al., 2010	Double blinded, crossover	11 WC	1 Hz rTMS at 90% AMT, in five sessions.	S1	Low frequency rTMS over S1 cortex can improve WC in both subjective and objective parameters.	7	Class III
Buttkus et al., 2010	Double blinded, sham controlled with crossover	10 MD	Cathodal/anodal tDCS for 20 min at 2 mA, in one session.	Left M1 with reference electrode over right supraorbital area	No change in control of fine movements.	8	Class III
Buttkus et al., 2011	Double blinded, sham controlled with crossover	9 MD	Cathodal/anodal tDCS for 20 min at 2 mA, in one session.	Left M1 (i.e. C3) with reference electrode over right supraorbital area	No change in control of fine movements.	8	Class III
Benninger et al., 2012	Double blinded, sham controlled	12 WC	Cathodal tDCS at 2 mA for 20 min, in three sessions over one week.	M1 contralateral to affected site; reference over mastoid	No benefit.	7	Class III
Huang et al., 2012	Single-blinded, sham controlled	18 WC, 8 HC	cTBS 3-pulse 50 Hz burst every 200 ms at 80% AMT for 40 s, in five sessions.	PMC	All subjects (including those in the sham arm) reported a subjective improvement, but no significant changes in two different writing tasks were observed.	6	Class III
Kimberley et al., 2013	Single-blinded, sham controlled with crossover (but only data prior to crossover were used for the analysis)	7 WC, 5 MD	rTMS 1 Hz rTMS at 80% RMT in five consecutive 20 min sessions + rehabilitation.	dPMC	No significant differences between real and sham rTMS.	4	Class III
Furuya et al., 2014	Double blinded, sham controlled with crossover	10 MD, 10 healthy musicians	tDCS 2 mA stimulation for 24 min (electrode size 35 cm ²) during motor retraining, in one session.	Bilateral M1	There is therapeutic potential for behavioral training assisted by bihemispheric M1 stimulation, since it improves rhythmic accuracy of sequential finger movements	8	Class III

Table 2. Cont.

Author, year	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Sadnicka et al., 2014	Single-blinded, sham controlled with crossover	10 WC	tDCS anodal stimulation at 2 mA for 15 min (electrode size 25 cm ²), in one session.	Ipsilateral cerebellum	No subjective improvement nor changes in the WCERS or timed writing assessment	7	Class III
Kimberley et al., 2015	Randomized, sham controlled, with crossover	8 FHD	rTMS 1 Hz rTMS at 90% RMT, in five consecutive 30 min sessions + training	dPMC	No additional benefit from sensorimotor retraining	7	Class III
Rosset-Llobet et al., 2015	Double blinded, sham controlled	30 MD	tDCS 2 mA stimulation (electrode size 35 cm ²) during first 20 min of 1 h rehabilitation session. Total of 10 sessions over 2 weeks.	Bilateral SMC (i.e. C3) with cathode contralateral to the affected arm	Biparietal tDCS with left-side cathode can increase the effectiveness of rehabilitation in MD.	8	Class III
Bradnam et al., 2015	Double blinded, sham-controlled with crossover	8 FHD (5 WC; 3 MD), 8 HC	tDCS anodal/cathodal tDCS for 20 min at 2 mA (electrode size 25 cm ²), in one session.	Ipsilateral cerebellum (3 cm laterally and 1 cm inferiorly to theinion, reference over the buccinator muscle)	No change in clinical outcomes.	8	Class II

WC: writer's cramp; HC: healthy controls; FHD: focal hand dystonia; DT: dystonic tremor; dPMC: dorsal premotor cortex; SMA: supplementary motor area; MD: musician's dystonia; cTBS: continuous theta burst stimulation.

Table 3. Characteristics of studies investigating cervical dystonia.

