

Non-Invasive Brain Stimulation for Treatment of Focal Hand Dystonia: Update and Future Direction

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ABSTRACT

Focal hand dystonia (FHD) is characterized by excessive and unwanted muscle activation in both the hand and arm resulting in impaired performance in particular tasks. Understanding the pathophysiology of FHD has progressed significantly for several decades and this has led to consideration of other potential therapies such as non-invasive brain stimulation (NIBS). A number of studies have been conducted to develop new therapy for FHD using transcranial magnetic stimulation and transcranial direct current stimulation. In this paper, we review previous studies and describe the potential therapeutic use of NIBS for FHD. We also discuss the future direction of NIBS to treat FHD.

Key Words

Focal hand dystonia; Non-invasive brain stimulation; Transcranial magnetic stimulation; Transcranial direct current stimulation.

INTRODUCTION

Focal hand dystonia (FHD) is characterized by excessive and unwanted muscle activation in both the hand and arm resulting in impaired performance in particular tasks. Writer's cramp (WC) and musician's dystonia (MD) are the most common forms of FHD, but numerous other occupational FHD have been identified.¹ FHD generally occurs in people who have spent a long period of time per-

forming repetitive skilled fine motor tasks. Botulinum toxin is usually the most effective treatment² for FHD whereas oral medications are often limited in efficacy and cause side effects. However, FHD has a lower overall response rate to botulinum toxin, with about 50% of WC patients receiving at least mild benefit compared to 80% for cervical dystonia and over 90% for blepharospasm.³ This may be due to complex patterns of the hand movements, numbers of muscles involved, and challenges in discriminating primary abnormal movements from compensatory movements. Clearly, new therapeutic measures are needed for FHD patients.

Understanding the pathophysiology of FHD has progressed significantly for several decades and this has led to consideration of other potential therapies such as non-invasive brain stimulation (NIBS). There are several general abnormalities that appear to play a role in the pathophysiology of dystonia including loss of inhibition, sensory dysfunction, and abnormal plasticity.⁴ FHD is thought to be a network disorder involving large areas of the brain, not confined to the striatum. Many studies demonstrated increased excitability or loss of inhibition at multiple levels including motor cortex (M1), premotor cortex (PMC), somatosensory cortex (S1), and cerebellum.⁵⁻⁸ Hence, a reasonable aim of treatment is to reverse these pathological abnormalities in the aforementioned areas of the brain to restore normal physiology associated with improved behavior. With this idea, a number of studies have been conducted to develop new therapy for FHD using repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).

NIBS can induce plastic changes in the brain in a variety of ways (Figure 1). Current rTMS protocols apply low- (< 1 Hz) or high-frequency (≥ 5 Hz) stimulation. Generally, high-frequency stimulation induces increased cortical excitability⁹ and low-frequency stimulation decreases cortical excitability.¹⁰ M1 plasticity can be also induced by paired associative stimulation (PAS) which employs repetitive pairs of TMS over M1 and peripheral nerve stimulation. Amplitude of motor-evoked potential (MEP) can be facilitated by using interval of ~25 ms (PAS 25) between the nerve stimulation and the TMS and MEP amplitude is inhibited by using interval of ~10 ms (PAS 10). This plastic facilitation and inhibition resembles characteristics of long-term potenti-

