CARINA CURA FRANÇA

Efeitos da estimulação magnética transcraniana profunda nas ataxias cerebelares: um ensaio clínico randomizado, duplo-cego e cruzado

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutora em Ciências

Programa de Neurologia

Orientador: Dr. Rubens Gisbert Cury

Coorientador: Prof. Dr. Daniel Ciampi Araujo de Andrade

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CARINA CURA FRANÇA

Effects of deep transcranial magnetic stimulation of the cerebellum on cerebellar ataxias: a randomized, double-blind, cross-over clinical trial

Thesis presented to the Faculdade de Medicina, Universidade de São Paulo to obtain the title of Doctor in Sciences

Neurology Program

Advisor: Dr. Rubens Gisbert Cury

Co-advisor: Prof. Dr. Daniel Ciampi Araujo de Andrade

São Paulo
2021

Aos meus filhos, Daniel e Oliver, que dividiram sua mãe com este trabalho desde o nascimento. Vocês são a razão da minha vida. Nunca houve ou haverá um projeto mais importante do que participar do crescimento de vocês.

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“I was taught that the way of progress is neither swift nor easy.”

— Marie Curie

“In madness lies change, in change is opportunity, and in opportunity are riches.”

— Bernard Cornwell, Lords of the North

“Success is not final; failure is not fatal: it is the courage to continue that counts.”

— Winston Churchill

NORMALIZAÇÃO ADOTADA

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ABBREVIATIONS

DBS: deep brain stimulation

d-rTMS: deep repetitive transcranial magnetic stimulation

ET: essential tremor

FHD: focal hand dystonia

GPi: globus pallidus internus

ICARS: International Cooperative Ataxia Rating Scale

LIM-62: Surgical Pathophysiology Laboratory

M1: motor cortex

MSA-c: multiple systems atrophy cerebellar type

PD: Parkinson's disease

PSP: progressive supranuclear palsy

rTMS: repetitive transcranial magnetic stimulation

SCA: spinocerebellar ataxia

SCA3: spinocerebellar ataxia type 3

TBS: theta burst stimulation

tDCS: transcranial direct current stimulation

TMS: transcranial magnetic stimulation

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Resumo

França CC. *Efeitos da estimulação magnética transcraniana profunda nas ataxias cerebelares:* um ensaio clínico randomizado, duplo-cego e cruzado [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2021.

A ataxia cerebelar é atualmente um sintoma neurológico órfão de intervenções terapêuticas, apesar de ser prevalente e incapacitante. Estudos prévios investigaram de forma exploratória os efeitos da neuromodulação cerebelar em pacientes atáxicos. O presente estudo randomizado, placebo-controlado e cruzado incluiu pacientes com pontuação maior que 6 na *Scale for the Assessment and Rating of Ataxia* e diagnóstico genético de ataxia espinocerebelar do tipo 3, diagnóstico clínico de atrofia de múltiplos sistemas ou história de ataxia pós-lesão cerebelar ou pós-acidente vascular cerebelar. Os pacientes incluídos receberam 5 sessões de estimulação magnética transcraniana ativa neuronavegada para o núcleo denteado e 5 sessões placebo, em ordem randômica, com um intervalo mínimo de 28 dias entre as duas fases (washout). O objetivo do presente estudo foi avaliar os efeitos da estimulação magnética transcraniana repetitiva do cerebelo com uma bobina de alcance profundo em sintomas atáxicos. O desfecho primário foi a comparação da pontuação da *Scale for the Assessment and Rating of* Ataxia entre as fases ativa e placebo. Desfechos secundários incluíram a *International Cooperative Ataxia Rating Scale*, também utilizada para quantificar sintomas atáxicos, e outras escalas motoras, cognitivas, e de qualidade de vida. Este estudo foi registrado no *clinicaltrials.gov* sob o protocolo NCT03213106. Vinte e quarto pacientes com idades variando de 29–74 anos foram incluídos neste estudo. Após a fase ativa, a pontuação da *Scale for the Assessment and Rating of Ataxia* foi significativamente menor se comparada à pontuação após a fase placebo [mediana (interquartis 25 e 75) de 10.2 (6.2, 16.2) para a fase ativa e 12.8 (9.6, 17.8) para a fase placebo; p = 0.002]. Também houve melhora significativa nos sintomas atáxicos de acordo com a *International Cooperative Ataxia Rating Scale* comparando as fases ativa e placebo [mediana (interquartis 25 e 75) de 29.0 (21.0, 43.5) para a fase ativa e 32.8 (22.0, 47.0) para a fase placebo; p = 0.005]. Os outros sintomas avaliados (motores, de qualidade de vida e cognitivos) não demonstraram melhora significativa. Nenhum paciente apresentou efeitos colaterais severos, e apenas nove apresentaram efeitos colaterais leves e

transitórios. Os achados do presente estudo sugerem que a estimulação magnética transcraniana repetitiva cerebelar é capaz de melhorar sintomas atáxicos em pacientes com ataxias de diferentes etiologias. Além disso, nosso protocolo de estudo mostrou-se seguro e bem tolerado. Tais resultados sugerem segurança deste protocolo para prática clínica. Estudos futuros devem avaliar o tempo de duração dos benefícios e seu efeito a longo prazo.

Descritores: Ataxia; Estimulação magnética transcraniana; Cerebelo; Ataxia espinocerebelar tipo 3; Atrofia de múltiplos sistemas; Acidente vascular encefálico.

Abstract

França CC. *Effects of deep transcranial magnetic stimulation of the cerebellum on cerebellar ataxias:* a randomized, double-blind, cross-over clinical trial [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2021.

Cerebellar ataxia remains a neurological symptom orphan of treatment interventions, despite being prevalent and incapacitating. Previous studies have investigated the effects of cerebellar neuromodulation in ataxic patients in an exploratory manner. In this randomized, sham-controlled, crossover trial, we included patients with scores > 6 on the Scale for the Assessment and Rating of Ataxia and genetic diagnosis of spinocerebellar ataxia type 3, clinical diagnosis of multiple systems atrophy cerebellar type, or post-lesion ataxia due to neurosurgery or stroke. Patients received five sessions each of sham and active neuronavigated 1 Hz deep repetitive transcranial magnetic stimulation of the cerebellum in randomized order with a 28-day minimum washout period between phases. We aimed to study whether cerebellar deep repetitive transcranial magnetic stimulation could improve ataxia. Our primary outcome was the Scale for the Assessment and Rating of Ataxia comparing phases (active x sham). Secondary outcomes measures included the International Cooperative Ataxia Rating Scale, and other motor, cognitive, and quality of life scales. This study was registered at the clinicaltrials.gov under protocol NCT03213106. Twenty-four patients aged 29–74 years were included in our trial. After active stimulation, the Scale for the Assessment and Rating of Ataxia score was significantly lower than the score after sham stimulation [median (interquartile range) of 10.2 (6.2, 16.2) versus 12.8 (9.6, 17.8); p = 0.002]. The International Cooperative Ataxia Rating Scale score also decreased after active stimulation versus sham [median (interquartile range) of 29.0 (21.0, 43.5) versus 32.8 (22.0, 47.0); p = 0.005]. Ratings of other motor scales, quality of life, and cognitive measures were not significantly modified by stimulation. No patient presented severe side effects, and nine presented mild and self-limited symptoms. These findings suggest that deep repetitive transcranial magnetic stimulation of the cerebellum may improve ataxic symptoms in patients with different types of ataxia. These results provide

reassurance about safety for clinical practice, and future studies should establish possibility to maintain these effects in the long-term.

Descriptors: Ataxia; Transcranial magnetic stimulation; Cerebellum; Spinocerebellar ataxia type 3; Multiple systems atrophy; Stroke.

1 INTRODUCTION

1 INTRODUCTION

Cerebellar ataxia is a prevalent and disabling neurological symptom with diverse etiologies, ranging from hereditary to acquired. The personal economic burden of spinocerebellar ataxia (SCA) alone is estimated to be around 18,776 euros per annum.[1] Currently there is no significant evidence-based treatment able to relieve ataxic symptoms although many therapeutic strategies have been tested in the past years.[2] Considering its safety, and the potential to alleviate ataxic symptoms, non-invasive neuromodulation therapies can be considered a promising treatment strategy for this symptom.[2]

Despite having different etiologies, ataxic symptoms can have a common physiopathological basis.[1] Because the cerebellum is highly connected to important areas related to motor function, it has emerged as an attractive and promising neuromodulation target for controlling movement disorders.[3] Technological improvements have allowed targeting deeper structures non-invasively.[4] Deep repetitive transcranial magnetic stimulation (d-rTMS) using a double-cone coil is capable of reaching structures as deep as the dentate nucleus.[5,6] Correction of a disruptive cerebellar network is believed to lead to changes in distant brain sites, such as sensorimotor areas, and bring about subsequent symptomatic control.[7–11]

In this study, we sought to investigate the effects of cerebellar d-rTMS on ataxic patients. We included patients with both hereditary and acquired diseases in a randomized, prospective, crossover, double-blind, sham-controlled phase II trial.

2 OBJECTIVES

2 OBJECTIVES

a) Evaluate the effects of d-rTMS aimed at the dentate nucleus on ataxic symptoms in patients with multiple systems atrophy cerebellar type (MSA-c), spinocerebellar ataxia type 3 (SCA3) and post-lesion ataxia.
b) Investigate if other symptoms such as tremor, dystonia, gait, quality of life, anxiety, depression, and cognition could improve after cerebellar d-rTMS.
c) Correlate changes in ataxia to cerebellar volume.
d) Investigate if cortical excitability parameters would change after cerebellar d-rTMS, compared with sham stimulation.
e) Evaluate the safety of cerebellar d-rTMS.

3 LITERATURE REVIEW

3 LITERATURE REVIEW

3.1 An overview of cerebellar diseases

Ataxia, originally derived from Greek “lack of order”, refers to poorly coordinated movements. Dysfunction of the cerebellum and its input or output tracts can lead to ataxia, which is usually partially responsive to rehabilitation treatments and can lead to a significant impact in functionality and quality of life.[12] Cerebellar ataxia is a clinically heterogeneous group of disorders, which includes several well-characterized genetic diseases as well as sporadic ataxias, and ataxia due to stroke, and trauma.

Stroke is one of the most important cases of ataxia in terms of prevalence: it is currently the second leading cause of death worldwide, and the third greatest cause of disability-adjusted life years, a sum of years of life lived with disability and years lost due to premature death.[13,14] The incidence of stroke in low-income countries seems to be rising, affecting around 33 million people in 2010.[15,16] Of all brain strokes, cerebellar stroke accounts for only 2-3%, but it has a disproportionate share of the resulting morbidity and mortality, with near twice the mortality rate of supratentorial strokes.[17] Severe complications in these cases include brain edema, obstructive hydrocephalus, and death.[17–20]

Genetic and acquired neurodegenerative diseases can also affect the cerebellum. Among the genetic causes, SCAs are the most common. The overall ataxia occurrence rate is 26/100,000 in children.[21,22] To date, there are over 40 different types of autosomal dominant SCAs, with estimated prevalence of 2.5 cases in 100,000.[23] The estimated prevalence of autosomal recessive SCAs is 3.3 cases in 100,000.[23] Regarding acquired neurogenerative causes of cerebellar ataxia, multiple systems atrophy is one of the most prevalent (4-5 cases in 100,000).[24] Although these are rare diseases, their high social impact must be considered, once they are inevitably progressive and do not have real therapeutic options thus far.

3.2 Principles of transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was introduced by Barker et al in 1985, following the success of transcranial electric stimulation in modulating the motor cortex, as a less painful way to deliver the electric current to the brain.[25] Based on the electromagnetic induction principle described in 1831 by Faraday, it can generate up to 2T magnetic field that lasts for 100μs, and that is able to go unattenuated through scalp structures and then generate an electric field in the brain.

The electric field, and consequently the neural structures affected, can be shaped through several variables, such as coil geometry, current orientation, and intensity. Circular coils were the first types of coils used and allow a large, albeit not deep, area of cortical stimulation.[26] For a more focal stimulation, figure-of-eight and double-cone coils are preferred. Double-cone coils also are selected for deeper stimulation fields, although there is a rapid attenuation of the electric field in depth, which implies that more superficial structures receive most of the electric field.[26] The stimulation of deeper structures, however, can increase depending on the delivered stimulation intensity, since the intensity of the induced current diminished with the square distance to the stimulation site. Regarding current orientation, it is known TMS stimulates preferentially axons than cell bodies, and the former are best stimulated by a parallel current. However, additionally to depth, shape, and intensity of stimulation, the effects of TMS must be accounted also for structures distant from the stimulation site, since TMS acts by circuit activation.[27] After axonal excitation by TMS, the changes in neuronal membrane spread in both orthodromic and antidromic directions, activating postsynaptic and presynaptic structures, respectively.[28] Although the effects of TMS are not exclusively consequence of local effects, but also distant circuit effects, it is important to precisely determine the stimulation target, and for this purpose the use of neuronavigated systems seems to be preferred over skull landmarks.[28]

The use of TMS in repetitive pulses – repetitive TMS (rTMS) – has a modulatory effect over neural structures possibly through long-term depression

and long-term potentiation, and can generate plastic synaptic changes.[29,30] Hight frequency rTMS (≥ 5Hz) is considered to be excitatory, while low frequency rTMS (≤ 1Hz) is inhibitory. This concept is not always straightforward, since it can vary depending on the stimulation target and the prior state of circuits activation.[31,32] As dictated by the Bienenstock-Cooper-Munro model, if postsynaptic activity is high, it is more likely to be depressed; if it is low, it is more likely to be potentiated.[33] Therefore, the effects of rTMS are more dependent of baseline excitability levels than stimulation frequency.[34] This is probably one of the reasons why atypical plastic responses and altered excitability modifications to cortical stimulation have been reported in various neuropsychiatric diseases.[35–37] The effects after one rTMS session are usually faint and short-lasting, but its effectiveness can be enhanced if patient is submitted to repeated sessions, especially in consecutive days.[38]

3.3 The cerebellum as a window to the whole brain

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, the modulation of these different neuronal networks could potentially treat pathologic neuronal oscillations and thus influence motor and sensory integration (Figure 1).

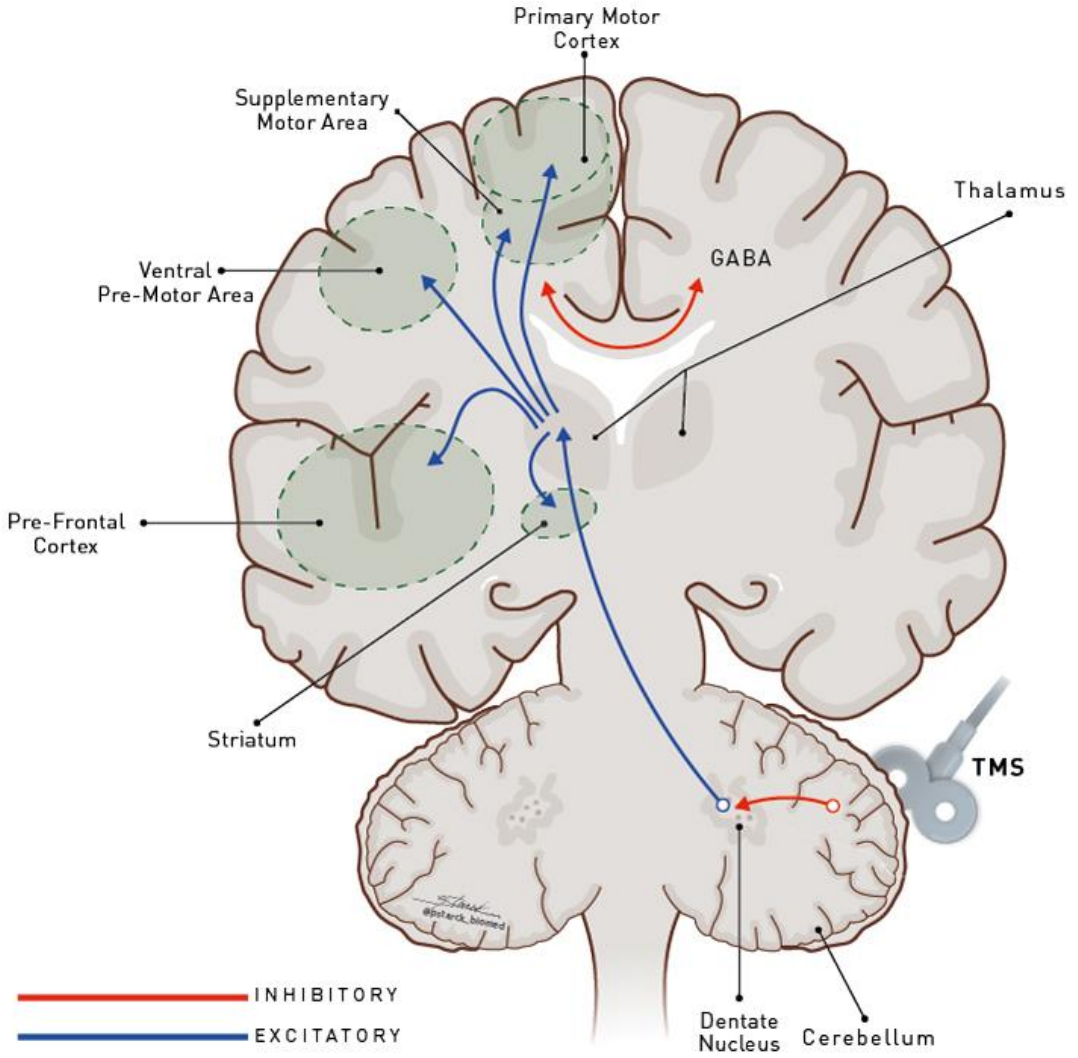


Figure 1 – Schematic representation of cerebellar cortical and subcortical connections. Network model showing cerebellar connections to distant regions. The dentate nucleus receives inhibitory input from Purkinje cells and modulates other brain areas, including contralateral primary motor cortex (facilitatory tonus). There is intracortical inhibition between both motor cortices, which is related to maintaining the integrity of axial, and limbs movements. The modulation of the dentate nucleus activity through transcranial magnetic stimulation could restore changes in motor cortex excitability that is seen in some ataxic syndromes. Adapted from França C, de Andrade DC, Silva V, Galhardoni R, et al. Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial. Parkinsonism Relat Disord. 2020 Nov;80:1–6.

Since the cerebral cortex is connected to the cerebellum only by polysynaptic circuits, and hence there are no monosynaptic connections, traditional techniques of anterograde and retrograde tracing cannot explore the topographic relationship between these two structures.[39–41] Instead, inferences from deficits after specific lesions, as well as physiological and transneuronal

tracing techniques, and functional neuroimaging could be used to investigate correlated areas.

Coherence is a spectral measure of the neural synchrony that can suggest communication between brain areas and can be measured using intrinsic low-frequency functional correlations by functional magnetic resonance imaging (MRI). Buckner et al. used this technique to create a complete functional map of the human cerebellum, and found functional connections between the cerebellum and the entire cerebral cortex, except perhaps primary visual and auditory cortices.[42] The cerebellum holds hubs of major functional brain networks, including Somatomotor Network, Default Mode Network, Limbic Network, Frontal Control Network, Ventral Attention Network, and Dorsal Attention Network.[42] Although the previous concept of the cerebellum as a structure related to motor control, somatomotor regions occupy only a small portion of the cerebellum; functional connections to cerebral association networks are by far larger.[42] Moreover, the cerebellum has at least two complete homotopic maps of all aforementioned cortical networks: one inverted representation in the anterior lobe, and one mirrored upright representation in the posterior lobe. The size of a cerebellar region dedicated to a network is in fact proportionate to its representation in the cerebral cortex, meaning the largest cerebral networks are associated with the greatest representations in the cerebellum.[42] This evidence points to a comprehensive cortical representation in the cerebellum.

In addition to cortical areas, several brainstems structures receive cerebellar outputs: nucleus reticularis tegmenti pontis, basilar pontine nuclei, pontine and medullary reticular formation, inferior olive, red nucleus, periaqueductal gray area, prerubral area, accessory oculomotor nuclei and superior colliculus.[43] The nucleus reticularis tegmenti pontis is associated with motor learning,[44] while the inferior olive plays a role not only in motor learning, but also in motor timing.[45] Since the red nucleus receives fibers from the dentate nucleus and is connected to both motor cortex and spinal cord, it is associated with motor control, especially postural control.[46]

Recent studies in patients with basal ganglia deep brain stimulation (DBS) have attempted to evaluate subcortical local field potentials through DBS

electrodes and compare them to data from cortical whole head magnetoencephalography in order to characterize cerebro-cerebral coherence. Neumann and colleagues described a series of nine patients with cervical dystonia and bilateral globus pallidus internus (GPi) DBS in which coherence was measured.[47] They reported pallidal coherence to ipsilateral temporal (theta band) and sensorimotor (beta band) areas, but also to the cerebellum (alpha band). More interestingly, the degree of pairing in the alpha band was inversely proportional to the severity of dystonia symptoms before surgery. This finding, though observational, could suggest that this neuronal synchrony between the cerebellum and basal ganglia is somehow involved in cervical dystonia pathophysiology. This hypothesis could shed light on why all studies to date showed improvement of cervical dystonia after cerebellar modulation.[48–51] Another study reported that, during writing, coherence between the ipsilateral cerebellum and contralateral posterior parietal cortex was reduced in patients with writing dystonia, compared to healthy controls.[52] Furthermore, patients with essential tremor (ET) performing hand motor tasks had a different coherence pattern than patients with age-related tremor, since the former showed a significant coupling between motor cortex (M1) in the contralateral cerebellum, while the latter did not,[53] corroborating the findings of a previous study. Parkinson's disease (PD) patients with tremor also showed signs of increased cerebellar coherence with M1.[54] Casula et al, analyzing data from electroencephalography after cerebellar theta burst stimulation (TBS) pulses, reported not only changes in M1, but also in the posterior parietal cortex. Similarly to previous findings in M1, continuous TBS would increase, while intermittent TBS would decrease local TMS-evoked activity and long-interval intracortical inhibition in the posterior parietal cortex, which demonstrates in humans a direct projection from cerebellum to a cortical non-motor area.[55]

The cerebellum is an important source of excitatory input to M1 via the dentato-thalamo-cortical pathway (Figure 1) and when this input is diminished, there is a reduction in cortical excitability (increase in intracortical inhibition and decrease in intracortical facilitation).[56] Injury in the dentato-thalamo-cortical pathway reduces excitability in the contralateral cortex,[57] whereas stimulation of the dentate nucleus increases cortical excitability and consequently promotes

motor facilitation (Figure 2).[7] Therefore, cerebellar neuromodulation techniques can modulate cortical excitability, since the cerebellum is a subcortical structure deputed to plastic mechanisms of motor learning.[58] It is not yet known whether cerebellar stimulation affects the dentate nucleus or Purkinje cells, structures with different roles in the cerebello-talamo-cortical activation.

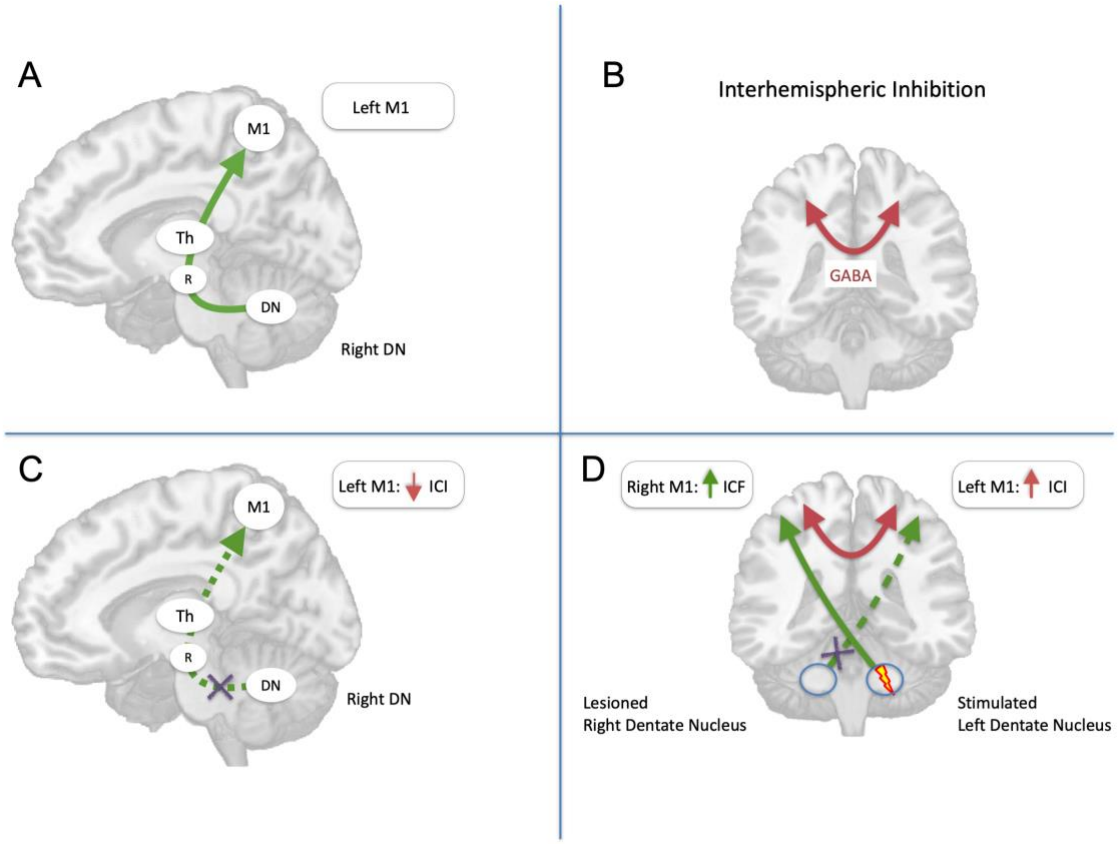


Figure 2 – Schematic representation of the rational of stimulating the Dentate Nucleus and its influence on restoring the primary motor area activity. Panel A shows the excitatory cerebellum-cortico pathway passing through the red nucleus and thalamus. There is an ICI between both M1 cortices (panel 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, that initially causes depression, but ultimately leads to 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).
Abbreviations: DN = Dentate Nucleus, R = Red Nucleus, Th = Thalamus, M1 = Motor Cortex, ICI = Intracortical Inhibition, ICF =Intracortical Facilitation, DRTT = dentate-rubro-thalamic tract, green arrow = Excitatory projection, red arrow = 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.

3.4 Little brain, big expectations: cerebellar modulation in movement disorders

The foundation behind the hypothesis of cerebellar stimulation in improving movement disorder symptoms is still unclear and theoretical. It lies on the fact that the cerebellum has been linked to the pathophysiology of numerous movement disorders, such as ataxia, dystonia,[59] PD tremor,[60] levodopa-induced dyskinesias,[61] ET,[62] and progressive supranuclear palsy (PSP).[63] Those are disorders with sometimes challenging treatments and are capable of gravely impairing the patient's quality of life.

Patients with dystonia present neuroimaging that is suggestive of cerebellar grey matter abnormalities,[64] microstructural deficits in cerebellar outflow [65], and augmented cerebellar metabolic activity.[59] Additionally, eye blink classical conditioning, linked to cerebellar function, is abnormal in dystonia.[66] There has also been pathological evidence supporting cerebellar involvement in cervical dystonia, including the loss of Purkinje cells, areas of focal gliosis, and torpedo bodies.[67]

Some features of PD have also been linked to cerebellar abnormalities. The dimmer-switch model proposes that resting tremor in PD is a consequence of anomalies in connections between the basal ganglia and the cerebello-thalamo-cortical circuit, especially regarding tremor amplitude.[60] Another study found a correlation between cerebellar circuits and resting tremor in PD, but not postural tremor.[68] Levodopa-induced dyskinesias are also associated with the cerebellum, since cerebellar sigma-receptors might be involved in its pathogenesis.[69] Patients with PD treated with pallidotomy or GPi-DBS, procedures that alleviate levodopa-induced dyskinesias, also exhibited functional and metabolic changes in the cerebellum after surgery.[61]

Evidence from clinical and neuroimaging studies show that the cerebellum is also involved in the pathophysiology of ET.[62] Studies report increased activity of the cerebellar cortex and deep cerebellar nuclei[70] and cerebellar degenerative changes in ET patients.[71]

Despite the fact that no frequent clinical symptoms point to cerebellar involvement in PSP, there is evidence to suggest otherwise. Shirota and

colleagues reported a dampening in cerebellar-brain inhibition in PSP patients, when compared to PD patients, which might insinuate a dentato-thalamo-cortical pathway or Purkinje cell impairment.[63]

3.4.1 Effects of cerebellar modulation on ataxia

To date, seventeen trials evaluated the effects of different types of cerebellar modulation in ataxias (Table 1).

Overall, these studies included patients with cerebellar ataxia due to stroke,[5,72–74] degenerative causes,[75–84] or cerebral palsy,[85] with a total of 237 patients. Nine studies were double-blind.[5,73,74,76,80,82–85] Eight studies used TMS stimulation,[5,72,73,75–77,84,86] seven used transcranial direct current stimulation (tDCS),[78–83,85] and 1 implanted a DBS device.[74] The time of evaluation after the intervention ranged from immediately after the stimulation to 1 year after the stimulation. Out of seventeen studies with cerebellar ataxia, only one reported no improvement, although it is important to point out the great variability in clinical improvement, probably reflecting the heterogeneity of the studied population, the number of sessions, and the type of technique used. In addition, the long-term effects have not been assessed.[78]

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Shimizu et al., 1999 [75]	(4) Spinocerebellar degeneration (2 SCA6, 1 SCA1 and 1 SCA7)	Cerebellum (tangentially over the inion, 4 cm to the right, and 4cm to the left)	Single pulse TMS (1 pulse of 0.1ms every >5s, 10 pulses per site, total 30 pulses per session) 21 sessions with 9cm circular coil at 100% of maximum stimulator output	Baseline + 21 days	None	Open label	Decrease in time and number of steps required for a 10m walk examination; increase in number of feasible steps in tandem; decrease in total length of tracing body balance.
Shiga et al., 2002 [76]	(74) Spinocerebellar degeneration (cerebellar type x OPCA type): 39 active, 35 placebo	Cerebellum (over the inion, 4cm to the left and 4cm to the right)	Single pulse TMS (1 pulse every 6s, 10 pulses per site, total 30 pulses per session) 21 sessions with 14cm circular coil at 250% RMT	Baseline + 3 weeks	None	Double-blind sham-controlled	Improvement in 10m time, 10m steps, tandem steps and standing capacities, especially in the cerebellar type.

continues

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias (continuation)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Ihara et al., 2005[86]	(20) Spinocerebellar degeneration (10 OPCA, 6 CCA, 4 SCA6)	Cerebellum (over the inion, 4cm to the left and 4cm to the right)	Single-pulse TMS (1 pulse every 5s, 10 pulses per site, total 30 pulses per session), 24 sessions with 70mm figure-of-eight coil at 100% maximum stimulator output.	Baseline + 1 day	Not mentioned	Single-blind, uncontrolled	Improvement in ataxia (ICARS).
Farzan et al., 2013 [77]	(1) Idiopathic late-onset cerebellar atrophy	Cerebellum (over the inion, 4cm to the left and 4cm to the right)	Single pulse TMS (1 pulse every 6s, 10 pulses per site, total 30 pulses per session) 21 sessions with 14cm circular coil at 250% RMT	Baseline + 3 weeks + 8 months	Not mentioned	Open label	Improvement of 9% in timed up-and-go test and gait speed. Decrease in stride duration variability and double support time.

continues

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias (continuation)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Grimaldi and Manto, 2013 [78]	(9) Cerebellar ataxias (1 immune ataxia; 1 paraneoplastic ataxia; 3 SAOA; 1 autosomal recessive ataxia; 3 dominant ataxia)	Right cerebellum hemisphere and vermis (over the inion and 3cm right)	Anodal tDCS 1 session with 1mA	Baseline + immediately after	Not mentioned	Single-blind sham-controlled crossover (> six days washout)	No change in posturography and upper limb dexterity.
Bonnì et al., 2014 [72]	(6) Posterior circulation stroke with ataxia	Cerebellar hemisphere (ipsilateral to the lesion)	rTMS (iTBS, 3 pulses at 50 Hz repeated at a rate of 5 Hz; 20 trains of 10 bursts delivered at 8-sec inter-vals; total duration: 190 sec, 600 pulses) 10 sessions with 70mm figure-of-eight coil at 80% RMT + physical therapy	Baseline + 2 weeks	Not mentioned	Open label	Ataxia improvement (MICARS), especially posture and gait subscales.

continues

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias (continuation)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Kim et al., 2014 [73]	(32) Posterior circulation stroke with ataxia	Cerebellar hemisphere (2cm under the inion and 2cm ipsilateral to the lesion)	rTMS (1Hz, 15 min duration, total 900 pulses per session), 5 sessions with 75mm figure-of-eight coil at 100% RMT	Baseline + 5 days + 1 month	None	Double-blind sham-controlled	Improvement in the 10m walk test 1 month after. BBS improved after 5 days and after 1 month
Grimaldi et al., 2014 [79]	(2) SCA 2	Right cerebellar hemisphere (3cm right of the inion) and motor cortex (hand representation area)	Anodal tDCS 1 session with 1mA	Baseline + immediately after	Not mentioned	Single-blind sham-controlled	Improvement in postural and action tremor. Improvement in limb hypermetria.
Grecco et al., 2015 [85]	(1) Ataxic Cerebral Palsy	Cerebellum	Anodal tDCS 1 session + treadmill training	Baseline + immediately after + 1 month	Not mentioned	Double-blind sham-controlled	Improvement in balance.

continues

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias (continuation)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Cury et al., 2015 [5]	(1) Cerebellar ataxia, cerebellar tremor and dystonia (cerebellar stroke)	Contralateral dentate nucleus - neuronavigated	rTMS 1Hz, 2 sessions (active and sham) with double-cone coil at 90% of RMT	Baseline + 1 week	None	Double-blind sham-controlled crossover (four weeks washout)	Improvement in tremor (FTMTRS) and ataxia (SARA). No improvement in dystonia (UDRS)
Teixeira et al., 2015 [74]	(1) Cerebellar ataxia, cerebellar tremor and dystonia (cerebellar stroke)	Contralateral dentate nucleus (contralateral)	DBS with bipolar setting (1.4 mA, 2.8 V, 60 ms pulse width at 20 Hz, and 2031 Ω)	Baseline + 1 year (ON and OFF)	None	Double-blind sham-controlled crossover (same day)	Improvement in tremor (FTMTRS) and ataxia (SARA) comparing ON and OFF. No improvement in dystonia (UDRS)
Benussi et al., 2015 [80]	(19) Cerebellar ataxia (5 SCA2; 1 SCA1; 2 SCA 38; 1 Friedreich's ataxia; 1 AOMA2; 6 MSA-C; 1 FXATAS and 2 SAOA)	Cerebellum	Anodal tDCS 1 session with 2mA	Baseline and immediately after	Not mentioned	Double-blind sham-controlled crossover (one week washout)	Improvement in SARA, ICARS, 9HPT and 8MW

continues

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias (continuation)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Grecco et al., 2016 [87]	(6) Ataxic cerebral palsy	Cerebellum (1cm under the inion)	Anodal tDCS 20min duration 10 sessions with 1mA + treadmill training	Baseline + 1 week + 1 month + 3 months	Present, mild (tingling and pain, tolerable)	Single-blind, sham-controlled, crossover (three months washout)	Improvement in hip oscillation during eyes-closed gait (stabilometric evaluation)
Bodranghien et al., 2017 [81]	(1) Cerebellar ataxia associated with ANO 10 mutation	Right cerebellar hemisphere (3cm right of the inion)	Anodal tDCS 1 session with 1.5mA	Baseline + 30min	None	Single-blind sham-controlled crossover (same day)	Improvement in postural tremor and slight improvement in dysmetria.
Benussi et al., 2017 [82]	(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	Cerebellum (2cm under the inion)	Anodal tDCS 10 sessions with 2mA	Baseline + immediately after + 1 month + 3 months	None	Double-blind sham-controlled	Improvement lasting at least 3 months in SARA, ICARS, 8MW and 9HPT (only in the non-dominant hand).

continues

Table 1 – Characteristics of studies investigating clinical effects of cerebellar neuromodulation on ataxias (conclusion)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Benussi et al., 2018 [83]	(20) Neurodegenerative ataxias (7 SCA 2; 5 MSA-C; 1 SCA38;1 SCA14; 1 Friedreich ataxia; 1 AOMA2; 4 SAOA)	Cerebellum (2cm under the inion) and spinal cord (2cm under T11)	Anodal tDCS (cerebellum) and cathodal tDCS (spinal cord) 10 sessions with 2mA	Baseline + immediately after + 1 month + 3 months	Not mentioned	Double-blind sham-controlled crossover (three months washout)	Improvement lasting at least 3 months in SARA, ICARS, 8MW, 9HPT, and SF-36.
Manor et al., 2019 [88]	(20) Spinocerebellar ataxia	Cerebellum (over the inion, 4cm to the left and 4cm to the right)	Single pulse TMS (1 pulse every 6s, 10 pulses per site, total 30 pulses per session) 20 sessions with 14cm circular coil at 100% maximum stimulator output.	Baseline + immediately after + 1 month	None	Double-blind sham-controlled	Improvement only in stance sub-score of SARA and standing postural sway metrics.

Abbreviations: 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; cTBS = continuous theta burst stimulation; DBS = deep brain stimulation; tDCS = transcranial direct current stimulation; FTMTRS = Fahn Tolosa Marin Tremor Rating Scale; FXATAS; fragile-X-associated tremor/ataxia syndrome; ICARS: International Cooperative Ataxia Rating Scale; M1 = primary motor cortex; MICARS = Modified International Cooperative Ataxia Rating Scale; MSA-C: multiple system atrophy cerebellar type; OPCA = olivopontocerebellar atrophy; SARA = scale for the assessment

and rating of ataxia; SAOA = sporadic adult-onset ataxia; SF-36 = short-form 36; TMS = transcranial magnetic stimulation; UDRS = unified dystonia rating scale.

The largest cohort included 74 patients with SCA, which were allocated into two arms: active or sham stimulation.[76] Participants underwent the following cerebellar single-pulse TMS stimulation protocol for 21 days: 10 pulses with 6-s interpulse intervals first over the inion, 4cm laterally to the right, and finally 4cm laterally to the left. In the active group, the authors found significant improvements in the 10-meter-walk time, number of tandem steps, and standing capacities. In one of the most recent studies,[82] Benussi and colleagues applied 10 sessions of anodal tDCS over the cerebellum of 20 patients with cerebellar ataxia in a double-blind design and reported a marked improvement in ataxic symptoms. No study reported major side effects.

3.4.2 Effects of cerebellar modulation on dystonia

In the nine studies that investigated the effects of cerebellar modulation on dystonia, 112 patients with cervical dystonia or focal hand dystonia (FHD) were included (Table 2).[48–51,89–93] Five trials used TMS stimulation,[48,50,51,92,93] three used tDCS,[49,89,90] and one implanted a DBS device.[91] All four studies with cervical dystonia reported good outcomes, while none of the five trials with FHD observed a significant improvement. Koch et al conducted a double-blind, placebo-controlled trial with 20 cervical dystonia patients and applied 10 sessions of continuous TBS, a specific TMS protocol, in 10 consecutive weekdays.[50] At the end of the last session, patients had a small (15%) but significant improvement, according to the Toronto Western Spasmodic Torticollis Rating Scale, although no difference was found using the Burke-Fahn-Marsden Dystonia Rating Scale. Another open-label study found greater improvement – 39% as measured by the Toronto Western Spasmodic Torticollis Rating Scale.[49] Sokal et al implanted a deep anterior cerebellar lobe DBS in 10 patients with spasticity and dystonia secondary to cerebral palsy and retrospectively observed a 25% dystonia improvement in 5 of them.[91] Only one study reported infectious complications after DBS implantation.[91]

Table 2 – Characteristics of studies investigating effects of cerebellar neuromodulation on dystonia

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Hoffland et al., 2013 [48]	(11) Cervical dystonia + (8) healthy controls	Right cerebellum	cTBS 1 session with figure-of-eight coil	5 min	None	Open label	Improvement of EBCC
Bradnam et al., 2014 [49]	(1) Cervical dystonia	Cerebellar hemispheres (bilateral) and M1	Anodal tDCS, 20 sessions + botulinum toxin A injection	Baseline + 4, 8 and 12 weeks	None	Open label	Dystonia improvement of 39% (TWSTRS)
Koch et al., 2014 [50]	(20) Cervical dystonia	Left and right lateral cerebellum	cTBS 10 sessions with 70mm figure-of-eight coil	Baseline + 2,4 and 6 weeks	None	Double-blind sham-controlled	Clinical improvement only in the 2-week evaluation as measured by the TWSTRS (15%), but not by the BFMDRS
Sadnicka et al., 2014 [89]	(10) Writing dystonia	Right cerebellar cortex	Anodal tDCS 1 session with 2mA	Baseline + immediately after + 30 min	Not mentioned	Double-blind sham-controlled crossover (one week washout)	No statistical difference between dystonia improvement in sham and active stimulations

continues

Table 2 – Characteristics of studies investigating effects of cerebellar neuromodulation on dystonia (continuation)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Bradnam et al., 2015 [90]	(8) FHD + (8) healthy controls	Lateral cerebellum (3 cm lateral and 1 inferior to the inion)	Anodal and cathodal tDCS 1 session with 2mA	Baseline + 5min	None	Double-blind sham-controlled crossover (five days washout)	Decrease of mean stroke frequency and average pen pressure
Sokal et al., 2015 [91]	(10) Cerebral palsy with secondary dystonia	Deep anterior cerebellar lobe	DBS	Retrospective evaluation	3 infectious complications	Open label	Improvement of 25% in dystonia (UDRS) in 5 patients
Linssen et al., 2015 [92]	(10) Writing dystonia	Cerebellar hemisphere ipsilateral to the dominant hand	cTBS 1 session with figure-of-eight coil	Baseline + immediately after	Not mentioned	Double-blind sham-controlled	No significant differences in writing performance
Bologna et al., 2016 [93]	(13) FHD + (13) CD + (13) healthy controls	Cerebellar hemisphere ipsilateral to the affected side of the body	cTBS 1 session with figure-of-eight coil	Baseline + 5min + 45 min	None	Double-blind sham-controlled	No changes in clinical scores or reaching and neck movements

continues

Table 2 – Characteristics of studies investigating effects of cerebellar neuromodulation on dystonia (conclusion)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Bradnam et al., 2016 [51]	(16) Cervical dystonia	Lateral cerebellum, bilaterally	iTBS 10 sessions with 70mm figure-of-eight coil + motor control training	Baseline + 5 days + 10 days	None	Double-blind sham-controlled	Reduction in total TWSTRS score and time to perform the grooved pegboard task

Abbreviations: Ass. TP: assessment time points; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; cTBS: continuous theta burst stimulation; DBS: deep brain stimulation; tDCS: transcranial direct current stimulation; EBCC: eyeblink classical conditioning; FHD: focal hand dystonia; iTBS: intermittent theta burst stimulation; M1: primary motor cortex; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale.