Author, year	Study design	Population	Intervention	Target	Main findings	Pedro score	Class of evidence
Koch et al., 2014	Double-blinded, sham-controlled	18 CD patients (9 real cTBS; 9 sham cTBS)	cTBS - five sessions per week for two weeks.	Bilateral lateral cerebellum	Small but significant clinical improvement as measured by TWSTRS, of approximately 15%.	9	Class III
Pirio Richardson et al., 2015	Single-blinded, sham-controlled	8 CD	rTMS - 0.2 Hz at 85% of RMT for 15 min in randomized sessions (one session per target, at least two days apart).	Left ACC, M1, dPMC, SMA and sham dPMC	All sites except ACC showed non-significant improvement in TWSTRS scores, with the greatest improvement seen over dPMC and M1.	7	Class IV
Zittel et al., 2015	Open	12 CD patients and 8 HC	rTMS - 1 Hz at 90% RMT in two 20 min sessions.	Left M1 and S1 (2 cm posteriorly and 1 laterally to M1)	No influence on symptoms severity.	4	Class IV

CD: cervical dystonia; dPMC: dorsal premotor cortex; PMC: premotor cortex; SMA: supplementary motor area; cTBS: continuous theta burst stimulation; ACC: anterior cingulate cortex.

Table 4. Characteristics of essential tremor studies.

Author, year	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Gironell et al., 2002	Double-blind sham-controlled, crossover (washout of one week)	10 ET	rTMS (1 Hz, 20 min, total 300 pulses per session), in one session with 70 mm butterfly coil at 100% of maximum stimulator output.	Posterior cerebellum (2 cm below theinion)	Tremor improvement according to the FTM (17%), and accelerometry evaluation on the +5 min assessment	10	Class II
Avanzino et al., 2009	Open-label on five patients and single-blind sham-controlled crossover (washout of two weeks) on seven patients	11 ET + 11 HC	rTMS (1 Hz, 10 min, total 600 pulses per session), in one session with 90 mm figure-of-eight coil at 90% RMT.	Right lateral cerebellum (3 cm laterally and 1 cm beneath theinion)	Decrease of TD values, increase of ITI values and decrease of the coefficient of variation of ITI. No change in frequency or magnitude of accelerometer signal. No change in tremor (FTM)	6	Class IV
Helriegel et al., 2012	Single-blind sham-controlled, crossover (washout of one week)	10 ET + 10 HC	rTMS (cTBS, two 20 s trains with 60 s pauses, repeated at every 200 s), in one session with 70 mm figure-of-eight coil, at 80% AMT (sham at 30% AMT).	Left M1 (hand area)	Decrease in tremor amplitude according to accelerometry evaluation on all post-treatment assessments. No significant reduction in clinical tremor (FTM).	7	Class III
Popa et al., 2013	Open-label	11 ET + 11 HC	rTMS (1 Hz, 15 min, total 900 pulses per session), in five sessions with figure-of-eight coil at 90% RMT.	Posterior cerebellum (bilateral) – neuronavigated to lobule VIII	Tremor improvement (27%) that built up until day 12 and persisted for 3 weeks (FTM: baseline 43.8 ± 12.5 vs one month 31.8 ± 12). Decrease in tremor amplitude.	6	Class IV
Gironell et al., 2014	Double-blind sham-controlled crossover (washout of three months)	10 ET	Cathodal tDCS, in 10 sessions with 2 mA.	Cerebellar hemispheres, bilaterally	No acute or long-lasting benefit (FTM and accelerometric recordings).	7	Class III
Chuang et al., 2014	Open-label sham-controlled crossover (washout of one week)	13 ET + 18 HC	rTMS (cTBS, 50 Hz burst, 40 s train; repeated at every 200 ms), 1 session with 70 mm figure-of-eight coil at 80% AMT	Left M1 + premotor cortex (2.5 cm anteriorly to the motor hot-spot)	Improvement in tremor amplitude, but not in tremor frequency.	7	Class IV
Bologna et al., 2015	Double-blind sham-controlled crossover (washout of one week)	16 ET + 11 HC	rTMS (cTBS, 40 s train; repeated at every 200 ms), in one session with figure-of-eight coil at 80% AMT.	Right cerebellar hemisphere (3 cm laterally and 1 cm under theinion)	No change in tremor severity and reaching movements (FTM and accelerometer).	9	Class III
Badran et al., 2016	Double-blind sham-controlled	10 ET (5 active; 5 sham)	rTMS (1 Hz, 20 min, total 1200 pulses per session), in 15 sessions with 75 mm figure-of-eight coil at 110% RMT.	Pre-SMA (sagittal midline, 50% of distance between EEG positions Fz and FCz)	Improvement in tremor (26.11% active x 18.82% sham according to FTM). Improvement was sustained 4 and 8 weeks afterwards, only in active group (17.77%).	9	Class III
Shin et al., 2019	Single-blind sham-controlled	22 ET (12 active; 10 sham)	rTMS (1 Hz, 20 trains with a duration of 30 s each, separated by 10 s, total 1200 pulses per session), in five sessions with 70 mm figure-of-eight coil at 90% RMT.	Cerebellum bilaterally (3 cm laterally and 1 cm inferiorly to theinion)	Improvement in tremor immediately afterwards (33% active x 20% sham according to FTM) and 4 weeks afterwards (31% active x 17% sham). No significant difference between groups. No improvement in functions of daily living.	6	Class III

