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Effects of cerebellar neuromodulation in movement disorders: A systematic review

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ABSTRACT

Background: The cerebellum is involved in the pathophysiology of many movement disorders and its importance in the field of neuromodulation is growing.
Objectives: To review the current evidence for cerebellar modulation in movement disorders and its safety profile.
Methods: Eligible studies were identified after a systematic literature review of the effects of cerebellar modulation in cerebellar ataxia, Parkinson's disease (PD), essential tremor (ET), dystonia and progressive supranuclear palsy (PSP). Neuromodulation techniques included transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS). The changes in motor scores and the incidence of adverse events after the stimulation were reviewed.
Results: Thirty-four studies were included in the systematic review, comprising 431 patients. The evaluation after stimulation ranged from immediately after to 12 months after. Neuromodulation techniques improved cerebellar ataxia due to vascular or degenerative etiologies (TMS, tDCS and DBS), dyskinesias in PD patients (TMS), gross upper limb movement in PD patients (tDCS), tremor in ET (TMS and tDCS), cervical dystonia (TMS and tDCS) and dysarthria in PSP patients (TMS). All the neuromodulation techniques were safe, since only three studies reported the existence of side effects (slight headache after TMS, local skin erythema after tDCS and infectious complication after DBS). Eleven studies did not mention if adverse events occurred.
Conclusions: Cerebellar modulation can improve specific symptoms in some movement disorders and is a safe and well-tolerated procedure. Further studies are needed to lay the groundwork for new researches in this promising target.

Introduction

The cerebellum has emerged as an attractive and promising target for neuromodulation in neurological disorders over the last few years. Because cerebellar areas present several connections with important cortical and subcortical structures, including the primary motor cortex (M1), the supplementary motor area, the cingulate cortex, and the basal ganglia [1], the modulation of these different neuronal networks could potentially treat pathologic neuronal oscillations and thus influence motor and sensory integration.

Prevalent and disabling conditions like cerebellar ataxia have no pharmacological or rehabilitation evidence-based treatment so far, and patients remain highly symptomatic and disabled despite receiving the best medical treatment available. In addition to cerebellar ataxia, the cerebellum has been linked to the pathophysiology of numerous movement disorders, such as dystonia [2], Parkinson's disease (PD) tremor [3], levodopa-induced dyskinesias (LID) [4], essential tremor (ET) [5], and progressive supranuclear palsy (PSP) [6]. Those are disorders with sometimes challenging

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treatments and are capable of gravely impairing the patient's quality of life. One could hypothesize that acting on dentate-thalamo-cortical circuits at the cerebellar level would help control symptoms in these patients.

The dentate nucleus has a tonic facilitatory influence on the M1, and transcranial magnetic stimulation (TMS) or electrical stimulation of the cerebellum given 5–8 ms before a TMS pulse is administered to the contralateral M1 results in M1 inhibition, which is reflected in decreased motor evoked potential amplitudes [7]. This is either related to the excitation of Purkinje cells, which inhibit the dentate nucleus, or to a direct disruptive effect of the TMS pulse upon the output axons that exit the cerebellum via the dentate nucleus. While acute ischemic damage to the deep cerebellar nuclei results in decreased excitatory input to the contralateral M1, chronic cerebellar ischemic lesions have been associated with reemerging increases in intracortical inhibition in the contralesional M1, leading to marked inter-hemispheric asymmetry in cortical excitability, which could account for part of the functional impairment seen after stroke [8]. We have recently shown that neuronavigated repetitive TMS to the normal dentate nucleus (and posterior deep brain stimulation, DBS) can correct altered M1 intracortical inhibition and improve ataxia in the long term (Fig. 1) [9,10].

Based on these promising findings, we reviewed the current evidence of clinical effects after cerebellar modulation in patients with movement disorders and the safety profile of cerebellar modulation.

Materials and methods

Protocol and registration: This review follows the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines and was prospectively registered with PROSPERO CRD42016043536.

Types of studies: We included published reports of clinical trials that examined the clinical improvement of movement disorders after neuromodulation interventions over the posterior fossa. No publication date or publication status restrictions were imposed.