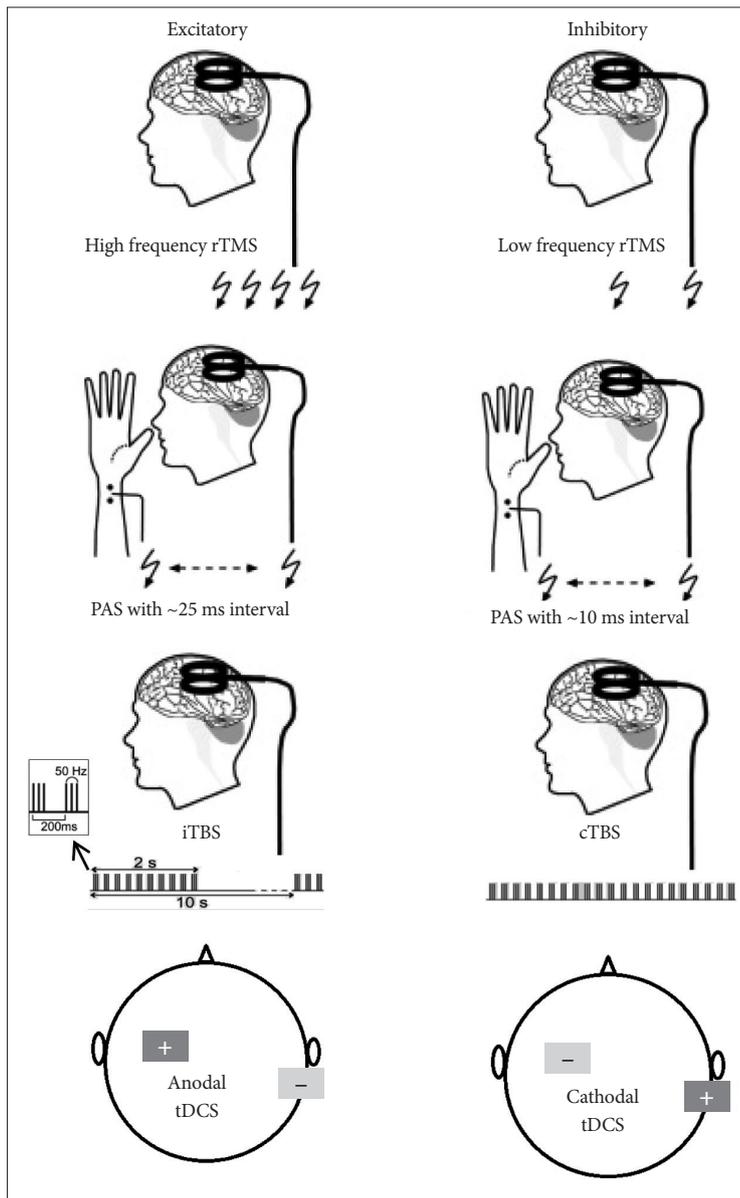


Figure 1. Summary of NIBS methods for excitation and inhibition. rTMS: repetitive transcranial magnetic stimulation, PAS: paired associative stimulation, iTBS: intermittent theta burst stimulation, cTBS: continuous theta burst stimulation, tDCS: transcranial direct current stimulation, NIBS: non-invasive brain stimulation.

ation (LTP) and long-term depression.¹¹ An alternative method of rTMS is theta burst stimulation (TBS), consisting of short, repeated bursts of TMS pulses at high frequency.¹² A typical paradigm would be a burst of three stimuli at 50 Hz with the burst repeated at 5 Hz. Continuous TBS decreases excitability while intermittent TBS increases excitability. As for tDCS, anodal stimulation is known to increase excitability of the stimulated area whereas cathodal stimulation decreases excitability.¹³ These modalities were applied to various brain targets that are thought to be involved in pathophysiology of FHD. In recent years, rTMS and tDCS have received significant attention as potential new therapeutic measures because of their safety and potential efficacy.¹⁴

In this paper, we will review previous studies and describe the potential therapeutic use of NIBS for FHD. We will also discuss the future direction of NIBS to treat FHD.

NIBS TO TREAT FHD

Fourteen articles were selected from those identified by a Pubmed search using the keywords ‘focal hand dystonia’, ‘writer’s cramp’, ‘musician’s dystonia’, ‘noninvasive brain stimulation’, ‘transcranial magnetic stimulation’, and ‘transcranial direct current stimulation’. Studies that measured clinical outcome were chosen for this review article. Seven studies performed rTMS (Table 1) and seven studies applied tDCS (Table 2) for therapeutic use in FHD.

rTMS STUDIES FOR THERAPEUTIC PURPOSE

Among seven rTMS studies, five studied WC patients and three had a mixed group of patients with MD and WC (Table 1). Various study designs were used, either single- or double-blinded mostly with sham control, crossover or parallel randomization.