AMT: action motor threshold; cTBS: continuous theta burst stimulation; tDCS: transcranial direct current stimulation; ET: essential tremor; FTM: Fahn Tolosa Marin tremor rating scale; HC: healthy controls; ITI: inter tapping interval; M1: primary motor cortex; RMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation; TD: touch duration.

weeks afterwards^{48,51,55}. All three used 1 Hz rTMS: two over the cerebellum and one over the motor cortex^{48,51,55}. Seven studies also analyzed tremor characteristics using accelerometric records and, after considering the data from three additional studies, demonstrated positive short-term results ranging from immediate to 40 min after the procedure^{49,50,53}. Two used cTBS over the motor cortex, and one used cerebellar 1 Hz rTMS⁵³. No cTBS study reported any improvement in clinical tremor scales, although two had positive accelerometric outcome data^{50,53}. Among the studies with the highest PEDro scores (9-10)^{48,54,55}, two were positive and one was negative. Four studies (three reporting positive accelerometric results) did not mention the presence or absence of side effects, although we believe that side effects are particularly important in clinical trials^{49,50,53,55}. Out of the remaining studies, only two reported mild side effects, including one with positive clinical results^{48,52}.

Interpretation

Through gathering the available data, low-frequency rTMS over the cerebellum was seen to be possibly effective in improving tremor in ET (studies with class II and III evidence). The outcomes from tDCS studies do not support any conclusions and, thus, tDCS cannot be recommended⁵². Overall, the heterogeneity of the reports and outcomes is still an obstacle in systematically implementing noninvasive neuromodulation for ET in clinical practice.

Cerebellar ataxia

Eleven clinical trials included patients with cerebellar ataxia (n = 238) and evaluated clinical changes after noninvasive stimulation (Table 5). Different ataxia etiologies were included: eight studies included patients with hereditary degenerative ataxias (n = 155)^{22,57,58}, four included patients with sporadic adult-onset ataxia (n = 14)^{58,59}, three included patients with cerebellar-type multiple-system atrophy (n = 15)^{22,58}, two included patients with cerebellar ataxia due to stroke (n = 38)^{60,61}, two included immune-mediated ataxias (n = 10)^{22,62} and one included cases of ataxia in the setting of cerebral palsy (n = 6)⁶³. Overall, the population included tended to be heterogeneous throughout the studies, and was limited to a single diagnosis in only four studies (multiple sclerosis in one, stroke in two and cerebral palsy in one)^{22,62}.

Two studies provided class IV evidence, while seven provided class III, and two provided class II. PEDro scores ranged from 4 to 9 (6.7 ± 1.9), considering all the studies. Studies using tDCS had higher PEDro scores (TMS mean = 6; and tDCS mean = 7.6).

Almost all the studies used the cerebellum as the target; only one study targeted the motor cortex (M1)⁶². Regarding the neuromodulation technique, four studies used single-pulse TMS (two of them were double-blind)^{57,64-66}, three used rTMS (two double-blind)⁶⁰⁻⁶² and five used anodal tDCS (three

double-blind)^{59,63,67-69}. The chosen stimulation frequency ranged from 1 to 50 Hz, and the number of sessions ranged from one to ten. All five tDCS studies used anodal stimulation, with currents ranging from 1 to 2 mA and numbers of sessions from one to ten. No study involved maintenance sessions, and none measured long-term effects, although it could be argued that three months of follow-up would constitute long-term in noninvasive neuromodulation.

