Opinion

Little Brain, Big Expectations

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Abstract: The cerebellum has been implicated in the mechanisms of several movement disorders. With the recent reports of successful modulation of its functioning, this highly connected structure has emerged as a promising way to provide symptomatic relief not yet obtained by usual treatments. Here we review the most relevant papers published to date, the limitations and gaps in literature, discuss why several papers have failed in showing efficacy, and present a new way of stimulating the cerebellum. References for this critique review were identified by searches on PubMed for the terms “Parkinson’s disease”, “ataxia”, “dystonia”, “tremor”, and “dyskinesias” in combination with the type of stimulation and the stimulation site. Studies conducted thus far have shed light on the potential of cerebellar neuromodulation for attenuating symptoms in patients with some forms of isolated and combined dystonia, dyskinesia in Parkinson’s disease, and neurodegenerative ataxia. However, there is still a high heterogeneity of results and uncertainty about the possibility of maintaining long-term benefits. Because of the complicated architecture of the cerebellum, the modulation techniques employed may have to focus on targeting the activity of the cerebellar nuclei rather than the cerebellar cortex. Measures of cerebellar activity may reduce the variability in outcomes.

Keywords: ataxia; cerebellum; dystonia; neuromodulation; Parkinson’s disease

1. Introduction

Current neuromodulation techniques to treat Parkinson’s disease (PD), essential tremor, and isolated dystonia are mainly based on targeting deep basal ganglia nuclei. Despite well-defined benefits of such intervention, some symptoms, such as gait and balance impairments in PD, and complex syndromes, such as combined dystonia and cerebellar ataxia, are only marginally influenced by basal ganglia-based approaches, fueling the quest for novel targets to improve long-term control of these so far ill-controlled symptoms.

Traditionally, the study of the basal ganglia and thalamus have been used to map movement disorders into specific subcortical regions [1]. However, many neurologic symptoms correspond more closely to networks of connected distant regions [2]. Likewise, targeting other nodes of the movement circuitry could influence functionally and structurally interconnected regions, leading to new treatment targets for complex neurological syndromes [3].

In this scenario, the connectivity power of the cerebellum has motivated the study of its modulation among many teams worldwide, and it has been so far explored in a range of well-conducted preclinical and clinical studies [4,5]. The appeal of the cerebellum for neuromodulation strategies is easy to
understand: it is a fascinating structure that boasts more neurons than all of the other brain regions combined, and it is implicated in virtually all movement disorders known to date.

2. Search Strategy and Selection Criteria

References for this article were identified by searches on PubMed, and references from relevant articles. We searched for the terms “Parkinson’s disease”, “ataxia”, “dystonia”, “tremor”, and “dyskinesias” in combination with terms describing the type of stimulation (transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), or deep brain stimulation (DBS)) and the stimulation site (cerebellum, posterior cranium fossa, or cerebellar nuclei). Information was extracted from each included trial on the (1) characteristics of study population (number, type of movement disorder, and severity of disease), (2) type of intervention, (3) intervention targets, (4) assessment time points, (5) side effects, and (6) outcomes. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this article.

3. A Window to Connect the Whole Brain

There is growing evidence that the ideal area for neuromodulation is rather heterogenous within the same “anatomical” target, and influencing the activity of subregions within the same target may provide different clinical results based on the distinct, functionally related networks [2]. For example, parkinsonian patients respond better to subthalamic deep brain stimulation (STN DBS) when the stimulation site is functionally connected to the supplementary motor area [2], while tics in patients with Gilles de la Tourette syndrome are better controlled when the frontal middle gyrus and cingulate are more intensely connected with thalamic stimulation [6]. Cerebellar modulation opens the possibility of modulating the dentato-thalamic pathway and the activities of distant areas, such as the prefrontal, parietal and temporal lobes, and basal ganglia, due to its largely cortical and subcortical connections [5] (Figure 1).