Table 1. rTMS studies for therapeutic purpose

References	Patient group	Study design	Intervention	Target of the stimulation	Effect
Siebner et al. ¹⁶	16 WC patients and 11 HV	Open-label	Single session of 1 Hz rTMS at 10% below the RMT (1,800 biphasic stimuli)	Left M1	Significantly reduced mean writing pressure, normalization of the deficient cortico-cortical inhibition, and prolongation of the cSP
Murase et al. ¹⁵	9 WC and 7 HV	Single-blinded	Single session of 0.2 Hz rTMS at 85% RMT (250 monophasic stimuli) vs. sham	M1, PMC, and SMA	Decreased tracking error and pen pressure with PMC stimulation, prolongation of cSP with PMC stimulation
Borich et al. ¹⁷	6 FHD (3 WC and 3 MD) and 9 HV	Single-blinded partial cross-over	1 Hz rTMS at 90% RMT (900 monophasic stimuli) vs. sham for 5 days	PMC	Improved handwriting performance and reduced cortical excitability 10 days post treatment
Havrankova et al. ¹⁸	11 WC	Double-blinded cross-over	1 Hz at 90% AMT (biphasic 1,800 stimuli) vs. sham-rTMS for 5 days	SI contralateral to affected hand	Subjective and objective improvement in writing 2 weeks post treatment associated with increased task-related BOLD in fMRI
Huang et al. ¹⁹	18 WC and 8 HV	Single-blinded randomized parallel	cTBS (3-pulse 50 Hz burst every 200 ms at 80% AMT for 40 sec) vs. sham daily for 5 days	Left PMC	More subjective improvement in writing with real rTMS Restoration of SICl, PMC-M1 interaction, and reduced M1 plasticity
Kimberley et al. ²⁰	12 FHD	Single-blinded randomized with partial cross-over	1 Hz rTMS with 90% RMT (biphasic 1,800 stimuli) vs. sham during non-dystonic writing movement for 5 days	Contralateral PMC	Prolonged cSP and reduced pen force
Kimberley et al. ²¹	9 FHD	Randomized with cross-over	5 days 1 Hz rTMS at 80% RMT (biphasic 1,200 pulses) + sensorimotor retraining vs. rTMS + control therapy	PMC	No additional benefit from sensorimotor retraining

rTMS: repetitive transcranial magnetic stimulation, WC: writer’s cramp, HV: healthy volunteer, RMT: resting motor threshold, cSP: cortical silent period, PMC: premotor cortex, SMA: supplementary motor area, FHD: focal hand dystonia, MD: musician’s dystonia, AMT: active motor threshold, BOLD: blood oxygenation level dependent, fMRI: functional magnetic resonance imaging, cTBS: continuous theta burst stimulation, SICl: short latency intracortical inhibition, M1: motor cortex.