Only one study, using one session of 1 mA anodal tDCS, reported no clinical improvement after neuromodulation⁶⁷; the remainder described positive results. Many studies assessed ataxia exclusively through axial measures of gait and balance, and only six studies applied validated ataxia scales^{57,59,60,66,68,69}. Both studies with the highest PEDro scores (9 and 10) used anodal tDCS and reported clinical improvement: one with validated scales and the other with gait evaluation. Out of the three studies with PEDro scores of 8, two used anodal tDCS and one used single-pulse TMS^{22,57,58}; all of these reported positive outcomes with validated scales.

Reporting of adverse effects was far from ideal, since half of the studies did not mention them^{59,60,62,66,67,69}. Among the remaining studies, five reported none^{57,61,64,65,68}, while one reported only mild transient side effects after anodal tDCS⁶³.

Interpretation

Overall, the studies on cerebellar ataxia were of moderate quality, and all but one reported short-term positive results. As such, there is insufficient evidence so far to support the use of rTMS to treat ataxia. Anodal cerebellar tDCS is possibly effective in treating degenerative cerebellar ataxia, but multicenter trials and meta-analyses are needed. Considering that cerebellar ataxia is currently an orphan symptom, and that these procedures are noninvasive and safe, off-label treatment could be attempted in selected cases.

Tourette syndrome (TS)

The pathological mechanism underlying TS is a matter of debate, but some studies have proposed that the primary motor (M1?) cortex and the SMA are hyperexcitable in these patients⁷⁰. These findings have led to the hypothesis that normalizing the excitability of these areas would be a potential treatment for tics. Accordingly, low-frequency rTMS applied over bilateral SMA was found to improve tic severity for up to six months in two open-label trials^{71,72}. On the other hand, two randomized controlled trials using the same target did not show any significant improvement in tics after TMS^{73,74}, although in one of them an additional three-week open-label active treatment (for those patients initially randomized to active rTMS) resulted in an overall 29.7% reduction in tic severity, compared with baseline⁷⁴. Additionally, active TMS induced significant inhibition in the primary motor cortex network. Other targets such as motor and pre-motor cortex were found to have effect on tics in TS patients^{75,76} (Table 6).

Table 5. Characteristics of studies investigating cerebellar ataxia.