In primates, deep cerebellar nuclei exert a primarily facilitatory effect on excitability in the contralateral primary motor cortex (M1) through dentothalamocortical projections [7]. In healthy individuals, a transcranial magnetic stimulation (TMS) pulse delivered to the cerebellum a few milliseconds before a TMS pulse is administered to the contralateral M1 results in M1 inhibition, revealed by decreased motor-evoked potential amplitude responses (cerebellar brain inhibition) [8]. This is thought to occur due to disruption of the tonic cerebellar facilitatory output to the contralateral M1 under physiologic conditions [3,8]. This normal balance is perturbed by disease (i.e., degenerative ataxia, cerebellar stroke, and dystonia) [3,5,8], and may affect the physiologic interhemispheric inhibition (how both M1s interact with one another) (Figure 1). For example, abnormal asymmetry in cortical excitability between the right and left hemispheres has been related to the motor impairment seen in cerebellar ataxia [7,8], which was normalized after cerebellar stimulation, improving the symptoms. This network connectivity allows for the construction of models to explain how the modulation of a normal or diseased cerebellum can restore the function of a dysfunctional network due to neurodegeneration or lesions to one of its hubs [3].
Figure 1. There is an intracortical inhibition between both M1 cortices that is related to maintaining the integrity of axial and limbs movements. The modulation of dentate nucleus activity through tDCS, TMS, or DBS could restore the changes in M1 cortical excitability that are present in some syndromes, such as degenerative ataxia, cerebellar stroke, and dystonia. Additionally, the recent disynaptic connection from the cerebellum to the striatum opens up the possibility of directly modulating aberrant electricity activity in the basal ganglia seen in a range of movement disorders. M1: primary motor cortex; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; DBS: deep brain stimulation (adapted from França et al. [9]).

4. Why Target the Cerebellum in Movement Disorders?

Neuroanatomical studies using transneuronal virus tracers in monkeys have demonstrated that substantial interactions exist between the basal ganglia and the cerebellum [10]. Probabilistic diffusion tractography has confirmed that dentato–thalamo–striato–pallidal and subthalamo–cerebellar connections also exist in the human brain [11]. Consequently, abnormal cerebellar output could alter activity in the basal ganglia and drive aberrant electricity activity, causing or worsening movement disorders [12]. Furthermore, basal ganglia activity may influence the cerebellum via projections of the subthalamic nucleus to pontine nuclei, which then project to the cerebellum, demonstrating bidirectional connections between these structures [12]. Functional perturbation in these connections may underlie the pathophysiology of dystonia, PD, and spinocerebellar ataxia [3].

It has been shown, for example, that abnormal bursts of cerebellar electroencephalographic activity are correlated with dystonic postures [13]. Notably, disruption of the disynaptic connections between the cerebellum and basal ganglia have been shown to alleviate dystonia in a mouse model [13]. Furthermore, studies of patients with genetic isolated dystonia DYT-TOR1A (formerly known as DYT1) have shown that patients exhibit specific changes in cerebellar connectivity compared with controls.
and unaffected mutation carriers [14]. Because the non-responder rate of globus pallidus internus DBS in isolated dystonia can reach 25% in clinical trials [15], and patients with combined dystonia, such as cerebral palsy, are typically poor responders to pallidal stimulation [15], novel primary targets for dystonia or rescue treatments must be explored.

In PD, cerebellar brain inhibition is reduced, suggesting that cerebellar function or transmission along the cerebello-thalamocortical pathway is compromised [16]. Additionally, PD patients have deficient short-latency and long-lasting cerebellar–thalamocortical inhibitory interactions [3]. Previous TMS studies for tremor have suggested that the cerebellum–thalamo–cortical circuit may play a pivotal role in the pathogenesis of parkinsonian tremor, and neuroimaging studies have found hyperactivity in the cerebellum in PD [3,5].

Besides its widespread connections, unlike the deeply located basal ganglia and brainstem targets already tested for DBS, the cerebellum can be preoperatively and non-invasively modulated. Thus far, except for the preoperative use of levodopa challenge prior to surgery in PD, there are no other consistent ways of preoperatively predicting surgery outcomes.

5. What Recent Positive Studies Have Revealed

Cerebellar stimulation could alleviate some aspects of dystonia, especially those related to posture, as has been recently shown in rodents [17]. There is also evidence from clinical studies that TMS of the cerebellum may alleviate symptoms in cervical dystonic patients (Table 1) [12]. Cerebellar anodal transcranial direct current stimulation (tDCS) improved handwriting and circle-drawing tasks in patients with writing dystonia [18]. Another study demonstrated that bilateral deep anterior cerebellar stimulation in patients with secondary dystonia reduces both dystonic symptoms and spasticity [19]. More recently, a patient with generalized fixed dystonia, having failed bilateral pallidotomy, presented significant benefits after high-frequency bilateral superior cerebellar peduncles and dentate nuclei DBS, highlighting that cerebellar DBS may be a new option for fixed dystonia, refractory to classical DBS approaches [20]. In PD, cerebellar continuous theta burst stimulation has been found to change local intracortical circuits in the primary motor cortex and reduce levodopa-induced dyskinesias [21].