Types of participants: We included participants at any age with any of the following movement disorders: PD, cerebellar ataxia, dystonia, tremor, dyskinesias, or PSP.

Types of intervention: Trials examining the clinical benefits and safety of neuromodulation in patients with movement disorders. Neuromodulation techniques included TMS, transcranial direct current stimulation (tDCS), and DBS.

Types of outcome measures: Only studies with clearly stated and measured clinical outcomes were included. The primary outcome was improvement in clinical movement disorder scales. The secondary outcome was the occurrence of adverse effects.

Information sources: Studies were identified by searching electronic databases and scanning the reference lists of articles. Only articles in English were included. We systematically searched Medline (Pubmed), Embase, Cochrane, and Google Scholar. The last search was run on May 27th, 2017. The reference and citations lists of relevant studies were manually screened for potential eligible articles.

Search: We searched for the terms Parkinson's disease, ataxia, dystonia, tremor, dyskinesias, and progressive supranuclear palsy in combination with terms describing the type of stimulation (TMS, tDCS, and DBS) and the stimulation site (cerebellum, posterior cranium fossa, and cerebellar nuclei).

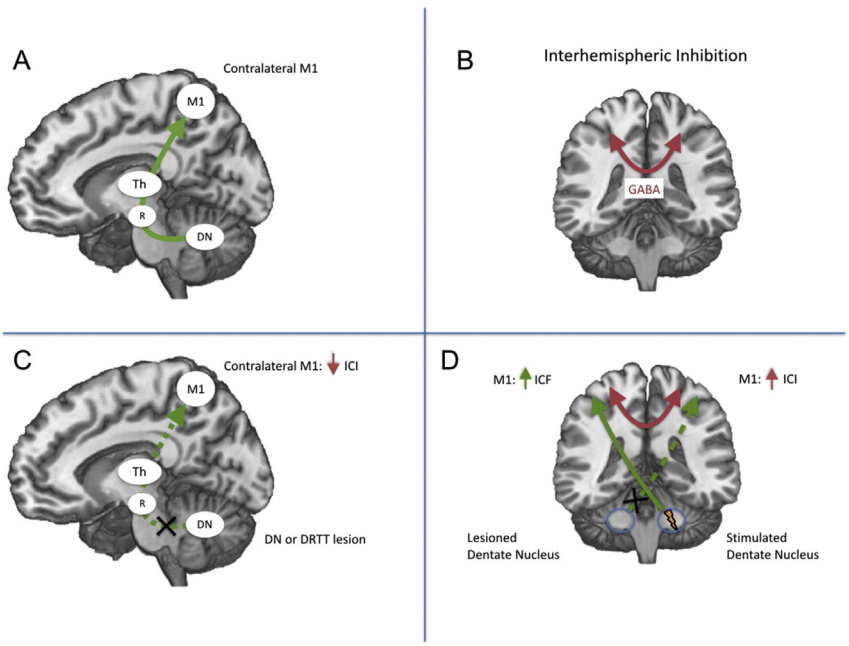

Fig. 1. Schematic representation of the rational of stimulating the Dentate Nucleus and its influence on restoring the primary motor area activity. Panel A shows the excitatory cerebellum-cortico pathway passing through the rubro nucleus and thalamus. There is an ICI between both M1 cortices (panel B) that is related to maintaining the integrity of axial and limbs movements. Panel C shows a progression of changes in intracortical motor function over time following a contralateral cerebellar lesion leading toward progressive disinhibition of the primary motor cortex (the ICI of contralesional M1 decreases). Panel D shows the restoration of the interhemispheric asymmetry after DBS of the left DN (ICF of the ipsilesional M1 and ICI of the contralesional M1 both increase).
DN = Dentate Nucleus, R = Rubro Nucleus, Th = Thalamus, M1 = Motor Cortex, ICI = Intracortical Inhibition, ICF = Intracortical Facilitation, DRTT = dentate-rubro-thalamic tract, → Excitatory projection, → Inhibitory projection.
Adapted from Teixeira MJ, Cury RG, Galhardoni R, et al. Deep brain stimulation of the dentate nucleus improves cerebellar ataxia after cerebellar stroke.Neurology. 2015;85:2075–2076 [10].

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