Author, year	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Shiga et al., 2002	Double-blind sham-controlled	74 spinocerebellar degeneration cases (cerebellar type x OPCA type): 39 active, 35 placebo	Single pulse TMS (1 pulse every 6 s, 10 pulses per site, total 30 pulses per session), in 21 sessions with 14 cm circular coil at 250% RMT.	Cerebellum (over the inion; 4 cm to the left and 4 cm to the right)	Improvement in 10 m time, 10 m steps, tandem steps and standing capacities, especially regarding cerebellar type.	7	Class III
Ihara et al., 2005	Single-blind, uncontrolled	20 spinocerebellar degeneration cases (10 OPCA, 6 CCA, 4 SCA6)	Single-pulse TMS (1 pulse every 5 s, 10 pulses per site, total 30 pulses per session), in 24 sessions with 70 mm figure-of-eight coil at 100% maximum stimulator output.	Cerebellum (over the inion; 4 cm to the left and 4 cm to the right)	Improvement in ataxia (ICARS) by 13.5% (38.15 ± 18.43 vs 33.01 ± 17.26, p = 0.003)	5	Class III
Koch et al., 2008	Open-label sham-controlled crossover (one day of washout)	8 multiple sclerosis cases with cerebellar symptoms + 7 healthy subjects	5 Hz rTMS (18 trains of 50 stimuli, with 40 s pause, total 900 pulses per session), in one session with 90 mm figure-of-eight coil at 100% RMT.	M1 (contralateral to the dominant limb)	Improvement in hand dexterity (9HPT) immediately after and 10 min after.	4	Class IV
Grimaldi and Manto et al., 2013	Single-blind sham-controlled crossover (> 6 days of washout)	9 cerebellar ataxia cases (1 immune ataxia; 1 paraneoplastic ataxia; 3 SAOA; 1 autosomal recessive ataxia; 3 dominant ataxia)	Anodal tDCS, in one session at 1 mA.	Right cerebellum hemisphere and vermis (over the inion and 3 cm to right)	No change in posturography and upper limb dexterity.	4	Class III
Bonni et al., 2014	Open-label	6 posterior circulation stroke cases with ataxia	rTMS (iTBS, 3 pulses at 50 Hz repeated at a rate of 5 Hz; 20 trains of 10 bursts delivered at 8-sec intervals; total duration: 190 sec, 600 pulses), in 10 sessions with 70 mm figure-of-eight coil at 80% RMT + physiotherapy.	Cerebellar hemisphere (ipsilateral to the lesion)	Improvement in ataxia (MICARS) by 18%, especially posture and gait subscales. Total score: pre-iTBS = 53.4 ± 13.0 vs post-iTBS = 43.8 ± 12.1	5	Class IV
Kim et al., 2014	Double-blind sham-controlled	32 posterior circulation stroke cases with ataxia	rTMS (1 Hz, 15 min duration, total 900 pulses per session), in five sessions with 75 mm figure-of-eight coil at 100% RMT.	Cerebellar hemisphere (2 cm under the inion and 2 cm ipsilateral to the lesion)	Improvement in the 10 m walk test 1 month afterwards. Balance (BBS) improved after five days and after one month.	7	Class III
Benussi et al., 2015	Double-blind sham-controlled crossover (one week of washout)	19 cerebellar ataxia cases (5 SCA2; 1 SCA1; 2 SCA 38; 1 Friedreich's ataxia; 1 AOMA2; 6 MSA-C; 1 FXATAS and 2 SAOA)	Anode tDCS 1 session with 2 mA.	Cerebellum	Improvement in ataxia by 10% (SARA) and 12.2% (ICARS). Hand dexterity also improved by 8% (9HPT) and gait by 10.7% (8MW)	9	Class III
Grecco et al., 2016	Single-blind, sham-controlled, crossover (three months of washout)	6 ataxic cerebral palsy patients	Anodal tDCS 20 min duration, in 10 sessions with 1 mA + treadmill training.	Cerebellum (1 cm under the inion)	Improvement in hip oscillation during eyes-closed gait (stabilimeter evaluation)	9	Class III

Table 5. Cont.

Author, year	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Benussi et al., 2017	Double-blind sham-controlled	20 neurodegenerative ataxias (5 SCA 2; 2 SCA 38; 1 SCA 14; 1 Friedreich's ataxia; 1 AOMA2; 4 MSA-C; 1 FXATAS; 5 SAOA) + 10 healthy controls	Anodal tDCS, in 10 sessions with 2 mA.	Cerebellum (2 cm under theinion)	Improvement lasting at least three months in SARA (17.4%), ICARS (20.2%), gait (27%) and handwriting (8.5%)	8	Class III
Benussi et al., 2018	Double-blind sham-controlled crossover (three months of washout)	20 neurodegenerative ataxia cases (7 SCA2; 5 MSA-C; 1 SCA38; 1 SCA14; 1 Friedreich ataxia; 1 AOMA2; 4 SAOA)	Anodal tDCS (cerebellum) and cathodal tDCS (spinal cord), in 10 sessions with 2 mA.	Cerebellum (2 cm under theinion) and spinal cord (2 cm under T11)	Improvement lasting at least 3 months in SARA (20.3%), ICARS (16.6%), 8MW (10.6%), 9HPT (6.6%) and SF-36 (10.5%).	8	Class II
Manor et al., 2019	Double-blind sham-controlled	20 spinocerebellar ataxia cases	Single pulse TMS (1 pulse every 6 s, 10 pulses per site, total 30 pulses per session), in 20 sessions with 14 cm circular coil at 100% maximum stimulator output.	Cerebellum (over theinion; 4 cm to the left and 4 cm to the right)	Improvement only in stance sub-score of SARA and standing postural sway metrics.	8	Class II