3.4.3 Effects of cerebellar modulation on essential tremor

Six trials studied the effects of cerebellar stimulation in 68 ET patients,[94–99] three of which used a double-blind design (Table 3). Only three studies found a significant clinical benefit (range: 9% to 27%) in tremor scales, two of them using TMS and one using cathodal tDCS.[95,96,99] The improvement was larger and lasted longer in patients that underwent more sessions. In the longest trial, improvement (20%) was only significant after 15 cathodal tDCS sessions, but not after 10.[99] Other studies failed to find any clinical benefit.[94,97,98] One study reported local skin erythema and chemosis as a side effect,[97] while another reported mild headache in one patient.[95] There were no other side effects.

Table 3 – Characteristics of studies investigating effects of cerebellar neuromodulation on essential tremor

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Avanzino et al., 2009 [94]	(15) Essential tremor + (11) Healthy controls	Right lateral cerebellum	rTMS 1 session with 90mm figure-of-eight coil	Baseline + immediately after + 5 min + 30 min	Not mentioned	Open label in 8 patients and single blind sham controlled in 7 patients; cervical stimulation in 5 patients	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.
Gironell et al., 2002 [95]	(10) Essential tremor	Posterior cerebellum	rTMS 1 session with 70mm butterfly coil	Baseline + 5min + 60min	Slight headache in one patient	Double-blind sham-controlled	Tremor improvement according to the TCRS, (17%) and accelerometry evaluation on the + 5min assessment
Popa et al., 2013 [96]	(11) Essential tremor + (11) healthy controls	Posterior cerebellum (bilateral) – neuronavigated	rTMS 5 sessions with figure-of-eight coil	Baseline + 5 days + 12 days + 29 days	None	Open label	Tremor improvement that built up until day 12 and persisted for 3 weeks.
Gironell et al., 2014 [97]	(10) Essential tremor	Cerebellar hemispheres, bilaterally	Cathodal tDCS 10 sessions with 2mA	Baseline + 10 min + 15min + 70min + 10 days + 40 days	Local skin erythema and chemosis	Double-blind sham-controlled	No acute or long-lasting benefit

continues

Table 3 – Characteristics of studies investigating effects of cerebellar neuromodulation on essential tremor (conclusion)

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Bologna et al., 2015 [98]	(16) Essential tremor + (11) healthy controls	Right cerebellar hemisphere	TMS (cTBS) 1 session with eight-shaped coil	Baseline + 5min + 45 min	None	Double-blind sham-controlled	No change in tremor severity and reaching movements.
Yilmaz et al., 2016 [99]	(6) Essential tremor	Cerebellum	Cathodal tDCS 10 sessions with 2mA; 5 more sessions after 1 month	Baseline + 20 days + 50 days	None	Open label	Improvement of tremor according to the TETRAS score (20%) only after 50 days

Abbreviations: Ass. TP: assessment time points; cTBS: continuous theta burst stimulation; ITI: inter tapping interval; rTMS: repetitive transcranial magnetic stimulation; TCRS: tremor clinical rating scale; tDCS: transcranial direct current stimulation; TETRAS: essential tremor rating scale assessment; TD: touch duration; TMS: transcranial magnetic stimulation

3.4.4 Effects of cerebellar modulation on Parkinson's disease

All five trials that examined effects of cerebellar modulation on Parkinson's disease (n=70) used double-blind designs (Table 4).[100–104] There was a great variation in the outcomes and symptom subtypes studied. Two studies examined the acute effect of continuous cerebellar TBS in 28 PD patients with levodopa-induced dyskinesias – both of them reported positive outcomes, with the improvement of dyskinesia after stimulation. [100,102] Ferrucci et al compared nine PD patients with levodopa-induced dyskinesias who underwent five sessions of anodal tDCS over the cerebellum to five daily sessions of M1 stimulation in a double-blind, sham-controlled design and found a significant decrease in the Unified Parkinson's Disease Rating Scale part IV (dyskinesia section) scores after both active stimulations, but not after the sham stimulation. This improvement was observed only immediately after the last session and did not persist after 1 week.[104] Another group assessed the acute effect of cerebellar continuous TBS on resting tremor and found no clinical benefit.[103] Minks et al evaluated dexterity in 20 PD patients after one session of TMS and reported improvements in gross upper limb movement, but impairment in fine motor finger and hand function.[101] No study reported side effects.

Table 4 – Characteristics of studies investigating effects of cerebellar neuromodulation on Parkinson's disease

Author	(n) Population	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Koch et. al., 2009 [100]	(20) PD with peak-dose dyskinesia	Lateral cerebellum ipsilateral (1) and bilateral (2)	cTBS 1 session with 70mm figure-of-eight coil	Baseline + 2, 4 and 6 weeks	None	Double-blind sham-controlled	Decrease in waking time spent as ON with dyskinesias.
Minks et. al., 2011 [101]	(20) PD	Right lateral cerebellum - neuronavigation	rTMS 1 session with a conic coil	Baseline + 2 – 6min	None	Double-blind sham-controlled	Less time to complete de ball test (gross upper limb movement); more time to complete the nine-hole peg test (fine motor finger and hand function).
Brusa et. al., 2012 [102]	(8) PD with levodopa-induced dyskinesias	Lateral cerebellum (bilateral)	cTBS 5 sessions with 70mm figure-of-eight coil	Baseline + 1 week	None	Double-blind sham-controlled	Reduction of dyskinesias.
Bologna et. al., 2015 [103]	(13) PD resting tremor + (10) healthy controls	Cerebellar hemisphere (ipsilateral)	cTBS 1 session with 8-shaped coil	Baseline + 5 min + 45 min	None	Double-blind sham-controlled	No changes in tremor amplitude, frequency or magnitude.
Ferrucci et. al., 2016 [104]	(9) PD with levodopa-induced dyskinesias	Cerebellum and M1	Anodal tDCS 5 sessions with 2mA	Baseline + 5 days + 12 days + 33 days	Not mentioned	Double-blind sham-controlled	Improvement in UPDRS IV (dyskinesias section).

Abbreviations: Ass. TP: assessment time points; cTBS: continuous theta burst stimulation; tDCS: transcranial direct current stimulation; PD: Parkinson disease; rTMS: repetitive transcranial magnetic stimulation; UPDRS: Unified Parkinson's Disease Rating Scale.

3.4.5 Effects of cerebellar modulation on progressive supranuclear palsy

Only one open-label trial included 10 PSP patients and performed 10 sessions of intermittent TBS over the lateral cerebellum.[105] Patients were evaluated using the PSP-Rating Scale, which is comprised of 6 sections: daily activity, behavior, bulbar, oculomotor, limb motor, and gait/midline abnormalities. This study described a significant improvement in all patients only in dysarthria, an item in section III Bulbar. Two out of 10 patients also showed improved gait. No side effects were observed.

4 METHODS

4 METHODS

4.1. Trial design

This is a randomized, prospective, double-blind, cross-over, sham-controlled trial that assessed patients with cerebellar ataxia treated with d-rTMS aimed at the cerebellar dentate nucleus.

4.2. Ethics

The Institutional Review Board of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo approved the study, and all patients provided informed consent before implementing any study protocol. This study was registered at the clinicaltrials.gov under protocol NCT03213106.

4.3. Participants

4.3.1 Eligibility criteria

(a) Diagnosis of cerebellar ataxia based on clinical history and neurological examination.
(b) Refractoriness to clinical treatment involving physical therapy, speech, and occupational therapy.
(c) Cerebellar lesion of vascular or surgical etiology; or diagnosis of SCA3 or MSA-c.
(d) Symptoms for at least six months (chronic ataxia).
(e) Symptoms of moderate ataxia with scale for the assessment and rating of ataxia (SARA) > 6.
(f) Intellectual ability to understand and sign the consent form.

(g) Availability and willingness to attend all follow-up visits.

4.3.2 Exclusion criteria

(a) Age < 18 years old.
(b) Active infection or other uncontrolled pre-existing medical conditions (e.g., diabetes, hypertension, symptomatic heart disease, malignant neoplasia, or psychiatric illnesses).
(c) Concomitant treatment with other experimental drugs.
(d) Cardiac pacemakers, electronic devices, or intra-cranial metallic objects;
(e) Pregnancy or breastfeeding.

4.3.3 Settings and location

This study was conducted in the Psychiatry Institute of the University of São Paulo. Stimulation sessions were performed on the Surgical Pathophysiology Laboratory (LIM-62).

4.4. Interventions

The target was the dentate nucleus contralateral to the most clinically affected side. If the patient had symmetric ataxia, we arbitrarily established the target as the right dentate nucleus [5]. Patients were evaluated at baseline and the location of the dentate nucleus was mapped through neuronavigation using Polaris Vicra, Brainsight software and T2 weighted volumetric MRI (Figure 3), as previously reported.[5] Briefly, patients comfortably sat in a chair in front of the neuronavigation camera. MRI image was uploaded in Brainsight and the following landmarks were marked both in the image and in the patient (using the neuronavigation pointer): right tragus, left tragus, occipito, and bregma. The dentate nucleus of interest was, then, found by moving the neuronavigation pointer in patient's occipital area. After found, the exact spot was marked in

patient's skull using red marker. The distance between the point marked and the landmarks previously mentioned was then measured using a measuring tape. These values were then used to locate the hotspot in future sessions.

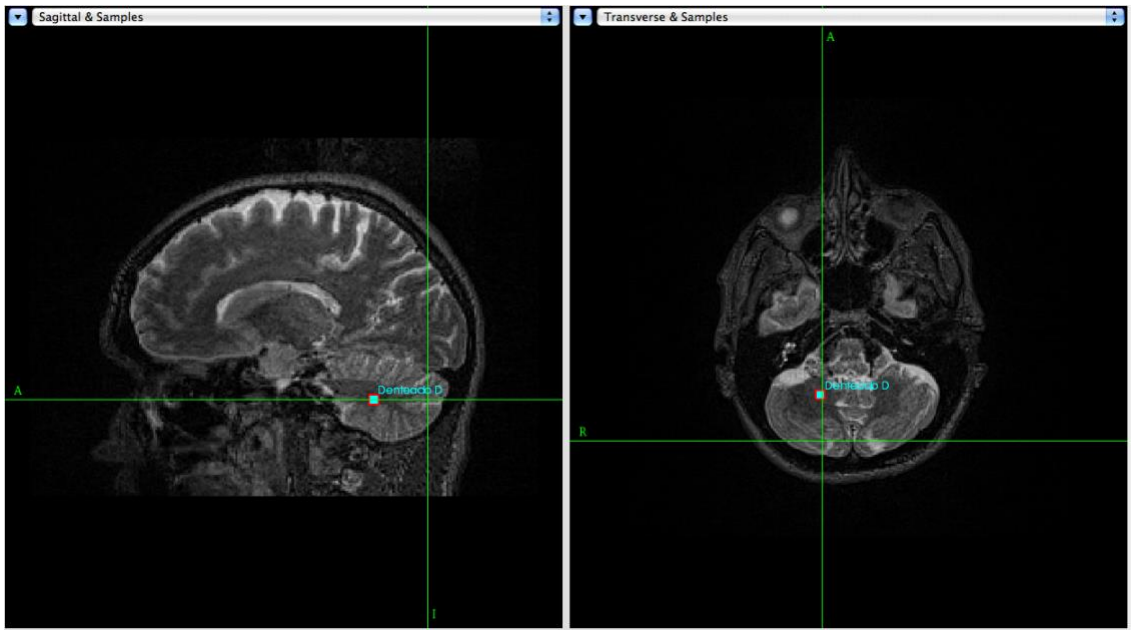


Figure 3 – Neuronavigation of the dentate nucleus in sagittal and transverse samples using T2 volumetric magnetic resonance imaging.

Participants were then randomly assigned to an intervention group (sham or active d-rTMS) for five consecutive days. Following a minimum of four weeks washout (in order to guarantee the return to baseline values), assignments were then switched, and participants underwent five additional stimulation sessions; those on active d-rTMS were switched to sham, while the ones on sham were switched to active d-rTMS (Figure 4). All interventions were administered during the morning period.

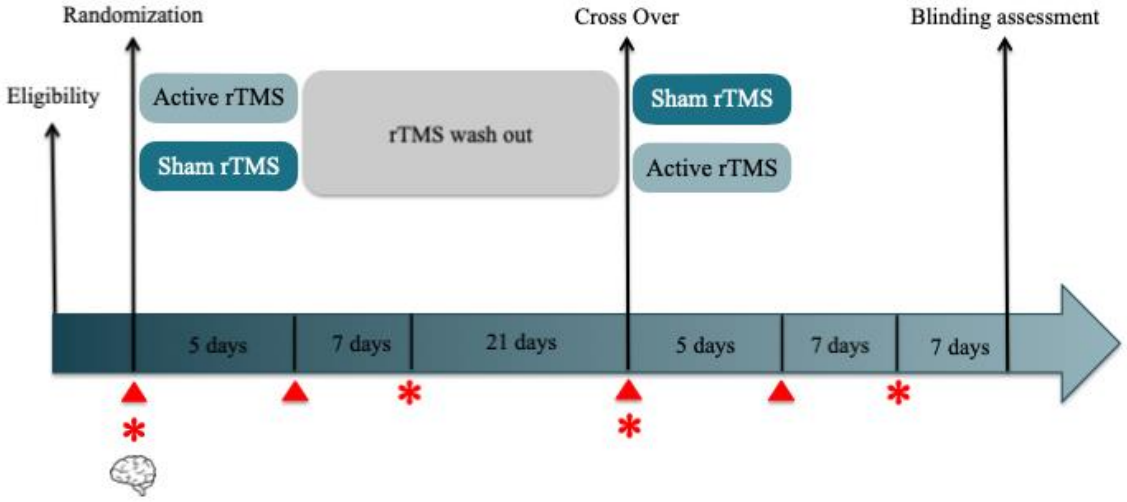


Figure 4 – Study design. Triangles represent assessment of the following outcomes: ataxia, tremor, dystonia, cognition, and cortical excitability. Asterisks represent assessment of quality of life, anxiety, and depression. Brain drawing represents neuronavigation. d-rTMS = deep repetitive transcranial magnetic stimulation.

Active d-rTMS was performed with neuronavigation coordinates using a MagPROX100 machine (Magventure® Tonika Elektronik, Farum, Denmark). A butterfly double-cone D-B80 cooled coil was oriented at a tangent to the scalp with the main phase of the induced current in the anterior-to-posterior direction. Intensity was set at 90% of the rest motor threshold of the abductor pollicis brevis muscle.[106] The stimulation session consisted of 20 series of 60-sec pulses at 1 Hz and inter-train-pulses of 1 sec (for a total of 1200 pulses per session). The sham stimulation was executed with a sham coil identical to the active d-rTMS, which was positioned in the exact same way. Sessions were performed with patients reclined in an armchair with both feet up. Patients were advised not to change any rehabilitation therapy or medication throughout the study.

Patients were evaluated at baseline and then were randomly assigned to the intervention (sham or active d-rTMS) for five consecutive days. Following a 28 days minimum washout period, assignments were then switched, and participants underwent five additional stimulation sessions: those on active d-rTMS were switched to sham while the ones on sham were switched to active d-rTMS.

4.5. Outcomes

The primary outcome measure was the difference between SARA scales, comparing active versus sham phases. SARA is a clinical scale that measures clinical cerebellar ataxia on an impairment level, and ranges from zero to 40 points (Supplementary material C).[107] Higher scores indicate higher levels of impairment. Currently, it is one of the most commonly used clinical scale to quantify ataxia, as was for this reason chosen as primary outcome. There are eight items: the first four items (gait, stance, sitting, and speech) measure axial ataxic symptoms, while the following four items (finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide) measure appendicular symptoms and are bilaterally graded (while only the mean value of both sides should be added to the total score).

Secondary outcome measures included:

(a) Ataxia measured with International Cooperative Ataxia Rating Scale (ICARS), a different, more comprehensive ataxia clinical scale (Supplementary material D).[107] It ranges from zero to 100, and is divided in four subscales: 1) postural and gait disturbances (seven items, ranging 0 – 34), 2) limb ataxia (seven items, ranging from 0 – 52), 3) dysarthria (two items, ranging 0 – 8), and 4) oculomotor disorders (three items, ranging 0 – 6). Higher scores indicate higher levels of impairment.

(b) Tremor measured with the Fahn-Tolosa-Marin Tremor Rating Scale, a clinical scale that measures tremor on an impairment level, and ranges from zero to 144 (Supplementary material E).[108] Higher scores indicate higher levels of impairment. This scale is divided in three parts. In part A (nine items, ranging 0 – 80), the examiner assesses tremor amplitude at rest, posture, and intention in several anatomic locations. In part B (five items, ranging 0 – 36), tremor is quantified during writing, pouring, and drawing. Part C (seven items, ranging 0 – 28) weights the impact of tremor in activities of daily living.

(c) Dystonia measured with the Unified Dystonia Rating Scale, a clinical scale that rates 14 body regions for dystonia severity and duration, ranging from 0 – 60. (Supplementary material F).[109] Higher scores indicate higher levels of impairment.

(d) Gait speed measured with the timed up and go test, in which two chairs were assembled 3 meters apart. Patients started the test sited in one chair, and were instructed to stand up, walk to the other chair, go around it, come back to the first chair, and sit down. The time between stand up and sit down was measured. Three trials were performed, and the smallest time was considered. If patient needed walking aids in his/her daily life, the same aids were allowed during the test. Higher scores indicate higher levels of impairment.[110]

(e) Quality of life measured by the short version of the World Health Organization Quality of Life scale, a self-reported questionnaire of 26 questions comprising four areas: physical, psychological, social interactions, and environment (Supplementary material G).[111,112] This scale ranges from 0 – 100, and higher scores indicate lower levels of impairment.

(f) Anxiety and depression, measured with the Hospital Anxiety and Depression Scale, a questionnaire that comprises seven questions for anxiety and seven questions for depression (Supplementary material H).[113] This questionnaire ranges from 0 – 21 for both anxiety and depression, that should be ranked separately. Higher scores indicate higher levels of impairment.

(g) Cognition, measured with the Frontal Assessment Battery, direct and indirect order digit span, in addition to verbal fluency using animal names and words with the letter F. The Frontal Assessment Battery includes several instruments to screen for frontotemporal dementia, including similarities, S-word verbal fluency, Luria's test, grasp reflex, and the Go-No-Go test (Supplementary material I).[114] It ranges from 0 – 18 and higher scores indicate lower levels of impairment.

(h) Cerebellar volume measured by a trained neuroradiologist with volumetric T2 sequences using volBrain system.[115]

(i) Cortical excitability measured bilaterally over the primary motor cortex immediately before the first session and immediately after the fifth session in both active and sham groups, and the following parameters were obtained: 1) Rest motor threshold, 2) Motor-evoked potential at 120% of rest motor threshold and at 140% of rest motor threshold, 3) Short interval intracortical inhibition, and 4) Intracortical facilitation. We classified each cortical excitability parameter as normal, low, or high after comparison with healthy controls.[116]

(j) Safety was assessed periodically during d-rTMS sessions by a trained nurse capable of identifying seizures. Additionally, patients answered a questionnaire after the end of the study with questions regarding discomfort, pain, headache, and seizures. In this same survey, there was a free text space in which patients could describe other sensations they deemed relevant.

The baseline evaluation included all previously described scales, demographic data, MRI, and cortical excitability. At the end of the first five days of intervention (active or sham), all scale tests and cortical excitability were repeated (evaluation number two), except for the short version of the World Health Organization Quality of Life scale and Hospital Anxiety and Depression Scale, which were answered remotely after seven days. After the washout period, patients were called for a third clinical evaluation identical to baseline. On the last day of the following five-day intervention (sham or active, crossover), there was a fourth evaluation identical to the second evaluation. Again, the short version of the World Health Organization Quality of Life scale and Hospital Anxiety and Depression Scale were repeated seven days after the fourth evaluation. After 14 days of the last intervention, patients were contacted by telephone for the blinding assessment (Figure 4). There was no follow-up visit after the blinding assessment.

4.6. Sample size

Sample size was calculated using G*Power 3 software, based on our preliminary study.[5,117] To detect a 4-point difference in SARA scale comparing active and sham stimulations, and to achieve 80% power with an alpha level of 5%, assuming a standard deviation of 5, twenty two subjects were required.

4.7. Randomization

Our random sequence was generated by randomization.com using randomly permuted blocks with size of four per block.

4.8. Blinding

Researchers were specifically instructed not to attempt to break the randomization schedule in any manner. Different researchers performed subject allocation, randomization, and clinical evaluation. A single movement disorder specialist blinded to the type of stimulation (active/sham) performed all clinical evaluations. Patients were blinded regarding randomization and were never scheduled on the same day and time, so they were not able to exchange information in the waiting room.

4.9. Statistical methods

Our exploratory analysis started with a visual assessment of all variables to evaluate the frequencies, percentages, and near-zero variance for categorical variables (such as gender, education, comorbidities), distribution for numeric variables (including age and the scale scores), and their corresponding missing value patterns.[118] A near zero variance was found when a categorical variable had a small percentage of a given category and was addressed by combining different variable categorizations. Missing values were handled through imputation algorithms followed by sensitivity analyses in order to verify whether our results were stable with and without imputation. When evaluating the balance of baseline variables between intervention arms, numeric variables were compared through t-tests and categorical variables though chi-squared tests. We assumed an alpha error of 0.5, a power of 80%, a 4-point difference in the SARA scale, and a standard deviation of 5. A sample size of twenty-two participants was obtained.

Period, carry-over, and treatment effects were initially evaluated with Mann–Whitney tests for SARA and ICARS.[119] A paired Mann–Whitney test was used because the variables did not present a normal distribution, which was confirmed through a Shapiro–Wilk test. Period effects were calculated as the difference

between the outcome values after the treatment in periods two and one (period two minus period one). Carry-over effects were calculated as the sum of outcome values after treatment in periods one and two (period one plus period two). The treatment effect was evaluated by using a paired Mann–Whitney test to compare the means of patients exposed to active d-rTMS to those exposed to sham conditions in each period. In order to explore the correlation between cerebellar volume and ataxia outcomes (SARA and ICARS changes) we used Spearman coefficient.

Finally, we performed subgroup analyses by testing the same association between our intervention and outcomes within specific subgroups of our sample, based on patient diagnoses (post-lesion ataxia, SCA3, and MSA-c) and laterality (clinical evaluation with SARA, ICARS, and Fahn-Tolosa-Marin Tremor Rating Scale ipsilateral and contralateral to the stimulation site). We used the same linear mixed-effects model applied to the whole population to evaluate primary and secondary outcomes within each subgroup. Since these were post-hoc analyses, they should be interpreted with caution. All analyses were performed using the statistical language R.

4.10. Funding

This study was funded by the Pain Center and LIM-62 medical research lab (research assistant scholarship and TMS/neuronavigation machines). Image study was performed through accordance with the Radiology department.

5 RESULTS

5 RESULTS

5.1 Participant flow

Two participants dropped out of the study after randomization: one after five d-rTMS sessions, and another after three sessions, both for personal reasons not related to the protocol itself. Figure 5 displays our study flowchart. Our sample consisted of 24 individuals and presented a distribution of 54.2% in the active/sham and 45.8% in the sham/active orders. All 24 patients were included in the final primary outcome analysis.

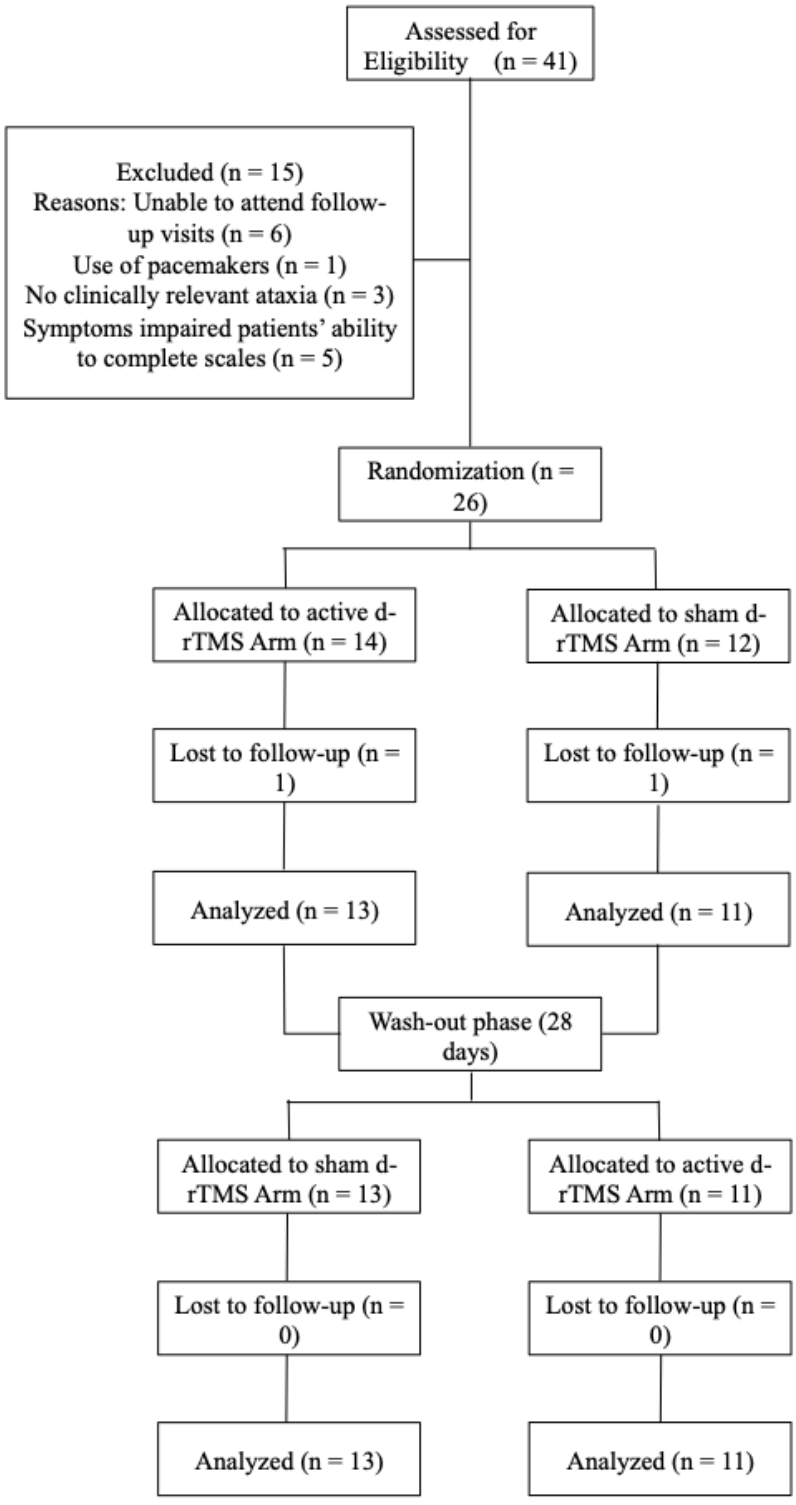


Figure 5 – Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram for Randomization of Patients with Ataxia Enrolled in the Study. d-rTMS = deep repetitive transcranial magnetic stimulation

5.2 Recruitment

Data were collected between July 2016 and April 2019. The trial ended when previously calculated sample size was reached with two additional patients to compensate for potential dropouts. No interim analysis was conducted during the protocol.

5.3 Baseline Data

Baseline demographic characteristics results were similar between groups (Table 5).

Table 5 – Description of the overall study sample

Variable	Total (n = 24)	Active/Sham d-rTMS (n = 13)	Sham/Active d-rTMS (n = 11)	P value
Age	49 (13.8)	53.4 (11.2)	44.5 (15.6)	p = 0.131
Female	16 (66.7%)	8 (61.5%)	8 (72.7%)	p = 0.885
Diagnosis				p = 0.368
- MSA-c	8 (33.3%)	5 (38.5%)	3 (27.3%)	
- Post-lesion ataxia	7 (29.2%)	5 (38.5%)	2 (18.2%)	
- SCA 3	9 (37.5%)	3 (23.0%)	6 (54.5%)	
Employment status				p = 0.346
- Employed	4 (16.7 %)	3 (25 %)	1 (10 %)	
- Retired	14 (58.3 %)	8 (66.7 %)	6 (60 %)	
- Others	4 (16.7 %)	1 (8.33 %)	3 (30 %)	
Education				p = 0.547
- Elementary	1 (4.17 %)	1 (7.69 %)	0 (0 %)	
- High school	8 (33.3 %)	3 (23.1 %)	5 (45.5 %)	
- College	8 (33.3 %)	5 (38.5 %)	3 (27.3 %)	
- Graduate	7 (29.2 %)	4 (30.8 %)	3 (27.3 %)	
Years of education	15 (+- 4.6)	15 (+- 4.2)	14.9 (+- 5.3)	p = 0.981
Cardiovascular diseases	11 (45.8%)	8 (61.5%)	3 (27.3%)	p = 0.205
Depression	14 (58.3%)	10 (76.9%)	4 (36.4%)	p = 0.111

Values are mean (SD) or n (%). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, MSA-c: multiple systems atrophy cerebellar type, SCA 3: spinocerebellar ataxia type 3.

Regarding the stimulation side, 14 patients received d-rTMS directed to the right cerebellum (six active/sham and eight sham/active), while 10 patients received it to the left (seven active/sham and three sham/active) (p = 0.3). Distances from stimulation hotspot to skull landmarks are depicted in Table 6.

Table 6 – Distance in centimeters from the coil hotspot to skull landmarks

	Right ear helical root	Left ear helical root	Bregma	Occipito
Right dentate nucleus	11.0 (11, 12.3)	16.5 (15.6, 18.3)	21.0 (20.1, 21.5)	5.0 (4.0, 5.3)
Left dentate nucleus	16.0 (15.0, 17.3)	11.2 (11.0, 11.8)	20.0 (19.0, 19.8)	5.0 (3.6, 5.5)

Values are median (interquartile range).

5.4 Outcomes

5.4.1 Clinical efficacy of the stimulation

Table 7 displays the main results of our evaluation instruments at baseline, after active d-rTMS and after sham, in addition to the p-values (active x sham). Since it was not found any statistical differences between baseline data (evaluations one and three), we depicted only one.

Table 7 – Outcome measures at baseline, post-sham and post-active phases

Variable [missing]	Baseline	Sham d-rTMS	Active d-rTMS	P value for treatment effect (sham vs active)
SARA [0]	13.5 (9.7, 17.6)	12.8 (9.6, 17.8)	10.2 (6.2, 16,2)	p = 0.002
ICARS [2]	34.0 (25.0, 43.7)	32.8 (22.0, 47.0)	29.0 (21.0, 43.5)	p = 0.005
ICARS posture and gait disturbances [2]	16.0 (10.5, 19.5)	15.0 (9.2, 21.5)	14.0 (9.5, 19.5)	p = 0.086
ICARS kinetic function [2]	16.0 (10.7, 20.5)	14.5 (9.0, 19.7)	10.5 (7.7, 17.5)	p = 0.005
ICARS speech disorders [2]	3.5 (1.7, 5.0)	2.0 (2.0, 4.7)	2.5 (1.7, 5.0)	p = 0.285
ICARS oculomotor disorders [2]	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 3.2)	p = 0.305
FTM score [0]	11.0 (2.5, 29.2)	9.5 (3.0, 29.2)	8.5 (3.0, 23.5)	p = 0.415
UDRS score [0]	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	p = 0.172
TUG [12]	15.5 (10.5, 28.2)	14.0 (11.5, 26.0)	12.0 (11.0, 24.5)	p = 0.106
WHOQOL-BREF score [1]	53.0 (48.0, 60.0)	55.0 (46.0, 62.0)	53.0 (44.0, 62.0)	p = 0.791
Anxiety HADS score [2]	6.0 (2.0, 8.2)	4.5 (2.0, 8.0)	5.0 (2.8, 8,2)	p = 0.447
Depression HADS score [2]	8.0 (2.8, 9.5)	5.5 (4.0, 9.2)	7.0 (3.0 – 0.9)	p = 0.527
FAB [0]	15.0 (12.2, 17.0)	17.0 (15.2, 18.0)	17.0 (15.2, 18.0)	p = 0.228
Digit span direct order [0]	5.0 (4.0, 5.7)	5.0 (5.0, 5.7)	5.0 (5.0, 5.7)	p = 0.515
Digit span indirect order [0]	4.0 (3.0, 4.0)	3.0 (3.0, 4.0)	4.0 (3.0, 4.0)	p = 0.515

continues

Table 7 – Outcome measures at baseline, post-sham and post-active phases (conclusion)

Variable [Missing]	Baseline	Sham d-rTMS	Active d-rTMS	P value for treatment effect (sham vs active)
Phonemic fluency (letter F) [0]	10.5 (7.2, 13.5)	12.0 (9.0, 14.0)	12.0 (9.0, 15.0)	p = 0.921
Semantic fluency (animals) [0]	15.5 (12.2, 19.5)	17.0 (13.2, 20.7)	15.5 (14.0, 20.0)	p = 0.476

Values are median (interquartile range). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, FAB: frontal assessment battery, FMT: Fahn-Tolosa Marin tremor rating scale, HADS: hospital anxiety and depression score, ICARS: international cooperative ataxia rating scale, MBS: most bothersome symptom, SARA: scale for the assessment and rating of ataxia, TUG: time up-and-go, UDRS: unified dystonia rating scale, WHOQOL-BREF: short version of the World Health Organization quality of life scale.

We found a significant improvement in ataxia according to the SARA scale after active cerebellar d-rTMS with a 2.6-point difference between medians of active and sham groups (p = 0.002, Table 7, Figure 6) and 3.3-point between baseline and active group (p < 0.005, Table 7). The difference in SARA between baseline and sham groups did not change significantly (p = 0.480).

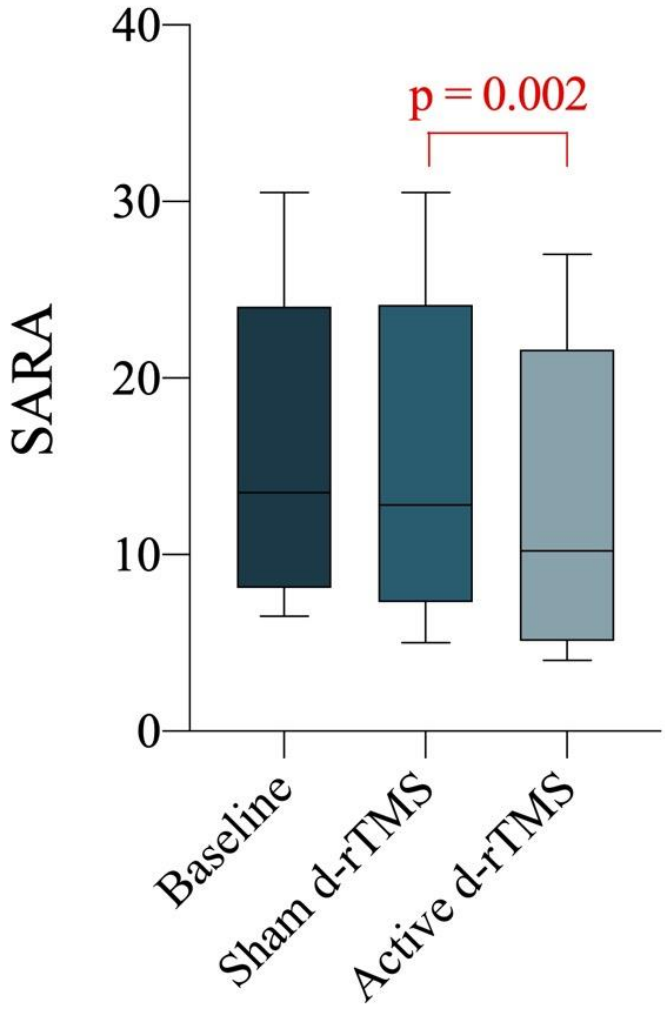


Figure 6 – Median (central mark), interquartile range (bottom and top edges of the box), maximum and minimum values (whiskers) of Scale for the Assessment and Rating of Ataxia (SARA) values at baseline, post-sham, and post-active modulation.

Similar to the SARA results, ICARS (measured in 22 out of 24 patients) also significantly improved in patients after active cerebellar d-rTMS compared to sham (3.8-point difference; p = 0.005, Table 7, Figure 7) and to baseline (6.08-point difference; p = 0.001).

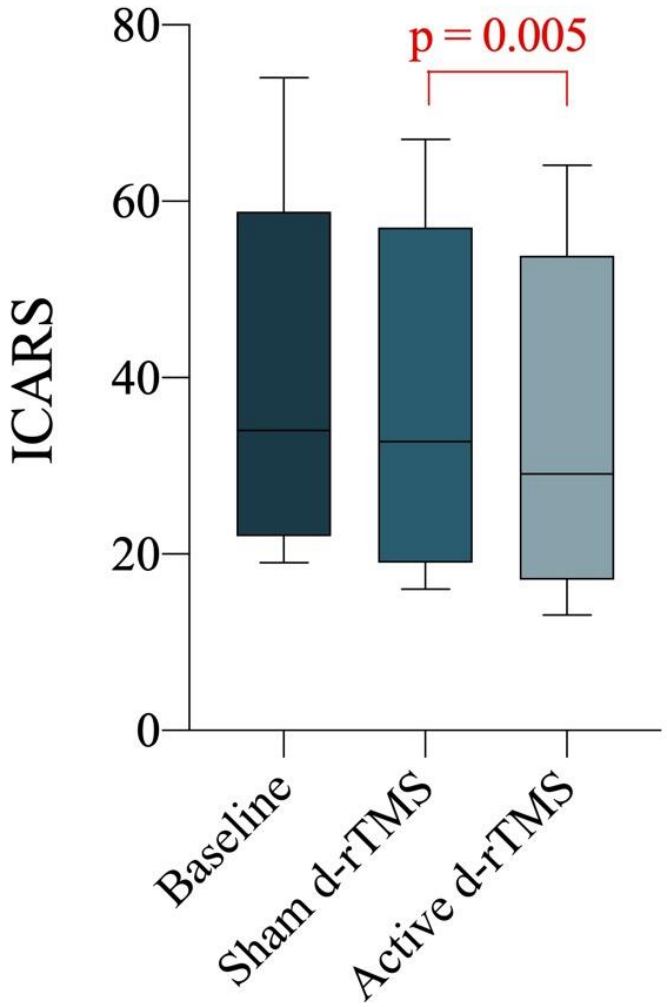


Figure 7 – Median (central mark), interquartile range (bottom and top edges of the box), maximum and minimum values (whiskers) of International Cooperative Ataxia Rating Scale (ICARS) values at baseline, post-sham, and post-active modulation.

Regarding ICARS sub scores, only in “kinetic function”, which measures appendicular abilities, there was significant improvement after active d-rTMS compared to sham (p = 0.020, Table 7). Axial functions, such as gait, balance, oculomotor abilities, and speech did not show significant improvement after d-rTMS.

Both SARA and ICARS improved bilaterally, regardless of the unilateral d-rTMS (Table 8).

Table 8 – Treatment effects of SARA, ICARS and Fahn-Tolosa-Marin Tremor Rating Scale between sham and active d-rTMS treatments regarding the laterality of the stimulation

Variable	Baseline	Active d-rTMS	Sham d-rTMS	P value for treatment effect (sham vs active)
Ipsilateral				
SARA limb score	4.0 (3.0, 6.0)	3.0 (1.2, 4.0)	4.5 (3.0, 6.0)	p = 0.005
ICARS limb score	5.0 (3.0, 8.2)	4.0 (2.0, 6.0)	4.5 (3.0, 7.2)	p = 0.013
FTM limb score	2.5 (0.25, 6.7)	2.0 (1.0, 4.7)	2.0 (1.0, 6.7)	p = 0.083
Contralateral				
SARA limb score	7.0 (4.2, 9.7)	4.5 (3.0, 7.7)	6.0 (4.0, 7.7)	p = 0.044
ICARS limb score	9.0 (5.0, 11.0)	4.5 (3.0, 8.7)	8.0 (4.0, 11.0)	p = 0.001
FTM limb score	3.5 (2.0, 7.0)	2.5 (1.0, 5.7)	3.5 (1.5, 8.7)	p = 0.084

Values are median (interquartile range). For SARA, it was considered right and left values for items five to eight (total range 0-16 each side). For ICARS, we considered right and left values for bilateral items of kinetic function (items eight to fourteen, total range 0-24 each side). For FTM, we considered right and left values for bilateral items (items five, eight, and eleven to fourteen, range 0-40 each side). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, SARA: scale for the assessment and rating of ataxia, ICARS: international cooperative ataxia rating scale, FMT: Fahn-Tolosa-Marin tremor rating scale.

When analyzing the subgroups outcomes (post-hoc analysis) comparing to baseline scores, SCA3, MSA-c, and post-lesion ataxia showed improvement in SARA and ICARS after d-rTMS. However, only MSA-c was significantly influenced by the stimulation when comparing sham and active d-rTMS ($p < 0.05$) (Table 9, Figure 8).