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Design</th>
<th>Diagnosis, n</th>
<th>Intervention</th>
<th>Main Clinical Findings</th>
<th>Class of Evidence</th>
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<tbody>
<tr>
<td>Koch et al., 2009 [21]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>PD with dyskinesias, 10</td>
<td>rTMS (cTBS) single session with figure-of-eight coil</td>
<td>Decrease in waking time spent as ON with dyskinesias</td>
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<td>Minks et al., 2011 [22]</td>
<td>Single-blind, sham-controlled, crossover</td>
<td>PD, 20</td>
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<td>Bologna et al., 2015 [23]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>PD, 13 + healthy controls, 10</td>
<td>Unilateral TMS (cTBS) single session with figure-of-eight coil</td>
<td>No changes in tremor amplitude, frequency, or magnitude</td>
<td>III</td>
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<tr>
<td>Ferrucci et al., 2016 [24]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>PD with dyskinesias, 9</td>
<td>Two mA anodal tDCS, five sessions</td>
<td>Improvement in UPDRS IV (dyskinesias section)</td>
<td>III</td>
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<tr>
<td>Sanna et al., 2020 [25]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>PD with dyskinesias, 11</td>
<td>rTMS (cTBS) single session with circular coil</td>
<td>Decrease in dyskinesias and serum BDNF in active group</td>
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<tr>
<td>Workman et al., 2020 [26]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>PD, 7</td>
<td>Two or 4 mA, unilateral or bilateral tDCS single session</td>
<td>Significant improvement in balance score in bilateral 4 mA group against sham; no gait improvement</td>
<td>II</td>
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## Table 1. Cont.