8MW: 8-meter walking time; 9HPT: 9-hole peg test; AOMA2: ataxia with oculomotor apraxia type 2; Ass. TP: assessment time points; BBS: Berg balance scale; BFMDRS: Burke-Fahn-Marsden dystonia rating scale; CCA: cortical cerebellar atrophy; cTBS: continuous theta burst stimulation; tDCS: transcranial direct current stimulation; EBCC: eyeblink classical conditioning; FXATAS: fragile-X associated tremor/ataxia syndrome; ICARS: international cooperative ataxia rating scale; iTBS: intermittent theta burst stimulation; ITI: inter tapping interval; M1: primary motor cortex; MICARS: modified international cooperative ataxia rating scale; MSA-C: multiple system atrophy cerebellar type; OPCA: olivopontocerebellar atrophy; PD: Parkinson disease; RMT: resting motor threshold; SARA: scale for the assessment and rating of ataxia; SAOA: sporadic adult-onset ataxia; TMS: transcranial magnetic stimulation.

Table 6. Characteristics of studies investigating Tourette syndrome.

Author, y	Study design	Population	Intervention	Target	Main clinical findings	Pedro score	Class of evidence
Münchau et al., 2002	Single-blinded, crossover	16 patients with TS	1 Hz rTMS	Motor and Pre-motor cortex	There was no significant improvement of symptoms after any of the rTMS conditions as assessed	05	III
Le et al., 2012	Open-label, not controlled	25 patients with TS	1 Hz rTMS	SMA	There was a significant reduction in Tic severity at the end of the week 4 of treatment. Seventeen children had sustained improvements at the 6-month follow-up.	03	IV
Kwon et al., 2011	Open-label, not controlled	10 patients with TS patients	1 Hz rTMS	SMA	Tic symptoms improved significantly over the 12 weeks of the study.	03	IV
Orth et al., 2014	Single blinded, crossover	5 patients with TS	1 Hz rTMS	Pre-motor cortex	No significant effect after stimulation protocol	06	III
Wu et al., 2014	Randomized-controlled trial	12 patients with TS	Theta burst stimulation	SMA	No significant difference in tic severity was detected between the two groups. Active TMS induced significant inhibition in the motor network.	10	Class I
Landeros-Weisenberger et al., 2015	Randomized-controlled trial	20 patients with TS	1 Hz rTMS	SMA	After 3 weeks of the TMS protocol, no difference was observed between the active and sham group	10	Class I

TS: Tourette syndrome; rTMS: repetitive transcranial magnetic stimulation; SMA: supplementary motor area.

Predictors of efficacy of TMS for TS have been recently discussed, and it has been pointed out that rTMS is more effective in TS with comorbidities (such as obsessive-compulsive disorder and attention deficit hyperactivity disorder), compared with “purer” TS forms⁷⁰. In accordance with the mechanism for TMS, a higher degree of brain electrical activity in individuals with TS and comorbidities (for example, ADHD has been associated with excess theta activity) might constitute a variable that is predictive of good response⁷⁰.

Studies using tDCS in TS are scarce. A recent sham-controlled trial showed that a single session of tDCS over SMA was not effective, with regard to time conditions (pre/post) and stimulation conditions (cathodal/sham), in ten patients⁷⁷.

The mean total PEDro score for the reports on these trials was 6.1 (3.1 ± 3). Three studies were considered to present moderate/high quality (> 5 points).

Interpretation

Repetitive TMS over the SMA is likely to be ineffective in reducing tics in TS. The lack of available data regarding other targets and the use of tDCS do not allow any conclusions to be reached regarding these techniques. Two points about the studies need to be addressed. First, the amount of stimulation given (rTMS or tDCS) seems to be an important consideration, since multiple sessions appear to be more effective than a single session. Likewise, a downstream effect from TMS has been demonstrated after repetitive stimulation over the SMA⁷⁴. Second, the high phenotypic variation and comorbidities might have contributed to the disparity of the study outcomes. Besides clinical characteristics, the baseline electrical brain activity has been associated with different TMS responses⁷⁰. How rTMS and tDCS affect this interplay between clinical and electrophysiological patients' characteristics should be addressed in further studies.