Table 9 – Motor outcomes for the subgroup analysis according to diagnosis

Outcome	Baseline	Sham d-rTMS	Active d-rTMS	P value active *versus* baseline	P value active *versus* sham
Multiple system atrophy cerebellar type (n = 8)					
SARA	14.0 (12.6, 22.8)	14.7 (11.6, 23.5)	11.0 (6.3, 22.6)	0.025	0.021
ICARS (total score)	37.5 (27.2, 55.0)	37.4 (24.0, 55.5)	30.5 (23.0, 51.0)	0.024	0.011
ICARS (posture and gait disturbances)	16.5 (10.5, 23.7)	17.5 (8.7, 27.2)	15.5 (8.0, 26.7)	0.609	0.157
ICARS (kinetic function)	17.0 (12.0, 22.0)	16.5 (9.0, 20.5)	12.0 (8.5, 15.0)	0.017	0.020
ICARS (speech disorders)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	3.5 (2.0, 4.7)	0.564	0.998
ICARS (oculomotor disorders)	3.0 (2.0, 3.7)	2.5 (2.0, 3.7)	3.0 (1.2, 3.0)	0.480	0.655
FTM	12.0 (4.0, 28.7)	12.0 (4.0, 29.2)	9.5 (4.2, 21.5)	0.108	0.176

continues

Table 9 – Motor outcomes for the subgroup analysis according to diagnosis (continuation)

Outcome	Baseline	Sham d-rTMS	Active d-rTMS	P value active *versus* baseline	P value active *versus* sham
Spinocerebellar ataxia type 3 (n = 9)					
SARA	12.0 (6.7, 13.5)	10.0 (7.7, 13.2)	7.5 (6.0, 10.5)	0.030	0.063
ICARS (total score)	32.0 (22.5, 40.0)	28.0 (21.0, 36.5)	23.0 (19.5, 28.0)	0.017	0.202
ICARS (posture and gait disturbances)	11.0 (10.0, 17.0)	11.0 (9.5, 19.5)	11.0 (8.5, 16.0)	0.111	0.334
ICARS (kinetic function)	13.0 (7.5, 16.5)	9.0 (6.5, 13.5)	9.0 (3.5, 9,5)	0.028	0.399
ICARS (speech disorders)	2.0 (1.0, 3.5)	2.0 (1.0, 2.0)	2.0 (0.5, 2.5)	0.157	0.890
ICARS (oculomotor disorders)	3.0 (2.0, 4.5)	3.0 (2.0, 5.0)	3.0 (2.5, 4.5)	0.157	0.589
FTM	4.0 (1.0, 10.5)	3.0 (2.0, 8.0)	3.0 (1.5, 7.0)	0.865	0.764

continues

Table 9 – Motor outcomes for the subgroup analysis according to diagnosis (conclusion)

Outcome	Baseline	Sham d-rTMS	Active d-rTMS	P value active *versus* baseline	P value active *versus* sham
Post-lesion ataxia (n = 7)					
SARA	18.5 (14.0, 28.5)	17.5 (10.5, 29.0)	16.5 (10.0, 27.0)	0.027	0.293
ICARS (total score)	46.0 (26.5, 72.5)	43.0 (17.0, 66.0)	40.0 (23.5, 63.0)	0.043	0.109
ICARS (posture and gait disturbances)	23.5 (12.5, 30.7)	17.0 (3.0, 31.0)	21.5 (11.7, 30.5)	0.180	0.109
ICARS (kinetic function)	22.0 (17.0, 32.0)	20.0 (9.0, 25.0)	19.0 (15.0, 24.0)	0.042	0.680
ICARS (speech disorders)	5.0 (2.0, 5.5)	4.0 (2.0, 5.0)	5.0 (2.5, 5.5)	0.564	0.414
ICARS (oculomotor disorders)	3.0 (1.5, 4.5)	3.0 (2.0, 4.0)	2.0 (1.0, 2.5)	0.102	0.157
FTM	49.0 (10.0, 53.0)	38.0 (10.0, 42.0)	44.0 (10.0, 48.0)	0.492	0.058

Values are median (interquartile range). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, FMT: Fahn-Tolosa-Marin tremor rating scale, ICARS: international cooperative ataxia rating scale, SARA: scale for the assessment and rating of ataxia.

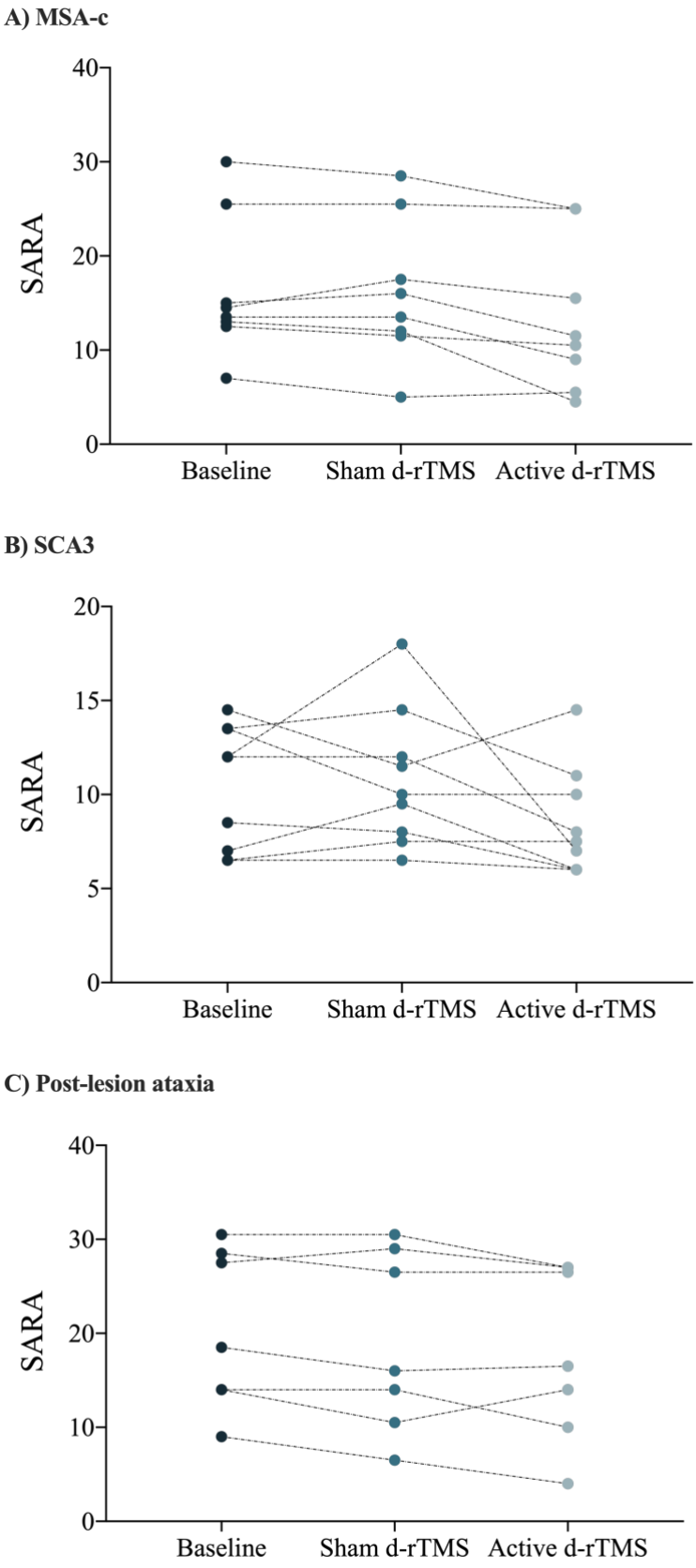


Figure 8 – Individual analysis of Scale for the Assessment and Rating of Ataxia (SARA) values at baseline, after sham and after active d-rTMS in patients with A) MSA-c; B) SCA3; and C) post-lesion ataxia.

Regarding individual analysis, after active d-rTMS, four patients did not present improved or had slightly worse SARA scores (range 0 to 1 point) while 20 patients showed improvements (range 0.5 to 8.5 points, Table 10, Figure 8).

Table 10 – Individual analysis from the 24 patients

Patient No.	Sex	Age	Diagnosis	SARA baseline	SARA after active treatment	ICARS baseline	ICARS after active treatment
1	F	74	MSA-c	13	4.5	26	21
2	F	49	MSA-c	14.5	15.5	43	45
3	F	70	MSA-c	13.5	9	31	29
4	F	59	MSA-c	25.5	25	62	60
5	M	62	MSA-c	12.5	10.5	33	29
6	F	56	MSA-c	7	5.5	25	13
7	M	67	MSA-c	15	11.5	42	32
8	M	52	MSA-c	30	25	59	53
9	F	40	SCA 3	6.5	6	23	21
10	F	29	SCA 3	13.5	10	40	30
11	F	29	SCA 3	15.5	11	34	26
12	F	49	SCA 3	6.5	7.5	20	18
13	M	48	SCA 3	12	7	40	22
14	F	36	SCA 3	8.5	6	32	25
15	M	37	SCA 3	12	8	25	18
16	F	48	SCA 3	14.5	14.5	43	43
17	F	44	SCA 3	7	6	22	23
18	M	46	Cerebellar lesion after tumor resection	14	14	34	30

continues

Table 10 – Individual analysis from the 24 patients (conclusion)

Patient No.	Sex	Age	Diagnosis	SARA baseline	SARA after active treatment	ICARS baseline	ICARS after active treatment
19	F	20	Cerebellar lesion after tumor resection	28.5	26.5	74	62
20	M	54	Left cerebellar stroke	14	10	..	..
21	F	36	Left cerebellar stroke	9	4	19	17
22	F	67	Cerebellar lesion after tumor resection	18.5	16.5	46	40
23	F	51	Unilateral hemorrhagic cerebellar stroke	30.5	27	71	64
24	M	59	Left cerebellar stroke	27.5	27	--	--

Abbreviations: ICARS: international cooperative ataxia rating scale, MSA-c: Multiple Systems Atrophy cerebellar type, SARA: scale for the assessment and rating of ataxia, SCA 3: spinocerebellar ataxia type 3.

There was no significant carryover effect in SARA ($p = 0.9$) and in ICARS scores ($p = 0.9$), showing that the effect of the active sessions did not persist after the washout period (Table 11). Patients who received active stimulation in the first five days (active/sham) did not show different effects when comparing with the patients randomized to receive sham stimulation first (sham/active) with $p = 0.5$ for the period effect of SARA and $p = 0.2$ for ICARS. Differences between groups were evaluated through paired Mann–Whitney tests.

Table 11 – Paired Mann-Whitney test comparing the mean period, carry-over, and treatment effects of SARA and ICARS between patients exposed to sham and active d-rTMS treatments

Outcome	Sham d-rTMS	Active d-rTMS	p
SARA period effect	2.0 (0.2, 3.8)	2.0 (-0.5, 3.5)	0.560
SARA carry-over effect	22.0 (18.0, 29.0)	24.5 (16.0, 32.0)	0.908
ICARS period effect	3.0 (2.0, 5.0)	2.0 (0.0, 4.0)	0.274
ICARS carry-over effect	60.0 (42.0, 79.0)	60.0 (48.0 – 82.0)	0.974

Values are median (interquartile range). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, SARA: scale for the assessment and rating of ataxia, ICARS: international cooperative ataxia rating scale.

The other secondary outcomes did not change when comparing active to sham stimulation (Table 3). Timed up and Go Test was only evaluated in 12 out of 24 patients since some patients could not perform the task, and although the difference between active and sham groups was 7.2 sec, it was not statistically significant (p = 0.1).

5.4.2 Cortical excitability

At the baseline evaluation, only three patients (patients 5, 11, and 21) had bilaterally normal rest motor threshold (Table 12). All others had highly altered rest motor threshold measurements. Moreover, all patients presented high values of paired pulse responses, such as short interval intracortical inhibition and intracortical facilitation. Active d-rTMS produced no significant changes in cortical excitability measurements, and no group differences were detected.

Table 12 – Individual values of cortical excitability

Patient No.	Right RMT	Left RMT	Right MEP_120	Left MEP_120	Right MEP_140	Left MEP_140	Right SICI	Left SICI	Right ICF	Left ICF
1	H	H	L	N	L	L	H	H	H	H
2	L	L	H	L	H	H	H	H	H	H
3	N	H	L	H	L	N	H	H	H	H
4	H	H	H	H	H	H	H	H	H	H
5	N	N	H	H	H	H	H	H	H	H
6	N	H	N	H	H	N	H	H	H	H
7	L	L	L	N	L	N	H	H	H	H
8	N	L	L	L	L	L	H	H	H	H
9	H	H	N	H	H	H	H	H	H	H
10	N	L	H	N	H	H	H	H	H	H
11	N	N	H	H	N	L	H	H	H	H
12	H	H	H	N	H	N	H	H	H	H
13	H	H	N	H	L	N	H	H	H	H
14	L	L	N	N	N	H	H	H	H	H
15	L	L	H	N	H	H	H	H	H	H
16	L	L	H	H	H	H	H	H	H	H
17	L	L	N	N	H	N	H	H	H	H
18	L	L	N	L	N	L	H	H	H	H
19	H	N	N	H	L	L	H	H	H	H
20	L	N	N	L	L	L	H	H	H	H
21	N	N	L	L	L	H	H	H	H	H
22	H	H	H	H	H	H	H	H	H	H
23	H	H	L	H	L	H	H	H	H	H
24	N	L	L	L	H	L	H	H	H	H

Abbreviations: H: high, ICF: intracortical facilitation, L: low, MEP: motor evoked potential, MSA-c: Multiple Systems Atrophy cerebellar type, N: normal, RMT: rest motor threshold, SCA 3: spinocerebellar ataxia type 3, SICI: short-interval intracortical inhibition.

5.4.3 Imaging analysis

MRI description of lesions in the seven patients with post-lesion ataxia can be found in Table 13.

Table 13 – MRI description of lesions in patients with post-lesion ataxia

Patient No	Lesion description
18	Median suboccipital craniotomy, gliosis / encephalomalacia in vermis and medial aspect of cerebellar hemispheres, affecting both dentate nuclei, and bilateral hypertrophic olivary degeneration. Cerebellar transverse diameter: 10.4 cm. Longitudinal diameter of the cerebellar vermis: 4.9 cm
19	Surgical manipulation in the posterior fossa, with loss of cerebral tissue and gliosis in the vermis, medial part of cerebellar hemispheres, and both dentate nuclei. Additionally, there is bilateral hypertrophic olivary degeneration. Cerebellar transverse diameter: 10 cm. Longitudinal diameter of the cerebellar vermis: 4.7 cm.
20	Gliosis / encephalomalacia of superior and anterior parts of left cerebellar hemisphere affecting the dentate nucleus, possibly secondary to ischemic insult of the superior cerebellar artery and the anterior inferior cerebellar artery. Additionally, there is contralateral hypertrophic olivary degeneration and minor supratentorial microangiopathy. Cerebellar transverse diameter: 10.5 cm. Longitudinal diameter of the cerebellar vermis: 4.8 cm.
21	Gliosis / encephalomalacia of posteroinferior part of the right cerebellar hemisphere, possibly secondary to ischemic insult in part of the posterior inferior cerebellar artery territory. Cerebellar transverse diameter: 9.7 cm. Longitudinal diameter of the cerebellar vermis: 4.6 cm
22	Signs of right retromastoid occipital craniotomy, with loss of cerebral tissue and encephalomalacia / gliosis in right cerebellar hemisphere and encephalomalacia/gliosis in the right arm of pons and in adjacent medium cerebellar peduncle (surgery to remove vestibular schwannoma). Cerebellar transverse diameter: 9.4 cm. Longitudinal diameter of the cerebellar vermis: 4.4 cm
23	Hemorrhagic sequelae in superior part of cerebellum, bilaterally, extending inferiorly to the dentate nucleus, mainly on right cerebellar hemisphere. Cerebellar transverse diameter: 8.5 cm. Longitudinal diameter of the cerebellar vermis: 4.5 cm
24	Signs of chronic hemorrhagic lesion on the left paramedian region of the pons tegmentum, bilateral asymmetric hypertrophic olivary degeneration (left > right), minor supratentorial microangiopathy. Cerebellar transverse diameter: 10 cm. Longitudinal diameter of the cerebellar vermis: 4.5 cm

Calculated cerebellar volume (median and interquartile range) was 89.3cm^3 (72.6, 113.4) for the MSA-c group, 94.8cm^3 (89.1, 105.7) for the SCA 3 group, and 96.4cm^3 (74.4, 113.0) for the post-lesion group. We found no significant correlation between the cerebellar volume and the difference in ataxia scores (SARA and ICARS) between sham and active phases ($p > 0.05$, Table 14).

Table 14 – Cerebellar volume in cubic centimeters and its correlation with ICARS and SARA scores when comparing sham and active phases

	Cerebellar volume (cm^3)	Correlation between SARA change (sham – active phases)		Correlation between ICARS change (sham – active phases)	
		r	p	r	p
All patients	94.7 (83.5, 105.1)	0.114	0.615	0.118	0.610
MSA-c	89.3 (72.6, 113.4)	0.707	0.051	(0.230)	0.583
SCA 3	94.8 (89.1, 105.7)	0.160	0.682	0.286	0.456
Post-lesion ataxia	96.4 (74.4, 113.0)	(0.700)	0.188	0.600	0.400

Values for cerebellar volume are median (interquartile range). Of note, the normal value for the cerebellar volume in adults is 128.35 cm^3.[120]

5.5 Safety

No patient suffered severe side effects. Out of 24 patients, nine presented mild side effects (five after active d-rTMS and four after sham). Two felt discomfort during sessions (patient 9 during sham and patient 22 during active d-rTMS); three suffered from mild headaches during or after sessions (patients 6, 10, and 16, all during active stimulation), and four patients presented other side effects, but only one did so during active stimulation (patient 20 presented short-lasting worsening of his chronic left leg pain).

5.6 Blinding assessment

At the end of the study, 66.7% of patients reported no differences between active and sham stimulations. Among the 33.3% of patients that perceived difference between sessions, when asked to guess the treatment, 75% guessed correctly. When all patients were asked to guess which sessions were active or sham, 50% did so correctly, and 83.4% based their response on stimulation effects rather than on different sensory perceptions during sessions.

6 DISCUSSION

6 DISCUSSION

In this double-blind, crossover trial, cerebellar d-rTMS caused a reduction in ataxic symptoms with no serious associated side effects in patients with different types of cerebellar ataxia. The improvement was self-limited, and reversible. Moreover, the clinical effects were consistent and specific, showing significant decreases on both the SARA and ICARS scales, but no significant effects on tremor, dystonia, gait, quality of like, anxiety, depression, cognition, or on cortical excitability measures. Individual outcomes varied greatly among patients, and no significant correlation was found between cerebellar volume and clinical improvement.

Previous studies have demonstrated that cerebellar modulation could improve ataxic symptoms. However, these studies had methodological limitations that compromised the external validity of their results. With the present study, we were able to confirm this benefit in a crossover and blinded manner. Although the effect size is small, and sometimes smaller than previous studies, our study design allowed us to minimize the placebo effect, since we compared post-active with post-sham ataxia scores, and not with baseline. Also, while the heterogeneity of our population can be seen as a limitation, it also reveals that cerebellar d-rTMS can benefit ataxia patients with different diagnosis and underlying mechanisms.

6.1 The choice of stimulation site

The rationale of stimulating the cerebellum is based on its widespread connections to several neurological sites, such as basal ganglia, prefrontal and cingulate cortices, supplementary area, and motor cortex (Figure 1).[121–123] Its modulation could reset pathological neuronal oscillations observed in different etiologies of ataxia and lead to subsequent symptomatic control. In recent years, the idea of network involvement in neurological symptoms, rather than a single neural structure, has arisen in the neuromodulation field.[124] This concept has already been proven in well-based neuromodulation therapies, such as deep brain stimulation (DBS) of subthalamic nucleus for patients with Parkinson's disease, in which several symptoms can improve by targeting a strategic network hub. Along this line, changes in brain metabolism and blood flow were reported after cerebellar transcranial magnetic stimulation.[75,76] Another study described a decrease in oxidative stress, which has been implicated in the pathophysiology of SCA and correlates with clinical severity,[86] after low-frequency cerebellar repetitive transcranial magnetic stimulation in ataxic patients. In MSA-c patients, cerebellar repetitive transcranial magnetic stimulation caused an improvement in motor scores and an increase in motor network resting-state complexity, an imaging finding that may correlate to functional decline.[125]

6.2 Cortical excitability

In this study, measurements of motor cortex excitability were employed to analyze the distant effects of cerebellar stimulation.[126] Patterns of abnormal cortical excitability in SCA, MSA-c, and cerebellar stroke have been previously described.[127–129] Also, previous studies have demonstrated changes in cortical

excitability parameters after cerebellar repetitive transcranial magnetic stimulation in normal humans.[8,9] Another group, when testing cortical excitability in patients with SCA type 6 and type 31 after cerebellar repetitive transcranial magnetic stimulation using a figure-of-eight coil (considered a superficial coil), found no change in cerebellar-brain inhibition.[130] Regarding MSA-c, one study found improvements in pathological disinhibition after cerebellar 1 Hz repetitive transcranial magnetic stimulation as demonstrated by a change in short-latency afferent inhibition.[10] All patients included in the present study had abnormal baseline cortical excitability parameters, but no significant changes in cortical excitability after d-rTMS were found despite clinical improvement. This finding could be due to the limited number of d-rTMS sessions to which patients were exposed in addition to stimulation parameters and/or the time between the end of the session and the cortical excitability assessment.[131] However, following previous single-patient d-rTMS study,[5] a DBS device was implanted in the dentate nucleus.[74,132] In this scenario, there was a change in cortical excitability when the DBS was switched on.

6.3 Purkinje cells or dentate nucleus: what is the real stimulation target

Distinguishing modulation of Purkinje cells and dentate nucleus is paramount, considering these two structures have opposite roles in cerebellar effects over the motor cortex. However, the determination of the exact brain area being influenced by the induced electric current is a major inherent limitation of non-invasive modulation techniques.[133] Most likely, more than one structure is being stimulated simultaneously, and that makes even more difficult to determine

which stimulated structure is actually responsible for the final result. This issue is even more complex if we add to the equation the concomitant activation of distant parts of the network, away from the stimulated target.[134,135] The double-cone transcranial magnetic stimulation coil used in the present study is considered a deep coil and is known to reach structures as deep as the foot motor cortex.[4] Since the dentate nucleus lies as deep from the skull surface as the foot motor cortex, it is safe to say double-cone coils are able to reach it.[5,6] However, between the dentate nucleus and the skull surface lie Purkinje cells on the cerebellar cortex that could be also modulated by the magnetic field. For the double-cone coil, the electric field diminishes as a function of coil distance; hence, it is possible that Purkinje and dentate nucleus, in addition to other cerebellar structures beneath the coil and its lateral wings, are concurrently modulated at different intensities.[136] However, since in SCA3 and MSA-c patients there is a severe loss of Purkinje cells, it is possible that the dentate nucleus would receive more electric current.[10] The insula lies at a similar depth from the scalp as the dentate nucleus (4.5–5.0 cm). Interestingly, a study using the same neuromodulation method as we did to target the human insula found antinociceptive effects only when using double-cone coils.[137,138] More importantly, this analgesic effect was clinically equivalent to the effect obtained by direct stimulation of the posterior insula using electrodes during electroencephalography in patients with refractory epilepsy.[137] These data point to a relatively good specificity and target accuracy when performing d-rTMS with a double-cone coil.[26] Another study comparing transcranial magnetic stimulation coils found no changes in cerebellar-brain inhibition after cerebellar 1 Hz repetitive transcranial magnetic stimulation with superficial figure-of-eight coil but only with deep-reaching ones, such as the one

used here.[6] Cury et al. previously reported improvement in the SARA score after cerebellar d-rTMS in one ataxic patient, and after this same patient received a dentate nucleus DBS implant, the improvement in SARA was identical.[5,74] Following this evidence, it is possible that the results in this current study were mainly due to the dentate nucleus modulation, although Purkinje cell involvement could also be contributing to the outcome.

6.4 The matter of frequency

In the present trial, 1 Hz d-rTMS was the chosen frequency, which is considered an inhibitory modulation. Overall, it is understood that baseline cerebellar disorders present with hyperactivity of the cerebellar output due to Purkinje loss, and previous experience revealed that this pattern of modulation is safe and potentially effective.[5] However, it is important to emphasize that the "inhibitory" and "excitatory" transcranial magnetic stimulation frequencies are not straightforward and that different frequencies can change abnormal oscillations in a diseased brain network. A more comprehensive understanding of this matter beyond excitation or inhibition is mandatory since in patients with cerebellar ataxia of the same etiology, cortical excitability is highly variable (Table 12). Also, despite the choice of unilateral modulation, patient presented bilateral improvement (Table 8). This is not a unique outcome in the field of neuromodulation. For instance, dystonic patients with unilateral DBS of GPI can improve symptoms bilaterally.[139] Most likely the effects of cerebellar d-rTMS are not constrained to a single cerebellar efferent pathway, but modulate the whole brain network that is influenced by the cerebellum (Figure 1), perhaps by

disrupting abnormal oscillations even in the ipsilateral cortex, possibly due to changes in transcallosal pathways mediated by GABA and responsible for interhemispheric inhibition.[127] Our choice for the unilateral modulation was mainly due to safety concerns, since we would use a deep coil in a structure in close proximity to the brainstem. However, since there were no severe side effects in the present trial, it is natural to wonder if a bilateral approach could lead to a superior clinical improvement.

6.5 Clinical improvement

Regardless of the structures being modulated or changes in cortical excitability, the improvement in ataxia measured not only by SARA, but also by ICARS, was significant (Table 7). There was great individual variability in those results, possibly due to different patterns of cerebellar connectivity impairment. Other variables, however, did not demonstrate significant improvement, such as quality of life, anxiety, and depression. Perhaps the short treatment regimen, adequate for a primary exploratory trial without maintenance sessions, as well as the lack of structured rehabilitation during the study protocol is in part responsible for these results. Studies with longer stimulation periods should provide definitive information on the effects of ataxia improvement in quality of life, anxiety, and depression. Importantly, cognition was not negatively affected according to the Frontal Assessment Battery, verbal fluency, and digit spam tests, which attests further to the safety of this approach, nor did the patients showed a learning curve, since both baseline measures (evaluations one and three) were not statistically different.[140] Yildiz et al. showed that cerebellar 1 Hz repetitive transcranial magnetic stimulation with a figure-of-eight coil improved short-latency afferent

inhibition, a variable that represents cholinergic cortical inhibition and is altered in patients with Alzheimer's disease, mild cognitive impairment, and MSA-c.[10] Also, despite ataxia improvement, there was no significant improvement in the Timed up and Go Test ($p = 0.1$). Since the mean difference between sham and active group was large (7 sec), it is possible that this result was due to the limited number of patients tested since the Timed up and Go Test could only be performed in 50% of our sample. The blinding assessment revealed that patients were effectively blinded, and allocation concealment was well performed since only 25% of the patients correctly reported detecting differences between active and sham stimulations.

It is vital to acknowledge that the treatment effect in the present study (2.6-point change in the primary outcome) was relatively low despite its statistical significance. Even so, the most encouraging results in other randomized trials with riluzole and valproic acid for ataxia were also modest. Romano et al. tested the efficacy of riluzole versus placebo in 55 patients in a highly variable population (different types of SCAs and Friedreich ataxia) and found a decrease in SARA scores by 1.02 points in patients.[141] Another group studied valproic acid in a smaller sample of 12 SCA3 patients and reported a 2.05-point decrease in SARA scores.[142] However, although an one point decrease in SARA, a scale with a 40-point range, may seem small, it was considered to be clinically relevant in previous studies.[143,144]

6.6 Limitations

This study has some limitations. While the patients had well-defined ataxia diagnoses, and this was an effectiveness trial, the study population was rather heterogeneous. However, since all patients had cerebellar ataxia as the main core symptom, they possibly shared similar network, or connectome, involvement.[145,146] Moreover, only 24 patients were included, and some tests could not be performed in all patients. Another important limitation was the short follow up after sessions, which could have impaired accuracy of quality of life evaluations and do not reveal the real duration of the beneficial effect. The lack of maintenance d-rTMS also prevents the analysis of long-term efficacy. The stimulation parameters were chosen based on a pathophysiological rationale, as well as on a previous study[5] and safety concerns, but the present data do not allow the conclusion of which parameters would produce better results. Additionally, the differences in SARA points between groups was small although it was larger than those reported in previous trials, and the mean difference between active and sham stimulations was significant. Larger and longer trials with different frequencies are necessary to confirm whether cerebellar d-rTMS is in fact a therapeutic alternative for ataxic patients and more importantly, which patients should benefit the most in addition to the optimal stimulation parameters.

6.7 Future perspectives

Although the present study was able show improvement in ataxic symptoms after cerebellar modulation, since scientific knowledge requires constant advancement, better and larger studies should tag along and explore different facets regarding this matter.

The heterogeneity of population is an issue that should be addressed. Studies with homogeneous populations are usually preferred. However, most of the diseases causing cerebellar ataxia are rare, and therefore gathering a significant number of patients with the exact same diagnosis is challenging. A possible way around this problem would be to perform a multicenter study, in which many centers around the globe could contribute with cases. In this situation, the challenges lie in standardize recruitment, modulation protocol, and assessment protocol. Well defined inclusion criteria, TMS training, and video assessment rated by a single trained neurologist should help in solving this issue.

The lack of maintenance sessions did not allow us to draw any conclusions about long term effects of this technique. Performing TMS in the long term can be very challenging in terms of costs and logistics, especially considering a large number of patients have mobility issues. A possible way of studying cerebellar modulation in the long term could be the use of invasive stimulation with a DBS electrode. However, since this invasive procedure carries more possible side effects compared to TMS, a screening tool should be used. Perhaps, good responders could be tracked down using TMS, and then evaluated regarding the possibility of DBS. In this line, the response to TMS and DBS should be compared to see if the former could predict de latter.

In order to move towards invasive modulation, a profile of good and bad responders should be drawn. In this study, we failed to find correlation between cerebellar volume and clinical response, but other variables should be tested. Is it a matter of cerebellar anatomy, or functional networks? Ideally, good and bad responders should be evaluated with functional MRI, and several areas of interest should be studied.

There are many unsolved questions about the modulation paradigms – what frequency is the best, what coil, and what location. In this study, for practical reasons, we could not solve these problems. Studies with noninvasive modulation techniques would take a very long time to assess what paradigms work best, not to mention the intrinsic limitation of these technics regarding the exact structure being modulated. While using DBS, one could more easily access patients' tendencies regarding parameters such as frequency, current, pulse width, and precise modulation spot – or hot spot. Using reconstruction software such as Lead DBS,[147] it is possible to estimate with a certain precision the volume of tissue activated, or the range of the electric modulation, and the structures being affected by it.[148] Going further, it would be even possible to use directional electrodes that allow current steering once a structure – or tract - is identified as being the most important for clinical benefit.[149,150]

Perhaps it is not just a question about a modulation hot spot. In Parkinson's disease, it is now known that the excess of beta oscillation is correlated with rigidity and bradykinesia.[151] Therefore, it is considered an oscillopathy. Both dopaminergic medications and DBS therapy can overwrite this pathological activity and improve symptoms. In ataxia there could be a similar diseased dominant frequency correlated with the symptoms, and this could potentially be overwritten by neuromodulation. Neurophysiological studies, and, in the future, studies using closed-loop DBS could aid in this matter.[152]

7 CONCLUSIONS

7 CONCLUSIONS

a) Low frequency cerebellar stimulation using d-rTMS aimed unilaterally at the dentate nucleus improves ataxic symptoms in ataxic patients.

b) Cerebellar d-rTMS, in the settings used in the present trial, is not able to improve tremor, dystonia, gait, quality of life, anxiety, depression, and cognition in ataxic patients.

c) There is no correlation between ataxia improvement and baseline cerebellar volume.

d) There is no change in cortical excitability categorical parameters after active d-rTMS.

e) Cerebellar d-rTMS is safe, with no severe side effects or cognition deterioration observed in the present study.

8 SUPPLEMENTARY MATERIALS

8 SUPPLEMENTARY MATERIALS

8.1 Supplementary material A – Demography

I.DADOS SÓCIODEMOGRAFICOS		
SEXO	IDADE	DATA DE NASCIMENTO
1.masculino ( ) 2.feminino ( )	_____ anos	/ /
Etnia:		
1. branco ( ) 2. Negro ( ) 3. Pardo ( ) 4. Amarelo ( )		
NÍVEL EDUCACIONAL:		
1.Analfabeto( ) 2. Ensino médio ( ) 3. Ensino fundamental ( ) 4.Superior ( ) 5.pós-graduação ( )		
ESTADO CIVIL:		
1.solteiro( ) 2.casado( ) 3.união consensual( ) 4.separado( ) 5.divorciado( ) 6.viúvo( )		
SITUAÇÃO CONJUGAL: 1.Com companheiro( ) 2.sem companheiro( )		
RELIGIÃO:		
1.ateu( ) 2.evangélico( ) 3.católico( ) 4.espírito( ) 5.Outro_____		
PRATICANTE:	SITUAÇÃO DE TRABALHO:	
0. não( ) 1. sim ( )	1.empregado( ) 2.desempregado( ) 3.aposentado( ) 4.dona de casa( ) 5.autônomo( ) 6.estudante( ) 7.Licença saúde( ) 8.informal( )	
Você está trabalhando atualmente? 0.não ( ) 1.sim ( )		
RENDA:		
I.individual(mensal):R$		
II.Suficiente para suprir necessidades? 0.não ( ) 1.sim ( )		
III.familiar (mensal): R$	IV.Nº de pessoas que vivem com esta renda:	
VI.Você é o principal responsável pelo sustento de sua família? 0.não ( ) 1.sim ( )		
CASO VOCÊ NÃO TENHA RENDA PRÓPRIA		
I. Como você se mantém?		
1. ajuda da família ( ) 2. ajuda de instituição ( ) qual?_____ 3. ajuda de vizinhos ou amigos ( ) 4. ajuda de pessoas estranhas ( )		
2.Você tem alguma das seguintes doenças:		

	Não 0	Sim1
1. Diabetes Mellitus		
2. Cerebrovascular		
3. Hipertensão arterial		
4. Doenças vascular periférica		
5. Doença renal crônica		
6. Neoplasia maligna		
7. Doença cardiocirculatória		
8. Doença hepática		
9.Depressão		
10. Doença do trato gastrointestinal		
11. Doença autoimune		
12.Outras:_____		

(Não)

Bebe?
Qto?_____

Fumante: (sim)

(sim) (Não)

8.2 Supplementary material B – Cortical excitability and neuronavigation

CORTICAL EXCITABILITY

RESTING MOTOR TRESHOLD: RIGHT_____ LEFT_____

80% RMT RIGHT_____LEFT_____
120% RMT RIGHT _____LEFT_____
140% RMT RIGHT_____LEFT_____

SINGLE PULSE

RMT_120%	1st		2nd		3rd		4th		Mean	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
RMT_140%	1st		2nd		3rd		4th		Mean	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left

PAIRED PULSES: CONDITIONING RMT80% / TEST RMT 120%

02mseg	1st		2nd		3rd		4th		Mean	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
15mseg	1st		2nd		3rd		4th		Mean	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
10mseg	1st		2nd		3rd		4th		Mean	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
04mseg	1st		2nd		3rd		4th		Mean	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left

8.3 Supplementary material C – Scale for the assessment and rating of ataxia (SARA)

1) Gait
Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.
0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
1 Slight difficulties, only visible when walking 10 consecutive steps in tandem
2 Clearly abnormal, tandem walking >10 steps not possible
3 Considerable staggering, difficulties in half-turn, but without support
4 Marked staggering, intermittent support of the wall required
5 Severe staggering, permanent support of one stick or light support by one arm required
6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
8 Unable to walk, even supported

2) Stance
Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.
0 Normal, able to stand in tandem for > 10 s
1 Able to stand with feet together without sway, but not in tandem for > 10s
2 Able to stand with feet together for > 10 s, but only with sway
3 Able to stand for > 10 s without support in natural position, but not with feet together
4 Able to stand for >10 s in natural position only with intermittent support
5 Able to stand >10 s in natural position only with constant support of one arm
6 Unable to stand for >10 s even with constant support of one arm

3) Sitting
Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.
0 Normal, no difficulties sitting >10 sec
1 Slight difficulties, intermittent sway
2 Constant sway, but able to sit > 10 s without support
3 Able to sit for > 10 s only with intermittent support
4 Unable to sit for >10 s without continuous support

4) Speech disturbance
Speech is assessed during normal conversation.
0 Normal

1 Suggestion of speech disturbance
2 Impaired speech, but easy to understand
3 Occasional words difficult to understand
4 Many words difficult to understand
5 Only single words understandable
6 Speech unintelligible / anarthria

5) Finger chase
Rated separately for each side (total result = mean).
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.
0 No dysmetria
1 Dysmetria, under/ overshooting target <5 cm
2 Dysmetria, under/ overshooting target < 15 cm
3 Dysmetria, under/ overshooting target > 15 cm
4 Unable to perform 5 pointing movements

6) Nose-finger test
Rated separately for each side (total result = mean).
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.
0 No tremor
1 Tremor with an amplitude < 2 cm
2 Tremor with an amplitude < 5 cm
3 Tremor with an amplitude > 5 cm
4 Unable to perform 5 pointing movements

7) Fast alternating hand movements
Rated separately for each side (total result = mean).
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.
0 Normal, no irregularities (performs <10s)
1 Slightly irregular (performs <10s)
2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s

3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
4 Unable to complete 10 cycles

7) Heel-shin slide
Rated separately for each side (total result = mean).
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.
0 Normal
1 Slightly abnormal, contact to shin maintained
2 Clearly abnormal, goes off shin up to 3 times during 3 cycles
3 Severely abnormal, goes off shin 4 or more times during 3 cycles
4 Unable to perform the task

8.4 Supplementary material D – International cooperative ataxia rating scale (ICARS)

I: POSTURE AND GAIT DISTURBANCE

1. WALKING CAPACITIES (observed during a 10 meter test including a half-turn, near a wall, at about 1,5meter.)
0: normal
1: almost normal naturally, but unable to walk with feet in tandem position
2: Walking without support, but clearly abnormal and irregular
3: Walking without support but with considerable staggering, difficulties in half turn
4: Walking with autonomous support no longer possible, the patient uses episodic support of the wall for a 10 meter test
5: Walking only possible with one stick
6: Walking only possible with two special sticks or with a stroller
7: Walking only with accompanying person
8: walking impossible even with accompanying person (wheelchair)

Score:_____

2: GAIT SPEED (observed in patients with preceeding scores 1-3, preceeding score 4 and up gives automatically score 4 in this test)
0: normal
1: slightly reduced
2: markedly reduced
3: extremely slow
4: walking with autonomous support no longer possible

Score:_____

3: STANDING CAPACITIES, *EYES OPEN* (the patient is asked first to stand on one foot
if impossible , to stand with feet in tandem position
if impossible to stand with feet together
for the natural position the patient is asked to find a comfortable standing position)
0: normal, able to stand on one foot more than 10 sec
1: able to stand with feet together, but no longer able to stand on one foot more than 10 sec.
2: able to stand with feet together, but no longer able to stand in tandem position
3: no longer able to stand with feet together, but able to stand in natural position without support, with no or moderate sway
4: standing in natural position without support, with considerable sway and considerable corrections
5: unable to stand in natural position without strong support of the arms
6: unable to stand at all, even with string support of the arms

Score:_____

4: SPREAD OF FEET IN NATURAL POSITION WITHOUT SUPPORT *EYES OPEN* (the patient is asked to find a comfortable position, then the distance between medial malleoli is measured)
0: normal <10cm
1: slightly enlarged >10cm
2: clearly enlarged 25cm < spread <35cm
3: severely enlarged >35cm
4: standing in natural position impossible

Score:_____

5: BODY SWAY WITH FEET TOGETHER *EYES OPEN*
0: normal
1: slightly oscillations
2: moderate oscillations (<10cm at the level of head)
3: severe oscillations (>10cm at the level of head), threatening the upright position
4: immediate falling

Score:_____

6: BODY SWAY WITH FEET TOGETHER *EYES CLOSED*
0: normal
1: slight oscillations
2: moderate oscillations (<10cm at the level of head)
3: severe oscillations (>10cm at the level of head), threatening the upright position
4: immediate falling

Score:_____

7: QUALITY OF SITTING POSITION (thighs together, on a hard surface, arms folded)
0: normal
1: with slight oscillations of the trunk
2: with moderate oscillations of the trunk and legs
3: with severe dysequilibrium
4: impossible

Score:_____

POSTURE AND GAIT SCORE (STATIC SCORE):	**/34**

II: KINETIC FUNCTIONS

8: KNEE-TIBIA TEST decomposition of movement and intention tremor.
(The test is performed in the supine position, but the head is tilted, so that visual control is possible. The patient is requested to raise one leg and place the heel on the knee, and then slide the heel down the anterior tibial surface of the resting leg towards the ankle. On reaching the ankle joint, the leg is again raised in the air to a height of approximately 40 cms and the action is repeated. At least 3 movements of each limb must be performed for proper assessment.)
0: normal

1: lowering of heel in continuous axis, but the movement is decomposed in several phases, without real jerks, or abnormally slow
2: lowering jerkily in the axis
3: lowering jerkily with lateral movements
4: lowering jerkily with extremely strong lateral movements or test impossible

Score:R_____L_____

9: ACTION TREMOR in the HEEL-TO-KNEE Test (Same test as preceeding one: the action tremor of the heel on the knee is specifically observed when the patient holds the heel on the knee for a few seconds before sliding down the anterior tibial surface; visual control is required)
0: No trouble
1: Tremor stopping immediately when the heel reaches the knee
2: Tremor stopping in less than 10 seconds after reaching the knee
3: Tremor continuing for more than 10 seconds after reaching the knee
4: uninterrupted tremor or test impossible

Score:R_____L_____

10: FINGER-TO-NOSE TEST - <u>decomposition and dysmetria</u> (the subject sits on a chair, the hand is resting on the knee before the beginning of the movement, visual control is required. Three movements of each limb must be performed for proper assessment.)
0: no trouble
1: Oscillating movement without decomposition of
the movement
2:Segmented movement in more than 2 phases and/or moderate dysmetria in reaching nose
3: segmented movement in more than 2 phases and /or considerable dysmetria in reaching nose
4: Dysmetria preventing the patient from reaching the nose

Score:R_____L_____

11: FINGER-TO-NOSE TEST - <u>intention tremor of the finger</u> (the studied tremor is that appeared during the ballistic phase of the movement; the patient is sitting comfortably, with his hands resting on his/her thigh; visual control is requires; three movements of each limb must be performed as proper assessment)
0: No trouble
1: simple swerve of the movement
2: moderate tremor with estimated amplitude <10cm
3: Tremor with estimated amplitude between 10cm und 40cm
4: severe tremor with estimated amplitude >40cm

Score:R_____L_____

12: FINGER-FINGER- TEST - <u>action tremor and/or instability</u> (the sitting patient is asked to maintain medially his/her index fingers pointing at each other for about 10 sec, at a distance of about 1cm, at the level of the thorax, under visual control.)