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<tr>
<td>Sadnicka et al., 2014 [27]</td>
<td>Single-blinded, sham controlled with crossover</td>
<td>WC, 10</td>
<td>Two mA ipsilateral anodal tDCS, single session</td>
<td>No subjective improvement or changes in the WCRS or timed writing assessment</td>
<td>III</td>
</tr>
<tr>
<td>Koch et al., 2014 [28]</td>
<td>Double-blind, sham-controlled</td>
<td>CD, 18 (9 active; 9 sham)</td>
<td>Bilateral rTMS (eTBS), 10 sessions</td>
<td>Small but significant clinical improvement as measured by the TWSTRS of approximately 15%</td>
<td>III</td>
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<tr>
<td>Bradnam et al., 2015 [18]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>FHD, 8 (WC = 5; MD = 5); healthy controls, 8</td>
<td>Two mA anodal/cathodal tDCS, single session</td>
<td>No change in clinical outcomes</td>
<td>II</td>
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<tr>
<td>Shiga et al., 2002 [29]</td>
<td>Double-blind, sham-controlled</td>
<td>Spinocerebellar degeneration, 74 (39 active, 35 sham)</td>
<td>Single-pulse TMS, 21 sessions with circular coil</td>
<td>Improvement in 10 m time, 10 m steps, tandem steps, and standing capacities, especially in the cerebellar type</td>
<td>III</td>
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<tr>
<td>Grimaldi and Manto et al., 2013 [31]</td>
<td>Single-blind, sham-controlled, crossover</td>
<td>Varied cerebellar ataxias, 9</td>
<td>One mA right anodal tDCS, single session</td>
<td>No change in posturography or upper limb dexterity</td>
<td>III</td>
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<tr>
<td>Bongini et al., 2014 [32]</td>
<td>Open label</td>
<td>Posterior circulation stroke with ataxia, 6</td>
<td>rTMS (tTMS, ipsilateral), 10 sessions with figure-of-eight coil + physical therapy</td>
<td>Ataxia improvement (MICARS), especially posture and gait subscales</td>
<td>IV</td>
</tr>
<tr>
<td>Kim et al., 2014 [33]</td>
<td>Double-blind, sham-controlled</td>
<td>Posterior circulation stroke with ataxia, 32</td>
<td>One Hz ipsilateral rTMS, five sessions with figure-of-eight coil</td>
<td>Improvement in the 10m walk test 1 month after; balance improved after 5 days and after 1 month</td>
<td>III</td>
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<tr>
<td>Benussi et al., 2015 [34]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>Varied cerebellar ataxias, 19</td>
<td>Two mA anodal tDCS, single session</td>
<td>Improvement in ataxia (SARA and ICARS), hand dexterity, and gait</td>
<td>III</td>
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<tr>
<td>Grecco et al., 2017 [35]</td>
<td>Single-blind, sham-controlled, crossover</td>
<td>Ataxic cerebral palsy, 6</td>
<td>One mA anodal tDCS, 10 sessions + treadmill training</td>
<td>Improvement in hip oscillation during eyes-closed gait (stabilometric evaluation)</td>
<td>III</td>
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<td>Benussi et al., 2017 [36]</td>
<td>Double-blind, sham-controlled</td>
<td>Varied neurodegenerative ataxias, 20; healthy controls, 10</td>
<td>Two mA anodal tDCS, 10 sessions</td>
<td>Improvement lasting at least 3 months in SARA, ICARS, gait, and hand dexterity (in non-dominant hand)</td>
<td>III</td>
</tr>
<tr>
<td>Benussi et al., 2018 [37]</td>
<td>Double-blind, sham-controlled crossover</td>
<td>Varied neurodegenerative ataxias, 20</td>
<td>Two mA anodal tDCS (cerebellum) and 2 mA cathodal tDCS (spinal cord), 10 sessions</td>
<td>Improvement lasting at least 3 months in SARA, ICARS, gait, hand dexterity, and quality of life</td>
<td>II</td>
</tr>
<tr>
<td>Manor et al., 2019 [38]</td>
<td>Double-blind, sham-controlled</td>
<td>Spinocerebellar ataxia, 20</td>
<td>Single-pulse TMS, 20 sessions with circular coil</td>
<td>Improvement only in stance sub-score of SARA and standing postural sway metrics</td>
<td>II</td>
</tr>
<tr>
<td>França et al., 2020 [9]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>Spinocerebellar ataxia type 3, 9; multiple system atrophy cerebellar type, 8; post-lesion ataxia, 7</td>
<td>One Hz unilateral rTMS, 10 sessions with double-cone coil</td>
<td>Improvement in SARA and ICARS</td>
<td>II</td>
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### Essential tremor

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<tr>
<th>Author, Year</th>
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<th>Diagnosis, n</th>
<th>Intervention</th>
<th>Main Clinical Findings</th>
<th>Class of Evidence</th>
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<tbody>
<tr>
<td>Gironell et al., 2002 [39]</td>
<td>Double-blind, sham-controlled, crossover (washout 1 week)</td>
<td>ET, 10</td>
<td>One Hz rTMS, single session with butterfly coil</td>
<td>Tremor improvement according to the FTM (17%), and accelerometry evaluation on the 5 min assessment</td>
<td>II</td>
</tr>
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Table 1. Cont.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Avanzino et al., 2009 [40]</td>
<td>Open label in five patients, and single-blind, sham-controlled, crossover in seven patients</td>
<td>ET, 10 + healthy controls, 11</td>
<td>One Hz right rTMS, single session with figure-of-eight coil</td>
<td>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, and no change in tremor (FTM)</td>
<td>IV</td>
</tr>
<tr>
<td>Popa et al., 2013 [41]</td>
<td>Open label</td>
<td>ET, 11; healthy controls, 11</td>
<td>One Hz rTMS, five sessions with figure-of-eight coil</td>
<td>Tremor improvement that built up until day 12 and persisted for 3 weeks (FTM); decrease in tremor amplitude</td>
<td>IV</td>
</tr>
<tr>
<td>Gironell et al., 2014 [42]</td>
<td>Double-blind, sham-controlled crossover</td>
<td>ET, 10</td>
<td>Two mA cathodal tDCS, 10 sessions</td>
<td>No acute or long-lasting benefit (FTM and accelerometric recordings)</td>
<td>III</td>
</tr>
<tr>
<td>Bologna et al., 2015 [43]</td>
<td>Double-blind, sham-controlled, crossover</td>
<td>ET, 16; healthy controls, 11</td>
<td>rTMS (cTBS), single session with eight-shaped coil</td>
<td>No change in tremor severity and reaching movements (FTM and accelerometer)</td>
<td>III</td>
</tr>
<tr>
<td>Shin et al., 2019 [44]</td>
<td>Single-blind, sham-controlled</td>
<td>ET, 22 (12 active, 10 sham)</td>
<td>One Hz rTMS, five sessions with figure-of-eight coil</td>
<td>Improvement in tremor immediately after (33% active × 20% sham, according to FTM) and 4 weeks after (31% active × 17% sham); no significant difference between groups; no improvement in functions of daily lives</td>
<td>III</td>
</tr>
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</table>