Discussion and future directions

In this review, we have summarized the evidence available regarding noninvasive stimulation therapies for managing the main movement disorders. We found that TMS is likely to be effective for motor symptoms, dyskinesia and depression in PD. Additionally, TMS is possibly effective in improving handwriting in FHD, tremor in ET and cerebellar ataxia and is likely to be ineffective in reducing tics in TS. tDCS is likely to be effective in improving gait in PD.

Despite good results in several studies and the robust background rationale for applying noninvasive stimulation in movement disorders, it remains to be determined how to optimize rTMS and tDCS protocols to give them relevance in routine clinical practice. The best stimulation paradigms and the best responder profiles are still coupled with uncertainties regarding the long-term genuine benefits⁴. Two major factors are determinant. First, there has been large heterogeneity among the protocols used, with different cortical targets and

numbers of sessions, which complicates the generalization of the current findings. In comparison, most studies relating to depression have focused on a single recommended site and protocol, producing consistent results. Second, there is still a lack of large-scale trials that could assess the placebo effects of stimulation and the real effects of stimulation in large samples of patients.

Noninvasive stimulation as an add-on therapy

In our view, because noninvasive stimulation has a low effect size, it should be seen as a “supporting actor,” and not as the “leading role”. This does not mean that it is less important than rehabilitation or medications, but it thus forms a complementary option, as in the case of botulinum toxin in dystonia or physiotherapy in FoG and ataxia, for example. In this era of personalized medicine, it is of paramount importance to note that noninvasive stimulation will probably serve a subset of patients with a subset of clinical characteristics and specific brain activity abnormalities or network disruption, but not all patients. Additionally, it could be a therapeutic tool for patients for whom surgical approaches are contraindicated, given the safety and lower rate of side effects shown by noninvasive stimulation. Another promising approach is the use of rTMS prior to a training intervention (e.g. prior to physiotherapy if treating gait in PD) or even during a given task in the case of tDCS (e.g. while performing physiotherapy for writer's cramp). In these cases, the rationale is to strengthen the effectiveness of synaptic connections and recruit fibers required to improve performance during a given task⁷.

New stimulation paradigms are needed

The classical targets explored so far (M1, supplementary area and prefrontal cortex) need to be investigated in multicenter clinical trials, and new paradigms need to be explored with combined or new targets. As discussed earlier, because of the great connectivity of the cerebellum, this has emerged as a potential hot spot for TMS and tDCS²². Along this line, because the spinal cord acts as a ‘highway’ of neural information and remotely regulates cortical areas relating to the pathophysiology of movement disorders, its modulation is theoretically interesting. A novel approach involving stimulation of the spinal cord noninvasively through a transcutaneous electrical or magnetic field applied to treat spasticity and urinary incontinence has recently emerged⁷. Its applicability is likely to catch the neurology community's attention over the coming years.

Lastly, network dysfunctions in movement disorders are not straightforward and involve multiple supraspinal circuits that are both distinct and overlapping^{6,8}. The presence of different underlying circuitries may explain the variability in cortical targets that have been pursued in the literature. An approach involving multiple/combined cortical targets, as recently explored in FoG, may be a key step forward. In

that investigation, stimulation of the dorsolateral prefrontal cortex simultaneously with M1 induced greater benefit for diminishing FoG severity, compared with M1 stimulation alone⁷.

Noninvasive stimulation approaches have the potential to be successfully applied in clinical practice, either as an adjunct therapy or as the protagonist in patients with contraindications for other treatments. Large-scale clinical trials focusing on targets previously attempted, from which positive results were obtained, are needed. The best scenario for this developing therapy will probably involve optimization of stimulation protocols, together with new paradigms looking to recruit fibers and neurons during rTMS and tDCS sessions to enhance rehabilitation effects.

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SUPPLEMENTARY MATERIAL

The following material is available online for this article:

- S1. PEDro scale - Internal Validity (8 Criteria).
- S2. American Academy of Neurology Classification of Evidence for the Rating of a Therapeutic Study and Recommendations.
- S3. Recommendations based on study classes.

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