0: normal
1: mild instability
2: moderate oscillations of finger with estimated amplitude <10cm
3: considerable oscillations of finger with estimated amplitude between 10 and 40cm
4: Jerky movement >40cm of amplitude

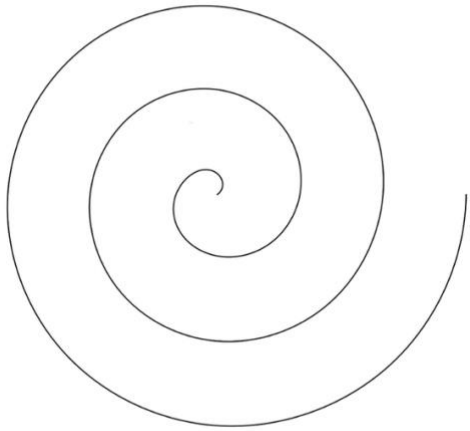
Score:R_____L_____

13: PRONATION- SUPINATION <u>altering movements</u> (the subject, comfortably sitting on a chair, is asked to raise his/her forearm vertically and to make alternative movements of the hand. Each hand is moved and assessed separately.)
0: normal
1: slightly irregular and slowed
2: clearly irregular and slowed, but without sway of the elbow
3: extremely irregular and slowed movement, with sway of the elbow
4: movement completely disorganized or impossible

Score:R_____L_____

14: DRAWING the Archimedes spiral on a predrawn pattern (the subject is comfortly setttled in front of the table, the sheet of paper is being fixed to avoid artefacts. The subject is asked to perform the task without timing requirements. The same condition of examination must be used at each examination.)
0: normal
1: impairment and decomposition, the line quitting the pattern slightly, but without hypermetric swerve
2: line completely out of the pattern without recrossing and/or hypermetric swerves
3: major disturbance due to hypermetria and decomposition
4: drawing completely disorganised or impossible

Score: _____



KINETIC SCORE (limb coordination):	**/52**

III: SPEECH DISORDERS

15: DYSARTHRIA: <u>fluency of speech</u> (The patient is asked to repeat several times a standard sentence, always the same.)
0: normal
1: mild modification of fluency
2: moderate modification of fluency
3: considerably slow and dysarthric speech
4: no speech

Score: _____

16: DYSARTHRIA: <u>clarity of speech</u>
0: normal
1: suggestion of slurring
2: definite slurring, most words understandable
3: severe slurring, speech not understandable
4: no speech

Score: _____	
DYSARTHRIA SCORE:	**/8**

IV: OCULOMOTOR DISORDERS

17: GAZE EVOKED NYSTAGMUS (the subject is asked to look laterally at the finger of the examiner: the movement assessed are mainly horizontal, but they may be oblique, rotatory, or vertical.)
0: normal
1: transient
2: persistent but moderate
3: persistent as severe

Score: _____

18: ABNORMALITIES OF THE OCULAR PURSUIT (the subject is asked to follow the slow lateral movement, performed by the finger of the examiner)
0: normal
1: slightly saccadic
2: clearly saccadic

Score: _____

19: DYSMETRIA OF THE SACCADE
the two index fingers of the examiner in each visual field, average overshoot/undershoot is estimated
0: absent
1: bilateral clear overshoot or undershoot of the saccade

Score: _____	
OCULOMOTOR MOVEMENT SCORE:	**/6**
TOTAL ICARS SCORE	**/100**

8.5 Supplementary material E – Fahn Tolosa Marin tremor rating scale

Fahn, Tolosa, Marin Tremor Rating Scale

1-9 Tremor (rate tremor)
- 1) At rest (in repose). For head and trunk, when lying down
- 2) With posture holding
  - UE: arms outstretched, wrists mildly extended, fingers spread apart
  - LE: legs flexed at hips and knees; foot dorsi-flexed
    - tongue: when protruded
    - head and trunk: when sitting or standing
- 3) with Action(ACT) and Intention(INT):
  - UE: finger to nose and other actions
  - LE: toe to finger in flexed posture

Definitions for 1-9

0 = None
1 = Slight. May be intermittent
2 = Moderate amplitude. May be intermittent
3 = Marked amplitude
4 = Severe amplitude

1. Face tremor	REST _____
2. Tongue tremor	REST _____
	POST _____
3. Voice tremor	ACT/INT _____
4. Head tremor	REST _____
	POST _____
5. Right upper extremity tremor	REST _____
	POST _____
	ACT/INT _____
6. Left upper extremity tremor	REST _____
	POST _____
	ACT/INT _____
7. Trunk tremor	REST _____
	POST _____
8. Right lower extremity tremor	REST _____
	POST _____
	ACT/INT _____

9. Left lower extremity tremor ..... REST ____

POST ____

ACT/INT ____

10. Handwriting ..... ____

Have patient write the standard sentence: "This is a sample of my best handwriting", sign his or her name and write the date.
0 = Normal
1 = Mildly abnormal. Slightly untidy, tremulous
2 = Moderately abnormal. Legible, but with considerable tremor.
3 = Marked abnormal. Illegible
4 = Severely abnormal. Unable to keep pencil or pen on paper without holding hand down with other hand.

11-13. Ask the patient to join both points of the various drawings without crossing the lines. Test each hand, beginning with the lesser, without leaning the hand or the arm on the table.

Definitions for 11-13
0 = Normal
1 = Slightly tremulous. May cross lines occasionally.
2 = Moderately tremulous or crosses lines frequently.
3 = Accomplishes the task with great difficulty. Many errors.
4 = Unable to complete drawing.

11. Drawing A

Right ____

Left ____

12. Drawing B Right ____

Left ____

13. Drawing C Right ____

Left ____

14. Pouring Right ____
Use firm plastic cups, about 8 cm tall, filled with water to 1 cm from top. Ask patient to pour water from one cup to another. Test each hand separately. Left ____
0 = Normal
1 = More careful that a person without tremor, but no water is spilled.
2 = Spills a small amount of water (up to 10% of the total amount).
3 = Spills a considerable amount of water (> 10-50%)
4 = Unable to pour water without spilling most of the water.

15. Speaking ____
This includes spastic dysphonia if present
0 = Normal
1 = Mild voice tremulousness when "nervous" only
2 = Mild voice tremor, constant
3 = Moderate voice tremor
4 = Severe voice tremor. Some words difficult to understand.

16. Feeding other than liquids ____
0 = Normal
1 = Mildly normal. Can bring all solids to mouth, spilling only rarely.
2 = Moderately abnormal. Frequent spills of peas and similar foods.
May bring head at least halfway to meet food.
3 = Markedly abnormal. Unable to cut or uses hands to feed.
4 = Severely abnormal. Needs help to feed.

17. Bringing liquids to mouth ____
0 = Normal
1 = Mildly abnormal. Can still use a spoon, but not if it is completely full
2 = Moderately abnormal. Unable to use spoon; uses cup or glass
3 = Markedly abnormal. Can drink from cup or glass, but needs two hands
4 = Severely abnormal. Must use a straw.

18 Hygiene ____
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person
2 = Moderately abnormal. Able to do everything, but with errors;
uses electric razor because of tremor
3 = Markedly abnormal. Unable to do most fine tasks, such as putting on lipstick or shaving
(even with electric razor), unless using two hands.
4 = Severely abnormal. Unable to do any fine-movement tasks.

19. Dressing ____
0 = Normal
1 = Mildly abnormal. Able to do everything, but is more careful than the average person.
2 = Moderately abnormal. Able to do everything, but with errors.
3 = Markedly abnormal. Needs some help with buttoning or other activities, such as tying shoelaces.
4 = Severely abnormal. Requires assistance even for gross motor activities.

20. Writing ____
0 = Normal
1 = Mildly abnormal. Legible. Continues to write letters
2 = Moderately abnormal. Legible, but no longer writes letters.
3 = Markedly abnormal. Illegible
4 = Severely abnormal. Unable to sign checks or other documents requiring a signature.

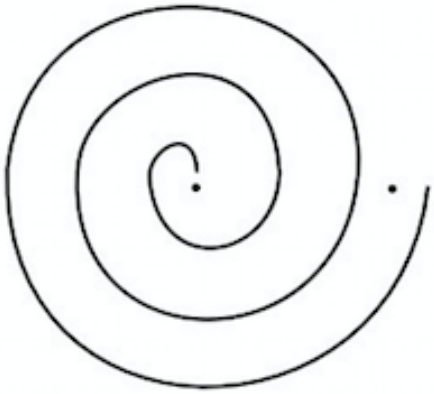
21.Working ____
0 = Tremor does not interfere with job
1 = Able to work, but needs to be more careful than the average person
2 = Able to do everything, but with errors. Poorer than usual performance because of tremor
3 = Unable to do regular job. May have changed to a different job because of tremor.
Tremor limits housework, such as ironing.
4 = Unable to do any outside job; housework is very limited.

Non-Dominant Hand

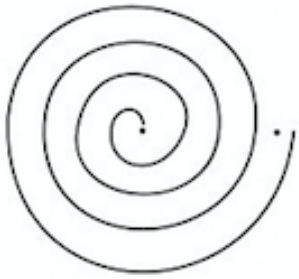
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

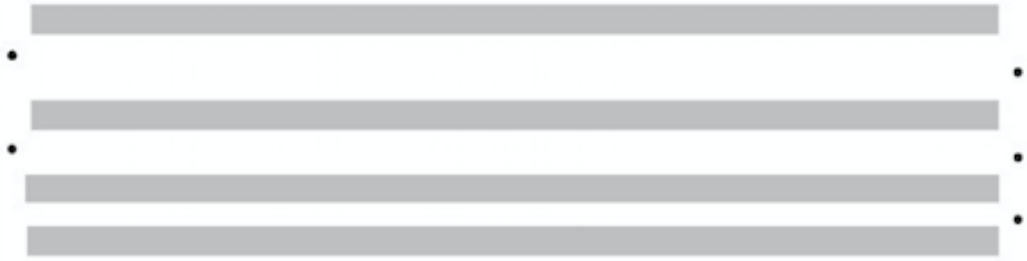
DRAWING A



DRAWING B



DRAWING C



Dominant Hand

Handwriting: This is a sample of my best handwriting

_____

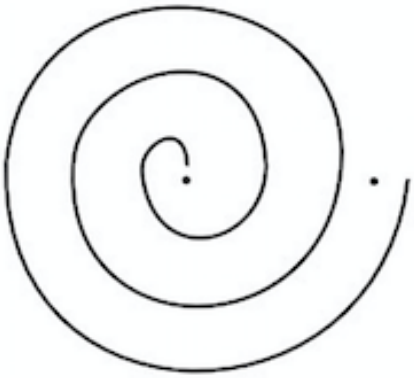
Signature: _____

Date: _____

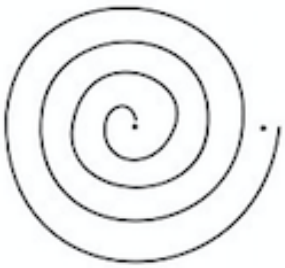
Drawings A, B, and C and make with the _____ Left Hand

_____ Right Hand

DRAWING A



DRAWING B



DRAWING C

8.6 Supplementary material F – Unified dystonia rating scale

1. Duration Factor
0 none
0.5 occasional (< 25% of the time); predominantly submaximal 1.0 occasional (< 25% of the time); predominantly maximal
1.5 Intermittent (25-50% of the time); predominantly submaximal 2.0 Intermittent (25-50% of the time); predominantly maximal 2.5 Frequent (50-75% of the time); predominantly submaximal 3.0 Frequent (50-75% of the time); predominantly maximal
3.5 Constant (> 75% of the time); predominantly submaximal
4.0 Constant (> 75% of the time); predominantly maximal

2. Motor Severity Factor

EYES AND UPPER FACE

0. none
1. mild: increased blinking and/or slight forehead wrinkling (< 25% maximal intensity)
2. moderate: eye closure without squeezing and/or pronounced forehead wrinkling (> 25% but < 50% maximal intensity)
3. severe: eye closure with squeezing, able to open eyes within 10 seconds and/or marked forehead wrinkling (>50% but < 75% maximal intensity)
4. eye closure with squeezing, unable to open eyes within 10 seconds and/or intense forehead wrinkling (> 75% maximal intensity)

LOWER FACE

0 none
1 mild: grimacing of lower face with minimal distortion of mouth (< 25% maximal)
2 moderate: grimacing of lower face with moderate distortion of mouth (> 25% but < 50% maximal)
3 severe: marked grimacing with severe distortion of mouth (> 50% but < 75% maximal)
4 extreme: intense grimacing with extreme distortion of mouth (> 75% maximal)

JAW AND TONGUE

0 none
1 mild: jaw opening and/or tongue protrusion < 25% of possible range or forced jaw clenching without bruxism
2 moderate: jaw opening and/or tongue protrusion > 25% but < 50%of possible range
or forced jaw clenching with mild bruxism secondary to dystonia
3 severe: jaw opening and /or tongue protrusion > 50% but < 75%of possible range or forced jaw clenching with pronounced bruxism secondary to dystonia
4 extreme: jaw opening and/or tongue protrusion > 75% of possible range or forced jaw clenching with inability to open mouth

LARYNX

0 none

1 mild: barely detectable hoarseness and/or choked voice and/or occasional voice breaks
2 moderate: obvious hoarseness and/or choked voice and/ or frequent voice breaks
3 severe: marked hoarseness and/or choked voice and/or continuous voice breaks
4 extreme: unable to vocalize

NECK
0 none
1 mild: movement of head from neutral position < 25% of possible normal range
2 moderate: movement of head from neutral position > 25% but < 50% of possible normal range
3 severe: movement of head from neutral position > 50% but < 75% of possible normal range
4 extreme: movement of head from neutral position > 75% of possible normal range

SHOULDER AND PROXIMAL ARM (Right and Left)
0 none
1 mild: movement of shoulder or upper arm < 25% of possible normal range
2 moderate: movement of shoulder or upper arm 25% but < 50% of possible normal range
3 severe: movement of shoulder or upper arm 50% but < 75% of possible normal range
4 extreme: movement of shoulder or upper arm 75% of possible normal range

DISTAL ARM AND HAND INCLUDING ELBOW (Right and Left)
0 none
1 mild: movement of distal arm or hand < 25% of possible normal range 2 moderate: movement of distal arm or hand 25% but < 50% of possible normal range
3 severe: movement of distal arm or hand 50% but < 75% of possible normal range
4 extreme: movement of distal arm or hand 75% of possible normal range

PELVIS AND PROXIMAL LEG (Right and Left)
0 none
1 mild: tilting of pelvis or movement of proximal leg or hip < 25% of possible normal range
2 moderate: tilting of pelvis or movement of proximal leg or hip 25% but < 50% of possible normal range
3 severe: tilting of pelvis or movement of proximal leg or hip 50% but < 75% of possible normal range
4. extreme: tilting of pelvis or movement of proximal leg or hip 75% of possible normal range

DISTAL LEG AND FOOT INCLUDING KNEE (Right and Left)

0 none
1 mild: movements of distal leg or foot < 25% of possible normal range 2 moderate: movements of distal leg or foot 25% but < 50% of possible normal range
3 severe: movements of distal leg or foot 50% but < 75% of possible normal range
4 extreme: movements of distal leg or foot 75% of possible normal range

TRUNK

0 none
1 mild: bending of trunk < 25% of possible normal range
2 moderate: bending of trunk 25% but < 50% of possible normal range
3 severe: bending of trunk > 50% but < 75% of possible normal range
4 extreme: bending of trunk > 75% of possible normal range

8.7 Supplementary material G – The short version of the World Health Organization quality of life scale

Por favor, leia cada questão, veja o que você acha e circule o número que lhe parece a melhor resposta.

	Muito ruim	Ruim	Nem ruim nem boa	Boa	Muito boa
1. Como você avaliaria sua qualidade de vida?	1	2	3	4	5

	Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito Satisfeito
2. Quão satisfeito(a) você está com a sua saúde?	1	2	3	4	5

As questões seguintes são sobre **o quanto** você tem sentido algumas coisas nas últimas duas semanas.

	Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
3. Em que medida você acha que sua dor (física) impede você de fazer o que você precisa?	1	2	3	4	5
4. O quanto você precisa de algum tratamento médico para levar sua vida diária?	1	2	3	4	5
5. O quanto você aproveita a vida?	1	2	3	4	5
6. Em que medida você acha que a sua vida tem sentido?	1	2	3	4	5
7. O quanto você consegue se concentrar?	1	2	3	4	5
8. Quão seguro(a) você se sente em sua vida diária?	1	2	3	4	5
9. Quão saudável é o seu ambiente físico (clima, barulho, poluição, atrativos)?	1	2	3	4	5

As questões seguintes perguntam sobre **quão completamente** você tem sentido ou é capaz de fazer certas coisas nestas últimas duas semanas.

	Nada	Muito pouco	Medio	Muito	Completamente
10. Você tem energia suficiente para seu dia-a- dia?	1	2	3	4	5
11. Você é capaz de aceitar sua aparência física?	1	2	3	4	5
12. Você tem dinheiro suficiente para satisfazer suas necessidades?	1	2	3	4	5

13. Quão disponíveis para você estão as informações que precisa no seu dia-a-dia?	1	2	3	4	5
14. Em que medida você tem oportunidades de atividade de lazer?	1	2	3	4	5

As questões seguintes perguntam sobre **quão bem ou satisfeito** você se sentiu a respeito de vários aspectos de sua vida nas últimas duas semanas.

	Muito ruim	Ruim	Nem ruim nem bom	Bom	Muito Bom
15. Quão bem você é capaz de se locomover?	1	2	3	4	5

	Muito insatisfeito	Insatifeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito Satisfeito
16. Quão satisfeito(a) você está com o seu sono?	1	2	3	4	5
17. Quão satisfeito(a) você está com sua capacidade de desempenhar as atividades do seu dia-a-dia?	1	2	3	4	5
18. Quão satisfeito(a) você está com sua capacidade para o trabalho?	1	2	3	4	5
19. Quão satisfeito(a) você está consigo mesmo?	1	2	3	4	5
20. Quão satisfeito(a) você está com suas relações pessoais (amigos, parentes, conhecidos, colegas)?	1	2	3	4	5
21. Quão satisfeito(a) você está com sua vida sexual?	1	2	3	4	5
22. Quão satisfeito(a) você está com o apoio que você recebe de seus amigos?	1	2	3	4	5
23. Quão satisfeito(a) você está com as condições do local onde mora?	1	2	3	4	5
24. Quão satisfeito(a) você está com o seu acesso aos serviços de saúde?	1	2	3	4	5
25. Quão satisfeito(a) você está com o seu meio de transporte?	1	2	3	4	5

As questões seguintes referem-se a **com que freqüência** você sentiu ou experimentou certas coisas nas últimas duas semanas.

	Nunca	Algumas vezes	Frequentemente	Muito frequentemente	Sempre
26. Com que freqüência você tem sentimentos negativos tais como mau humor, desespero, ansiedade, depressão?	1	2	3	4	5

8.8. Supplementary material H – Escala Hospitalar de Ansiedade e Depressão

Este questionário ajudará o seu médico a saber como você está se sentindo. Leia todas as frases. Marque com um “X” a resposta que melhor corresponder a como você tem se sentido na ÚLTIMA SEMANA. Não é preciso ficar pensando muito em cada questão. Neste questionário, as respostas espontâneas têm mais valor do que aquelas em que se pensa muito. Marque apenas uma resposta para cada pergunta.

A 1) Eu me sinto tenso ou contraído:
3 ( ) A maior parte do tempo
2 ( ) Boa parte do tempo
1 ( ) De vez em quando
0 ( ) Nunca

D 2) Eu ainda sinto gosto pelas mesmas coisas de antes:
3 ( ) Já não sinto mais prazer em nada
2 ( ) Só um pouco
1 ( ) Não tanto quanto antes
0 ( ) Sim, do mesmo jeito que antes

A 3) Eu sinto uma espécie de medo, como se alguma coisa ruim fosse acontecer:
3 ( ) Sim, e de um jeito muito forte
2 ( ) Sim, mas não tão forte
1 ( ) Um pouco, mas isso não me preocupa
0 ( ) Não sinto nada disso

D 4) Dou risada e me divirto quando vejo coisas engraçadas:
3 ( ) Não consigo mais
2 ( ) Atualmente bem menos
1 ( ) Atualmente um pouco menos
0 ( ) Do mesmo jeito que antes

A 5) Estou com a cabeça cheia de preocupações:
3 ( ) A maior parte do tempo
2 ( ) Boa parte do tempo
1 ( ) De vez em quando
0 ( ) Raramente

D 6) Eu me sinto alegre:
3 ( ) Nunca
2 ( ) Poucas vezes
1 ( ) Muitas vezes
0 ( ) A maior parte do tempo

A 7) Consigo ficar sentado à vontade e me sentir relaxado:
3 ( ) Nunca
2 ( ) Poucas vezes
1 ( ) Muitas vezes
0 ( ) Sim, quase sempre

D 8) Eu estou lento para pensar e fazer as coisas:
3 ( ) Quase sempre
2 ( ) Muitas vezes
1 ( ) De vez em quando
0 ( ) Nunca

A 9) Eu tenho uma sensação ruim de medo, como um frio na barriga ou um aperto no estômago:
3 ( ) Quase sempre
2 ( ) Muitas vezes
1 ( ) De vez em quando
0 ( ) Nunca

D 10) Eu perdi o interesse em cuidar da minha aparência:
3 ( ) Completamente
2 ( ) Não estou mais me cuidando como deveria
1 ( ) Talvez não tanto quanto antes
0 ( ) Me cuido do mesmo jeito que antes

A 11) Eu me sinto inquieto, como se eu não pudesse ficar parado em lugar nenhum:
3 ( ) Sim, demais
2 ( ) Bastante
1 ( ) Um pouco
0 ( ) Não me sinto assim

D 12) Fico esperando animado as coisas boas que estão por vir:
3 ( ) Quase nunca
2 ( ) Bem menos do que antes
1 ( ) Um pouco menos do que antes
0 ( ) Do mesmo jeito que antes

A 13) De repente, tenho a sensação de entrar em pânico:
3 ( ) A quase todo momento
2 ( ) Várias vezes
1 ( ) De vez em quando
0 ( ) Não sinto isso

D 14) Consigo sentir prazer quando assisto a um bom programa de televisão, de rádio ou quando leio alguma coisa:
3 ( ) Quase nunca
2 ( ) Poucas vezes
1 ( ) Várias vezes
0 ( ) Quase sempre

8.9 Supplementary material I – Frontal Assessment Battery

1. Similaridades (conceituação)
"De que maneira eles são parecidos?" "Uma banana e uma laranja".
(Caso ocorra falha total: "eles não são parecidos" ou falha parcial: "ambas têm casca", ajude o paciente dizendo: "tanto a banana quanto a laranja são..."; mas credite 0 para o item; não ajude o paciente nos dois itens seguintes).
"Uma mesa e uma cadeira". "Uma tulipa, uma rosa e uma margarida".
Escore (apenas respostas de categorias [frutas, móveis, flores] são consideradas corretas).

Três corretas: 3 ☐
Duas corretas: 2 ☐
Uma correta: 1 ☐
Nenhuma correta: 0 ☐

2. Fluência lexical (flexibilidade mental)
"Diga quantas palavras você puder começando com a letra 'S', qualquer palavra exceto sobrenomes ou nomes próprios".
Se o paciente não responder durante os primeiros 5 segundos, diga: "por exemplo, sapo".
Se o paciente fizer uma pausa de 10 segundos, estimule-o dizendo: "qualquer palavra começando com a letra 'S'". O tempo permitido é de 60 segundos.
Escore (repetições ou variações de palavras [sapato, sapateiro], sobrenomes ou nomes próprios não são contados como respostas corretas).

Mais do que nove palavras: 3 ☐
Seis a nove palavras: 2 ☐
Três a cinco palavras: 1 ☐
Menos de três palavras: 0 ☐

3. Série motora (programação)
"Olhe cuidadosamente para o que eu estou fazendo".
O examinador, sentado em frente ao paciente, realiza sozinho, três vezes, com sua mão esquerda a série de Luria "punho-borda- palma".
"Agora, com sua mão direita faça a mesma série, primeiro comigo, depois sozinho".
O examinador realiza a série três vezes com o paciente, então diz a ele/ela: "Agora, faça sozinho".

Paciente realiza seis séries consecutivas corretas sozinho: 3 ☐
Paciente realiza pelo menos três séries consecutivas corretas sozinho: 2 ☐
Paciente fracassa sozinho, mas realiza três séries consecutivas corretas com o examinador: 1 ☐
Paciente não consegue realizar três séries consecutivas corre- tas mesmo com o examinador: 0 ☐

4. Instruções conflitantes (sensibilidade a interferência)
"Bata duas vezes quando eu bater uma vez".
Para ter certeza de que o paciente entendeu a instrução, uma série de três tentativas é executada: 1-1-1.
"Bata uma vez quando eu bater duas vezes".
Para ter certeza de que o paciente entendeu a instrução, uma série de três tentativas é executada: 2-2-2.
O examinador executa a seguinte série: 1-1-2-1-2-2-2-1-1-2.

Nenhum erro: 3 ☐
Um ou dois erros: 2 ☐
Mais de dois erros: 1 ☐
Paciente bate como o examinador pelo menos quatro vezes consecutivas: 0 ☐

5. Vai-não vai (controle inibitório)
"Bata uma vez quando eu bater uma vez"
Para ter certeza de que o paciente entendeu a instrução, uma série de três tentativas é executada: 1-1-1.
"Não bata quando eu bater duas vezes". Para ter certeza de que o paciente entendeu a instrução, uma série de três tentativas é executada: 2-2-2.
O examinador executa a seguinte série: 1-1-2-1-2-2-2-1-1-2.

Nenhum erro: 3 ☐
Um ou dois erros: 2 ☐
Mais de dois erros: 1 ☐
Paciente bate como o examinador pelo menos quatro vezes consecutivas: 0 ☐

6. Comportamento de preensão (autonomia ambiental)
"Não pegue minhas mãos"
O examinador está sentado em frente ao paciente. Coloca as mãos do paciente, com as palmas para cima, sobre os joelhos dele/dela. Sem dizer nada ou olhar para o paciente, o examinador coloca suas mãos perto das mãos do paciente e toca as palmas de ambas as mãos do paciente, para ver se ele/ela pega-as espontaneamente. Se o paciente pegar as mãos, o examinador tentará novamente após pedir a ele/ela: "Agora, não pegue minhas mãos".

Paciente não pega as mãos do examinador: 3 ☐
Paciente hesita e pergunta o que ele/ela deve fazer: 2 ☐
Paciente pega as mãos sem hesitação: 1 ☐
Paciente pega as mãos do examinador mesmo depois de ter sido avisado para não fazer isso: 0 ☐

9 BIBLIOGRAPHY

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APPENDICES

Appendix 1 – Informed consent

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO AO PACIENTE

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA (PACIENTE) OU RESPONSÁVEL LEGAL

1. NOME (paciente): .:..... .....

DOCUMENTO DE IDENTIDADE Nº : ..... SEXO : .M ☐ F ☐
DATA NASCIMENTO: ...../...../.....
ENDEREÇO ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE .....
CEP:..... TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL .....
NATUREZA (grau de parentesco, tutor, curador etc.) .....

DOCUMENTO DE IDENTIDADE :.....SEXO: M ☐ F ☐
DATA NASCIMENTO.: ...../...../.....
ENDEREÇO: ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE: .....
CEP: ..... TELEFONE: DDD (.....).....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA: "Estimulação do Núcleo Denteado do Cerebelo para Tratamento de Ataxia".

PESQUISADOR: Dra Carina C. França

CARGO/FUNÇÃO: Médico INSCRIÇÃO CONSELHO REGIONAL Nº CRM-SP: 153569

UNIDADE DO HCFMUSP: Instituto de Psiquiatria (IPQ HCFMUSP)

3. AVALIAÇÃO DO RISCO DA PESQUISA:

RISCO MÍNIMO ☐ RISCO MÉDIO ☐
RISCO BAIXO X RISCO MAIOR ☐

4.DURAÇÃO DA PESQUISA: 13 meses

Rubrica do sujeito de pesquisa ou responsável_____

Rubrica do pesquisador_____

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

1- Convidamos o Senhor/Senhora a participar de um estudo clínico de pesquisa a ser realizado no Hospital de Clínicas da Universidade de São Paulo, visando à melhora do conhecimento relacionado à modulação do cerebelo no tratamento de ataxias de diversas causas, associadas ou não a quadros distônicos e espásticos. Este estudo pode ser de grande valor para a melhora do entendimento desta doença neurológica, bem como para melhora do seu tratamento, com potencial melhora dos resultados. Este termo será elaborado em duas vias, sendo que uma ficará retida com o pesquisador responsável e outra via será fornecida ao Senhor/Senhora.

2- Essas informações estão sendo fornecidas para sua participação voluntária como paciente neste estudo, que visa melhorar o entendimento sobre a ataxia, uma doença neurológica muitas vezes grave e incapacitante caracterizada por incoordenação dos movimentos, por vezes associada a tremores, tentando melhorar sua forma de tratamento que nos dias atuais é ainda muito insatisfatória. Estas novas informações sobre esta condição e tratamento serão obtidas após realização de consultas ambulatoriais (entrevistas) antes e depois do procedimento, com realização de exame físico e neurológico associado a aplicações de escalas. Após, você será submetido a 10 sessões de Estimulação Magnética Transcraniana (TMS) do núcleo denteado do cerebelo, um método não-invasivo de estimulação de regiões específicas do cérebro, com efeito temporário.

3 – Os procedimentos realizados serão: entrevista com o Senhor/Senhora com uso de diversos questionários (aplicação de escalas). Os questionários avaliam através de perguntas simples e objetivas o grau de ataxia, tremor, distonia, qualidade de vida, cognição, e grau de ansiedade e depressão. O exame complementar a ser realizado é apenas a Ressonância Magnética. A ressonância magnética da cabeça será realizada antes do TMS e mais duas vezes após (total de 3 vezes). Após o TMS, o Senhor/Senhora será reavaliado (a) do ponto de vista clínico, com as mesmas escalas explicadas anteriormente, 1 e 4 semanas após as sessões de TMS. Em qualquer momento, o Senhor/Senhora terá direito de se retirar do estudo.

3 – Questionários (escalas) serão realizados por neurologista ou neurocirurgião habilitados em sala de consulta adequada. O exame físico geral e neurológico será realizado por médico habilitado em sala de exames adequada. As ressonâncias magnéticas serão realizadas em local adequado da Radiologia.

4 – Durante todas as fases da pesquisa pode haver risco de dano ao paciente (danos à dimensão física, psíquica, moral, intelectual, social, cultural ou espiritual). Durante os questionários e avaliações clínicas pode haver risco ou desconforto psíquico, moral, intelectual, social ou cultural para o paciente. O exame de Ressonância Magnética pode causar desconforto para pacientes ansiosos e com dificuldade em

tolerar ambientes fechados e pequenos (claustrofobia). As sessões de TMS podem causar desconforto local e tem risco teórico de indução de crises convulsivas auto-limitadas.

5 – Em caso de dor o senhor/senhora poderá o paciente ter acesso a medicações analgésicas de diversas classes (ex. anti-inflamatórios, opióides e outros) a fim de obter alívio da dor. Os pacientes manterão as técnicas de tratamento atuais que incluem o tratamento médico convencional.

6 – Garantia de acesso: em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é a Dra. Carina C França que pode ser encontrada no endereço Av. Dr. Enéas de Carvalho Aguiar, 155 Telefone (11) 2661 6188 . Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5º andar – tel.: (11)2661-6442 ramais 16, 17, 18 ou 20 – e-mail: cappesq@hcnet.usp.br, horário de funcionamento das 8:00 as 17:00h de segunda a sexta-feira;

7 – É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição;

8 – Direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgado a identificação de nenhum paciente;

9 –Todos os sujeitos da pesquisa terão acesso a qualquer momento aos resultados do estudo;

10 – Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação.

11 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo "Estimulação do Núcleo Denteado do Cerebelo para Tratamento de Ataxia".

Eu discuti com o Dra. Carina C. França e/ou com Dr. Rubens Cury sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem

realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste serviço.

Assinatura do paciente/representante legal Data ___/___/___

Assinatura da testemunha Data ___/___/___

para casos de pacientes menores de 18 anos, analfabetos, semianalfabetos ou portadores de deficiência auditiva ou visual.

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo Data ___/___/___

Appendix 2 – Ethics committee approval

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA USP - HCFMUSP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Estimulação do Núcleo Denteado do Cerebelo para Tratamento da Espasticidade Refratária com ou sem e Distonia

Pesquisador: Guilherme Alves Lepski

Área Temática:

Versão: 2

CAAE: 32779514.5.0000.0068

Instituição Proponente: HOSPITAL DAS CLINICAS DA FACULDADE DE MEDICINA DA U S P

Patrocinador Principal: Secretaria de Estado da Saúde de São Paulo

DADOS DO PARECER

Número do Parecer: 1.310.275

Apresentação do Projeto:

O projeto número 719.854 intitulado Estimulação do Nucleo Denteado do Cerebelo para Tratamento da Espasticidade Refratária com ou sem Distonia, já aprovado pela comissão de ética, está em andamento, e consiste na realização de estimulação magnética transcraniana (TMS) do nucleo denteado de pacientes com quadros espásticos, com ou sem distonia

Objetivo da Pesquisa:

já aprovado

Avaliação dos Riscos e Benefícios:

já aprovado

Comentários e Considerações sobre a Pesquisa:

já aprovado

Considerações sobre os Termos de apresentação obrigatória:

já aprovado

Recomendações:

Ciencia do adendo que solicita inclusão de escalas de avaliação de tremor e ataxia no estudo atual (Fahn, Tolosa, Marin Tremor Rating Scale e a scale for the assessment and rating of ataxia [SARA])

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências

Considerações Finais a critério do CEP:

O projeto número 719.854 intitulado Estimulação do Nucleo Denteado do Cerebelo para Tratamento da Espasticidade Refratária com ou sem Distonia, já aprovado pela comissão de ética, está em andamento, e consiste na realização de estimulação magnética transcraniana (TMS) do nucleo denteado de pacientes com quadros espásticos, com ou sem distonia, prevendo a inserção eletródios de estimulação cerebral profunda em caso de melhora sintomática após o TMS. Como encontramos evidências na literatura que sugiram resposta favorável também em quadros atáxicos após a estimulação do núcleo denteado, e observamos uma melhora significativa em um paciente após a estimulação, inclusive com a publicação do caso1, propomos incluir escalas de avaliação de tremor e ataxia no estudo atual (Fahn, Tolosa, Marin Tremor Rating Scale e a scale for the assessment and rating of ataxia [SARA]). Nexte contexto, serão avaliados tanto pacientes com lesões corticais e cerebelares isquêmicas quanto lesões cerebelares degenerativas, sendo que os questionários de tremor e ataxia não trarão qualquer risco aos pacientes. Os questionários serão aplicados com a colaboração dos médicos Rubens Gisbert Cury, doutor em ciências pela FMUSP e Carina França, neurologista e especializanda do ambulatório de Distúrbios do Movimento da FMUSP.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_587113_E1.pdf	07/10/2015 11:41:14		Aceito
Outros	adendopesquisa.pdf	07/10/2015 11:39:10	Guilherme Alves Lepski	Aceito
Recurso Anexado pelo Pesquisador	Adendo0809.docx	08/09/2015 15:16:45	Guilherme Alves Lepski	Aceito
Outros	Lepski.Humberto.cadastro.12242.0001.pdf	25/06/2014 15:31:55		Aceito
Folha de Rosto	Lepski.Humberto.FR.12242.0001.pdf	25/06/2014 15:31:03		Aceito
Outros	Formula¿rio Plano de Trabalho Estimulação Denteado -Termo aditivo 29.05.2014.doc	11/06/2014 22:54:29		Aceito
TCLE / Termos de Assentimento /	Consentimento Livre e Esclarecido TCLE 01.05.2014.doc	05/05/2014 13:18:41		Aceito

Justificativa de Ausência	Consentimento Livre e Esclarecido TCLE 01.05.2014.doc	05/05/2014 13:18:41		Aceito
Projeto Detalhado / Brochura Investigador	Projeto de Pesquisa Estimulacao do Denteado 24.04.2014.doc	24/04/2014 22:34:30		Aceito
Outros	Cotação Pesquisa Denteado.pdf	23/04/2014 17:16:47		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 05 de Novembro de 2015

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador)

Appendix 3 – Effects of cerebellar neuromodulation in movement disorders: A systematic review. Review article on cerebellar neuromodulation published in Brain Stimulation.

Brain Stimulation 11 (2018) 249–260

Contents lists available at ScienceDirect

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journal homepage: http://www.journals.elsevier.com/brain-stimulation

Effects of cerebellar neuromodulation in movement disorders: A systematic review

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Neuromodulation
Transcranial magnetic stimulation

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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1935-861X/

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).

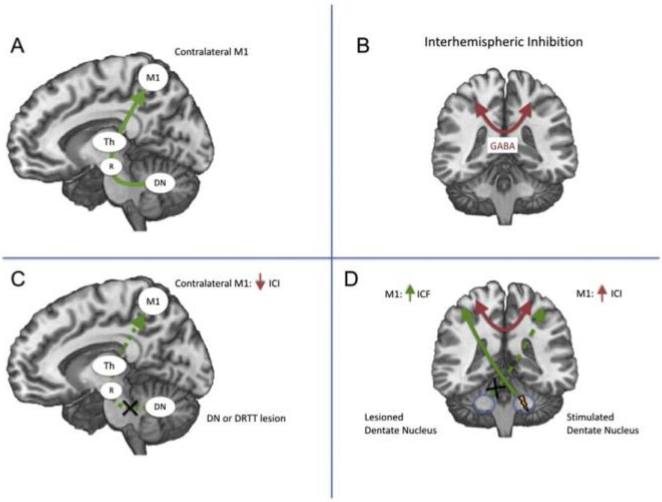

Fig. 1. Schematic representation of the rational of stimulating the Dentate Nucleus and its influence on restoring the primary motor area activity. Panel A shows the excitatory cerebellum-cortico pathway passing through the rubro nucleus and thalamus. There is an ICI between both M1 cortices (panel B) 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].

Study selection: Two reviewers (C.F. and R.G.C.) performed the eligibility assessment independently. Disagreements between reviewers were resolved by consensus.

Data collection process: We developed a data extraction sheet and one author (C.F.) obtained the data from the included studies. A second author (R.G.C.) checked the extraction data.

Data items: Information was extracted from each included trial regarding the: 1) characteristics of the study population (number of subjects and type of movement disorder), 2) intervention targets, 3) type of intervention, 4) assessment time points, 5) side effects, 6) blinding, and 7) outcomes.

Results

Study selection

The database search provided 933 studies; screening of references and citations provided other 8 studies, for a total of 941 studies screened. Based on title and abstract, 897 records were excluded. The full texts of the remaining 44 articles were examined by two authors (C.F. and R.G.C.). Review articles, trials without clinical endpoints, and trials with neuromodulation targets outside the posterior fossa were excluded. A total of 34 studies were included in this review (Fig. 2).

Study characteristics (Table 1 and Table 2)

A total of 533 participants were involved in all 34 studies, including 431 patients and 102 controls. Inclusion criteria varied greatly among the studies, but all the patients had a diagnosis that involved a movement disorder as described. There was great variability regarding the duration of the intervention, from 1 day to 1 year.

All trials used neuromodulation techniques (TMS, tDCS, or DBS) targeting the posterior fossa. Of the 34 studies included, 24 had blinded designs and 10 were open label.

Contemplating the clinical evaluation, the scales varied according to the movement disorder and even between studies with the same population.

We found trials that included patients with cerebellar ataxia, PD, ET, dystonia, and PSP. There were no studies with dyskinesias other than LID.

Cerebellar ataxia

Thirteen trials included patients with cerebellar ataxia due to stroke [9–12], spinocerebellar degeneration [13–20], or cerebral palsy [21], with a total of 171 patients; seven of them were double-blind studies [9,10,12,14,18,20,21]. Six studies used TMS stimulation [9,11–15], 6 used tDCS stimulation [16–21], and 1 implanted a DBS device [10]. The time of evaluation after the intervention ranged from immediately after the stimulation to 1 year after the stimulation. All studies reported favorable clinical outcomes (Supplementary item 1). The largest cohort [14] included 74 patients with spinocerebellar degeneration, which were allocated into two arms: active or sham stimulation. Participants underwent the following cerebellar TMS stimulation protocol for 21 days: 10 pulses with 6-s interpulse intervals first over the inion, 4 cm laterally to the right, and finally 4 cm laterally to the left. In the active group, the authors found significant improvements in the 10-m-walk time, number of tandem steps, and standing capacities. In the most recent study [20], Benussi and colleagues applied 10 sessions of anodal tDCS over the cerebellum of 20 patients with cerebellar ataxia in a double-blind design and reported a marked improvement in ataxic symptoms. No study reported major or minor side effects.

Dystonia

To date, only patients with focal dystonia were included in trials on cerebellar neuromodulation. The nine studies that were assessed included 112 patients with cervical dystonia or focal hand dystonia (FHD) [22–30]. Five trials used TMS stimulation [22,24,28–30], 3 used tDCS [23,25,26], and 1 implanted a DBS device [27]. All four studies with cervical dystonia reported good outcomes, while none of the five trials with FHD observed a significant improvement. Koch et al. conducted a double-blind, placebo-controlled trial with 20 cervical dystonia patients and applied 10 sessions of continuous theta burst stimulation (TBS), a specific TMS protocol, in 10 consecutive weekdays [24]. At the end of the last session, patients had a small (15%) but significant improvement, according to the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), although no difference was found using the Burke-Fahn-Marsden Dystonia Rating Scale. Another open-label study found greater improvement − 39% as measured by the

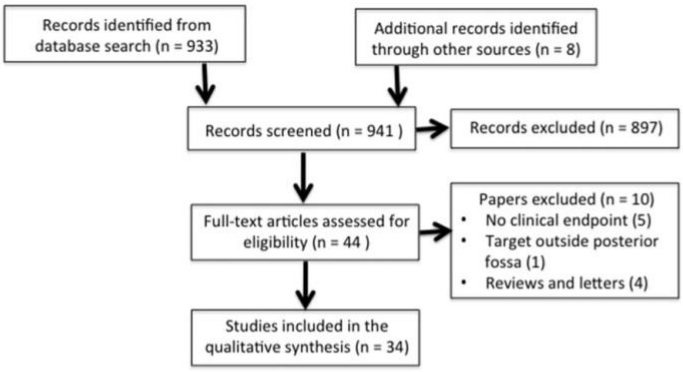

Fig. 2. Flow diagram of study selection.

