Non-invasive Brain Stimulation Therapy in Dystonia

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Introduction

Dystonia is defined as a "movement disorder characterised by sustained or intermittent muscle contractions resulting in abnormal, often repetitive, movements, postures, or both" Dystonia is a heterogeneous group of syndromes that can be divided into focal, segmental, multifocal, hemidystonia, and generalised dystonia based on anatomical distribution.

Furthermore, dystonia can be classified as inherited (autosomal dominant, recessive, X-linked, or mitochondrial), acquired (vascular, iatrogenic, neoplastic, traumatic, or psychogenic), or idiopathic (sporadic or familiar) based on its aetiology .Although clinical heterogeneity suggests that dystonia may be a multifactorial disease, the pathophysiology of the disease remains highly speculative. The scarcity of symptomatic animal models is one of the reasons why dystonia pathophysiology remains largely unknown [1].

Recent symptomatic animal models have also established the cerebellum's critical role in dystonia, implying that the basal ganglia and cerebellum are nodes in a dysfunctional integrated network in dystonia. Dystonia treatment can only partially alleviate symptoms and is primarily based on the injection of botulinum toxin into hyperactive muscles, while levodopa, anticholinergic, and antiepileptic drugs have been shown to be largely ineffective. Deep Brain Stimulation (DBS) of the internal portion of the Globus Pallidus (GPi) is the gold standard of functional neurosurgical interventions for dystonia in the most severe patients, with numerous studies demonstrating its efficacy and safety. However, because it is an invasive procedure, alternative treatments are required .In recent years, gamma-knife and focused ultrasound lesions, which do not require a surgical incision of the skull, have posed a challenge to the routine use of both classic radiofrequency lesions and DBS. However, the application of dystonia is very limited .Finally, Transcranial Magnetic Stimulation (TMS) has been used in the last 20 years to investigate non-invasive cortical excitability, providing important new insights into the pathophysiology of dystonia [2].

Furthermore, TMS is a valuable technique that has the potential to be used for both diagnostic and therapeutic purposes in dystonia. However, the inter-subject variability in TMS after-effects and the different pathophysiological mechanisms in different types of dystonia limit diagnostic and therapeutic applications. Nonetheless, TMS can be used to distinguish between organic and psychogenic dystonia.

TMS has been proposed as a noninvasive treatment option for focal hand dystonia, where pharmacological options or botulinum toxin injections are frequently ineffective. Finally, TMS can be used as an adjunctive treatment in patients with cervical dystonia, with botulinum toxin remaining the gold standard of care.TMS and tDCS can stimulate the cerebral cortex painlessly through the intact skull and produce long-lasting changes in cortical excitability.TMS was originally conceived as a non-invasive method for testing the efficiency of motor pathways from the cortex to the spinal cord [3].

Several experimental evidences suggest that TMS activates axons of excitatory and inhibitory interneurons that synapse into pyramidal output neurons. In this way, TMS responsiveness may represent an indirect measure of the excitability of intrinsic cortical circuits. When the pulses are delivered repeatedly, TMS can produce long-term changes in cortical excitability.The aftereffects of rTMS are dependent on the frequency of stimulation used: pulses at 5 Hz or higher facilitate excitability, whereas pulses at 1 Hz or lower depress excitability for at least 30-60 minutes . TBS is a protocol derived from animal studies that consists of repetitive sequences of short bursts applied in the frequency range of EEG theta rhythms.

There are two major protocols to consider. Intermittent TBS (iTBS), which has facilitative effects, and Continuous TBS (cTBS), which has inhibitory effects. Their effect can last for up to 1 hour after the conditioning protocol is completed.

As a result, in this narrative review, we will discuss how TMS can be used as a therapeutic tool in dystonia in comparison to other noninvasive brain techniques such as Transcranial Direct Current Stimulation (tDCS) [4].

The mechanisms of action of TMS that are responsible for the long-term effects on cortical excitability are still unknown. Based on human pharmacological studies, changes in the effectiveness of synapses between cortical neurons, such as Long Term Depression (LTD) and Long Term Potentiation (LTP), have been proposed. A single dose of the NMDA antagonist dextromethorphan effectively eliminates the aftereffects of rTMS . Similarly, another NMDA antagonist, memantine, can inhibit the aftereffects of some rTMS protocols. Furthermore, nimodipine, an L-type voltage-gated Ca2+-channel blocker, reverses the LTD-like depression caused by PAS10 . Finally, several evidences suggest that TMS modulation of the BDNF-TrkB pathway may play a permissive role in determining the NMDA dependent.

Dystonia pathophysiology can be a difficult puzzle to solve because dystonia aetiology is so diverse.Despite the fact that the basal ganglia have traditionally been implicated in dystonia, several studies in animal models and in humans suggest that dystonia is a network disorder .

Although it is tempting to attribute neuronal damage to a single node of the cortico-subcortical loop, there is now compelling evidence that, from a network perspective, it is also important to consider how distant healthy nodes of the brain may react and rearrange themselves in response to the primary damage. This type of plastic reorganisation can be adaptive, compensatory, or maladaptive, exacerbating the deficit.

Approaches to dystonia treatment

In accordance with the pathophysiological considerations discussed above, NIBS has been applied over the primary motor cortex (M1), PMC, ACC, and cerebellar cortex, which are important relays of the cortico-striatal and cerebello-thalamic loops.Because TMS affects the superficial layers of the cerebral cortex, it is unlikely that it will directly stimulate basal ganglia structures. rTMS over the human PFC, on the other hand, has been shown to have remote effects on the ipsilateral caudate nucleus via a cortico-striatal dopamine release . Furthermore, when compared to rTMS of the left occipital cortex, rTMS over M1 causes a decrease in raclopride binding in the left putamen.

Similarly, 1 Hz rTMS over PMC improved handwriting velocity and hand discomfort while writing. Furthermore, the effect of rTMS was compared in three different motor areas, including PMC, in patients with FHD. This study discovered that rTMS (20 min 0.2 Hz rTMS) over PMC is more effective than M1 and SMA repetitive stimulation . The clinical effects

were mirrored by increased cortical inhibition, as measured by a prolonged cortical silent period . The authors of the same study did not report any therapeutic effect of rTMS over M1 ; the discrepancy with Siebner's study could be due to the different stimulation parameters [5].

Another study compared rTMS to PMC , but the lack of a control arm makes data interpretation difficult. In this study, the authors used inhibitory rTMS over PMC for 5 consecutive days in patients with generalised secondary dystonia, and the reduction of the Burke-Fahn-Marsden scale demonstrated a significant clinical effect .

It is worth noting that TMS-measured cortical excitability parameters can be used to predict response to rTMS. It has been reported, for example, that only patients who have cortical inhibition modulation respond to rTMS treatment .

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