Table 2. tDCS studies for therapeutic purpose

References	Patient group	Study design	Intervention	Target of the stimulation	Effect
Buttkus et al. ²⁶	10 MD (guitarists)	Double-blinded randomized with cross-over	Single session of cathodal tDCS (2 mA for 20 min) vs. placebo	Left M1	No change in fine motor control after 30 min
Benninger et al. ²⁴	12 WC	Double-blinded randomized, sham-controlled with parallel	Prolonged sessions (3 in 1 week) of cathodal tDCS	M1 contralateral to FHD	No positive effects in clinical measures nor handwriting and cortical excitability
Buttkus et al. ²⁵	9 MD (pianists)	Double-blinded sham-controlled with cross-over	Anodal tDCS, cathodal tDCS (2 mA for 20 min) during sensorimotor retraining	Left M1	No favorable result in behavior
Furuya et al. ²⁷	10 MD, 10 healthy musicians (pianists)	Double-blinded sham-controlled with cross-over	tDCS (2 mA for 24 min) during bimanual mirrored finger movements	Bihemispheric motor cortices	Improved rhythmic accuracy of sequential finger movements with cathodal-affected and anodal- unaffected tDCS
Sadnicka et al. ²⁹	10 WC	Single-blinded sham-controlled with cross-over	Single session anodal tDCS (sham-controlled)	Cerebellum	No changes in clinical symptoms nor in M1 plasticity
Bradnam et al. ²⁸	8 FHD (5 WC, 3 MD) and 8 HV	Double-blinded randomized sham-controlled with cross-over	Anodal, cathodal (2 mA, 20 min) or sham tDCS	Cerebellum	Improved writing kinematics and decreased CBI with anodal tDCS
Rosset-Llobet et al. ³⁰	30 MD	Parallel double-blind randomized design	tDCS (real vs. sham) for 30 min coupled with 1 hr sensory motor retraining therapy for 2 weeks (10 days)	Cathode over left and anode over right parietal regions	Improved dystonia severity score in both groups; more benefit in real tDCS than sham group

tDCS: transcranial direct current stimulation, MD: musician's dystonia, WC: writer's cramp, HV: healthy volunteer, FHD: focal hand dystonia, CBI: cerebellar inhibition, M1: motor cortex.

Crossover design seems to have been used most frequently, likely due to small sample size. In terms of the intervention, all studies used low-frequency subthreshold rTMS to enhance cortical inhibition. Early studies used single-session inhibitory rTMS and measured the outcome right after the intervention for proof of concept.^{15,16} More recent studies applied prolonged sessions for 5 consecutive days or longer and assessed the outcome at more than one time point.¹⁷⁻²¹ Although small effects of a single session were reported, repetitive sessions over consecutive days seem to be required for clearer therapeutic effects.

Different brain areas were used as a target of stimulation including M1, PMC, and S1, on the contralateral side to dystonia. The first study done by Siebner et al.¹⁶ showed that inhibitory rTMS on M1 might have potential benefit, but Murase et al.¹⁵ showed that PMC was a better target when compared with M1 and supplementary motor area (SMA). Subsequently, four more studies used PMC as the target^{17,19-21} and all studies showed promising results either by physiologic or behavioral measures

or both. Kimberley et al.²¹ studied whether sensorimotor retraining in addition to rTMS on PMC would add further benefit, but failed to prove any additional benefit from sensorimotor retraining. One study targeting S1 showed improved writing associated with rTMS-induced blood oxygenation level dependent (BOLD) signal increase bilaterally in the SI cortex, posterior parietal cortex, and the SMA.¹⁸

Why does it work?

To determine outcome, some studies also measured changes of physiological markers in neurophysiology or neuroimaging in addition to a subjective and/or objective writing assessment. This might help demonstrate why rTMS would work if it did. The pathological hallmark of FHD is increased cortical excitability that can be demonstrated as reduced intracortical inhibition⁵ and a cortical silent period.²² Several studies showed reversal of this abnormal physiology by applying low-frequency rTMS.^{15-17,19,20} Havrankova et al.¹⁸ examined changes in functional magnetic resonance imaging in 'responders' to an

rTMS protocol and found bilateral BOLD signal increase in the posterior parietal cortex, SMA, and right anterior insula. In one positron emission tomography study, there was a greater decrease of regional cerebral blood flow (rCBF) in lateral and medial premotor areas, putamen, and thalamus, including the stimulated PMC, and a larger increase in cerebellar rCBF after one session of premotor rTMS in FHD patients compared to healthy controls.²³ These imaging studies prove that rTMS affects regional synaptic activity in widespread areas of the motor system, but it is not clear how they explain the therapeutic effect.

What are the limitations?