TWSTRS [23]. Sokal et al. implanted a deep anterior cerebellar lobe DBS in 10 patients with spasticity and dystonia secondary to cerebral palsy and retrospectively observed a 25% dystonia improvement in 5 of them [27]. Only one study reported infectious complications after DBS implantation [27].

Essential tremor (ET)

Six trials studied the effects of cerebellar stimulation in 68 ET patients [31–36], three of which used a double-blind design. Only three studies [32,33,36] found a significant clinical benefit (range: 9%–27%) in tremor scales, two of them using TMS and one using cathodal tDCS. The improvement was larger and lasted longer in patients that underwent more sessions. In the longest trial, improvement (20%) was only significant after 15 cathodal tDCS sessions, but not after 10 [36]. Other studies failed to find any clinical benefit [31,34,35]. One study reported local skin erythema and chemosis as a side effect [34], while another reported mild headache in one patient [32]. There were no other side effects.

Parkinson's disease (PD)

All five trials (n = 70) used double-blind designs [37–41]. There was a great variation in the outcomes and symptom subtypes studied. Two studies [37,39] examined the acute effect of continuous cerebellar TBS in 28 PD patients with LID – both of them reported positive outcomes, with the improvement of dyskinesia after stimulation. Ferrucci et al. compared nine PD patients with LID who underwent five sessions of anodal tDCS over the cerebellum to five daily sessions of M1 stimulation in a double-blind, sham-controlled design and found a significant decrease in the Unified Parkinson's Disease Rating Scale part IV (dyskinesia section) scores after both active stimulations, but not after the sham stimulation. This improvement was observed only immediately after the last session and did not persist after 1 week [41]. Another group [40] assessed the acute effect of cerebellar continuous TBS on resting tremor and found no clinical benefit. Minks et al. evaluated dexterity in 20 PD patients after one session of TMS and reported improvements in gross upper limb movement, but impairment in fine motor finger and hand function [38]. No study reported side effects.

Progressive supranuclear palsy (PSP)

Only one open-label trial included 10 PSP patients and performed 10 sessions of intermittent TBS over the lateral cerebellum [42]. Patients were evaluated using the PSP-Rating Scale, which is comprised of 6 sections: daily activity, behavior, bulbar, oculomotor, limb motor, and gait/midline abnormalities. This study described a significant improvement in all patients only in dysarthria, an item in section III Bulbar. Two out of 10 patients also showed improved gait. No side effects were observed.

Discussion

This systematic review analyzed the clinical effects and the safety of three neuromodulation techniques (TMS, tDCS and DBS) in patients with movement disorders. Our findings suggest that cerebellar neuromodulation could be a promising therapeutic option to relieve some specific symptoms in certain movement disorders. Overall, the studies showed that cerebellar stimulation improved: i) cerebellar ataxia (of vascular and degenerative etiologies); ii) cervical dystonia; iii) tremor in ET; iv) LID in PD patients; v) gross upper limb movement in PD patients; and vi) dysarthria in PSP patients. Overall, all the neuromodulation techniques were safe and well tolerated, with only 3 out of 23 studies reporting side effects (11 of 34 studies did not mention if adverse events were observed) [27,32,34]. Of those adverse events, only one (DBS device infection) was considered potentially dangerous [27].

The most robust motor effect was seen in patients with cerebellar ataxia, which was the most studied movement disorder regarding cerebellar modulation. Out of 13 studies with cerebellar ataxia, only one reported no improvement, although it is important to point out the great variability on clinical improvement (supplementary item 1), probably reflecting the heterogeneity of the studied population, the number of tDCS or TMS sessions, and the type of technique used. In addition, the long-term effects have not been assessed [16]. Concerning dystonia, most studies included patients with cervical or hand dystonia (including writer's cramp). One study reported effects of cerebellar DBS in 10 patients with cerebral palsy presenting focal or segmental dystonia [27]. No trial testing cerebellar modulation for hand dystonia reported clinical improvement [25,26,28,35], though none performed more than 1 neuromodulation session. Therefore, it can't be ruled out a possible good clinical outcome if patients were exposed to more sessions. Cervical dystonia patients were included in 5 studies, and only one failed to show clinical improvement [29]. Though some treatment strategies for cervical dystonia are currently effective (botulin toxin, GPI-DBS) [43], refractory patients could benefit from a different approach. Larger number of patients and longer follow-up, including isolated generalized dystonia, would be of great interest to the neurological community. Essential tremor showed dubious results, since there was clinical improvement in half of the studies [32,33,36]. No technique appeared superior, since 4 studies used TMS (2 negative, 2 positive) and 2 used tDCS (1 negative, 1 positive) (Table 2). Considering the number of sessions, only 1 negative study, but two positive studies performed 5 or more sessions. Furthermore, two positive studies were open label versus one negative. In studies with PD patients, the only clinical improvement reported was regarding LID, since all three trials analyzing LID had positive outcomes [37,39,41].

The foundation behind the hypothesis of cerebellar stimulation in improving movement disorder symptoms is still unclear and theoretical. It lies in the participation of the cerebellum in those disorders' pathophysiological mechanisms and is supported by its motor cortex influence, structural changes in brain blood flow and metabolism, and electrophysiological coupling with several brain areas.

Patients with dystonia present neuroimaging that is suggestive of cerebellar grey matter abnormalities [44], microstructural deficits in cerebellar outflow [45], and augmented cerebellar metabolic activity [2]. Additionally, eye blink classical conditioning, linked to cerebellar function, is abnormal in dystonia [46]. There has also been pathological evidence supporting cerebellar involvement in cervical dystonia, including the loss of Purkinje cells, areas of focal gliosis, and torpedo bodies [47].

Some features of PD have also been linked to cerebellar abnormalities. The dimmer-switch model proposes that resting tremor in PD is a consequence of anomalies in connections between the basal ganglia and the cerebello-thalamo-cortical circuit (CTC), especially regarding tremor amplitude [3]. Another study found a correlation between cerebellar circuits and resting tremor in PD, but not postural tremor [48]. LID are also associated with the cerebellum, since cerebellar sigma-receptors might be involved in its pathogenesis [49]. Patients with PD treated with pallidotomy or pallidus internus (GPi)-DBS, procedures that alleviate LID, also exhibited functional and metabolic changes in the cerebellum after surgery [4].

Evidence from clinical and neuroimaging studies show that the cerebellum is also involved in the pathophysiology of ET [5]. Studies

Table 1
Study characteristics.

Author	Year	N	Movement disorder(s)	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Cerebellar Ataxia									
Shimizu et al. [13]	1999	4	Spinocerebellar degeneration (2 SCA6, 1 SCA1 and 1 SCA7)	Cerebellum (right hemisphere, middle and left hemisphere)	TMS 21 sessions with 14 cm circular coil	Baseline + 21 days	None	Open label	Decrease in time and number of steps required for a 10 m walk examination; increase in number of feasible steps in tandem; decrease in total length of tracing body balance.
Shiga et al. [14]	2002	74 (39 active, 35 placebo)	Spinocerebellar degeneration (cerebellar type x OPCA type)	Cerebellum	TMS 21 sessions with 9 cm circular coil	Baseline + 3 weeks	None	Double-blind sham-controlled	Improvement in 10 m time, 10 m steps, tandem steps and standing capacities, especially in the cerebellar type.
Farzan et al. [15]	2013	1	Idiopathic late-onset cerebellar atrophy	Cerebellum	TMS 21 sessions with 14 cm circular coil; 45 days after, once a week for 6 months	Baseline + 3 weeks + 8 months	Didn't mention	Open label	Improvement of 9% in timed up-and-go test and gait speed. Decrease in stride duration variability and double support time.
Grimaldi et al. [16]	2013	9	Cerebellar ataxias (1 immune ataxia; 1 paraneoplastic ataxia; 3 SAOA; 1 autosomal recessive ataxia; 3 dominant ataxia)	Right cerebellar hemisphere and cerebellar vermis	Anodal tDCS 1 session with 1 mA	Baseline + immediately after	Didn't mention	Single-blind sham-controlled	No change in posturography and upper limb dexterity.
Bonnì et al. [11]	2014	6	Posterior circulation stroke with ataxia	Cerebellar hemisphere (ipsilateral)	rTMS (cTBS) 10 sessions with 70 mm figure-of-eight coil + physical therapy	Baseline + 2 weeks	Didn't mention	Open label	Ataxia improvement (MICARS), especially posture and gait subscales.
Kim et al. [12]	2014	32	Posterior circulation stroke with ataxia	Cerebellar hemisphere (ipsilateral)	rTMS 5 sessions with 75 mm figure-of-eight coil	Baseline + 5 days + 1 month	None	Double-blind sham-controlled	Improvement in the 10 m walk test 1 month after. BBS improved after 5 days and after 1 month
Grimaldi et al. [17]	2014	2	SCA 2	Right cerebellar hemisphere and motor cortex	Anodal tDCS 1 session with 1 mA	Baseline + immediately after	Didn't mention	Single-blind sham-controlled	Improvement in postural and action tremor. Improvement in limb hypermetria.
Grecco et al. [21]	2015	1	Ataxic Cerebral Palsy	Cerebellum	Anodal tDCS 1 session + treadmill training	Baseline + immediately after + 1 month	Didn't mention	Double-blind sham-controlled	Improvement in balance.
Cury et al. [9]	2015	1	Cerebellar ataxia, cerebellar tremor and dystonia (cerebellar stroke)	Dentate nucleus (contralateral) - neuronavegation	TMS, 2 sessions with double-cone coil	Baseline + 1 week	None	Double-blind sham-controlled	Improvement in tremor (FTMTRS) and ataxia (SARA). No improvement in dystonia (UDRS)
Teixeira et al. [10]	2015	1	Cerebellar ataxia, cerebellar tremor and dystonia (cerebellar stroke)	Dentate nucleus (contralateral) - neuronavegation	DBS with bipolar setting (1.4 mA, 2.8 V, 60 ms pulse width at 20 Hz, and 2031 Ω)	Baseline + 1 year	None	Double-blind sham-controlled	Improvement in tremor (FTMTRS) and ataxia (SARA). No improvement in dystonia (UDRS)
Benussi et al. [18]	2015	19	Cerebellar ataxia (5 SCA2; 1 SCA1; 2 SCA 38; 1 Friedreich's ataxia; 1 AOMA2; 6 MSA-C; 1 FXATAS and 2 SAOA)	Cerebellum	Anode tDCS 1 session with 2 mA	Baseline and immediately after	Didn't mention	Double-blind sham-controlled	Improvement in SARA, ICARS, 9HPT and 8 MW
Bodranghien et al. [19]	2017	1	Cerebellar ataxia associated with ANO 10 mutation	Right cerebellar hemisphere (cathode over contralateral M1)	Anodal tDCS 1 session with 1.5 mA	Baseline + 30min	None	Single-blind sham-controlled	Improvement in postural tremor and slight improvement in dysmetria.
Benussi et al. [20]	2017	20 patients + 10 controls	Neurodegenerative ataxias (5 SCA 2; 2 SCA 38; 1 SCA 14; 1 Friedreich's ataxia; 1 AOMA2; 4 MSA-C; 1 FXATAS; 5 SAOA)	Cerebellum	Anodal tDCS 10 sessions with 2 mA	Baseline + immediately after + 1 month + 3 months	None	Double-blind sham-controlled	Improvement lasting at least 3 months in SARA, ICARS, 8 MW and 9HPT (only in the non-dominant hand).

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Table 1 (*continued*)

Author	Year	N	Movement disorder(s)	Target	Intervention	Ass. TP	Side effects	Blinding	Main findings
Dystonia									
Hoffland et al. [22]	2013	11 + 8 controls	Cervical dystonia	Right cerebellum	cTBS 1 session with figure-of-eight coil	5 min	None	Open label	Improvement of EBCC
Bradnam et al. [23]	2014	1	Cervical dystonia	Cerebellar hemispheres (bilateral) and M1	Anodal tDCS, 20 sessions + botulinum toxin A injection	Baseline + 4, 8 and 12 weeks	None	Open label	Dystonia improvement of 39% (TWSTRS)
Koch et al. [24]	2014	20	Cervical dystonia	Left and right lateral cerebellum	cTBS 10 sessions with 70 mm figure-of-eight coil	Baseline + 2,4 and 6 weeks	None	Double-blind sham-controlled	Clinical improvement only in the 2-week evaluation as measured by the TWSTRS (15%), but not by the BFMDRS.
Sadnicka et al. [25]	2014	10	Writing dystonia	Right cerebellar cortex	Anodal tDCS 1 session with 2 mA	Baseline + 30 min	Didn't mention	Double-blind sham-controlled	No statistical difference between dystonia improvement in sham and active stimulations.
Bradnam et al. [26]	2015	8 patients + 8 controls	FHD	Lateral cerebellum	Anodal and cathodal tDCS 1 session with 2 mA	Baseline + 5min	None	Double-blind sham-controlled	Decrease of mean stroke frequency and average pen pressure.
Sokal et al. [27]	2015	10	Cerebral palsy with secondary dystonia	Deep anterior cerebellar lobe	DBS	Retrospective evaluation	3 infectious complications	Open label	Improvement of 25% in dystonia (UDRS) in 5 patients.
Linssen et al. [28]	2015	10	Writing dystonia	Cerebellar hemisphere ipsilateral to the dominant hand	cTBS 1 session with figure-of-eight coil	Baseline + immediately after	Didn't mention	Double-blind sham-controlled	No significant differences in writing performance.
Bologna et al. [29]	2016	13 FHD + 13 CD + 13 healthy	Focal Dystonia (cervical and hand)	Cerebellar hemisphere ipsilateral to the affected side of the body	cTBS 1 session with figure-of-eight coil	Baseline + 5min + 45 min	None	Double-blind sham-controlled	No changes in clinical scores or reaching and neck movements
Bradnam et al. [30]	2016	16	Cervical dystonia	Lateral cerebellum, bilaterally	iTBS 10 sessions with 70 mm figure-of-eight coil + motor control training	Baseline + 5 days + 10 days	None	Double-blind sham-controlled	Reduction in total TWSTRS score and time to perform the grooved pegboard task.
Essential Tremor									
Avanzino et al. [31]	2009	15 patients + 11 controls	Essential tremor	Right lateral cerebellum	rTMS 1 session with 90 mm figure-of-eight coil	Baseline + immediately after + 5 min + 30 min	Didn't mention	Open label in 8 patients and single blind Sham controlled in 7 patients; cervical stimulation in 5 patients	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.
Gironell et al. [32]	2002	10	Essential tremor	Posterior cerebellum	rTMS 1 session with 70 mm butterfly coil	Baseline + 5min + 60min	Slight headache in one patient	Double-blind sham-controlled	Tremor improvement according to the TCRS, (17%) and accelerometry evaluation on the + 5min assessment
Popa et al. [33]	2013	11 patients + 11 controls	Essential tremor	Posterior cerebellum (bilateral) – neuronavegation	rTMS 5 sessions with figure-of-eight coil	Baseline + 5 days + 12 days + 29 days	None	Open label	Tremor improvement that built up until day 12 and persisted for 3 weeks.
Gironell et al. [34]	2014	10	Essential tremor	Cerebellar hemispheres, bilaterally	Cathodal tDCS 10 sessions with 2 mA	Baseline + 10 min + 15min + 70min + 10 days + 40 days	Local skin erythema and chemosis	Double-blind sham-controlled	No acute or long lasting benefit
Bologna et al. [35]	2015	16 patients + 11 healthy	Essential tremor	Right cerebellar hemisphere	TMS (cTBS) 1 session with eight-shaped coil	Baseline + 5min + 45 min	None	Double-blind sham-controlled	No change in tremor severity and reaching movements.
Yilmaz et al. [36]	2016	6	ET	Cerebellum	Cathodal tDCS 10 sessions with 2 mA; 5 more sessions after 1 month	Baseline + 20 days + 50 days	None	Open label	Improvement of tremor according to the TETRAS score (20%) only after 50 days

Parkinson's Disease									
Koch et al. [37]	2009	20	PD with peak-dose dyskinesia	Lateral cerebellum ipsilateral (1) and bilateral (2)	cTBS 1 session with 70 mm figure-of-eight coil	Baseline + 2, 4 and 6 weeks	None	Double-blind sham-controlled	Decrease in waking time spent as ON with dyskinesias.
Minks et al. [38]	2011	20	PD	Right lateral cerebellum - neuronavegation	rTMS 1 session with a conic coil	Baseline + 2 − 6min	None	Double-blind sham-controlled	Less time to complete de ball test (gross upper limb movement); more time to complete the nine-hole peg test (fine motor finger and hand function).
Brusa et al. [39]	2012	8	PD with levodopa-induced dyskinesias	Lateral cerebellum (bilateral)	cTBS 5 sessions with 70 mm figure-of-eight coil	Baseline + 1 week	None	Double-blind sham-controlled	Reduction of dyskinesias.
Bologna et al. [40]	2015	13 patients + 10 controls	PD resting tremor	Cerebellar hemisphere (ipsilateral)	TMS (cTBS) 1 session with 8-shaped coil	Baseline + 5 min + 45 min	None	Double-blind sham-controlled	No changes in tremor amplitude, frequency or magnitude.
Ferrucci et al. [41]	2016	9	PD with levodopa-induced dyskinesias	Cerebellum and M1	Anodal tDCS 5 sessions with 2 mA	Baseline + 5 days + 12 days + 33 days	Didn't mention	Double-blind sham-controlled	Improvement in UPDRS IV (dyskinesias section).
Progressive Supranuclear Palsy									
Brusa et al. [42]	2014	10 patients + 20 controls (10 PD + 10 healthy)	Progressive Supranuclear Palsy	Lateral cerebellum, bilaterally	iTBS 10 sessions with 70 mm figure-of-eight coil	Baseline + 2 weeks	Didn't mention	Open label	Improvement of dysarthria.

Abbreviations: **8 MW**: 8-m 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; **cTBS** = continuous theta burst stimulation; **DBS** = deep brain stimulation; **tDCS** = transcranial direct current stimulation; **EBCC** = eyeblink classical conditioning; **ET** = Essential Tremor; **FHD** = focal hand dystonia; **FTMTRS** = Fahn Tolosa Marin Tremor Rating Scale; **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's disease; **SARA** = scale for the assessment and rating of ataxia; **SAOA** = sporadic adult-onset ataxia; sporadic; **TCRS** = tremor clinical rating scale; **TETRAS** = essential tremor rating scale assessment; **TD** = touch duration; **TMS** = transcranial magnetic stimulation; **TWSTRS** = Toronto Western Spasmodic Torticollis Rating Scale; **UDRS** = unified dystonia rating scale; **UPDRS**: Unified Parkinson's Disease Rating Scale.

Table 2
Effects separated by neuromodulation technique.

Technique	Proposed underlying mechanism	Movement disorder	Studies	Main outcome measures	Main findings
tDCS	Generation of electric field that changes neuronal membrane's polarity and therefore its threshold for triggering action potentials. Cathodal stimulation would increase this threshold (inhibitory) while anodal stimulation would decrease it (excitatory) [67].	Cerebellar ataxia	N = 6	# Computerized Posturography: balance [16]. # MCT: upper limb dexterity [16]. # Triaxial accelerometry: postural tremor [17,19]. # Mechatronic myohaptic device: action tremor and dysmetria [17,19]. # Pediatric Balance Scale: balance [21]. # SARA: ataxia scale (0–40) [18,20]. # ICARS: ataxia scale (0–100) [18,20]. # 9HPT: finger dexterity and upper-limb coordination [18,20]. # 8 MW: gait speed [18,20].	Improvement in postural tremor [17,19], action tremor [17], dysmetria [17,19], balance [21], ataxia scale [18,20], gait speed [18,20] and upper limb dexterity [18,20]. No changes in balance and upper limb dexterity [16].
		Focal dystonia	N = 3	# TWSTRS: dystonia scale (0–35) [23]. # WCRD: writer's cramp scale (0–30) [25]. # ADDS: focal dystonia scale (0–100) [26].	Improvement in CD [23]. No changes in writing dystonia [25] or FHD [26].
		Essential Tremor	N = 2	# TCRS: tremor scale (0–144) [34]. # Accelerometric recordings: tremor analysis [34]. # TETRAS: tremor scale (0–40) [36].	Improvement in tremor [36]. No changes in tremor [34].
		PD	N = 1	# UPDRS: PD scale (15–89) [41].	Improvement of dyskinesias [41].
TMS	Induces electric and magnetic fields that generate long-term potentiation (high frequency, >5 Hz) or long-term depression (low frequency, <1Hz) [68].	Cerebellar ataxia	N = 6	# 10 MW: gait speed [12–14]. # Number of tandem steps [13,14]. # Gravicometer: body balance [13]. # Standing capacities (0–6) [14]. # Walking capacities (0–6) [14]. # TUG: functional mobility [15]. # Stationary force platform: postural control [15]. # 90-s walk: gait speed and stride duration [15]. # MICARS: ataxia score (0–124) [11]. # BBS: balance scale (1–56) [12]. # SARA: ataxia scale (0–40) [9]. # TCRS: tremor scale (0–144) [9]. # UDRS: dystonia scale (0–120) [9].	Improvement in gait speed [12–14], number of tandem steps [13,14], body balance [12–14], ataxia scale [9,11], and tremor [9]. No changes in dystonia [9].
		Focal dystonia	N = 5	# EBCC: motor learning [22]. # TWSTRS dystonia scale (0–35) [24,29,30]. # BFMDRS: dystonia scale (0–120) [24]. # Circle drawing: writing performance [28]. # Dedicated optoelectronic device:	Improvement of motor learning [22], dystonia score [24,30], and hand dexterity [30]. No changes in writing performance [28], dystonia score [24,29], and reaching movements [29].

Table 2 (*continued*)

Technique	Proposed underlying mechanism	Movement disorder	Studies	Main outcome measures	Main findings
				reaching movement kinematics [29]. # Grooved pegboard test: hand dexterity [30].	
		Essential tremor	N = 4	# Finger tapping: motor performance [31]. # TCRS: tremor scale (0–144) [32,33]. # Accelerometer: tremor quantification [32,33]. # Kinematic recordings: postural tremor and reaching movement analysis [35].	Improvement of motor performance [31], tremor scale [32,33] and tremor quantification [32,33]. No changes in postural tremor severity and reaching movements [35].
		PD	N = 4	# UPDRS: PD scale (15–89) [37,39]. # Ball test: gross motor skills [38]. # 9HPT: fine motor skills [38]. # Kinematic recordings: resting tremor analysis [40].	Improvement in levodopa-induced dyskinesias [37,39] and gross upper limb skills [38]. No changes in resting tremor [40]. Worsening of fine motor upper limb skills [38].
		PSP	N = 1	# PSP-RS: PSP rating scale (0–100) [42].	Improvement in dysarthria [42].
DBS	Overrides abnormal neuronal oscillations, releases local neurotransmitters and alters action potentials thresholds [69].	Cerebellar ataxia	N = 1	# TCRS: tremor scale (0–144) [10]. # SARA: ataxia scale (0–40) [10]. # UDRS: dystonia scale (0–120) [10].	Improvement in tremor and ataxia [10]. No changes in dystonia [10].
		Dystonia	N = 1	# UDRS: dystonia scale (0–120) [27].	Improvement in dystonia [27].

Abbreviations: **8 MW**: 8-m walk; **9HPT**: 9-hole peg test; **10 MW**: 10-m walk; **ADDS**: Arm Dystonia Disability Scale; **BBS**: Berg Balance Scale; **BFMDRS**: Burke-Fahn-Marsden Dystonia Rating Scale; **CD**: cervical dystonia; **DBS** = deep brain stimulation; **EBCC**: eyeblink classical conditioning; **FHD**: focal hand dystonia; **ICARS**: International Cooperative Ataxia Rating Scale; **MCT**: mechanical counter test; **MICARS** = Modified International Cooperative Ataxia Rating Scale; **TCRS**: tremor clinical rating scale; **PD**: Parkinson's disease; **PSP**: progressive supranuclear palsy; **PSP-RS**: progressive supranuclear palsy rating scale; **SARA** = scale for the assessment and rating of ataxia; **tDCS**: transcranial direct current stimulation; **TETRAS**: Essential Tremor Rating Assessment Scale; **TMS** = transcranial magnetic stimulation; **TWSTRS** = Toronto Western Spasmodic Torticollis Rating Scale; **UDRS** = unified dystonia rating scale; **UPDRS**: Unified Parkinson's Disease Rating Scale; **WCRS**: Writer's Cramp Rating Scale.

report increased activity of the cerebellar cortex and deep cerebellar nuclei [50] and cerebellar degenerative changes in ET patients [51].

Despite the fact that no frequent clinical symptoms point to cerebellar involvement in PSP, there is evidence to suggest otherwise. Shirota and colleagues reported a dampening in cerebellar-brain inhibition (CBI) in PSP patients, when compared to PD patients, which might insinuate a dentato-thalamo-cortical (DTC) pathway or Purkinje cell impairment [6].

The cerebellum is an important source of excitatory input to M1 via the DTC pathway (Fig. 3) and when this input is diminished, there is a reduction in cortical excitability [7]. Injury in the DTC pathway reduces excitability in the contralateral cortex [52], whereas stimulation of the dentate nucleus increases cortical excitability and consequently promotes motor facilitation (Fig. 1) [53]. Therefore, cerebellar neuromodulation techniques can modulate cortical excitability, since the cerebellum is a subcortical structure deputed to plastic mechanisms of motor learning [54]. It is not yet known whether cerebellar stimulation affects the dentate nucleus or Purkinje cells, structures with different roles in CTC activation.

Bologna et al. observed a reduction in contralateral cortical excitability after one session of continuous cerebellar TBS in 13 PD patients and 10 controls [40]. The same group described similar

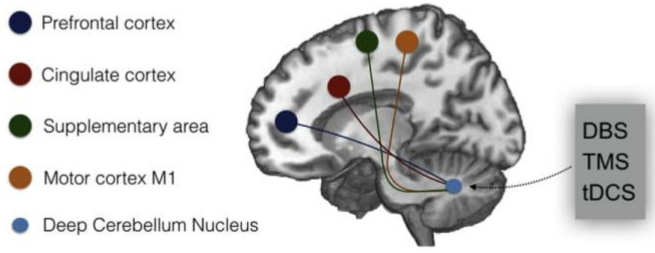

Fig. 3. Cerebellar connections.

findings in 11 healthy subjects, but not in 16 ET patients [35]. Another study [37], using the same stimulation protocol, found a reduction in short intracortical inhibition (SICI) and an increase in long intracortical inhibition (LICI) in the contralateral M1 of 20 dyskinetic PD patients, similar to the results reported in a previous study with healthy subjects [55] and after palidotomy [56]. Those findings are thought to reflect the activity of ϒ-aminobutyric acid type B ($GABA_b$) interneurons, since a single dose of baclofen, a $GABA_b$ receptor agonist, increases LICI and decreases SICI [57]. Brusa et al., after stimulating the cerebellums of PSP patients with 10 intermittent TBS sessions, reported impairment in paradoxical facilitation of the CBI, which could counteract the defective inhibitory projections expected in those patients [42]. Another group also reported decreases in CBI after cerebellar TMS in a patient with cerebellar ataxia [15].

Likewise, connections between the cerebellum and the brainstem could, in part, be responsible for the changes in motor performance after cerebellar modulation, since the precise physiological mechanisms of cerebellum participation in motor learning and motor coordination are not yet established. Several brainstems structures receive cerebellar outputs: nucleus reticularis tegmenti pontis, basilar pontine nuclei, pontine and medullary reticular formation, inferior olive, red nucleus, periaqueductal grey area, prerubral area, accessory oculomotor nuclei and superior colliculus [58]. The nucleus reticularis tegmenti pontis is associated with motor learning [59], while the inferior olive plays a role not only in motor learning, but also in motor timing [60]. Since the red nucleus receives fibers from the dentate nucleus and is connected to both motor cortex and spinal cord, it is associated with motor control, especially postural control [61].

Other than cortical excitability, cerebellar neuromodulation is believed to provoke changes in brain blood flow and metabolism. Patients with spinocerebellar degeneration submitted to single-positron emission computed tomography evaluation showed signs of increased brain blood flow in the cerebellum, putamen, and pons after 21 sessions of cerebellar TMS [13,14]. Another study reported decreased cerebellar metabolism through positron emission tomography imaging after 5 sessions of continuous bilateral cerebellar TBS in PD patients [39]. Popa et al. found, after 5 cerebellar TMS sessions, functional magnetic resonance imaging (fMRI) evidence of information flow reestablishment in the CTC network of ET patients, a result that predicted clinical improvement [33]. After 10 sessions of intermittent cerebellar TBS in PSP patients, the caudate nucleus fMRI activation increased [42], possibly as a consequence of thalamic activation and perhaps the explanation of why those patients reported improvement in dysarthria.

Recent studies in patients with basal ganglia DBS have attempted to evaluate subcortical local field potentials through DBS electrodes and compare them to data from cortical whole head magnetoencephalography in order to characterize cerebro-cerebral coherence. Coherence is a spectral measure of the neural synchrony that can suggest communication between brain areas. Neumann and colleagues described a series of nine patients with cervical dystonia and bilateral GPi DBS in which coherence was measured [62]. They reported pallidal coherence to ipsilateral temporal (theta band) and sensorimotor (beta band) areas, but also to the cerebellum (alpha band). More interestingly, the degree of pairing in the alpha band was inversely proportional to the severity of dystonia symptoms before surgery. This finding, though observational, could suggest that this neuronal synchrony between the cerebellum and basal ganglia is somehow involved in cervical dystonia pathophysiology. This hypothesis could shed light on why all studies to date showed improvement of cervical dystonia after cerebellar modulation [22–24,30]. Another study reported that, during writing, coherence between the ipsilateral cerebellum and contralateral posterior parietal cortex was reduced in patients with writing dystonia, compared to healthy controls [63]. Furthermore, patients with ET performing hand motor tasks had a different coherence pattern than patients with age-related tremor, since the former showed a significant coupling between M1 in the contralateral cerebellum, while the latter did not [64], corroborating the findings of a previous study. PD patients with tremor also showed signs of increased cerebellar coherence with M1 [65]. Casula et al., analyzing data from electroencephalography after cerebellar TBS pulses, reported not only changes in M1, but also in the posterior parietal cortex (PPC). Similarly to previous findings in M1, continuous TBS would increase, while intermittent TBS would decrease local TMS-evoked activity and LICI in PPC, which demonstrates in humans a direct projection from cerebellum to a cortical non-motor area [66].

There are several limitations in the literature data regarding cerebellar neuromodulation. Because of the small sample size evaluated in the majority of studies and the absence of controls, caution is warranted in the interpretation of the present data. It is important to emphasize that we included many different diagnosis in this review, which have different underlying mechanisms and therefore could not be fully explained nor corrected by targeting a single brain structure or pathway. Furthermore, the outcomes of the studies included were not uniformly reported and the types of stimulation were noticeably different (Table 2). Even when using the same kind of stimulation, protocols and coils (shape and size) were different. Another problem was the adverse events registration, since eleven out of 34 studies didn't mention if side effects were observed or not, which we deem to be a relevant issue. Moreover, many studies were not blinded and therefore could not rule out placebo effect. Only four trials used neuronavigation to target the cerebellum [9,10,33,38], a more precise technique than the use of skull landmarks. Eight studies reported negative clinical outcomes [16,25,26,28,29,34,35,40], but we believe there might be a publication bias in favor of positive clinical outcomes, since negative results tend to be less published. Considering this publication bias, perhaps more trials with negative outcomes were performed and their results were not made public. Finally, neuromodulation techniques vary among their underlying physiological mechanisms. While tDCS utilizes superficial electrical current to influence the threshold for actions potentials, TMS induces neuronal membrane's changes based on electrical and magnetic fields, and can reach deeper structures. DBS usually reaches even deeper targets, and has different electrical parameters (voltage, frequency, pulse width) to modulate the surround tissue. It is intuitive to consider DBS more effective (nevertheless with more potential side effects), but it is difficult to compare motor outcomes between these techniques, as there are no comparative studies available so far.

In conclusion, cerebellar neuromodulation seems to be a promising therapy with a safe profile, but more studies are needed to determine whether it could be established as a treatment tool in the field of movement disorders.

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Author contributions

Carina França and Rubens Gisbert Cury contributed to literature review, manuscript preparation, writing and revising.

Daniel Ciampi de Andrade, Manoel Jacobsen Teixeira, Ricardo Galhardoni and Egberto Reis Barbosa contributed to manuscript review and critique.

V. Silva contributed to research conception and manuscript review.

Disclosures

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Dr. Ciampi de Andrade reports no disclosures.
Dr. Teixeira reports no disclosures.
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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2017.11.015.

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Appendix 4 – Cerebellum as a possible target for neuromodulation after stroke. Letter on cerebellar modulation published in Brain Stimulation.

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Cerebellum as a possible target for neuromodulation after stroke

Dear Editor

We read with great interest the article entitled "Deep brain stimulation for stroke: Current uses and future directions," a systematic review of the current evidence for using neuromodulation as a rehabilitation tool after stroke [1]. This topic is of significant importance because stroke affects millions of people every year, leaving behind a large social burden in terms of medical costs. The rehabilitation techniques available to date often fail to restore a patient's previous quality of life. Although the present article thoroughly reviews the literature related to this matter, we believe some important points might have been overlooked regarding the cerebellar modulation, particularly concerning its role in ataxia and dystonia.

Because the cerebellum has direct and indirect connections with almost the entire central nervous system, especially the motor, premotor and parietal cortices, neuromodulation of this region would be of great interest in the motor domain and in the field of neurocognitive science [2]. Notably, low-frequency (LF) stimulation (which is known to enhance neuronal activity) of the excitatory efferent dentatothalamocortical pathway has been the subject of pre-clinical and clinical studies. Machado et al. reported that motor recovery after stroke in rats can be improved after chronic stimulation of dentate nucleus output at LF via augmentation of perilesional cortical excitability [3]. Moreover, stroke patients present reduced excitability of the ipsilesional hemisphere not only due to ischemic lesions but also due to the diaschisis-related hypoactivity of the dentatothalamocortical pathway. This finding was associated with poorer long-term outcomes, regardless of the severity of the stroke symptoms in the acute phase [4]. Taken together, cerebellar stimulation with implanted electrodes appears to be a reasonable option to increase cortical activity in cortical stroke, thereby enhancing motor outcomes.

Besides cortical stroke, cerebellar stroke has also been studied [5]. We recently reported a patient with cerebellar ataxia due to unilateral cerebellar infarction who improved in her symptoms after deep brain stimulation (DBS) implant to the healthy dentate nucleus [6]. Our hypothesis relied on the fact that chronic cerebellar ischemic lesions have been associated with a decrease in intracortical inhibition in the contralesional M1, leading to interhemispheric asymmetry in cortical excitability, which could contribute to motor impairment seen after stroke [7]. Cerebellar TMS and DBS targeting the healthy dentate nucleus can increase contralateral intracortical facilitation and restore cortical excitability symmetry [8].

Moreover, as noted by the authors, the cortico-striato-pallido-cortical circuit and the cerebello-thalamo-cortical circuit play a role in the pathophysiology of post-stroke dystonia. Although globus pallidus internus (GPI) is a well-established dystonia target, the outcome for secondary dystonia after GPI-DBS is poor. Other authors have attempted to approach dual targets, mainly the GPI and the thalamus [9]. Nonetheless, other brain targets are currently being explored. There is a firm link between cerebellum and dystonia established by functional imaging, neurophysiological and behavioral studies [10]. In addition, direct cerebellar lesions can lead to dystonia [6]. Previous studies have demonstrated that cerebellar modulation might be promising in dystonic patients [5] and could eventually be considered in a dual-target approach.

The current literature is still poor in terms of supporting DBS as an effective treatment in some disabling symptoms after stroke, such as dystonia and ataxia. Elias and colleagues highlight several unmet needs in neuromodulation for stroke, and larger studies exploring combined and new targets are crucial. We expect that modulating cortical excitability via cerebellar stimulation may be a promising way forward. However, additional comprehensive studies are required to lay the groundwork for its application in clinical practice.

Author contributions

Carina França, Daniel Ciampi de Andrade, Manoel Jacobsen Teixeira and Rubens Gisbert Cury contributed to literature review, manuscript preparation, writing and revising.

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Appendix 5 – Dentate nucleus stimulation in a patient with cerebellar ataxia and tremor after cerebellar stroke: A long-term follow-up. Original article on cerebellar modulation published in Parkinsonism and Related Disorders.

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Dentate nucleus stimulation in a patient with cerebellar ataxia and tremor after cerebellar stroke: A long-term follow-up

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Cerebellar modulation has emerged as a promise therapy in the movement disorders field, as cerebellum pathways present connections with critical cortical areas. We have previously reported the short-term outcome in a patient with unilateral cerebellar stroke who improved the ataxia after cerebellar neuromodulation [1,2]. The rational hypothesis lies on the fact that unilateral chronic cerebellar ischemic lesions were linked with a decrease in intracortical inhibition in the contralateral motor cortex, culminating to inter-hemispheric asymmetry in cortical excitability, which could contribute to the motor impairment [3]. Then, modulating the healthy dentate nucleus could increase contralateral intracortical facilitation, restoring cortical excitability symmetry (Fig. 1) [2]. We report here the 4-year results of this patient using a single-blinded evaluation.

A 53-year-old female patient underwent a resection of acoustic neuroma, complicated by stroke of the right cerebellar hemisphere. Due to the refractoriness of her ataxia, we conducted double-blind trial of 1 Hz, transcranial magnetic stimulation (TMS) to the left ("healthy") dentate nucleus (DN). Based on her clear response to TMS, after consent of the patient, she underwent DBS of the left DN. A double-blind assessment 12 months after surgery showed tremor improvement by 37% and ataxia by 33%. Motor cortex excitability showed restoration of the asymmetry between both hemispheres during on-condition (supplementary file 1). Details about the procedure have been described [1,2].

Four years after surgery, the patient (unware to DBS status) was assessed during on-stimulation (1.9 mA, 60 μs, 20 Hz) and 30 minutes after the DBS has been switched off. The tremor continued to further improve (Fahn, Tolosa, Marin Tremor Rating Scale [FTMRS] baseline = 38, after = 19/144 [50% reduction]) and the ataxia improvement stabilized (scale for the assessment and rating of ataxia [SARA] baseline = 25, after = 17/40 [33% reduction]) in the on-stimulation (video, supplementary file 2). When the DBS was switched off, the patient spontaneously reported worsening the symptoms, and the SARA worsened to 30/40 (supplementary file 3). No adverse events were reported. The patient's global impression of change was 6 (moderately improved).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.10.001.

The present case is the first prospective long-term report of DN-DBS in a patient with cerebellar stroke assessed in a blinded fashion. The findings suggest an initial and sustained benefit in tremor and ataxia of unilateral DN-DBS along with long-term safety and a good tolerability profile.

To date, only few studies have been designed to assess the effects of cerebellar modulation. A recent study showed that stimulation of dentate nucleus in rats with cortical stroke was associated with motor recovery, probably via intensification of perilesional excitability [4]. Two trials reported improvement in posture and gait in patients with cerebellar ataxia due to stroke after repetitive-TMS stimulation [4]. In regard to cerebellar DBS, there is no study focusing exclusively in ataxia outcomes.

In addition to the evidence that cerebellar modulation could restore the altered cortical excitability asymmetry seen between both motor cortices after a chronic cerebellar stroke, structural changes in brain blood flow and metabolism can also be involved in the pathophysiology [4]. Patients with spinocerebellar degeneration showed increased brain blood flow in the cerebellum, putamen, and pons after sessions of cerebellar TMS. A reduction in cerebellar metabolism after 5 sessions of cerebellar TBS in parkinsonian patients was observed through positron emission tomography imaging [5].

Despite the consistent result described in the present case, and a reasonable explanation for the improvement, at least in part, based on the restored cortical excitability, the hypothesis on why cerebellar stimulation could change motor symptoms after cerebellar lesions is still theoretical. This is the index case, and larger prospective studies are obviously necessary. The best target into the cerebellum (DN or the dentate-rubro-thalamic tracts or both), the stimulation parameters, and

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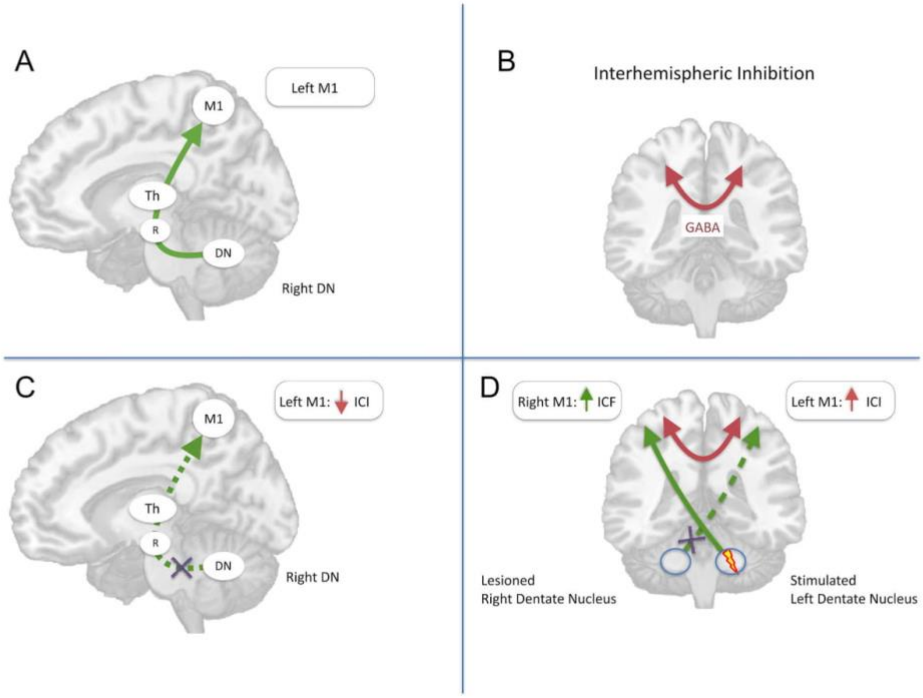

Fig. 1. Representation of the physiology of cerebellar cortical pathway and the effect of the dentate-deep brain stimulation after unilateral lesion of the cerebellum. Legend. Panel A displays the excitatory cerebellum-cortico pathway passing through the rubro nucleus and thalamus. There is an ICI between both M1 cortices that is related to preserving the integrity of limbs coordination (panel B). 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, Green arrow = Excitatory projection, Red arrow = Inhibitory projection (adapted from Teixeira et al., 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the baseline clinical characteristics predictive of response should be further explored. Interestingly, during the off-stimulation in the last follow-up (4 years) the SARA worsened when compared to the pre-operative score, i.e., after the stimulation has been switched off, the worsening of symptoms exceeded the baseline levels, probably reflecting a rebound phenomena. Defining whether the sudden interruption of stimulation affects the cerebellar-cortical circuitry and whether these rebound symptoms also occur when stimulation is tapered off slowly could help explain the mechanism behind the effects of cerebellar modulation.