Abbreviations: BDNF: brain-derived neurotrophic factor; CD: cervical dystonia; cTBS: continuous theta burst stimulation; ET: essential tremor; FHD: focal hand dystonia; FTM: Fahn Tolosa Marin Tremor Rating Scale; ICARS: International Cooperative Ataxia Rating; iTBS: intermittent theta burst stimulation; ITI: inter-tapping interval; MD: musician’s dystonia; MICARS: Modified International Cooperative Ataxia Rating Scale; PD: Parkinson’s disease; rTMS: repetitive transcranial magnetic stimulation; SARA: scale for the assessment and rating of ataxia; TD: touch duration; tDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; UPDRS: Unified Parkinson’s Disease Rating Scale; WC: writer’s cramp; WCRS: writer’s cramp rating scale.

To date, most trials involving ataxic patients have focused on degenerative ataxias. Studies have identified temporary and long-lasting (3 months) functional improvement after cerebellar tDCS in patients with ataxia [3,5,37]. Recently, we have demonstrated in a clinical trial that cerebellar TMS using a deep coil improved ataxia in patients with spinocerebellar ataxia type 3 (SCA3), multiple-system atrophy, and post-lesion ataxia (post-stroke or neurosurgery) [9].

Regarding invasive stimulation, low-frequency DBS of the dentate nucleus has been applied in a rat model of neurogenerative ataxia [4]. A frequency of 30 Hz improved motor symptoms, such as ataxia and tremor, and high-frequency stimulation worsened incoordination. This study is probably the most significant in suggesting that the “hot spot” for stimulation would be located at the dentate nucleus. The authors found that the dorsal part of the nucleus was the most effective target for stimulation. In humans, two case reports demonstrated improvement in ataxia after cerebellar DBS in SCA3 and post-lesion ataxia [45–47].

Overall, studies conducted thus far, despite having methodological flaws, have shed light on the possibility of relieving symptoms in patients with some forms of dystonia, dyskinesia in PD, and neurodegenerative ataxia.

6. Playing Devil’s Advocate

The recent inclusion of cerebellar stimulation as an option to treat refractory cerebellar ataxia is likely due to the absence of any safer, better treatment option, along with non-invasive stimulation being safe in these settings. However, despite some good outcomes of cerebellar modulation in treating movement disorders in general, there is still a high heterogeneity of parameters employed in the available studies. The best stimulation paradigms and the best profiles of responders are still coupled with uncertainties about the possibility of maintaining long-term benefits [5], which makes it still
It is still unknown exactly what type of activity we are triggering when we stimulate the dentate nucleus. There are probable antidromic effects within the cerebellar cortex, but it would be interesting to test whether there are different responses within the thalamus and other downstream targets, depending on the topography stimulated. If this is true, one must consider the possibility that direct dentate nucleus stimulation could have variable effects, according to which specific regions are recruited [5]. Evidence suggests that the hot spot of modulation is likely located in more dorsal parts of the dentate nucleus, the presumed motor domain [4]. The study of the volume of tissue activated through DBS contacts can represent a powerful research platform to study connectomics from distributed brain networks in the “human connectome” [2].

Additionally, knowledge about modifications in the cerebellum circuitry in each disease, both neuropathological and functional, should help practitioners make decisions about the ideal type of stimuli to apply over the cerebellum. Such work is necessary before proceeding to multicenter clinical trials. Measures of cerebellar activity using functional and Positron Emission Tomography studies and cortical excitability may help with this issue.

Whether the “little brain” will be a primary or a rescue/adjunctive therapy in movement disorders remains an open question. It could perhaps be an alternative target for patients for whom the risk of
surgery is high. Substantial changes in clinical practice are often tied to apprehension, but remarkable benefits may arise from innovations.


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