Most studies adapted a crossover design with randomization because of small patient sample size. However, it may not be the best study design due to the potential carry-over effect of rTMS. Most studies used a 1-week interval except Havrankova et al.¹⁸ who used 4–10 weeks; however, 1 week might not enough time for washout since some studies showed^{18,21} that more than one week was necessary to be effective. In Kimberley's study, patients did not return to their baseline even with a one-month washout period, which likely blurred the accurate outcome measure.²¹ Also, there are many methodological variations across the studies in terms of rTMS protocol. Accurate positioning of the coil on the brain target could be critical¹⁸ and different studies adopted different ways for the same target. For example, 2.5 cm anterior to the first dorsal interosseous (FDI) hotspot was set for PMC target in one study,¹⁹ whereas 1 cm medial and 2 cm rostral to the FDI hotspot was used in another study.²⁰ There are also variations in intensity (85–90% active motor threshold vs. 90% resting motor threshold), frequency (0.2 Hz or 1 Hz), and type of TMS (monophasic vs. biphasic). This variability makes it difficult to compare results across studies, but can be important for the future development of optimal treatment parameters.

In summary, PMC seems to be a promising target for a treatment protocol of rTMS and prolonged sessions may result in better clinical outcomes. However, it is still unclear how long rTMS treatment is needed to sustain significant clinical benefit and how long the benefit might last. There are less data for MD than for WC. Dedicated rTMS for MD might be necessary to refine a treatment protocol.

tDCS STUDIES FOR THERAPEUTIC PURPOSE

Of the seven tDCS studies, two were performed for WC, four for MD and two were mixed. Again, various study designs were used either with single or prolonged sessions. Four studies applied tDCS on M1, and three showed no clinical benefit when stimulating the affected M1 with cathodal tDCS.^{24–26} However, when cathodal tDCS on the affected M1 was combined with anodal tDCS on unaffected M1 in MD pianists, rhythmic accuracy of sequential finger movements was improved.²⁷ In the same study, the authors also tested whether tDCS during rest vs. motor training would be different; indeed, it was only effective when tDCS was applied combined with motor training. The cerebellum was the target location in two studies^{28,29} and the results were contradictory. The idea behind anodal tDCS on the cerebellum was to enhance cerebellar activity and modulate M1 plasticity which is abnormally increased in FHD patients. The study done by Sadnicka et al.²⁹ for WC patients could not demonstrate any changes in clinical symptoms and also failed to show changes in M1 plasticity to PAS 25. However, it was noted that PAS 25 response varied considerably among patients. Some patients had facilitation with PAS 25 as expected and others had inhibition to the same protocol. Interestingly, cerebellar tDCS reduced M1 plasticity only in 'facilitators' but not in 'inhibitors'. Another study showed that anodal tDCS on cerebellum in WC patients improved writing kinematics and reduced cerebellar inhibition (CBI), but clinical improvement was not correlated with changes in CBI.²⁸ Most recently, the largest double-blind controlled study done in 30 MD patients showed that bilateral parietal tDCS might hold potential therapeutic benefits.³⁰

Why does it work?

Only a few tDCS studies tried to address the underlying mechanism of either the tDCS effect or its absence.^{24,28,29} None of the studies showed changes in neurophysiology or neuroimaging that might be correlated with clinical benefit. Two studies examined neurophysiology, but there was neither clinical benefit nor positive changes in physiology. One study²⁸ showed reduced CBI after anodal tDCS but this was not correlated with symptom improvement;

therefore, this is likely not the underlying mechanism for clinical benefit. Further studies are required to elucidate the mechanism of tDCS effects in treating dystonia by combining tDCS with functional imaging or neurophysiology techniques such as electroencephalogram or TMS.

What are the limitations?