Continuous progress in our understanding of brain pathology, connectivity and biomarkers will certainly contribute to the field of movement disorders research, especially regarding new brain targets for neuromodulation. We showed that DN-DBS improved tremor and ataxia in a single patient with cerebellar stroke, and this effect is sustainable over time. The study protocol was safe and well tolerated. Additional comprehensive studies are required to bring evidences for its application in clinical practice.

Conflicts of interest

The authors report no conflict of interest involved in this article.

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Appendix A. Supplementary data

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Appendix 6 – Effects of dentate nucleus stimulation in spinocerebellar ataxia type 3. Original article on cerebellar modulation published in Parkinsonism and Related Disorders.

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Effects of dentate nucleus stimulation in spinocerebellar ataxia type 3

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Spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominantly progressive diseases that comprise more than 40 distinct subtypes [1]. Currently, there are no approved pharmacological treatments for treating SCAs [1]. Because the cerebellum has many connections with crucial cortical and subcortical structures (e.g., the primary motor cortex, supplementary motor area, and basal ganglia), the modulation of these different neuronal networks through the dentate nucleus (DN) could potentially repair pathological neuronal oscillations and thereby influence motor and sensory integration [2]. Cerebellar deep and superficial (non-invasive) stimulation promotes gait and balance recovery in patients with cerebellar or cortical stroke by acting on cerebello-cortical plasticity [3]. Cerebellar transcranial direct current stimulation can transiently improve symptoms in patients with degenerative ataxias, including SCAs [4]. Here, we tested whether chronic deep DN modulation could reduce symptoms in SCA-3 in a sham-controlled, double-blind n = 1 study.

A 31-year-old female with SCA-3 and refractory ataxia underwent a trial of neuronavigated, repetitive, low-frequency (1 Hz) transcranial magnetic stimulation (rTMS) on the left DN; both the patient and the evaluator were blinded to the treatment. Two (active or sham) stimulation sessions were randomly performed four weeks apart. For the sham procedure, the patient had the coil placed over the scalp and a second active coil was placed on it. This created noise and bumps from the pulses, similar to an active stimulation. The active stimulation resulted in significant improvement in ataxia (25%) and tremor (62.5%). After the patient signed the informed consent, she underwent bilateral DN deep brain stimulation (DBS) in a randomized, double-blind, cross-over design with two 3-month phases (active versus sham) (Fig. 1 illustrates the target) (St. Jude Medical, Plano, Tx, USA). During the active phase, we tested a range of frequencies, between 6 and 150 Hz, and pulse widths, between 60 μs and 210 μs. We observed improvements in tremor (Fahn, Tolosa, Marin Tremor Scale from 23/144 to 16/144; 30% reduction) and cerebellar ataxia (Scale for the Assessment and Rating of Ataxia [SARA] from 15.5/40 to 12.0/40; 22% reduction) during the active phase. No changes were observed during the sham phase. The patient's global impression of change was 5 (moderately better, with a slight but noticeable change). The best settings were bipolar and activated the most dorsal contacts (left DN = 2 mA, 182 μs, 16 Hz; right DN = 1.8 mA, 182 μs, 16 Hz). Stimulation frequencies above 80 Hz worsened gait coordination.

DBS is typically applied to treat medically refractory movement disorders, but it has been poorly studied for cerebellar disorders. The present case is the first to target the DN in a SCA-3 patient. The cerebellum is an important source of excitatory input to the motor cortex via the dentatothalamocortical tract. Degeneration in this pathway reduces excitability in the contralateral cortex; stimulation of the DN increases cortical excitability and consequently promotes motor facilitation [2]. Low-frequency stimulation (which enhances neuronal output) of the dorsal DN has been recently applied in a rat model of neurogenerative ataxia [5]. A frequency of 30 Hz improved motor symptoms; high-frequency stimulation worsened incoordination, as was noted in our case. It has been hypothesized that high-frequency stimulation blocks collateral signals in the vicinity of the stimulated area, thereby affecting fibers associated with motor coordination [5]. Another pre-clinical study reported that low-frequency DN DBS restored motor function after cortical stroke via augmentation of perilesional cortical excitability [2]. In summary, in this study, cerebellar TMS and DBS of the DN improved the patient's SCA symptoms, possibly by strengthening the connections between the cerebellum and several sensory and motor regions.

We observed a modest improvement in the SARA score (3.5 points), but the patient reported subjective slight improvement during the on-phase; for context, a 1-point change in the SARA score is believed to be clinically relevant [1]. The most robust trials of genetic ataxias (SCAs and Friedreich ataxia) showed that riluzole decreased SARA scores by 1.02 points [1]. The mean change in total SARA score in SCA-3 patients receiving a high dose of valproic acid was 2.05 [1].

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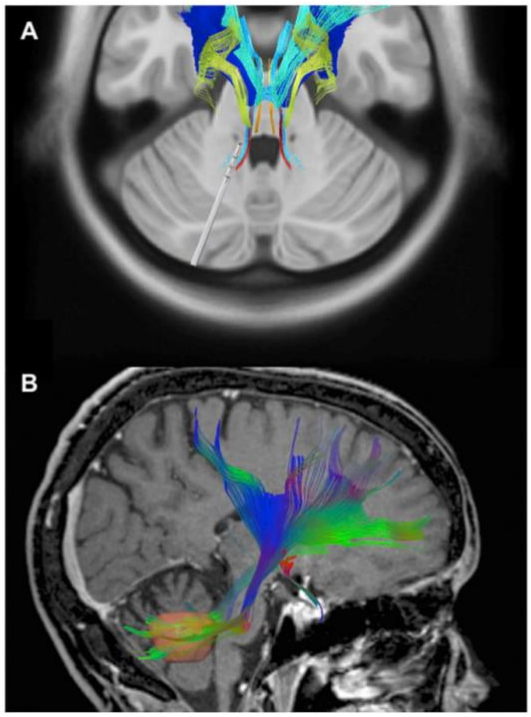

Fig. 1. (A) Three-dimensional demonstration of the DBS electrode displayed in the right cerebellum hemisphere achieving the dentate nucleus. The red and light blue fibers represent the dentate-rubro-thalamic tract derived from a normative structural human connectome. (B) Fiber tractography reconstruction in our neuromodulation laboratory during the dentate-DBS surgery planning. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Low-frequency cerebellar stimulation should be investigated further in larger studies to address whether it effectively treats degenerative ataxias over short- and long-term periods and to better explore the *hot spot* site of stimulation and electric parameters. Measurements of cortical excitability will be necessary, as its unbalancing has been implicated in causing ataxia and DN DBS seems to directly influence them [2]. Finally, studies pertaining to the use of TMS as a tool for predicting surgical responses appear to be promising [2].

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Appendix 7 – Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial. Original article with results of the present study published in Parkinsonism and Related Disorders.

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Effects of cerebellar transcranial magnetic stimulation on ataxias: A randomized trial

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ABSTRACT

Introduction: Cerebellar ataxia remains a neurological symptom orphan of treatment interventions, despite being prevalent and incapacitating. We aimed to study, in a double-blind design, whether cerebellar modulation could improve ataxia.

Methods: We included patients with diagnosis of spinocerebellar ataxia type 3, multiple systems atrophy cerebellar type, or post-lesion ataxia. Patients received five sessions each of sham and active cerebellar 1 Hz deep repetitive transcranial magnetic stimulation in randomized order. Our primary outcome was the decrease in the Scale for the Assessment and Rating of Ataxia when comparing phases (active x sham). Secondary outcomes measures included the International Cooperative Ataxia Rating Scale, and other motor, cognitive, and quality of life scales. This study was registered at clinicaltrials.gov (protocol NCT03213106).

Results: Twenty-four patients aged 29–74 years were included in our trial. After active stimulation, the Scale for the Assessment and Rating of Ataxia score was significantly lower than the score after sham stimulation [median (interquartile range) of 10.2 (6.2, 16.2) versus 12.8 (9.6, 17.8); $p = 0.002$]. The International Cooperative Ataxia Rating Scale score also improved after active stimulation versus sham [median (interquartile range) of 29.0 (21.0, 43.5) versus 32.8 (22.0, 47.0); $p = 0.005$]. Other secondary outcomes were not significantly modified by stimulation. No patient presented severe side effects, and nine presented mild and self-limited symptoms.

Conclusions: Our protocol was safe and well-tolerated. These findings suggest that cerebellar modulation may improve ataxic symptom and provide reassurance about safety for clinical practice.

1. Introduction

Cerebellar ataxia is a prevalent and disabling neurological symptom with diverse etiologies, ranging from hereditary to acquired. The personal economic burden of spinocerebellar ataxia alone is estimated to be around 18,776 euros per annum [1]. Currently there is no significant evidence-based treatment able to relieve ataxic symptoms although many therapeutic strategies have been tested in the past years [2]. Considering its safety, and the potential to alleviate ataxic symptoms, non-invasive neuromodulation therapies can be considered a promising treatment strategy for this symptom [2].

Despite having different etiologies, ataxic symptoms can have a common physiopathological basis [1]. Because the cerebellum is connected to important areas related to motor function, it has emerged as an attractive and promising neuromodulation target for controlling movement disorders [3]. Technological improvements have allowed targeting deeper structures non-invasively [4]. Deep repetitive transcranial magnetic stimulation (d-rTMS) using a double-cone coil is capable of reaching structures as deep as the dentate nucleus [5,6]. Correction of a disruptive cerebellar network is believed to lead to changes in distant brain sites and bring about subsequent symptomatic control [7–11].

In this study, we sought to investigate if cerebellar d-rTMS can improve ataxic symptoms. We included patients with both hereditary and acquired diseases in a double-blind phase II trial.

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2. Methods

2.1. Study design and participants

This was a randomized, prospective, double-blind, cross-over, sham-controlled trial conducted in the University of São Paulo to evaluate the efficacy of d-rTMS on clinical outcomes of patients with different etiologies of cerebellar ataxia. Data were collected between July 2016 and April 2019. Our study was designed and reported in accordance to the Consolidated Standards of Reporting Trials (CONSORT) extension to crossover trials [12] in addition to the CONSORT statement [13].

Eligible participants were all adults aged ≥18 who met several inclusion criteria: (a) cerebellar ataxia based on clinical history and neurological examination; (b) refractory to clinical treatment involving at least six months of physical therapy, speech, and/or occupational therapy; (c) cerebellar lesion seen by MRI and a history of cerebellar stroke or neurosurgery, spinocerebellar ataxia type 3 (SCA3) or multiple system atrophy cerebellar type (MSA-c); (d) duration of symptoms of at least six months (chronic ataxia); and (e) presence of symptoms of moderate ataxia with at least six points on the Scale for the Assessment and Rating of Ataxia (SARA). Exclusion criteria consisted of several parameters: (a) active infection or other pre-existing untreated medical conditions; (b) pregnancy; (c) concurrent treatment with other experimental drugs; and (d) cardiac pacemakers, electronic devices, and/or intra-cranial metallic objects.

The Institutional Review Board from the University of São Paulo approved the study, and all participants provided informed consent according to the Declaration of Helsinski before implementing any study protocol. This study was registered at clinicaltrials.gov under protocol NCT03213106.

2.2. Interventions

The target was the cerebellum contralateral to the most clinically affected side. If the patient had symmetric ataxia, we established the target arbitrarily as the right cerebellum [5]. Patients were evaluated at baseline and the location of the dentate nucleus was mapped through neuronavigation using Polaris Vicra, Brainsight software and MRI (Supplementary Fig. 1) as previously reported [5]. Participants were then randomly assigned to sham or active d-rTMS for five consecutive days. Following a minimum of four weeks washout (to attempt to return to baseline values), assignments were then switched, and participants underwent five additional stimulation sessions; those on active d-rTMS were switched to sham, while the ones on sham were switched to active (Fig. 1). All interventions were administered during the morning period. Active d-rTMS was performed with neuronavigation coordinates using a MagPROX100 machine (Magventure® Tonika Elektronik, Farum, Denmark). A butterfly double-cone D-B80 cooled coil was oriented at a tangent to the scalp with the handle facing upwards. Intensity was set at 90% of the rest motor threshold of the abductor pollicis brevis muscle identified under electroneuromyography control [14]. The stimulation session consisted of 20 series of 60-sec pulses at 1 Hz and inter-train-pulses of 1 s (for a total of 1200 pulses per session). The sham stimulation was executed with a sham coil identical to the active d-rTMS, which was positioned in the exact same way. Sessions were performed with patients reclined in an armchair with both feet up.

Patients were advised not to change any rehabilitation therapy or medication throughout the study.

2.3. Outcome measures

The primary outcome measure was the difference between SARA scales, comparing active versus sham phases. Secondary outcome measures included the International Cooperative Ataxia Rating Scale (ICARS), and several parameters: (a) gait speed measured with the Timed Up and Go Test; (b) quality of life measured by the short version of the World Health Organization Quality of Life scale; and (c) cognition, measured with the Frontal Assessment Battery. A sole blinded movement disorder specialist performed all of the tests for the different scales.

The baseline evaluation included all previously described scales. At the end of the first five days of intervention (active or sham), all scale tests were repeated (evaluation number two), except for the short version of the World Health Organization Quality of Life scale, which was answered remotely after seven days. After the washout period, patients were called for a third clinical evaluation identical to baseline. On the last day of the following 5-day intervention (sham or active, crossover), there was a fourth evaluation identical to the second evaluation. After 14 days of the last intervention, patients were contacted by telephone for the blinding assessment (Fig. 1). There was no follow-up visit after the blinding assessment.

2.4. Randomization and masking

Our random sequence was generated by randomization.com using randomly permuted blocks with size of four per block. Researchers were specifically instructed not to attempt to break the randomization schedule in any manner. Different researchers performed concealed subject allocation, randomization, and clinical evaluation. Patients were blinded regarding randomization and were never scheduled on the same day and time, so they were not able to exchange information in the waiting room.

2.5. Statistical analysis

Our exploratory analysis started with a visual assessment of all variables to evaluate the frequencies, percentages, and near-zero variance for categorical variables, distribution for numeric variables, and their corresponding missing value patterns. When evaluating the

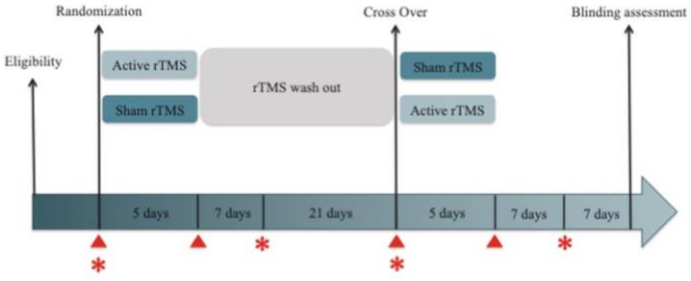

Fig. 1. Study design. Triangles represent assessment of the following outcomes: ataxia, gait speed, and cognition. Asterisks represent assessment of quality of life. d-rTMS = deep repetitive transcranial magnetic stimulation.

balance of baseline variables between intervention arms, numeric variables were compared through t-tests and categorical variables though chi-squared tests. We assumed an alpha error of 0.05, a power of 80%, a 4-point difference in the SARA scale, and a standard deviation of 5. A sample size of twenty-two participants was obtained.

Period, carry-over, and treatment effects were initially evaluated with Mann–Whitney tests for SARA and ICARS. A Mann–Whitney test was used because the variables did not present a normal distribution, which was confirmed through a Shapiro–Wilk test. Period effects were calculated as the difference between the outcome values after the treatment in periods two and one (period two minus period one). Carry-over effects were calculated as the sum of outcome values after treatment in periods one and two (period one plus period two). We evaluated the treatment effect by comparing sham vs. active stimulation across periods one and two through a paired Mann-Whitney test. Statistical significance was considered for the primary outcome as $p < 0.05$; for secondary outcomes, it was reduced according to Bonferroni correction for multiple comparisons.

Finally, we performed subgroup analyses by testing the same association between our intervention and outcomes within specific subgroups of our sample, based on patient diagnoses and laterality (clinical evaluation ipsilateral and contralateral to the stimulation site). We used the same linear mixed-effects model applied to the whole population to evaluate primary and secondary outcomes within each subgroup. Since these were post-hoc analyses, they should be interpreted with caution.

3. Results

3.1. Patients

Supplementary figure 2 displays our study flowchart. Two participants dropped out of the study after randomization, both for personal reasons not related to the protocol itself. Our sample consisted of 24 individuals and presented a distribution of 54.2% in the active/sham and 45.8% in the sham/active orders. All 24 patients were included in the final primary outcome analysis. Baseline demographic characteristics results were similar between groups (Table 1). Supplementary Table 1 displays the MRI description of lesions in patients with post-lesion ataxia. The trial ended when previously calculated sample size was reached with two additional patients to compensate for potential dropouts. No interim analysis was conducted during the protocol.

Regarding the stimulation side, 14 patients received d-rTMS directed to the right cerebellum (six active/sham and eight sham/active), while 10 patients received it to the left (seven active/sham and three sham/active) ($p = 0.3$).

Table 1
Description of the overall study sample.

Variable	Total (n = 24)	Active/Sham d-rTMS (n = 13)	Sham/Active d-rTMS (n = 11)	P value
Age	49 (13.8)	53.4 (11.2)	44.5 (15.6)	p = 0.131
Female	16 (66.7%)	8 (61.5%)	8 (72.7%)	p = 0.885
Cardiovascular diseases	11 (45.8%)	8 (61.5%)	3 (27.3%)	p = 0.205
Depression	14 (58.3%)	10 (76.9%)	4 (36.4%)	p = 0.111
Diagnosis				p = 0.368
- *MSA-c*	8 (33.3%)	5 (38.5%)	3 (27.3%)	
- *Post-lesion ataxia*	7 (29.2%)	5 (38.5%)	2 (18.2%)	
- *SCA 3*	9 (37.5%)	3 (23.0%)	6 (54.5%)	

Values are mean (SD) or n (%). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, MSA-c: multiple systems atrophy cerebellar type, SCA 3: spinocerebellar ataxia type 3.

3.2. Clinical efficacy of the stimulation

3.2.1. Primary outcome

Table 2 displays the main results of our evaluation instruments at baseline, after active d-rTMS and after sham, in addition to the p-values (active x sham). Since we did not find any statistical differences between baseline data (evaluations one and three), we depicted only one. We found a significant improvement in ataxia according to the SARA scale after active cerebellar d-rTMS with a 2.6-point difference (20.3%) between medians of active and sham groups ($p = 0.002$, Table 2, Fig. 2A) and 3.3-point (24.4%) between baseline and active group ($p < 0.005$). The difference in SARA between baseline and sham groups did not change significantly ($p = 0.480$). After active d-rTMS, four patients did not present improved or had slightly worse SARA scores (range 0–1 point) while 20 patients showed improvements (range 0.5–8.5 points) (Supplementary Table 2, Supplementary Fig. 3).

3.2.2. Secondary outcomes and post-hoc analysis

ICARS significantly improved in patients after active cerebellar d-rTMS compared to sham (3.8-point difference, 11.5%; $p = 0.005$, Table 2, Fig. 2B) and to baseline (6.08-point difference, 17.8%; $p = 0.001$). Regarding ICARS subscores, only in "kinetic function", which measures appendicular abilities, there was significant improvement after active d-rTMS compared to sham ($p = 0.005$, Table 2). Axial functions, such as gait, balance, oculomotor abilities, and speech did not show significant improvement after d-rTMS. The other secondary outcomes did not change when comparing active to sham stimulation (Table 2).

In the post-hoc analyses, both SARA and ICARS improved bilaterally, regardless of the unilateral d-rTMS (Supplementary Table 3). When analyzing the subgroups outcomes comparing to baseline scores, SCA3,

Table 2
Outcome measures at baseline, sham and active phases.

Variable [Missing]	Baseline	Sham d-rTMS	Active d-rTMS	P value for treatment effect (sham vs active)
SARA [0]	13.5 (9.7, 17.6)	12.8 (9.6, 17.8)	10.2 (6.2, 16,2)	$p = 0.002^a$
ICARS [2]	34.0 (25.0, 43.7)	32.8 (22.0, 47.0)	29.0 (21.0, 43.5)	$p = 0.005^b$
ICARS posture and gait disturbances [2]	16.0 (10.5, 19.5)	15.0 (9.2, 21.5)	14.0 (9.5, 19.5)	p = 0.086
ICARS kinetic function [2]	16.0 (10.7, 20.5)	14.5 (9.0, 19.7)	10.5 (7.7, 17.5)	$p = 0.005^b$
ICARS speech disorders [2]	3.5 (1.7, 5.0)	2.0 (2.0, 4.7)	2.5 (1.7, 5.0)	p = 0.285
ICARS oculomotor disorders [2]	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 3.2)	p = 0.305
TUG [12]	15.5 (10.5, 28.2)	14.0 (11.5, 26.0)	12.0 (11.0, 24.5)	p = 0.106
WHOQOL-BREF score [1]	53.0 (48.0, 60.0)	55.0 (46.0, 62.0)	53.0 (44.0, 62.0)	p = 0.791
FAB [0]	15.0 (12.2, 17.0)	17.0 (15.2, 18.0)	17.0 (15.2, 18.0)	p = 0.228

Values are median (interquartile range). Abbreviations: d-rTMS: deep repetitive transcranial magnetic stimulation, FAB: frontal assessment battery, FMT: Fahn-Tolosa Marin tremor rating scale, HADS: hospital anxiety and depression score, ICARS: international cooperative ataxia rating scale, MBS: most bothersome symptom, SARA: scale for the assessment and rating of ataxia, TUG: time up-and-go, WHOQOL-BREF: short version of the World Health Organization quality of life scale. Significance of the Wilcoxon set at [a] $p < 0.05$ for the primary outcome and at [b] $p < 0.006$ for secondary outcomes.

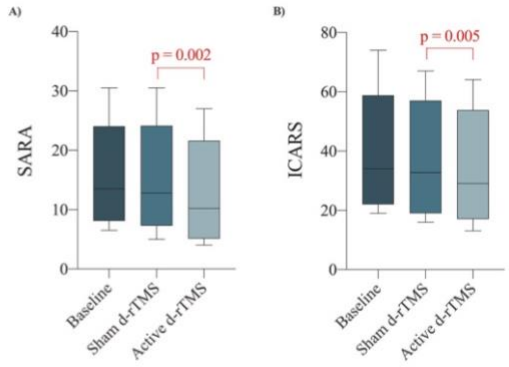

Fig. 2. Median (central mark), interquartile range (bottom and top edges of the box), maximum and minimum values (whiskers) of A) Scale for the Assessment and Rating of Ataxia (SARA) values, and B) International Cooperative Ataxia Rating Scale (ICARS) values at baseline, post-sham, and post-active modulation. SARA values were collected from 24 patients in all time points. ICARS values were collected from 22 patients in all time points.

MSA-c, and post-lesion ataxia showed improvement in SARA and ICARS after d-rTMS. However, only MSA-c was significantly influenced by the stimulation when comparing sham and active d-rTMS ($p < 0.05$) (Supplementary Table 4 and Supplementary Fig. 3).

There was no significant carryover effect in SARA ($p = 0.9$) and in ICARS scores ($p = 0.9$), showing that the effect of the active sessions did not persist after the washout period. Patients who received active stimulation in the first five days (active/sham) did not show different effects when comparing with the patients randomized to receive sham stimulation first (sham/active) with $p = 0.5$ for the period effect of SARA and $p = 0.2$ for ICARS.

3.3. Safety

No patient suffered severe side effects. Out of 24 patients, nine presented mild side effects (five after active d-rTMS and four after sham). Two felt discomfort during sessions (patient 9 during sham and patient 22 during active d-rTMS); three suffered from mild headaches during or after sessions (patients 6, 10, and 16, all during active stimulation), and four patients presented other side effects, but only one did so during active stimulation (patient 20 presented short-lasting worsening of his left leg pain).

3.4. Blinding assessment

At the end of the study, 66.7% of patients reported no differences between active and sham stimulations. Among the 33.3% of patients that perceived difference between sessions, when asked to guess the treatment, 75% guessed correctly. When all patients were asked to guess which sessions were active or sham, 50% did so correctly, and 83.4% based their response on stimulation effects rather than on different sensory perceptions during sessions.

4. Discussion

In this double-blind, crossover trial, cerebellar d-rTMS caused a temporary reduction in ataxic symptoms with no serious associated side effects in patients with different types of cerebellar ataxia. The improvement was self-limited and reversible. Moreover, the clinical effects were consistent, showing significant decreases on both the SARA and ICARS scales, and specific, showing no significant effects in other domains.

This trial supports previous findings in which cerebellar ataxia caused by different underlining mechanisms can improve after cerebellar modulation. A recent study reviewed six trials that investigated effects of cerebellar transcranial magnetic stimulation on ataxic patients [11]. Despite the high variability among reports they all reported positive outcomes [11]. Although these are encouraging results, all trials had important shortcomings. The largest study so far evaluated 74 ataxic patients after cerebellar single-pulse transcranial magnetic stimulation in a double-blind manner and reported improvement in walking and stance abilities [15]. The authors did not assess appendicular abilities and no MRI-navigated system was applied. Additionally, single-pulse transcranial magnetic stimulation is currently used to assess cortical excitability, and is not capable of providing consistent long-term clinical effects [16]. In the present study, each patient received a total of 6000 pulses (five sessions of 1200 pulses each) of d-rTMS. Moreover, we minimized the variation in the stimulation target through neuronavigation. Regardless of limitations, an important aspect of past trials was the absence of significant side effects, which supports the notion that cerebellar d-rTMS is safe [11,17]. In our trial, we observed only mild and self-limited side effects. Of the nine patients, four experienced side effects after sham stimulation, which could be explained by patients standing in uncomfortable positions during sessions or by nocebo effects.

The rationale of stimulating the cerebellum is based on its widespread connections to several neurological sites (Supplementary Fig. 4) [18–20]. Its modulation could reset pathological neuronal oscillations observed in different etiologies of ataxia and lead to symptomatic control. In recent years, the idea of network involvement in neurological symptoms, rather than a single neural structure, has arisen in the neuromodulation field [21]. This concept is already been proven in well-based neuromodulation therapies, such as deep brain stimulation (DBS) of subthalamic nucleus for patients with Parkinson disease, in which many symptoms can improve by targeting a strategic network hub.

In the present trial, we used 1 Hz d-rTMS, which is considered an inhibitory modulation. Our previous experience showed that this pattern of modulation is safe and potentially effective [5]. However, it is important to emphasize that the "inhibitory" and "excitatory" frequencies are not straightforward and that different frequencies can change abnormal oscillations in a diseased brain network. We believe a more comprehensive understanding of this matter beyond excitation or inhibition is mandatory. Also, despite our choice of unilateral modulation, patients presented bilateral improvement. Although these results are based on a post-hoc analysis and are, therefore, exploratory, this is not a unique outcome in the field of neuromodulation. For instance, dystonic patients with unilateral DBS of GPI can improve symptoms bilaterally [22]. We believe that the effects of cerebellar d-rTMS are not constrained to a single cerebellar efferent pathway, but modulate the whole brain network that is influenced by the cerebellum (Supplementary Fig. 4), perhaps by disrupting abnormal oscillations even in the ipsilateral cortex, possibly due to changes in transcallosal pathways mediated by GABA and responsible for interhemispheric inhibition [23]. Since there were no severe side effects in the present trial, we wonder if a bilateral approach could lead to a superior clinical improvement.

The improvement in ataxia measured not only by SARA, but also by ICARS, was significant (Table 2, Fig. 2). There was great individual variability in those results, possibly due to different patterns of cerebellar connectivity impairment. Other variables, however, did not demonstrate significant improvement, such as quality of life. We believe that our short treatment regimen, adequate for a primary exploratory trial without maintenance sessions, is in part responsible for these results. Studies with longer stimulation periods should provide definitive information on the effects of ataxia improvement in quality of life. Importantly, cognition was not negatively affected according to the

Frontal Assessment Battery, which attests further to the safety of this approach [24]. Our blinding assessment revealed that patients were effectively blinded, and allocation concealment was well performed since only 25% of our participants correctly reported detecting differences between active and sham stimulations.

We acknowledge that the treatment effect in the present study (2.6-point change in the primary outcome) was relatively low despite its statistical significance. Even so, the most encouraging results in other randomized trials with riluzole and valproic acid for ataxia were also modest. Romano et al. tested the efficacy of riluzole versus placebo in 55 patients in a highly variable population and found a decrease in SARA scores by 1.02 points in patients [25]. Another group studied valproic acid in a smaller sample of 12 SCA3 patients and reported a 2.05-point decrease in SARA scores [26]. However, although an one point decrease in SARA, a scale with a 40-point range, may seem small, it is considered to be clinically relevant [27,28].

This study has limitations. While our patients had well-defined ataxia diagnoses, our study population was heterogeneous. However, since all patients had cerebellar ataxia as the main core symptom, they possibly shared similar network, or connectome, involvement [29,30]. Another important limitation was the short follow up after sessions, which could have impaired accuracy of quality of life evaluations and did not allow us to determine the real duration of the beneficial effect, in addition to the lack of maintenance d-rTMS to analyze long-term efficacy. The stimulation parameters were chosen based on a pathophysiological rationale, as well as on a previous study [5] and safety concerns, but our data did not allow us to conclude if other parameters would not have produced better results. Additionally, the differences in SARA points between groups was small although it was larger than those reported in previous trials, and the mean difference between active and sham stimulations was significant. Larger and longer trials are necessary to confirm whether cerebellar d-rTMS is in fact a therapeutic alternative for ataxic patients and more importantly, which patients should benefit the most in addition to the optimal stimulation parameters. We believe different frequencies should be attempted in future trials.

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Author contributions

CF: patient's clinical evaluation and scales, study design, literature review, manuscript preparation, writing, revising. DCA: study design, manuscript review and critique. VS: acquisition and interpretation of data, literature search, critical revision of manuscript. RG: manuscript review and critique. ERB: manuscript review and critique. MJT: study design, manuscript review and critique. RGC: patient's randomization, statistical analysis, study design, literature review, manuscript preparation, writing and revising.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.09.001.

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Appendix 8 – Little Brain, Big Expectations. Opinion article on cerebellar neuromodulation published in Brain Sciences.

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MDPI

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].

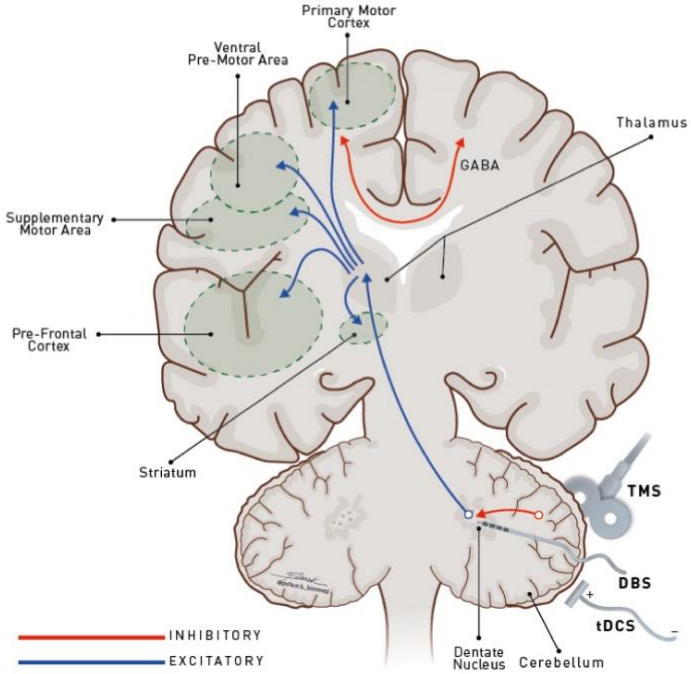

Figure 1. There is an intracortical inhibition between both M1 cortices that is related to maintaining the integrity of axial and limbs movements. The modulation of dentate nucleus activity through tDCS, TMS, or DBS could restore the changes in M1 cortical excitability that are present in some syndromes, 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 cerebellothalamocortical 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 cerebello–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 1. Clinical trials of cerebellar neuromodulation for Parkinson's disease, dystonia, cerebellar ataxia, and essential tremor.

Author, Year	Study Design	Diagnosis, *n*	Intervention	Main Clinical Findings	Class of Evidence
Parkinson's disease					
Koch et al., 2009 [21]	Double-blind, sham-controlled, crossover	PD with dyskinesias, 10	rTMS (cTBS) single session with figure-of-eight coil	Decrease in waking time spent as ON with dyskinesias	III
Minks et al., 2011 [22]	Single-blind, sham-controlled, crossover	PD, 20	One Hz rTMS, single session, with a double-cone coil	Improvement in gross upper limb movement; worsening in fine motor finger and hand function	III
Bologna et al., 2015 [23]	Double-blind, sham-controlled, crossover	PD, 13 + healthy controls, 10	Unilateral TMS (cTBS) single session with figure-of-eight coil	No changes in tremor amplitude, frequency, or magnitude	III
Ferrucci et al., 2016 [24]	Double-blind, sham-controlled, crossover	PD with dyskinesias, 9	Two mA anodal tDCS, five sessions	Improvement in UPDRS IV (dyskinesias section)	III
Sanna et al., 2020 [25]	Double-blind, sham-controlled, crossover	PD with dyskinesias, 11	rTMS (cTBS) single session with circular coil	Decrease in dyskinesias and serum BDNF in active group	II
Workman et al., 2020 [26]	Double-blind, sham-controlled, crossover	PD, 7	Two or 4 mA, unilateral or bilateral tDCS single session	Significant improvement in balance score in bilateral 4 mA group against sham; no gait improvement	II

Table 1. *Cont.*

Author, Year	Study Design	Diagnosis, *n*	Intervention	Main Clinical Findings	Class of Evidence
Dystonia					
Sadnicka et al., 2014 [27]	Single-blinded, sham controlled with crossover	WC, 10	Two mA ipsilateral anodal tDCS, single session	No subjective improvement or changes in the WCRS or timed writing assessment	III
Koch et al., 2014 [28]	Double-blind, sham-controlled	CD, 18 (9 active; 9 sham)	Bilateral rTMS (cTBS), 10 sessions	Small but significant clinical improvement as measured by the TWSTRS of approximately 15%	III
Bradnam et al., 2015 [18]	Double-blind, sham-controlled, crossover	FHD, 8 (WC = 5; MD = 3); healthy controls, 8	Two mA anodal/cathodal tDCS, single session	No change in clinical outcomes	II
Cerebellar ataxia					
Shiga et al., 2002 [29]	Double-blind, sham-controlled	Spinocerebellar degeneration, 74 (39 active, 35 sham)	Single-pulse TMS, 21 sessions with circular coil	Improvement in 10 m time, 10 m steps, tandem steps. and standing capacities, especially in the cerebellar type	III
Ihara et al., 2005 [30]	Single-blind, uncontrolled	Spinocerebellar degeneration, 20	Single-pulse TMS, 24 sessions with figure-of-eight coil	Improvement in ataxia (ICARS)	III
Grimaldi and Manto et al., 2013 [31]	Single-blind, sham-controlled, crossover	Varied cerebellar ataxias, 9	One mA right anodal tDCS, single session	No change in posturography or upper limb dexterity	III
Bonnì et al., 2014 [32]	Open label	Posterior circulation stroke with ataxia, 6	rTMS (iTBS, ipsilateral), 10 sessions with figure-of-eight coil + physical therapy	Ataxia improvement (MICARS), especially posture and gait subscales	IV
Kim et al., 2014 [33]	Double-blind, sham-controlled	Posterior circulation stroke with ataxia, 32	One Hz ipsilateral rTMS, five sessions with figure-of-eight coil	Improvement in the 1 0m walk test 1 month after; balance improved after 5 days and after 1 month	III
Benussi et al., 2015 [34]	Double-blind, sham-controlled, crossover	Varied cerebellar ataxias, 19	Two mA anodal tDCS, single session	Improvement in ataxia (SARA and ICARS), hand dexterity, and gait	III
Grecco et al., 2017 [35]	Single-blind, sham-controlled, crossover	Ataxic cerebral palsy, 6	One mA anodal tDCS, 10 sessions + treadmill training	Improvement in hip oscillation during eyes-closed gait (stabilometric evaluation)	III
Benussi et al., 2017 [36]	Double-blind, sham-controlled	Varied neurodegenerative ataxias, 20; healthy controls, 10	Two mA anodal tDCS, 10 sessions	Improvement lasting at least 3 months in SARA, ICARS, gait, and hand dexterity (in non-dominant hand)	III
Benussi et al., 2018 [37]	Double-blind, sham-controlled crossover	Varied neurodegenerative ataxias, 20	Two mA anodal tDCS (cerebellum) and 2 mA cathodal tDCS (spinal cord), 10 sessions	Improvement lasting at least 3 months in SARA, ICARS, gait, hand dexterity, and quality of life	II
Manor et al., 2019 [38]	Double-blind, sham-controlled	Spinocerebellar ataxia, 20	Single-pulse TMS, 20 sessions with circular coil	Improvement only in stance sub-score of SARA and standing postural sway metrics	II
França et al., 2020 [9]	Double-blind, sham-controlled, crossover	Spinocerebellar ataxia type 3, 9; multiple system atrophy cerebellar type, 8; post-lesion ataxia, 7	One Hz unilateral rTMS, 10 sessions with double-cone coil	Improvement in SARA and ICARS	II
Essential tremor					
Gironell et al., 2002 [39]	Double-blind, sham-controlled, crossover (washout 1 week)	ET, 10	One Hz rTMS, single session with butterfly coil	Tremor improvement according to the FTM (17%), and accelerometry evaluation on the 5 min assessment	II

Table 1. *Cont.*

Author, Year	Study Design	Diagnosis, *n*	Intervention	Main Clinical Findings	Class of Evidence
Avanzino et al., 2009 [40]	Open label in five patients, and single-blind, sham-controlled, crossover in seven patients	ET, 10 + healthy controls, 11	One Hz right rTMS, single session with figure-of-eight coil	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)	IV
Popa et al., 2013 [41]	Open label	ET, 11; healthy controls, 11	One Hz rTMS, five sessions with figure-of-eight coil	Tremor improvement that built up until day 12 and persisted for 3 weeks (FTM); decrease in tremor amplitude.	IV
Gironell et al., 2014 [42]	Double-blind, sham-controlled crossover	ET, 10	Two mA cathodal tDCS, 10 sessions	No acute or long-lasting benefit (FTM and accelerometric recordings)	III
Bologna et al., 2015 [43]	Double-blind, sham-controlled, crossover	ET, 16; healthy controls, 11	rTMS (cTBS), single session with eight-shaped coil	No change in tremor severity and reaching movements (FTM and accelerometer)	III
Shin et al., 2019 [44]	Single-blind, sham-controlled	ET, 22 (12 active, 10 sham)	One Hz rTMS, five sessions with figure-of-eight coil	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	III

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

difficult to currently advise the cerebellum as a new target. Although neurodegenerative ataxia remains orphaned of disease-modifying therapies, current results from cerebellar neuromodulation approaches may suffer from publication bias of positive results and small sample sizes, besides suboptimal blinding. Also, most studies have focused on stimulating still-imprecise areas within the cerebellar cortices, using tDCS or figure-of-eight TMS (i.e., superficial stimulations), with the goal of having an indirect effect on cerebellar–cortex connections [5]. There is currently a lack of information about the specific effects of cerebellar–cortex stimulation on various groups of neurons (e.g., Purkinje neurons, inhibitory interneurons of the cerebellar cortex, and granule cells) and afferent pathways (e.g., mossy fibers and climbing fibers) [5]. Because the cerebellum has a highly convoluted and completely different cytoarchitecture than the neocortex, generalizations of current density and geometry obtained from neocortical stimulation by TMS and tDCS are at least over-optimistic. This lack of specificity makes us rethink whether we are applying the stimulus at the right spot. Because of the complicated architecture of the cerebellum, the focus perhaps should shift from modulating the cerebellar cortex to targeting its output nuclei. This strategy could increase the stimulation's efficiency and reduce variability in the outcomes of cortical stimulation. On an organizational level, the fibers from the cerebellar nuclei directly regulate movement commands in the spinal cord and brainstem, increase motor signals in the cerebral cortex, and modulate signals for adaptive learning via connections to the inferior olive. Direct stimulus to the dentate nucleus via a double-cone coil TMS (which allows for the stimulation of deep structures) [8] and DBS could be more precise, resetting abnormal firing oscillations or enhancing cerebellar output activity, depending on the parameters [4].

Several studies using cerebellar tDCS have compared both anodal and cathodal stimulation with a sham condition. Varying results have been obtained. Most of the studies report a different effect for anodal and cathodal tDCS. Some studies [48] have reported increased cerebellar brain inhibition following anodal stimulation applied over the cerebellar cortex. On the other hand, cathodal stimulation has reduced cerebellar brain inhibition. Two studies found the opposite effect [49,50]. Other studies did not find any effect after either stimulation type [24,51]. Additionally, many studies evaluating the effects of cerebellar cortical stimulation have been negative for motor outcomes in PD [23], essential tremor [42], and dystonia [27] or these studies found considerable side effects [22]. A recent, randomized, sham-controlled study failed to show the efficacy of figure-of-eight TMS over the cerebellum in 22 essential tremor patients [44]. Again, the absence of Magnetic Resonance Imaging-navigated systems and the superficial TMS stimulation applied bring doubt upon which regions of this overpopulated brain area we are stimulating.

7. So, What Is Next?

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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Appendix 9 – Dentate nucleus stimulation for essential tremor. Original article on cerebellar neuromodulation for essential tremor published in Parkinsonism and Related Disorders.

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Dentate nucleus stimulation for essential tremor

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Thalamus ventral intermediate nucleus deep brain stimulation is a well-recognized therapy for refractory essential tremor (ET) [1]. However, cortical atrophy and microangiopathy may present a greater surgical risk especially in older patients. In this context, alternative targets for neuromodulation in ET may be relevant. Cerebellar neuromodulation has emerged with promising results in movement disorders [2]. Although there have been only a few studies, non-invasive and invasive stimulation over the cerebellum has been shown to potentially improve ataxia, dystonia, and tremor [2–5]. Here, we report the case of a patient with refractory ET who underwent dentate nucleus DBS (DN DBS).

A 76-year-old right-handed male presented with a 50-year history of tremor in uppers limbs and voice that became incapacitating over the last 20 years. He was diagnosed with essential tremor and had been taking 200 mg of primidone with initial improvement, but symptoms worsened over the last 5 years. Propranolol was not tolerated over 40 mg due to hypotension effect. By the time of his first visit he was not able to write, drink, or eat because of the high amplitude tremor (Motor part of Fahn, Tolosa, Marin Tremor Scale = 65/120). Considering the refractoriness of his symptoms and severity of the tremor he was referred to DBS surgery. However, because of his marked brain atrophy and leukoencephalopathy, considering the higher risks of bleeding, the dentate nucleus was proposed as a target. The study was approved by the local ethics committee and the patient provided written informed consent.

The surgical procedure was described elsewhere [3] and is detailed in supplementary file 1. Fig. 1 illustrates the target. The DBS was turned on one month after surgery. During the follow-up, we tested a range of frequencies between 6 and 150 Hz and pulse widths between 60 and 210 μs. We tested each electrode separately and then both sides together, first using monopolar and after using bipolar settings. The tremor improvement was seen ipsilateral to the stimulated lead when tested unilaterally. The patient was assessed every 28 days and parameters were changed in all visits according to tendencies, patient's improvement, or collateral effects. Once the best parameters were defined, nine months after surgery, the configuration was kept constant until the double-blind evaluation, at the one-year follow-up. During the double-blind evaluation, the patient was assessed under off- and on-stimulation conditions. Both conditions were introduced 30 min before the clinical ratings in randomized order, with both patient and evaluator blinded to the DBS status. The best settings were bipolar and activated the most proximal contacts (left DN = 1.6 mA, 78 μs, 138 Hz; right DN = 1.2 mA, 117 μs, 138 Hz).

We observed an improvement in tremor with a 48% reduction in Motor part of Fahn, Tolosa, Marin Tremor Scale (from 66/120 to 34/120) and a 71% reduction in tremor amplitude using the Weber-Fechner Relationship when comparing the active versus sham phases. Part of this evaluation can be seen at the supplementary video. Dizziness was noted with a higher pulse width on monopolar stimulation and some habituation could be seen over the months. Patients' global impression of change (PGIC scale) during the last follow-up was 6 (better, and definitive improvement that has made a real difference).

In this pilot case, DN DBS in a patient with ET was a safe and well-tolerated procedure with no major side effects during the 12-month follow-up period. The effect on tremor was remarkable in the blinded assessment one year after the surgery. Additionally, the stimulation significantly improved his functionally, including the handwriting (from 4 to 2 points in item 10 of Fahn, Tolosa, Marin Tremor Scale).

Thus far, clinical studies have only evaluated the effects of DN DBS in single cases. Although only small improvements were noted, DN DBS was effective for treating ataxia in SCA type 3 [3], cerebellar stroke [4], and dystonia [5]. To our knowledge, this is the first report for ET. Treatment involving DBS of the VIM and posterior subthalamic area targeting the fibers of the dentatothalamic tract (DTT) has been shown to be effective for treating ET. We postulate that DN stimulation can be effective in reducing tremor by modulating the nucleus excitatory activity and targeting the DTT at its origin. Larger studies are necessary to address whether DN DBS is in fact effective over short- and long-term periods for ET and to better determine the optimal site of electrode placement and parameters for stimulation.

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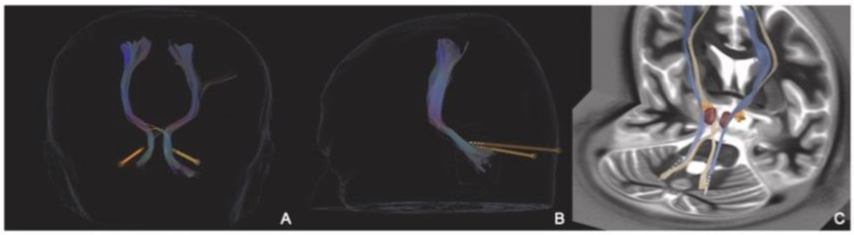

Fig. 1. Bilateral deep brain stimulation (DBS) of the dentate nucleus and relation with dentatorubrothalamic tracts (DRTT). Three-dimensional depictions of electrode placement in the dentate nucleus and its relations to the dentate-rubro-thalamic tract (DRTT). Fig. 1A and B result from a co-registration of pre-operative MRI with patient-specific deterministic tractography and post-operative CT (Elements Software, Brainlab AG, Germany). Fig. 1C originates from a co-registration of pre-operative MRI and post-operative CT, however normalized to the MNI space and comparing electrode position with a normalized DRTT projection (LEAD DBS Software, Horn & Kuehn, Germany).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2020.12.001.

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Appendix 10 – Long-Term Outcome of Dentatotomy in a Dystonic Patient. Case report in Arquivos Brasileiros de Neurocirurgia.

THIEME OPEN ACCESS

Case Report | Relato de Caso

Long-Term Outcome of Dentatotomy in a Dystonic Patient

Avaliação a longo prazo de paciente distônico submetido a dentatotomia

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Arq Bras Neurocir

Abstract

Dystonia is characterized by sustained or intermittent muscle contractions leading to abnormal movements and impairment in daily activities. Stereotactic dentatotomy has been a treatment option in cases of spasticity or dystonia, especially in patients with cerebral palsy, but the long-term effect of dentatotomy in dystonia is still unknown. Here we describe a dystonic patient who underwent dentatotomy for symptomatic treatment of refractory dystonia and whose 20-year follow-up showed improvement in symptoms.

Keywords
- dystonia
- dentatotomy
- cerebral palsy

Resumo

A distonia é caracterizada por contrações musculares intermitentes ou sustentadas que levam a movimentos anormais e ao comprometimento das atividades cotidianas. A dentatotomia estereotáxica tem sido uma opção de tratamento nos casos de espasticidade ou distonia, especialmente em pacientes com paralisia cerebral, mas o efeito a longo prazo da dentatotomia na distonia ainda é desconhecido. Descrevemos aqui um paciente submetido a dentatotomia para tratamento sintomático de distonia refratária e cujo acompanhamento por 20 anos demonstrou melhora nos sintomas.

Palavras-chave
- distonia
- dentatotomia
- paralisia cerebral

Introduction

Dystonia is a neurologic disorder characterized by sustained or intermittent muscle contractions causing abnormal movements and/or postures[1] and involves a heterogeneous group of disorders with many underlying causes, both known and unknown. Etiologic classification relates to whether dystonia is inherited, acquired, or due to identifiable brain abnormalities.[1] Dystonia can arise secondary to brain damage, including stroke, trauma, or adverse medication effect (tardive dystonia), or as a symptom of other diseases, such as Parkinson disease. Pharmacologic therapies, especially the anticholinergic agents, can provide modest symptomatic improvement but can lead to significant adverse effects. Botulinum toxin injections can provide relief in many patients.[1,2] However, the injections must be repeated every few

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months, patients can become resistant, and adverse effects, such as weakness, are not uncommon. Surgical interventions have included rhizotomy, for cervical dystonia; ablation of the thalamus (thalamotomy); internal globus pallidus (pallidotomy); dentate nucleus (dentatotomy), and deep brain stimulation for more generalized dystonias.[1–3]

For many decades, stereotactic dentatotomy has been a treatment option in cases of spasticity[4] or dystonia, especially in patients with cerebral palsy. Though vastly used in the past, in the last twenty years, published papers on the matter were rare. In this line, the long-term effect of dentatotomy in dystonia is still unknown. Here we describe a dystonic patient who underwent dentatotomy for symptomatic management and was monitored for 20 years.

Case Report

A 39-year-old right-handed man presented with dystonia since early childhood due to hypoxia during birth. His symptoms were mainly distal on four limbs, as well as on larynx, and significantly impaired his work, study and leisure activities. He had no cognitive disability, no motor involvement other than dystonia/dystonic tremor, and no remarkable neuroimaging findings. All the treatment attempts were frustrated, including physical therapy and medical therapy with diazepam, clonazepam, valproic acid and trihexyphenidyl. By the time the patient was 20 years-old, in 1995, due to refractory symptoms and with patient's consent, a left dentatotomy was performed. The stereotactic coordinates of the targets were determined based on previously published anatomical studies.[5,6] The target point was located 10–12 mm behind the fastigial point, 3–5 mm below the fastigial line, and 8–10 mm from the midline. The patient reported good outcome in the motor function, improvement in left side dystonia, action tremor, walking and performing manual tests, such as drinking. Despite the improvement in dystonia, our patient remained symptomatic on the right side, and in the same year, deep brain stimulation (DBS) was placed on the left subthalamic nucleus. Deep brain stimulation was set as bipolar (contact 0 as anode and 2 as cathode), at 2,1 V, 270 μs and 125 Hz. Twenty years after the first surgery (dentatotomy), the Unified Dystonia Rating Scale (UDRS) was 9,5 (highest score on this scale: 44), with symptoms predominantly in the distal parts of the upper limbs and larynx. He was otherwise asymptomatic.

The patient had the impression that the procedures improved $\sim$ 50% of his dystonia, mainly on his legs, now considered asymptomatic.

Discussion

Dentate lesions result in prolonged reaction time associated with a corresponding increase in the latency of movement and related responses of cortical neurons, and may affect movement programming through the cortico-neocerebellum cortical loop.[7] It may improve abnormal movements through decreasing in the facilitatory outflow of the dentate nucleus over the motor cortex.[8] Basal ganglia or cerebral cortex damage tend to lead the contralateral cortex to hyperexcitability that can be reduced with dentatotomy.[9,10]

In agreement with this hypothesis, Schneider and Crosby[9] found that the cerebellar cortex aided abnormal posturing and hypertonia in patients with cerebral palsy.

After those results, several studies showed benefits of dentatotomy in dystonia, choreoathetosis and spasticity in cerebral palsy patients.[11–14] Improvement seemed more substantial in the lower limbs,[15] which happened in our patient. A combination of dentatotomy and thalamo-subthalamotomies showed even better result in cases of spasticity than dentatotomy alone.[16] To our knowledge, the case reported is the first to show the association between dentatotomy and subthalamic deep brain stimulation.

Despite the report of good outcomes seen in the literature, the benefit over long periods is unknown. In 1970, Heimburger[17] reported improvement in 50 out of 61 patients submitted to dentatotomy, with benefits lasting from 4 months to 5 years and relapse in 11 cases. Siegfried and Verdie[18] described a reduction in improvement after months or years of the operation, with a failure rate of 10% in 6 months, 20% in 2 years and 24% in 3 years of follow-up. Our patient remained stable after 20 years follow-up.

Finally, although dentatotomy can be a safe treatment of spasticity and dystonia, the current trend is the DBS surgery, which usually brings better results with fewer side effects.[19] Even so, ablative surgery appears to be a good option for a proportion of patients to whom the DBS is contraindicated, as well as for those with social problems,[20].

Conclusion

This case report showed sustained benefit of dentatotomy associated with unilateral subthalamic DBS for secondary dystonia. The dentatotomy can be considered as a good option for refractory dystonia, which should be further explored in future studies. Our study protocol was safe; it laid the groundwork for larger studies regarding dentatotomy, with or without DBS, in this patient population.

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Appendix 11 – Interleaving Stimulation in Parkinson Disease: Interesting to Whom? Original article on neuromodulation published in World Neurosurgery.

ORIGINAL ARTICLE

Interleaving Stimulation in Parkinson Disease: Interesting to Whom?

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BACKGROUND: **Interleaving stimulation (ILS) is a stimulation strategy that can help the physician manage more challenging cases of patients with deep brain stimulation (DBS) for Parkinson disease (PD). It consists of altering 2 different programs on the electrode with the same frequency.**

OBJECTIVES: **Our objective was to overview our patients' experience with ILS and explore clinical scenarios in which ILS should be considered when programming DBS in patients with PD.**

METHODS: **We retrospectively reviewed medical charts from 120 patients with PD treated with DBS between 2011 and 2018.**

RESULTS: **Eighteen patients received ILS. One was excluded because of the medical chart was incomplete. The remaining 17 patients had subthalamic nucleus DBS ($n = 14$) and globus pallidus internus DBS ($n = 3$). Eight patients (47%) received ILS to improve rigidity and bradykinesia, 4 to improve dyskinesias, 4 because of refractory tremor, and 1 for gait management. Until the end of data collection, 13 of 17 patients (70%) were still on ILS, with a mean duration time of 28.8 months (range, 2–44 months). Four patients reported no benefit from ILS and had their program changed.**

CONCLUSIONS: **Overall, ILS is useful 1) to use 2 contacts that optimally improve 2 specific symptoms but have different therapeutic windows; 2) to avoid side effects related to current spreading to nearby areas; 3) to increase frequency in a small region; or 4) to stimulate a larger target area.**

INTRODUCTION

Deep brain stimulation (DBS) is considered a successful treatment for patients with Parkinson disease (PD) and motor fluctuations.[1] Most patients achieve good clinical results after surgery and keep this benefit for several years[2]; however, insufficient outcomes after DBS can occur and have been related to many issues, including inadequate selection of patients, unreal expectations, lead misplacement, or inadequate programming. Experienced movement disorder specialists are generally able to successfully troubleshoot programming errors and achieve a balance between inadequate motor outcomes and intolerable side effects, even when considering electrodes not optimally placed.[3] In this scenario, advanced programming, such as multiple cathodes, shorter pulse width, lower frequencies, and interleaving are the most commonly used strategies in clinical practice. Interleaving stimulation (ILS) is an approach that changes the electric field by rapidly alternating 2 stimulation programs and, in some patients, could help further improve their motor symptoms without eliciting adverse effects.[4-7] The amplitude, active contacts, and pulse width can differ between the 2 programs, but the frequency must be identical and is restricted to a maximum of 125 Hz. Despite being largely applied in clinical practice, few reports have addressed the applicability of ILS in PD. The aim of this study was to systematically report our clinical experience with ILS in our center and review the main uses of this advanced DBS program. It was not

Key words
- Deep brain stimulation
- Interleaving
- Parkinson disease

Abbreviations and Acronyms
DBS: Deep brain stimulation
GPi: Globus pallidus internus
HFS: High-frequency stimulation
ILS: Interleaving stimulation
LID: Levodopa-induced dyskinesia
PD: Parkinson disease
SNr: Substancia nigra pars reticulata
STN: Subthalamic nucleus
VTA: Volume of tissue activated
ZI: Zona incerta

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our goal to compare ILS with classic programming but to explore this type of stimulation as an option in the programming trial-and-error process.

METHODS

One hundred and twenty patients with PD underwent DBS surgery from 2011 to 2018 at the University of São Paulo, Brazil. All patients submitted to DBS surgery had motor fluctuations (incapacitating wearing off or dyskinesias), refractory tremor, or severe medication intolerance, along with good response (>35%) in the levodopa challenge and absence of severe cognitive decline (Mattis scale >130). From this cohort, we screened those treated with ILS. All patients with ILS had 3387 or 3389 Medtronic bilateral electrodes and double-channel implantable pulse generators (Activa [Medtronic, Minneapolis, Minnesota, USA]). Clinical and demographic data were collected from medical records, including reason for changing to ILS, DBS target, current programming status, duration of ILS, sex, age at PD onset, age at DBS surgery, time between surgery and ILS, and program tried immediately before ILS.

All patients, as per our clinical practice, go through contact testing 3 or 4 weeks after surgery and receive monopolar stimulation with 130 Hz frequency and 60 microseconds pulse width in the best contact as the first programming DBS strategy. The best contact is defined as the one with best clinical outcomes and largest therapeutic window. Amplitude is slowly increased over the next weeks until satisfactory clinical benefit or manifestation of side effects. When patients and physicians were satisfied with DBS outcomes, stimulation was left unchanged. If patients did not improve adequately or if there were adverse effects, other strategies were tested in a variable order individualized for each patient's needs. For instance, if a patient experiences side effects related to activation of internal capsule, the contact can be changed, current or pulse width decreased, or bipolar stimulation can be attempted. Sometimes, patients show great symptom control in one side of the body, whereas the other is inadequately improved (because of asymmetry of the disease of electrode unilateral misplacement). In those cases, we usually change only the contralateral electrode configuration, although bilateral changes can be made in selected cases.

RESULTS

From the entire cohort, 18 patients received ILS. One female patient had incomplete medical records and was therefore excluded from the analysis. The remaining 17 patients (8 female, 47%) had a mean of 14.82 (range, 7–27 years) from the PD diagnosis to DBS surgery (Table 1). The mean time between DBS surgery and ILS programming was 2.58 years (range, 1–7 years) (Table 1). Two targets were used: the subthalamic nucleus (STN) in 14 patients and the globus pallidus internus (GPI) in 3 patients. All patients initially received conventional programming strategies to relieve their symptoms before ILS, according to standard algorithms,[8] but achieved suboptimal results over time.

Thirteen patients had unilateral ILS, and only 4 had bilateral (patients 1, 2, 8, and 17). Eight patients (47%) received ILS to improve rigidity and bradykinesia (patients 1–8), 4 to improve dyskinesias (patients 9–12), 4 to improve refractory tremor (patients 13–16), and 1 for gait management (patient 17). Rigidity and bradykinesia were the main concerns of patient 8 before ILS, but he also experienced important tremor. Likewise, patient 11 had dyskinesia as the most bothersome symptom, but also faced troublesome rigidity and bradykinesia (Table 1).

Until the end of data collection, 13 of 17 patients (70%) were still on ILS, with a mean duration time of 28.8 months (range, 2–44 months) (Table 1). Four patients reported no benefit and therefore had their stimulation changed. Patient 3 reported apraxia of eyelid opening and was changed to monopolar stimulation of the left (L) lead (L, 0–00 2.7 V 90 microseconds 130 Hz). Patient 6 had ILS for 3.5 months and had his program changed on the left side to bipolar (L, 0+-0 3.5 V 90 microseconds 130 Hz) because of diplopia, as well as worsening in speech and gait. Patient 11 tried ILS for only 3 months, and in this period reported worsening in tremor, rigidity, and speech. This patient is testing 4 stimulation groups, none of which uses ILS. Patient 15 failed to improve tremor with ILS for 1 month and receives bilateral double monopolar stimulation (L, 0–0 3 V 90 milliseconds 130 Hz/right (R), 0–0 2.5 V 100 milliseconds 130 Hz).

DISCUSSION

In this study, we have reported the main issues concerning the use of ILS in 17 patients with PD after classic programming techniques failed to achieve optimal therapeutic benefit, in patients' and physicians' opinions. Clinicians should be aware of the applicability of ILS because although there are general guidelines available for programming, there is no validated and established programming protocol.

Inefficient programming can result in suboptimal clinical outcomes and lead to side effects. In a retrospective analysis of 41 patients evaluated in 2 DBS centers for the management of DBS failures, 15 patients (37%) were identified as inadequately programmed and improved significantly after reprogramming.[9]

ILS allows shifting of 2 sets of amplitude and pulse width parameters pulse to pulse and is a programming tool that could improve patients' symptoms. The main difference between ILS and classic techniques such as monopolar, double monopolar, and bipolar is the electric field generated, which can be distinctively shaped to modulate a larger portion of the targeted nucleus and avoid undesired areas.[10] By using different amplitudes and pulse widths, the physician can explore >1 contact, allowing unique current shaping.[7] This factor is especially helpful in small targets (e.g., STN) and also in electrodes that are not optimally located. Moreover, the offset of the 2 programs by itself could provide additional effect in the clinical outcomes, because using ILS with the same parameters in both programs is not essentially equal to using double monopolar, possibly because of differences in temporal integration.[5] Nevertheless, ILS may reduce battery life compared with monopolar stimulation, an important issue because DBS is still considered an expensive treatment option.

To date, only 7 studies have reported ILS in patients with PD (Table 2), all of whom had STN DBS.[4,10-15] Three articles are case reports[4,12,13] and 4 are case series.[10,11,14,15] In the first study reported on this matter, Wojtecki et al. reported a case in which monopolar stimulation on contact 1 improved hypokinesia, but

Table 1. Sociodemographic Information and Programming in 17 Patients

Patient	Sex	Age at Parkinson Disease Onset	Age at Deep Brain Stimulation	Target	Chief Symptom Before Surgery	Time Between Surgery and ILS (years)	Deep Brain Stimulation Program before ILS	ILS Program	ILS Duration (months)
ILS to improve rigidity and bradykinesia									
1	Female	38	57/60	STN	LID and wearing off	1	L: −000, 1.5 V, 90 microseconds, 130 Hz R: 0−00, 1.2 V, 90 microseconds, 130 Hz	L1: −000 2.2 V, 60 microseconds, 125 Hz L2: 00−0, 1.0 V, 90 microseconds, 125 Hz R1: 0−00, 2.2 V, 60 microseconds, 125 Hz R2: 000−, 1.4 V, 90 microseconds, 125 Hz	35
2	Male	29	56	STN	LID	2*	Not found	L1: 00−0, 4.3 V, 90 microseconds, 125 Hz L2: −000, 2.4 V, 60 microseconds, 125 Hz R1: 00−0, 1.5 V, 90 microseconds, 125 Hz R2: 0−00, 3.3 V, 60 microseconds, 125 Hz	64
3	Female	42	69	STN	LID and wearing off	3*	Not found	L1: 0−00, 3.0 V, 90 microseconds, 125 Hz L2: 00−0, 3.0 V, 90 microseconds, 125 Hz R 0−00, 3.0 V, 90 microseconds, 125 Hz	Not found
4	Female	50	70	STN	LID and wearing off	1	L: −00+, 2.0 V, 90 microseconds, 120 Hz R: 0−00, 3.6 V, 90 microseconds, 120 Hz	L1: 0−00, 1.6 V, 90 microseconds, 125 Hz L2: 00−0, 2.2 V, 90 microseconds, 125 Hz R 0−+0, 2.3 V, 90 microseconds, 125 Hz	30
5	Male	24	40	STN	Tremor	3	L: −−00, 3.4 V, 90 microseconds, 130 Hz R: −−00, 3.2 V, 90 microseconds, 130 Hz	L1: −−00, 3.6 V, 90 microseconds, 125 Hz L2: 00−0, 2.5 V, 90 microseconds, 125 Hz R −00, 3.4 V, 90 microseconds, 125 Hz	44
6	Male	37	49	STN	Levodopa intolerance	1	L: 00−+, 3.5 V, 90 microseconds, 130 Hz R: 00−0, 3.0 V, 60 microseconds, 130 Hz	L1: 0−00, 1.1 V, 60 microseconds, 125 Hz L2: 00−0, 2.4 V, 60 microseconds, 125 Hz R 00−0, 3.5 V, 60 microseconds, 125 Hz	3
7	Female	50	61	STN	Wearing off	5	L: 0−00, 3.4 V, 90 microseconds, 130 Hz R: 0−00, 2.4 V, 90 microseconds, 130 Hz	L1: 0−00, 3.2 V, 90 microseconds, 125 Hz L2: −000, 1.5 V, 90 microseconds, 125 Hz R: 0−00, 2.4 V, 90 microseconds, 125 Hz	2
8	Male	37	62	GPI	LID	4	L: 0−00, 2.8 V, 90 microseconds, 130 Hz R: 00−0, 1.8 V, 90 microseconds, 130 Hz	L1: 0−00, 2.8 V, 90 microseconds, 125 Hz L2: −000, 1.0 V, 90 microseconds, 125 Hz R1: −000, 1.2 V, 90 microseconds, 125 Hz R2: 00−0, 1.8 V, 90 microseconds, 125 Hz	7
ILS to improve dyskinesia									
9	Female	45	59	STN	LID	2	L: 0−00, 2.6 V, 90 microseconds, 130 Hz R: 0−00, 2.0 V, 90 microseconds, 130 Hz	L: 0−00, 2.6 V, 90 microseconds, 125 Hz R1: 000−, 1.5 V, 90 microseconds, 125 Hz R2: 0−00, 2.0 V, 90 microseconds, 125 Hz	25
10	Male	30	39	STN	LID and wearing off	3*	Not found	L: 0−00, 3.7 V, 90 microseconds, 125 Hz R1: 00−0, 1.5 V, 90 microseconds, 125 Hz R2: 000−, 3.7 V, 90 microseconds, 125 Hz	24

11	Male	42	49	GPI	LID	4	L: 000–, 4.7 V, 90 microseconds, 170 Hz R: ––00, 3.0 V, 90 microseconds, 170 Hz	L1: 000–, 4.7 V, 90 microseconds, 125 Hz L2: –000, 1.0 V, 90 microseconds, 125 Hz R: ––00, 3.0 V, 90 microseconds, 170 Hz	3
12	Female	25	41	GPI	LID	3*	Not found	L1: 00–0, 2.6 V, 90 microseconds, 125 Hz L2: 000–, 1.0 V, 90 microseconds, 125 Hz R: 0––+, 3.5 V, 70 microseconds, 125 Hz	36
ILS to improve tremor									
13	Male	25	34	STN	Tremor	3*	Not found	L: –000, 3.4 V, 90 microseconds, 125 Hz R1: 00–0, 1.7 V, 90 microseconds, 125 Hz R2: 000–, 3.4 V, 90 microseconds, 125 Hz	21
14	Female	30	42	STN	Tremor	1	L: 0–0+, 3.0 V, 90 microseconds, 210 Hz R: 0—0, 3.8 V, 90 microseconds, 210 Hz	L1: 0—0, 1.2 V, 60 microseconds, 125 Hz L2: 000–, 1.4 V, 60 microseconds, 125 Hz R: 0—00, 1.6 V, 120 microseconds, 125 Hz	42
15	Female	49	56	STN	LID	7	L: 00–0, 2.0 V, 90 microseconds, 130 Hz R: 00–0, 2.5 V, 90 microseconds, 130 Hz	L1: 0–00, 2.0 V, 80 microseconds, 125 Hz L2: 00–0, 2.5 V, 90 microseconds, 125 Hz R: 0—0, 2.5 V, 100 microseconds, 125 Hz	1
16	Male	52	66	STN	LID and wearing off	2	L: 0–00, 3.5 V, 90 microseconds, 130 Hz R: 0–00, 1.5 V, 90 microseconds, 130 Hz	L1: 0–00, 3.0 V, 60 microseconds, 125 Hz L2: 000–, 2.7 V, 90 microseconds, 125 Hz R: 0—00, 2.0 V, 90 microseconds, 130 Hz	23
ILS to improve gait									
17	Male	53	60	STN	Freezing of gait	2	L: 0–00, 3.0 V, 90 microseconds, 130 Hz R: 00–0, 2.7 V, 90 microseconds, 130 Hz	L1: 0–00, 3.0 V, 90 microseconds, 125 Hz L2: 000–, 0.5 V, 100 microseconds, 125 Hz R1: 000–, 0.5 V, 100 microseconds, 125 Hz R2: 0–00, 2.7 V, 90 microseconds, 125 Hz	22

ILS, interleaving stimulation; STN, subthalamic nucleus; LID, levodopa-induced dyskinesia; L, left lead configuration; L1, left lead first configuration; L2, left lead second configuration; R, right lead configuration; R1, right lead first configuration; R2, right lead second configuration; GPI, globus pallidus internus.
*Information not clear in medical chart, estimated with first record of ILS found.

Table 2. Studies Analyzing Interleaving Stimulation in Patients with Parkinson Disease

Reference	Number of Patients	Lead Location	Results Summary
Wojtecki et al., 2011[4]	1	Not mentioned	Good control of cardinal symptoms without side effects, allowing differential therapeutic effects on hypokinesia and tremor without SE
Miocinovic et al., 2014[10]	3	Suboptimal en case 1 and 2, optimal in case 3	Case 1: better tremor control without diplopia Case 2: tremor and bradykinesia control without diplopia and paresthesias Case 3: improvement in tremor and dyskinesia without worsening nocturnal rigidity
Ramirez-Zamora et al., 2015[11]	9	Well located in 8 patients; no information in 1 patient	ILS applied for 3 patients with dyskinesias, 4 patients with dysarthria, and 2 patients with partial benefit in parkinsonism who could not tolerate higher voltages. After ILS, improvement in symptoms and resolution of SE were reported
Brosius et al., 2015[12]	1	Not mentioned	Unilateral ILS with combined stimulation of subthalamic nucleus and substantia nigra pars reticulata significantly improved the time to walk 4 m
Tsukada et al., 2016[13]	1	Well located	ILS with a combination of monopolar and bipolar configurations improved wearing-off symptoms and gait disturbance without any SE
Zhang et al., 2016[14]	12	Well located	Four groups of patients, based on symptoms: 1) dysarthria, 2) dyskinesias, 3) gait disturbances, and 4) incomplete control of parkinsonism. After ILS, satisfactory improvement in Parkinson disease symptoms and alleviation of stimulation-induced SE were reported
Kern et al., 2018[15]	27	Variable	Three groups of patients, based on symptoms: 1) management of dyskinesias, 2) management of other adverse effects, and 3) improvement of parkinsonism. ILS was effective for the treatment of dyskinesias and parkinsonism, but ineffective for other adverse effects

SE, side effects; ILS, interleaving stimulation.

not tremor, and monopolar stimulation on contact 3 could improved only tremor.[4] The investigators, then, applied ILS with monopolar contacts 1 and 3 and achieved satisfactory control of cardinal symptoms. The largest case series reported ILS use in 27 patients with PD.[15] The investigators divided patients into 3 groups based on the motive for ILS, choosing 1) management of dyskinesias, 2) management of other adverse effects, and 3) improvement of parkinsonism. The most interesting finding was improvement of dyskinesias when more dorsal contacts within the zona incerta (ZI) region were used. However, this finding was based on clinicians' impressions, because no validated scales on dyskinesias were used. To date, case series reported about ILS are highly heterogeneous and report a small number of cases, all in a retrospective manner.

In the following sections, we discuss 4 main scenarios in which ILS could help further improvement in patients' symptoms.

Rigidity and Bradykinesia

Although DBS of the STN or GPI is an excellent surgical treatment for patients with PD, exact targeting of the motor area of the nucleus is paramount for surgical success because of the relation between target stimulated area and improvement in parkinsonian symptoms.[16] The Jaccard coefficient is a conformity index that measures the similarities between 2 sample sets.[17] It is defined as the size of the intersection divided by the size of the sum of the sample sets. Considering the 2 sample sets as the total volume of the motor nucleus and the volume of tissue activated (VTA), larger Jaccard coefficients would in most cases mean better motor outcome after DBS, although other factors can influence outcome. When the electrode is well positioned inside the target, monopolar stimulation might be sufficient to activate a larger portion of the nucleus and therefore control PD symptoms without provoking adverse effects. Because is not uncommon to have suboptimal placed electrodes, to increase the Jaccard coefficient, the physician might use ILS to spread and better fit the VTA and avoid areas that could lead to side effects (Figure 1B). In our cohort of 120 patients with PD, ILS was used for this purpose in 8 patients and was continued long-term in 6 (75%). In all 8 patients, ≥1 middle contact was used in the ILS.

Dyskinesias

STN-DBS–induced dyskinesias can be troublesome for some patients, despite good parkinsonism control. A useful strategy is decreasing the voltage or dopaminergic medication, but some patients might experience a worsening in parkinsonism as a consequence. Another approach in patients with STN-DBS is to explore more dorsal contacts in an attempt to reach the lenticular fasciculus, an efferent tract from the dorsal GPI.[18,19] In well-positioned STN electrodes, stimulation of dorsal (higher) contacts usually affects lenticular fasciculus fibers passing above the STN. Given our knowledge of GPI-STN connectivity, lenticular

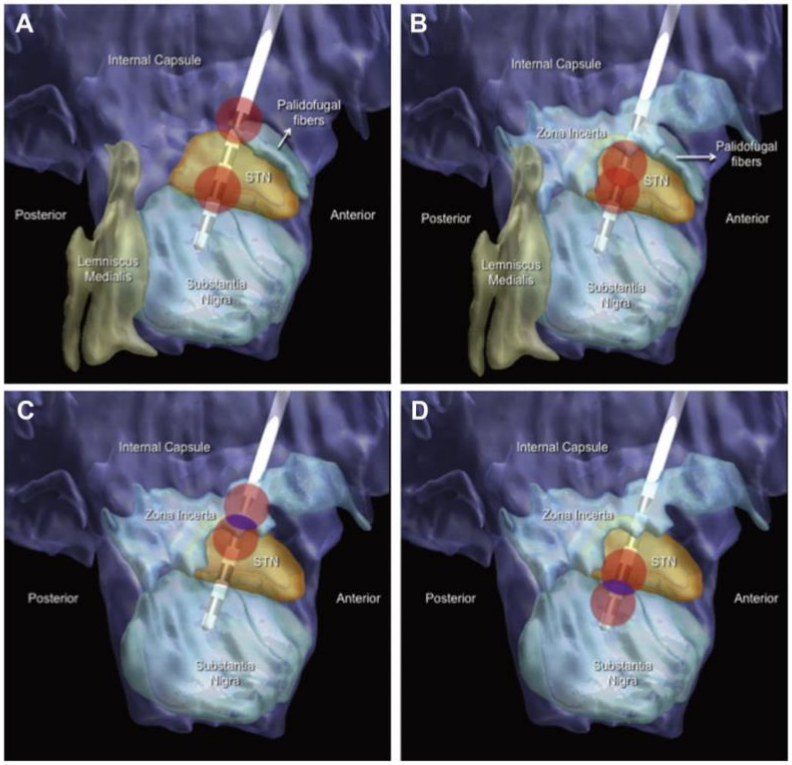

Figure 1. Anatomic illustration of subthalamic nucleus (STN) and its adjacent structures. (**A**) Pallidofugal fibers leaving the globus pallidus internus pass above the STN and could be reached using the most dorsal contact, whereas a more ventral contact would cover the STN area in cases of dyskinesias. (**B**) Stimulation area restricted inside the dorsolateral STN without compromising unwanted adjacent areas (e.g., the internal capsule and the leminiscus medialis) could be used to improve parkinsonism without stimulation-induced side effects. (**C**) Using adjacent contacts in high frequency creates an overlap area where frequency is doubled and can aid in tremor control, as well as targeting the zona incerta, an area above the STN. (**D**) Stimulation of the substantia nigra simultaneously with STN stimulation to improve gait disorders. Figures assembled using Lead-DBS.

fasciculus stimulation may mimic the effects of GPI stimulation and improve dyskinesias.[20] Exploring dorsal contacts in a monopolar or bipolar fashion might elicit side effects or, more commonly, might not be able to stimulate enough dorsolateral STN to improve parkinsonian symptoms. In those cases, ILS with lower amplitudes in the most dorsal contact (targeting the lenticular fasciculus) and higher amplitudes in a ventral contact (targeting the STN) might be able to control dyskinesias without worsening parkinsonism (Figure 1A). In addition, when using adjacent contacts in ILS, or 2 farther contacts with higher amplitudes, there is an overlap area where the frequency doubles, creating a small area of high-frequency stimulation (HFS) inside the total stimulation area. This approach could also help improve dyskinesias, because previous studies have suggested that continuous HFS of the STN has antidyskinetic effects.[21,22] Our cohort had 4 patients in whom this strategy was tested, and 3 are still on ILS (75%). In the 2 patients with STN-DBS, ≥1 ILS contact was the most dorsal.

Tremor

Although amplitude is the most important factor to improve tremor in patients with STN-DBS, its increase is limited by the occurrence of side effects. Frequency is also an important factor to control tremor, because better outcomes are observed when using frequencies ≥130 Hz, with further improvement >185 Hz.[23] HFS might help relieve tremor for keeping neurons in a refractory

state, producing a decrease in STN neurons firing rate.[24] As discussed earlier, ILS is capable of generating an HFS area inside the target, when the choice of contacts and amplitude allows an overlap of the VTA (Figure 1C). Three of our 4 patients receiving ILS for tremor control used adjacent contacts in which this overlap area would be expected. One patient was stimulated using farther contacts (ventral and most dorsal), but with moderately high voltages (3.0 V and 2.7 V). All patients had frequency set to 125 Hz.

Moreover, ILS could help improve tremor considering the modulation effects on ZI, a region immediately above the STN that is known to improve tremor but has a mild effect on rigidity and bradykinesia.[25] Hence, one could use ILS to stimulate ZI with the most dorsal contact, whereas a more ventral contact inside the motor STN improves rigidity and bradykinesia. All our patients had the STN as target of choice and all but 1 (patient 15) activated the most dorsal contact in the ILS. Three of the 4 patients (75%) who received ILS for tremor control kept this programming long-term.

Gait

Previous studies have postulated that gait impairment may be associated with errors in the mesencephalic locomotor pathway.[26,27] Stimulation of the substantia nigra pars reticulata (SNr) might modulate the nigropontine projections to spinal neurons involved in its pathogenesis and showed good outcomes in a previous study.[28] Because of the anatomic proximity between these 2 regions, STN-DBS stimulation of the most ventral contact could, depending on the radius of stimulation, spread to SNr. However, SNr stimulation alone does not improve classic parkinsonian symptoms. ILS with the most ventral contact in the SNr and a more dorsal one in the STN could help simultaneously improve gait disturbances and parkinsonism (Figure 1D).[29] Only 1 patient from our cohort with STN-DBS received ILS to improve gait dysfunction, but the most ventral contacts were not used in his programming. Retrospectively, we postulate that this patient had less trouble walking after ILS secondary to improvement in rigidity and bradykinesia. ILS does not allow different frequencies between the contacts. We propose that the most effective stimulation scenario is lower frequency (<100 Hz) into the SNr associated with higher frequency into the STN, and further studies exploring this hypothesis through the new devices are warranted.

Limitations

The limitations of this study include the retrospective analysis based on medical charts, as well as the relatively small cohort and lack of electrode positioning confirmation by VTA software. Comments about the anatomic location of our patients' active contacts were made based on postoperative computed tomography scan and stimulation effects, widely used on clinical practice. Another important limitation is the absence of Unified Parkinson's Disease Rating Scale values during the visits, because this information was not systematically reported in most patients' charts. Conclusions about efficacy were made based on written reports about patients' and physicians' impressions and if patients were left with the same stimulation or if another strategy was tried, reflecting a common clinical practice. Nonetheless, the aim of this study is not ILS effectiveness or its contrast with classic stimulation but its usefulness. The programming physician should be able to recognize in which scenarios ILS should be tried if the patient still has troublesome symptoms that could not be alleviated after DBS.

CONCLUSIONS

Although most patients with PD achieve good outcome after DBS, ILS must be considered when classic programming fails to achieve optimal outcomes. Overall, ILS is useful 1) to use 2 contacts that optimally improve 2 specific symptoms but have different therapeutic windows, 2) to avoid side effects related to current spreading to nearby areas, 3) to increase frequency in a small region, or 4) to stimulate a larger target area.

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Clinical short communication

Exploring the clinical outcomes after deep brain stimulation in Tourette syndrome

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ABSTRACT

Introduction: Deep brain stimulation (DBS) of the thalamic centromedian-parafascicular (CM-Pf) region is the most common target to treat refractory Tourette syndrome (TS), but the improvement among the patients is quite variable. This study describes the outcomes of stimulation in TS patients and attempts to determine whether the volume of tissue activated (VTA) inside the thalamus or the structural connectivity between the area stimulated and different regions of the brain is associated with tic improvement.

Methods: The DBS patient response was measured as the percentage change in the Yale Global Tic Severity Scale (YGTSS) before and 12 months after surgery. The sum of the two overlapping VTA/CM-Pf volumes from both hemispheres was correlated with the percent change in YGTSS scores to assess whether the area stimulated inside the CM-Pf affects the clinical outcome. Structural connectivity estimates between the VTA (of each patient) and different regions of the brain were computed using a normative connectome that was taken from healthy subjects.

Results: Five male patients aged 26.8 ± 9.3 years were included. No relationships were found between the areas stimulated and the changes in patient tics ($p = .374$). However, the right frontal middle gyrus ($R = 0.564$, $p = .03$), the left frontal superior sulci region ($R = 0.900$, $p = .030$) and the left cingulate sulci region ($R = 0.821$, $p = .045$) structurally correlated with tic improvement.

Conclusion: These data suggests that the volume of thalamic area that is stimulated does not explain the variance in outcomes in TS, however, the pattern of connectivity between the region stimulated and specific brain cortical areas is linked to patient outcome.

1. Introduction

Tourette syndrome (TS) is a chronic neuropsychiatric disease characterized by motor and phonic tics that begins during childhood [1]. TS is frequently associated with other neuropsychiatric comorbidities such as obsessive-compulsive disorder. Overall, treatment of TS with behavioral interventions and/or a variety of medications is effective. Nevertheless, in a subset of patients these approaches are ineffective. Deep brain stimulation (DBS) may be an alternative treatment for these refractory cases [2].

To date, DBS has been used on several TS patients and is typically targeted to the globus pallidus internus or the centromedian nucleus-parafascicular region (CM-Pf) in the thalamus. Although most studies have shown a beneficial effect of DBS on tics, the results also reveal wide variations in treatment outcome [1–3], which highlights the need to determine why some patients improve after surgery and others do not, i.e., which factors predict individual patient responsiveness. These heterogeneous outcomes of DBS in TS treatment reflect (in part) a multi-faceted disorder with motor and behavioral aspects that may not respond equally to a single intervention [4].

Recent studies have demonstrated that the benefit of DBS may rely on the modulation of distant brain areas that are connected to the stimulation spot [5,6]. This remote influence of DBS can be measured by studying the fiber tracts that structurally connect both the volume of the stimulated tissue and the corresponding distant area. In this way, hypothetically, the connectivity of the stimulation site to a specific brain network may be responsible for some of the DBS response. Here, we describe clinical outcomes of DBS that was applied to a few patients

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with TS in an attempt to determine whether the electrode location and the connectivity profile between each patient correlates with tic improvement.