Most tDCS studies adopted prolonged sessions, 1 or 2 weeks, with or without concomitant sensorimotor training. However, the duration of prolonged treatment sessions was not well studied. Furuya et al.²⁷ reported that the effect was retained 4 days after the intervention, but it is not clear whether the effect might have lasted longer. This is important to know in order to properly design future clinical trials. tDCS is known to cause lasting effects (up to 5 hr) from a single session if the stimulation is sufficiently long (10–30 min).¹³ The duration of the prolonged session needs to be studied. Also, there are many variations in experimental details as to how exactly tDCS was applied. Most of the studies used a 10–20 system to localize C3 and C4 as targets,^{25–27,30} but one study used the first dorsal FDI hotspot as the target.²⁴ It is clear that placement of the reference is very important to shape the electric flow³¹ and it may change the behavioral outcome as well. For an outcome measure, it is particularly difficult for MD to have a single uniform dystonia scale due to variable instruments and different skills. This issue needs to be addressed by experts in this area.

In summary, bi-hemispheric tDCS on sensorimotor cortices with cathodal tDCS on the affected hemisphere together with anodal tDCS on the unaffected hemisphere combined with sensorimotor retraining seem to be promising for therapeutic purposes. Further studies are required to elucidate the mechanism of the tDCS effect in treating dystonia using multimodal experiments.

FUTURE DIRECTION

While NIBS for treating dystonia seems to be promising, there are many unanswered questions that can be addressed in future studies. First, we need a properly designed large, multi-center, randomized controlled trial with longer duration of rTMS intervention to provide a greater opportunity for cumulative therapeutic and adverse effects to be expressed.

In rTMS trials for depression, 3–6 weeks duration has been typical³² and the effect seemed to last for 1 year based on the follow-up study.³³ FHD generally takes years of repetitive tasks to become apparent, and it is possible that it may take a long time to reverse the disordered motor program as seen in cases of deep brain stimulation.³⁴ Second, characterization of “responders” and “non-responders” would be useful to predict the response to NIBS intervention. Demographics, for example, age or disease duration might affect the responsiveness to NIBS. In fact, one study reported that age might be a predictor for a response to rTMS intervention.²⁰ Baseline neurophysiology might serve as an indicator of responsiveness. One study showed that patients who had LTP-like response to PAS 25 interval showed changes in M1 plasticity after cerebellar tDCS, but others who did not show LTP-like response elicited no changes in M1 plasticity with the same intervention.²⁹ Kimberley et al.³⁵ demonstrated in a small sample ($n = 2$) study that the individual with baseline TMS responses indicating impaired inhibition responded favorably to the rTMS intervention. These results point out that not everyone might have a desirable outcome from NIBS, and a more individualistic approach is required to determine therapeutic options. But, first, we need to study who might benefit from NIBS. Last, the benefit of combined neurorehabilitation with NIBS should be studied in more detail. Previous studies used NIBS with sensorimotor training under the assumption that neurorehabilitation with a sensorimotor retraining program could induce a synergistic benefit when given with NIBS,³⁶ but, to date, the results are mixed. It is necessary to explore an additive or synergistic effect of sensorimotor training program with the potential to transform clinical practice.

OTHER NON-INVASIVE NEUROMODULATION

Although they were not reviewed in this paper, there are other methods of non-invasive neuromodulation that have been tried in FHD other than rTMS or tDCS. Proprioceptive training using vibration was studied in MD patients, and it was shown to effectively restore sensorimotor organization.³⁷ Transcutaneous electrical nerve stimulation over forearm flexor muscles was tried in WC, and it decreased

MEP amplitude in the flexor carpi radialis and increased it in the extensor carpi radialis which was paralleled by improved handwriting.³⁸ Neurofeedback, using a brain-computer interface, is another method that has received attention for non-invasive neuromodulation. A preliminary study with two WC patients showed impressive results in one of them.³⁹ There may be more such studies in the future.

CONCLUSION

rTMS and tDCS can be powerful tools to better understand and treat FHD. Clear consensus on optimal protocols needs to be established, and multicenter randomized clinical trials with large numbers of patients are required to implement the technique in clinical practice.

Conflicts of Interest

The authors have no financial conflicts of interest.

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