2. Methods

Five patients with TS underwent CM-Pf DBS between 2011 and 2018 at the University of São Paulo, Brazil due to medically refractory TS and according to the Movement Disorders Society recommendation [2]. We retrospectively analyzed data from this cohort who underwent bilateral DBS (Medtronic, Minneapolis, MN, USA) after an informed consent was signed. Clinical variables including medications, age, sex and disease duration were recorded before surgery. The DBS response was measured as a percentage change in the Yale Global Tic Severity Scale (YGTSS) before and 12 months after surgery. Neuropsychological assessment was made before the surgery in all patients, which included the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). This study was approved by a local ethics committee.

2.1. Lead location and volume of tissue activated

Postoperative tomography was linearly coregistered to preoperative MRI using SPM12 and subsequently normalized into ICBM 2009b NLIN asymmetric space using the SyN method (http://stnava.github.io/ANTs/) using the baseline MRI. The DBS electrode contacts were located within MNI space using Lead-DBS software (www.lead-dbs.org) [7].

Once localized the electrode, the volume of tissue activated (VTA) of the active contact was estimated using a heuristic stimulation algorithm previously described by Dembek et al. [8]. The overlap between the VTA and the CM-Pf was calculated in mm^3. The sum of the two overlapping VTA/CM-Pf volumes from both hemispheres was correlated with the percent change in YGTSS scores to analyze whether the area stimulated inside the CM-Pf may have influenced the clinical outcome.

2.2. Connectivity analysis

Using VTAs as seed regions, structural connectivity estimates were analyzed using a normative structural connectome, which consists of high density normative fibertracts that are based on 20 subjects. Global fiber-tracking was performed using Gibb's tracking method [9]. Structural connectivity was calculated by extracting tracts passing through the VTA and calculating the fiber counts in a voxel-wise manner through the entire brain [10]. Brain parcellations were defined according to the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA), which includes pairs of homotopic regions of interest. One hundred and twenty-two regions of interest, anatomically belonging to 37 gyri, and 50 regions of interest overlapped with 14 sulci [11].

2.3. Statistical analysis

Clinical pre-operative factors (age at surgery, age at tic onset, disease duration, YGTSS at baseline) that could predict YGTSS changes after surgery were analyzed using a logistic regression. The connectivity from VTAs was calculated for each patient. Structural connectivity strength was defined as the number of fiber tracts between the VTA and the corresponding cortical area. The connectivity map of each VTA was designed to determine whether changes in tics (the independent variable was defined as the YGTSS change 12 months after surgery, expressed as %) were associated with different brain connectivity patterns. The correlation between the independent (YGTSS) and dependent variable (fiber tracts) was expressed as an R-value.

3. Results

All five patients were male (age at tic onset = 8 ± 2 years; age at surgery = 26.8 ± 9.3 years). The mean disease duration at the time of surgery was 18.4 ± 7.7 years. Medications were kept constant after surgery, except for the patient 3, who suspended all medications due to side-effects (Supplementary File 1). No comorbidities were related, except for patients 2 and 5, who presented mild obsessive-compulsive disorder (YBOCS = 13 and 11, respectively). Table 1 summarizes the clinical outcomes 12 months after surgery. Patients 1, 2 and 3 responded positively after surgery; the symptoms of patient 4 and 5 did not improve (poor responders). The changes in YGTSS after surgery could not be explained by patient age at the time of surgery, age at the time of tic onset, baseline YGTSS or disease duration ($p > .05$).

Table 1
Thalamic-DBS effect on tics before and 12 months after surgery.

	YGTSS total		
	Preoperative	Postoperative	Improvement (%)
Patient 1	79	43	45
Patient 2	96	45	53
Patient 3	72	36	50
Patient 4	78	81	−4
Patient 5	85	82	3

YGTSS = Yale Global Tic Severity Scale.

3.1. Imaging analysis

The active contacts and the VTAs of all patients reached the CM-Pf. Visually, there were no major differences between the active contacts and the clinical outcomes (Fig. 1).

There was no significant relationship between the VTA intersection of the CM-Pf and the YGTSS changes after surgery ($p = .374$, Fig. 2).

Using the connectivity between the VTAs and the cortical areas (described above), we determined that the frontal and limbic regions structurally correlated with YGTSS improvement. Unlike patient 4 and 5 (poor responders), the VTA of the three good responders correlated positively with the right frontal middle gyrus ($R = 0.564$, $p = .03$), the left frontal superior sulci region ($R = 0.900$, $p = .030$) and the left cingulate sulci region ($R = 0.821$, $p = .045$) (Fig. 3).

4. Discussion

Our primary conclusions are: i) the motor outcome after CM-Pf DBS in TS may differ between patients and the VTA inside the target (CM-Pf) does not explain this variability in clinical outcomes; ii) the pattern of the connectivity between the region stimulated and specific brain cortical area may be responsible for the variance in outcome. These two points reinforce recent evidence that, although the targets for DBS in neurological disorders are normally determined by specific anatomical regions (nucleus or tracts), the ideal target may not necessarily be an anatomical structure in itself, but rather, a structurally connected region.

We found a strong correlation between the connectivity of the VTA from the three good responders with the frontal and limbic areas. This is expected because TS presents with motor (probably more related to frontal areas) and behavioral symptoms (limbic areas). The poor responders (patients 4 and 5), despite having his VTAs inside the CM-Pf nucleus, had no activated fibers connected with these regions. Additionally, there were no notable differences between the active contacts inside the CM-Pf among the patients. This is crucial because a misplacement lead could account for the poor outcomes.

Functional imaging proposes that tic improvement is related to the activation of the prefrontal cortex. A PET study revealed an association between tics and brain activity in the dorsolateral-rostral prefrontal cortex and cingulate cortex. In addition, transcranial magnetic stimulation studies indicate that tics originate from compromised inhibition

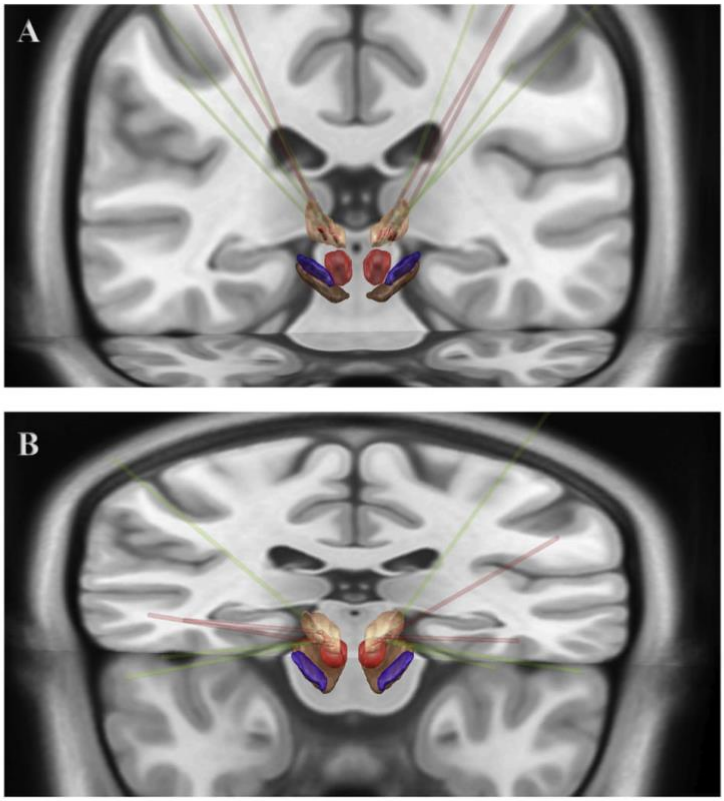

Fig. 1. The figure shows the lead placement and the active contact (red highlighted) between the good responders (green leads) and the poor responders (red leads). All the active contacts reached the centromedian nucleus-parafascicular region. A = Frontal view; B = Upper view. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in the motor cortex [12]. Taken together, we can hypothesize that the effectiveness of CM-Pf/dB is related to the effects of high-frequency stimulation of frontal and limbic cortical regions [13].

Recent data published by the International Deep Brain Stimulation Database and Registry revealed a mean improvement in the YGTSS of 45.1% in 157 patients with TS, 12 months after surgery [14]. Although individual data or interquartile ranges were not available, the large SD implies that the level of improvement among the TS patients was quite variable. A complex interplay between the severity and the chronicity of tics, baseline characteristics, psychiatry comorbidities, electrode placement and VTA connectivity may together account for this variability. Studies focusing on the most important predictive factors are

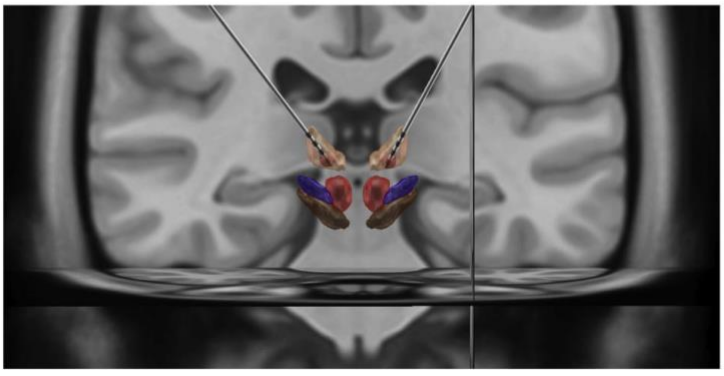

Fig. 2. Representation of the volume of tissue activated inside the centromedian nucleus-parafascicular region from Patient 2. The figure illustrates the VTA (red sphere) that reaches the centromedian nucleus-parafascicular region of patient 2. The volume of each VTA did not differ between patients. Pink nucleus = centromedian nucleus-parafascicular region; red nucleus = red nucleus; purple nucleus = subthalamic nucleus; brown nucleus = substantia nigra. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

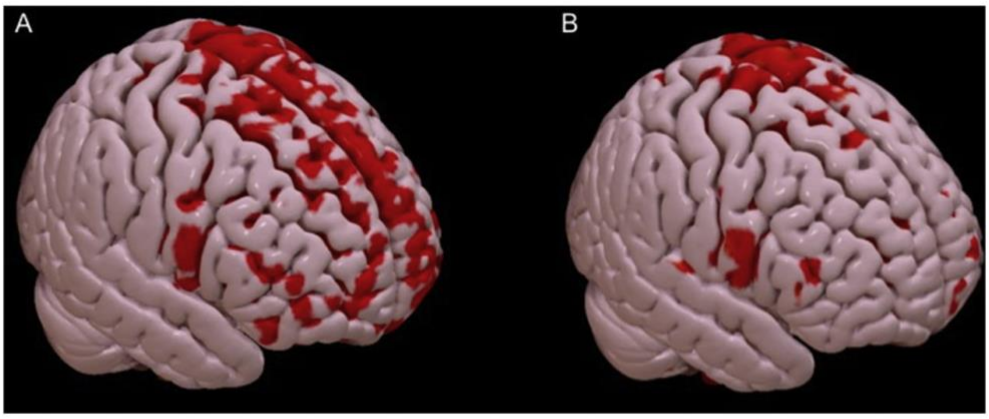

Fig. 3. Structural connectivity between the volume of tissue activated and the cortical areas.
The brain map represents the cortical areas that were structurally connected with the VTA in a good responder (patient 2, A) and a poor responder (patient 4, B). There is a stronger connectivity with the frontal areas in the good (compared to the poor) responder.

warranted.

This study has several clear limitations. Our goal was to present work conducted to test the hypothesis that the influence of thalamic-DBS on specific cortical regions may be, in part, responsible for motor outcomes in TS. This investigation is a proof-of-concept study with investigations of only five patients that attempted to determine why two patients did not improve after surgery, despite having their active contacts inside the CM-Pf.

5. Conclusion

Results in this study suggest that the thalamic volume stimulated does not explain the variance in outcome in TS, but rather, the pattern of connectivity between the region stimulated and specific brain cortical area does affect treatment outcome. Studies with larger patient cohorts will be necessary to confirm our initial findings.

Conflict of interests

The authors report no conflict of interest involved in this article.

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Appendix A. Supplementary data

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ORIGINAL RESEARCH
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Connectivity Patterns of Subthalamic Stimulation Influence Pain Outcomes in Parkinson's Disease

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Background: Pain is highly prevalent in Parkinson's disease and is associated with significant reduction in health-related quality of life. Subthalamic deep brain stimulation can produce significant pain relief in a subset of patients after surgery. However, the mechanism by which deep brain stimulation modulates sensory function in Parkinson's disease remains uncertain.

Objective: To describe the motor and pain outcomes of deep brain stimulation applied to a series of patients with Parkinson's disease and to determine whether the structural connectivity between the volume of tissue activated and different regions of the brain was associated with the changes of these outcomes after surgery.

Methods: Data from a long-term prospective cohort of 32 Parkinson's disease patients with subthalamic stimulation were combined with available human connectome to identify connections consistently associated with clinical improvement (Unified Parkinson Disease Rating Scale), pain intensity, and experimental cold pain threshold after surgery.

Results: The connectivity between the volume of tissue activated and a distributed network of sensory brain regions (prefrontal, insular and cingulate cortex, and postcentral gyrus) was inversely correlated with pain intensity improvement and reduced sensitivity to cold pain after surgery ($p < 0.01$). The connectivity strength with the supplementary motor area positively correlated with motor and pain threshold improvement ($p < 0.05$).

Conclusions: These data suggest that the pattern of the connectivity between the region stimulated and specific brain cortical area might be responsible, in part, for the successful control of motor and pain symptoms by subthalamic deep brain stimulation in Parkinson's disease.

Keywords: deep brain stimulation, connectivity, pain, sensibility, Parkinson's disease

INTRODUCTION

Pain has a prevalence of 40–85% in Parkinson's disease (PD) patients (1, 2) and is related with a significant reduction in their quality of life (3). Subthalamic deep brain stimulation (STN DBS) is an effective treatment for the motor symptoms of PD (4), but it also ameliorates non-motor symptoms, such as pain (5). It has been shown that STN DBS can produce significant pain relief in more than 80% of PD patients and might be a major driver of quality of life improvement in the long term after DBS (5, 6). Besides pain intensity reduction, some studies have proposed that DBS can modulate conscious perception of sensory function, increasing the abnormally low sensory detection and pain thresholds seen in PD toward normal values (7–9). However, the mechanism by which DBS modulates sensory function in PD remains uncertain. Studies have failed to find a correlation between the amount of motor improvement and pain improvement after surgery, which is inconsistent with the musculogenic theory of pain in PD and suggests a more complex relationship among pain improvement, sensory changes, and motor improvement after surgery (10, 11).

Studies have demonstrated that the benefit of locally applied DBS to the STN might rely on the modulation of distant brain areas connected to the stimulation spot, through antidromic activation of neuronal somas, passing fibers, and afferent terminals from the cortex (12, 13). These remote influences of DBS can be measured by studying the fiber tracts that structurally connect both the volume of the tissue activated (VTA) and the corresponding distant area. Recently, the strength of the connectivity between the VTA and the supplementary motor area (SMA) was positively correlated with the motor response in a cohort of PD patients receiving STN DBS (14). This opens the fascinating possibility of tailoring the exact hot spot stimulation site to obtain clinical effects that are meaningful for the patient. However, while this possibility starts to sprout for the control of motor symptoms, no information exists concerning that "hot connectivity spot" related to non-motor symptom improvement after surgery, and pain in particular.

In PD, there is an abnormal functional overactivity in pain processing regions, such as the insula, the cingulate cortex, and the prefrontal cortex (8, 11), and fibers from these areas are known to reach the STN (15). In light of such a network-based mechanism of DBS action and motivated by our preceding connectivity study on motor symptoms, we explored the pain outcomes of DBS applied to a cohort of PD patients previously reported by our group (5, 9) in an attempt to determine whether the connectivity profile between a patient's DBS-VTAs and specific brain regions could correlate with pain intensity and thermic pain threshold changes after surgery, using an available human connectome data set (16).

MATERIALS AND METHODS

Patients and Study Design

This study presents original imaging results from a previous clinical study on the effects of DBS on non-motor symptoms in PD (5, 9) In the present analyses, 32 patients with idiopathic PD according to the UKPD Society Brain Bank (17) who underwent STN DBS due to refractory motor complications were included. The patients had their motor (UPDRS-III) and pain scales prospectively evaluated before and 12 months after surgery. All implanted DBS electrodes were Medtronic 3387 (Minneapolis, MN, USA). This study was approved by our institution's ethics review board and registered in the clinical research database (# 0105/10). All patients were informed about the procedures in this protocol and gave informed consent to participate.

Pain Assessment

Detailed protocol has been previously published (5, 9). Briefly, all participants underwent a quantitative sensory testing intended to assess temperature pain thresholds. The evaluations were performed before surgery in an off-medication condition and 12 months after surgery during off-medication/on-stimulation conditions. Tests were performed bilaterally on thenar eminences. A contact thermode was placed over the thenar eminence at a neutral temperature (32°C). Heat and cold pain thresholds (HPT, CPT) were assessed by the methods of limits (1°C/s change from 32°C). Temperatures were maintained within the range of 0–50°C to protect participants from thermal cutaneous injuries (9). Besides quantitative sensory testing analysis, all patients were classified as having pain directly related to PD (triggered by PD), i.e., pain temporally related to the disease course and that fluctuates according to the motor status and/or improves with antiparkinsonian drugs (18, 19). Non-parkinsonian-pain (pain related to etiologies other than PD) was not included. Pain intensity was measured with a 100-mm visual analog scale (0 = no pain, 100 = worst pain) (3) and the concerned patient's "pain in general."

Lead Location and Volume of Tissue Activated

Postoperative tomography was coregistered to preoperative T1- and T2-weighted MRI using SPM12 and then normalized into ICBM 2009b NLIN asymmetric space using the SyN method (http://stnava.github.io/ANTs/) (20). Brainshift was corrected when present. The DBS electrode contacts were located within Montreal Neurological Institute space using Lead-DBS software (http://www.lead-dbs.org) (21). Once the electrode was localized, the VTA of the active contact (cathode) was estimated using a heuristic stimulation algorithm previously described by Dembek et al. (22). The VTA was based on patient-specific stimulation parameters recorded 12 months after surgery. The overlap between the VTA and the STN was calculated in mm^3. The sum of the two overlapping VTA/STN volumes from both hemispheres was correlated with the percent change in VAS and cold pain threshold in order to analyze whether the area stimulated inside the STN could influence pain outcomes.

Connectivity Analysis

Using VTAs as seed regions, structural connectivity estimates were analyzed using a normative structural connectome, which consists of high-density normative fibertracts based on 20 subjects (16). Global fiber-tracking was performed using Gibb's tracking method (23). Structural connectivity was calculated by

extracting tracts passing through VTA and calculating the fiber counts in a voxel-wise fashion in specific brain areas (16). Brain parcellations were defined according to the human Harvard-Oxford atlas, a probabilistic atlas covering 48 cortical and 21 subcortical structural areas, derived from structural data and segmentations (24). For pain correlation, we included pairs of sensory regions of interest related to classic pain circuitry and previously reported to be affected in PD (25–27): prefrontal cortex, insular cortex, cingulate gyrus anterior division, and post central gyrus (**Supplementary Figure 1**) (8, 28). Finally, for pain and DBS motor response, we also analyzed the correlation of VTA with the SMA, previously associated with the improvement of motor symptoms in PD (14) but also linked with pain modulation (discussed below).

Statistical Analysis

Motor function (UPDRS-III), pain intensity (VAS), and sensory thresholds (HPT and CPT) were expressed as average ± standard deviation. Because the Kolmogorov–Smirnov test disclosed that the values did not have a normal distribution, Wilcoxon signed rank test was applied. Spearman coefficients were used to assess the variables' correlations. The level of statistical significance was set at $p < 0.05$ and was then lowered according to the Bonferroni correction for multiple comparisons (for VAS, the p value was set at <0.005 and for pain thresholds at <0.01).

The connectivity from VTAs was calculated for each patient. Structural connectivity strength was defined as the number of fiber tracts between VTA and the corresponding cortical area. This procedure resulted in R-maps with Spearman's rank-correlation coefficients for each voxel. The independent variable was defined as the VAS change (expressed in %), CPT change (CPT before–after), and DBS motor response (UPDRS-III in the off-medication before surgery–UPDRS-III off-medication/on-stimulation) 12 months after surgery. We did not include in the analysis the HPT because it did not change after the surgery.

RESULTS

All 32 patients were included in the analysis. The mean duration of the disease was 15.4 ± 8.1 years, and the Hoehn & Yahr off-medication score was 2.7 ± 0.6. Preoperative UPDRS-III scores were 45.1 ± 12.3 in the off-medication and 16.8 ± 7.6 in the on-medication conditions. After STN DBS, the UPDRS-III scores in the off-stimulation/off-medication condition were 46.9 ± 13.4 and 23.9 ± 10.6 in the on-stimulation/off-medication condition (49% of improvement).

Pain Outcomes

Twenty-three patients (71.9%) had pain related to PD before the surgery. After STN DBS, eight patients (28.1%) remained with pain under their regular pharmacological treatment ($p < 0.001$). In those who remained symptomatic, there was significant reduction in pain intensity after surgery (VAS: before = 66.0 ± 24.1, after $r = 42.5 \pm 19.0$, $p = 0.011$). One patient developed dystonic pain after surgery in the left arm. Comparing to baseline, STN DBS significantly decreased the CPT (reduced sensitivity to cold pain) after surgery in both hands (left side before = 18.4 ± 7.8, after = 13.0 ± 8.4; right side before = 18.1 ± 7.0, after = 10.3 ± 6.4; $p = 0.007$ and 0.003, respectively). There were no changes in the HPT after surgery (left side before = 41.1 ± 5.1, after = 41.7 ± 4.7; right side before = 41.4 ± 4.4, after = 42.0 ± 5.6, $p > 0.05$). No correlation was found between the change in pain intensity (VAS) and the CPT (left side, $r = 0.221$, $p = 0.800$; right side, $r = 0.114$, $p = 0.123$) and between VAS and the CPT with motor response to STN DBS ($p > 0.05$).

Once it was determined that both VAS and the CPT changed after surgery, but did not correlate with each other, imaging analysis was performed based on these two variables in order to determine whether the STN volume was stimulated and the connectivity pattern between the VTA and sensory cortical areas could account for these changes.

Contact Position and Imaging Analysis

For both sides, the ventral contacts were the most frequently utilized as cathode (**Table 1** shows the contacts and the parameters applied in each brain sides). Spatially, most contacts were located in the dorsal part of the STN (**Figure 1** and **Supplementary Figure 2** illustrate the electrode position). The patient with *de novo* pain after surgery had the electrodes set posteriorly (**Figure 1**).

There was no relation between the VTA intersection of the STN with VAS ($n = 23$, $p = 0.174$) or CPT changes ($n = 32$, $p = 0.362$) after surgery (**Figure 2**). Using the structural connectivity between the VTAs and cortical areas described above, we identified that the left prefrontal cortex ($r = -0.528$, $p = 0.001$) and the right post-central gyrus ($r = -0.323$, $p = 0.004$) correlated negatively with VAS improvement ($n = 23$). Additionally, the right prefrontal cortex ($r = -0.517$; $p = 0.008$) correlated negatively with left CPT improvement (n=32). The left prefrontal cortex ($r = -0.666$; $p = 0.002$), the left insular cortex ($r = -0.548$; $p = 0.003$), and the left cingulate gyrus anterior division ($r = -0.547$; $p = 0.003$) correlated negatively with right CPT reduction, whereas there was a strong positive correlation with the left SMA ($r = 0.676$; $p = 0.002$) (**Figure 3**). Finally, there was a positive correlation between the DBS motor response with the left SMA ($r = 0.404$; $p = 0.011$).

DISCUSSION

Our primary findings were that: (i) STN DBS alleviates pain intensity and reduces CPT 12 months after surgery in PD, but these changes differed between patients and were not correlated with each other; (ii) the VTA inside the STN does not explain the variance in pain change after surgery; and (iii) the pattern of the connectivity between the stimulated region and specific brain cortical areas may be responsible for this variance in outcome. This latter point reinforces the recent, growing evidence that, although the targets for DBS in neurological disorders are normally determined by specific anatomical regions (e.g., nucleus or tracts), the ideal target may not necessarily be an anatomical structure itself but rather a structurally connected region. This has an obvious surgical targeting implication, but also highlights the importance of postoperative symptom-oriented

TABLE 1 | Cathode distribution and parameters applied in each subthalamic nucleus at 12 months after surgery.

	Most ventral (–)	Ventral (–)	Dorsal (–)	Most dorsal (–)	Current (mA)	Pulse width (μs)	Frequency (Hz)
Left STN	12	15	04	01	2.5 ± 0.5	76.8 ± 17.4	131.8 ± 23.3
Right STN	11	17	13	01	2.6 ± 0.5	80.6 ± 20.7	131.8 ± 23.3

STN, subthalamic nucleus.

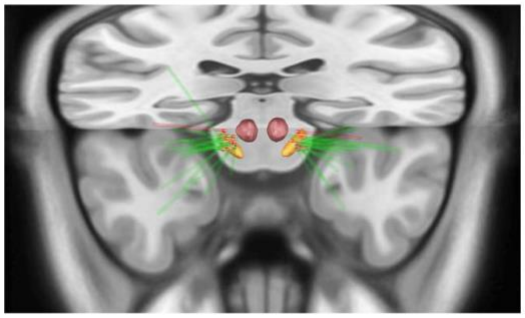

FIGURE 1 | Upper view of the lead placement and the active contact (red highlighted) from all patients with pain before surgery (green electrodes) localized in the subthalamic nucleus (STN). The red electrode represents the patient who developed painful dystonia after surgery, showing the contact posteriorly to the STN. Orange = STN, red = red nucleus.

programming in looking for the desired network within the same structural DBS target.

It is well-known that STN DBS not only produces motor improvements but also influences a set of non-motor symptoms, including pain related to PD (5). In addition to pain relief, STN DBS has also been associated with improved sensory detection and pain thresholds, which are modified toward normal values after surgery (7–9, 29). What is uncertain is whether the remote effect of DBS mediated through structural connectivity could account for those non-motor symptom changes or whether those changes are due to a global improvement in motor function after surgery. Accordingly, the current study utilized a DBS cohort (n = 32) to explore the relationship between their sensory changes and the structural connectivity of the VTA with specific brain regions. We have found that the brain regions responsible for central pain processing (11) were negatively correlated with the effectiveness of STN DBS in ameliorating pain intensity and induced cold pain, meaning that the higher the influence of the STN on these areas, the lower the improvement in spontaneous or induced pain after surgery. Interestingly, STN DBS affects more the CPT than the HPT, probably reflecting the fact that the HPT is usually less affected in PD patients (9). Additionally, there are qualitative differences between thermal pain thresholds. CPTs are highly modulated by top-down systems, such as the opioidergic and cannabinoid ones, known to be influenced by DBS (30, 31). Also, the CPT and the HPT are differentially conveyed to the SNC, with the CPT being mediated by C and A delta fibers, while the HPT being mainly dependent on unmyelinated C fibers (32).

A functional study demonstrated, in PD, an abnormal pain-induced activation in both sensory discriminative processing of pain, as occurs in the insula, in affective motivational processing of pain, as occurs in the cingulate cortex, and in cognitive areas, such as the prefrontal cortex (28). In addition, levodopa reduced pain-induced activation in those same overactive sensory areas. Remarkably, we have recently shown in a different model (central neuropathic pain), where the insula and anterior cingulate cortex are known to be hyperactive, that non-invasive deep transcranial magnetic stimulation of these structures not only was ineffective in alleviating pain but also actually aggravated some aspects of pain, especially in the insula group (33).

The STN is a small nucleus that projects fibers to both pallidal divisions and to the substantia nigra and uses the excitatory neurotransmitter glutamate to mediate its function (34). In PD, the loss of GPe inhibition over the STN culminates with high-level activity in this nucleus, leading to the distinctive motor impairments seen in PD. The delivery of high-frequency electrical impulses to the dorsolateral STN through DBS interferes with the function of the STN and reduces its output, alleviating the symptoms (orthodromic effect). In addition to the decrement in STN output, DBS exerts its activity by modulating passing fibers and afferent terminals, including those from the cortex (antidromic effect). The stimulation of incoming fibers could antidromically activate several cortical areas in a retrograde manner, leading to widespread and heterogeneous effects at distal sites (13). Along this line, the question raised by the present study is whether the local stimulation of these different fibers that project to the STN could influence pain outcomes, particularly those fibers coming from sensory areas.

Most of the cortical afferents to the STN arise from the primary motor cortex, SMA, and the dorsal and ventral premotor cortex and predominantly innervate the dorsal aspects of the nucleus (35). The limbic ventromedial portion of the STN receives fibers from the prelimbic-medial orbital areas of the prefrontal cortex (36). Somatosensory projections from the cingulate cortex, somatosensory cortex, and insular cortex also primarily project to the medial part of the STN, but a specific somatotopy organization has not been described (37–40). We have shown an anticorrelation between the activation of these fibers and the improvement of pain after surgery. It is worth highlighting that, overall, the patients experienced improved pain intensity (except for one patient whose electrodes were located posteriorly) and reduced CPT after surgery, but the degree of this improvement among the patients was quite variable. We hypothesized that avoiding stimulating sensory/pain-related

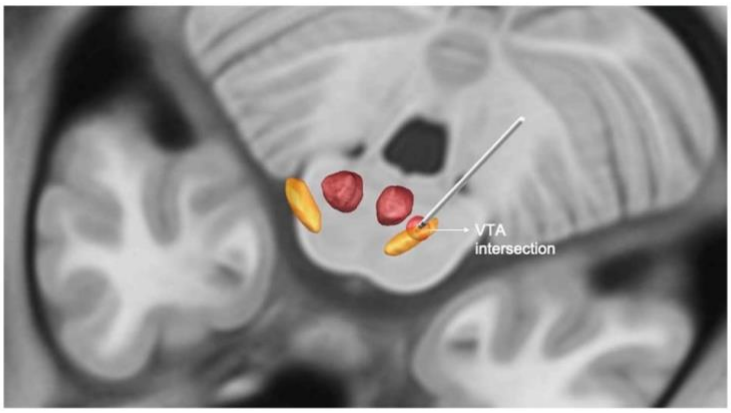

FIGURE 2 | Illustration of the intersection between the volume of tissue activated (VAT) and subthalamic nucleus (STN) in mm^3. Orange = STN, red = red nucleus, circumferential red circle around the electrode = VTA.

afferents to the STN seems to be reasonable in patients with moderate/severe pain related to PD at baseline in order to optimize the results. Because most of the sensory afferents enter in the medial part of the STN, we hypothesize that the ideal VTA should be located more laterally.

The present study was not intended or designed to find the stimulation "hot spot" for pain improvement. The STN DBS in PD probably modulates not only the nucleus itself but also a brain network of converging neural pathways from different brain regions as well as the nucleus outputs. It will probably be very difficult to define a specific area of stimulation that is ideal for improving both the motor and non-motor symptoms because it is impossible to disentangle them with certainty, which highlights the importance of personalized polarity and parameter trials in each electrode based on individual responses and symptoms.

In line with a previous study where stronger connectivity between the site of stimulation and the SMA was associated with better motor improvement in PD patients (14), we found a positive connection between the VTA and the SMA in terms of the DBS motor response. Interestingly, the VTA–SMA connectivity was also correlated with the CPT change after surgery. Although we found that motor and non-motor (CPT) changes may be correlated with the same brain area, previous studies showed that there are no correlations between pain and motor improvement after STN DBS (5, 11, 29). The changes in pain and sensory thresholds after STN probably are a patchwork of motor improvement and changes in motivation drive, in the capacity of patients to perform more physical activity, central mechanisms, and connectivity pattern (11).

Clinical and preclinical studies show that motor cortex stimulation induces analgesia by activating descending analgesic pathways (41). Motor cortex stimulation improves the nociceptive threshold in rats via endogenous opioids, inhibiting thalamic nuclei and activating the periaqueductal gray (42). Additionally, electrophysiology and functional imaging studies have shown that motor cortex stimulation activates the brain regions involved in the perception and/or emotional aspects of pain, including the lateral thalamus, anterior cingulate cortex, anterior insula, and periaqueductal gray (43). Interestingly, it has been repetitively shown that precentral gyrus stimulation by transcranial magnetic stimulation preferentially affects the CPT toward analgesia (44) and that this effect is dependent on endogenous opioids (45) and the availability of N-methyl-D-aspartate receptors (46). This suggests that CPT changes may occur due to motor/premotor back-stimulation and possibly serve as a marker of the stimulation that is delivered to more dorsal-motor-related areas instead of more medial-sensory/affective regions. Even so, because there is no correlation between changes in motor and non-motor symptoms after STN DBS, including pain and the CPT (5, 11), this assumption should be interpreted with caution and clearly remains to be determined in further studies.

In clinical practice, exploring the individual connectivity profile between the chosen cathodes and corresponding activated cortical regions would imply a more effective therapy based on the patient's motor and non-motor baseline status. For instance, in patients with significant pain related to PD at baseline, the cathode with higher SMA and lower sensory area connectivity would be the best option. Along this line, considering the new directional devices with more cathodes and consequently more VTA options, more personalized programming based on the patient's connectivity profile could bring better clinical results.

Our study has several limitations. First, the brain regions correlated with the VTA varied between the pain dimensions analyzed (VAS vs. pain thresholds) and between the sides (right and left), which limits us from drawing a more robust conclusion. In addition, due to the low alpha value after Bonferroni correction, many important correlations should be missed (type II error). Therefore, connectivity patterns that look

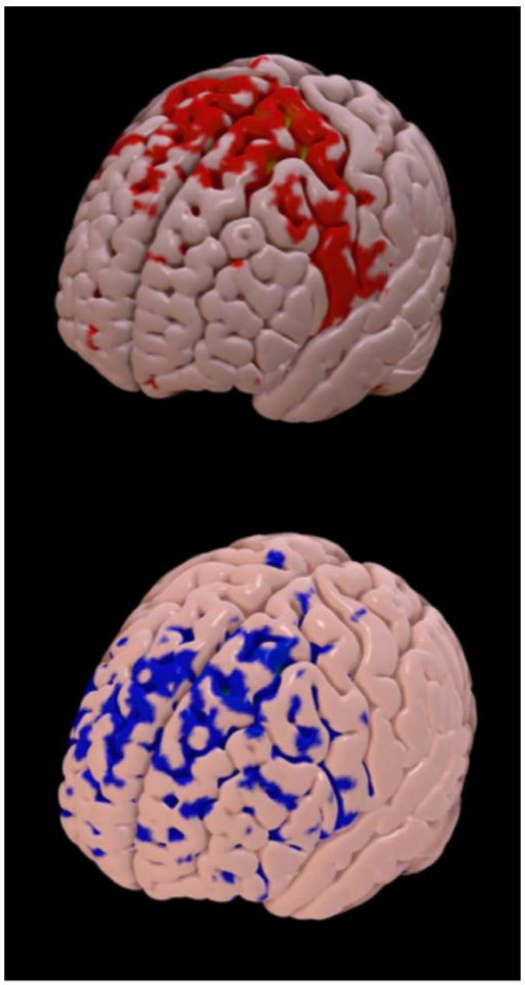

FIGURE 3 | Structural connectivity between the volume of tissue activated and cortical areas. The brain map represents the cortical areas structurally connected with the volume of tissue activated from a good responder (improvement in pain intensity and cold pain threshold after surgery; red areas, mainly located in the supplementary motor area) and a poor responder (blue areas, mainly located anteriorly in the frontal lobe).

at pain and other non-motor symptoms should be explored in larger studies. Second, the present study did not use a patient-based connectome, which would be preferable and more reliable, considering the possible anatomic variances in PD patients. Therefore, future studies using patients' connectomes should be performed to confirm our data. On the other hand, normative connectomes from healthy subjects have the benefit of large participant numbers, high-quality signal-to-noise ratios, and acquisition that involves operating unique high-power MRI scanners that are particularly designed for connectivity imaging. The connectome used in our study was created using the Gibbs global tracking algorithm (16), which has the advantage of reconstructing multiple fiber tracts passing through the ROIs and VTAs we analyzed. The method is very computationally consuming compared to other deterministic algorithms and, although the fact that we did not use the DTI data of each patient is a limitation to the study, it allowed us to identify interesting structural relations among different brain regions in this exploratory work. Moreover, a recent study evaluated the connectivity between the VTA and brain regions through both normative connectome from healthy subjects and a connectome that was age, sex, and disease matched (PD) (14). Their connectivity results (to predict motor outcome after STN DBS) were highly correlated across patients using the normative vs. PD connectome.

We decided to use a broad brain map parcellation, which spans large parts of the cortex. Subsequently, a more specific brain area connected to the VTA could not be identified, and further studies using brain parcellation with smaller and more specific cortical areas would be helpful in this issue. Finally, another important point concerns the current models of calculating the VTA. The models assume that the whole VTA is activating the tissue, but, instead, the VTA represents the volume of the electrostatic field, where the axons and cell bodies receive electrons but may or may not be activated. This limitation is intrinsic to the VTA models and should be refined in future studies.

Taking our findings and the literature review together, we can summarize that PD patients have higher pain prevalence and abnormal pain thresholds compared to controls and that the supraspinal areas involved in the nociceptive process are, overall, overactivated. Deep brain stimulation improves pain intensity and decreases sensitivity to cold pain and, in part, the amount of this change occurs through antidromic activation of the SMA (an area related to analgesia) and is associated with the avoidance of activation of subcortical/cortical sensory circuitry areas. Metabolic, electrophysiologic, and functional studies on this matter could confirm our preliminary findings. Further clinical studies are necessary to define how to work together with the strengths of normative connectomes and connectivity data from individual patients.

DATA AVAILABILITY STATEMENT

Anonymized data are available and will be shared upon reasonable request from any qualified investigator.

ETHICS STATEMENT

This study was approved by our institution's ethics review board and registered in the clinical research database (# 0105/10). Ethical Committee: Comissão de Ética para Análise de Projetos de Pesquisa do HCFMUSP, Address: Rua Ovídio Pires de Campos, 225 – 5° andar – Prédio da Administração, Phone:

55 11 26 61 75 85, e-mail: cappesq.adm@hc.fm.usp.br. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RC: conception, organization, and execution of Research Project, execution and data analysis of Clinical Assessments, writing of the first draft and review and critique of Letter. MT, RG, VS, RI, and EB: organization of Research Project, execution of Clinical Assessments, review and critique of Letter. CF, DA, EF, and EB: organization and execution of Research Project, execution of Clinical Assessments, review and critique of Letter. DC: conception, execution, and supervision of Research Project, data analysis of Clinical Assessments, review and critique of Letter.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00009/full#supplementary-material

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Appendix 14 – Medical management after subthalamic stimulation in Parkinson's disease: a phenotype perspective. Review article published in Arquivos de Neuropsiquiatria.

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Medical management after subthalamic stimulation in Parkinson's disease: a phenotype perspective

Manejo medicamentoso após estimulação subtalâmica na doença de Parkinson: uma perspectiva fenotípica

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ABSTRACT

Subthalamic nucleus deep brain stimulation (STN DBS) is an established treatment that improves motor fluctuations, dyskinesia, and tremor in Parkinson's disease (PD). After the surgery, a careful electrode programming strategy and medical management are crucial, because an imbalance between them can compromise the quality of life over time. Clinical management is not straightforward and depends on several perioperative motor and non-motor symptoms. In this study, we review the literature data on acute medical management after STN DBS in PD and propose a clinical algorithm on medical management focused on the patient's phenotypic profile at the perioperative period. Overall, across the trials, the levodopa equivalent daily dose is reduced by 30 to 50% one year after surgery. In patients taking high doses of dopaminergic drugs or with high risk of impulse control disorders, an initial reduction in dopamine agonists after STN DBS is recommended to avoid the hyperdopaminergic syndrome, particularly hypomania. On the other hand, a rapid reduction of dopaminergic agonists of more than 70% during the first months can lead to dopaminergic agonist withdrawal syndrome, characterized by apathy, pain, and autonomic features. In a subset of patients with severe dyskinesia before surgery, an initial reduction in levodopa seems to be a more reasonable approach. Finally, when the patient's phenotype before the surgery is the severe parkinsonism (wearing-off) with or without tremor, reduction of the medication after surgery can be more conservative. Individualized medical management following DBS contributes to the ultimate therapy success.

Keywords: deep brain stimulation; medical management; Parkinson's disease; phenotype; subthalamic nucleus.

RESUMO

A estimulação cerebral profunda do núcleo subtalâmico (ECP NST) é um tratamento estabelecido para doença de Parkinson (DP), que leva à melhora das flutuações motoras, da discinesia e do tremor. Após a cirurgia, deve haver uma estratégia cuidadosa de programação da estimulação e do manejo medicamentoso, pois um desequilíbrio entre eles pode comprometer a qualidade de vida. O gerenciamento clínico não é simples e depende de vários sintomas motores e não motores perioperatórios. Nesta revisão, discutimos os dados da literatura sobre o tratamento clínico agudo após a ECP NST na DP e propomos um algoritmo clínico baseado no perfil fenotípico do paciente no período perioperatório. Em geral, nos estudos clínicos, a dose diária equivalente de levodopa é reduzida em 30 a 50% um ano após a cirurgia. Em pacientes que recebem altas doses de medicações dopaminérgicas ou com alto risco de impulsividade, recomenda-se redução inicial do agonista dopaminérgico após a ECP NST, para evitar síndrome hiperdopaminérgica, particularmente a hipomania. Por outro lado, uma rápida redução de agonistas dopaminérgicos em mais de 70% durante os primeiros meses pode levar à síndrome de abstinência do agonista dopaminérgico, com apatia, dor e disautonomia. Em pacientes com discinesia grave antes da cirurgia, é recomendada redução inicial na dose de levodopa. Finalmente, quando o fenótipo do paciente antes da cirurgia é o parkinsonismo grave (flutuação motora) com ou sem tremor, a redução da medicação após a cirurgia deve ser mais conservadora. O tratamento médico individualizado após a ECP contribui para o sucesso final da terapia.

Palavras-chave: estimulação encefálica profunda; manejo medicamentoso; doença de Parkinson; fenótipo; núcleo subtalâmico.

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Parkinson's disease (PD) is a progressive neurodegenerative disorder, which affects several regions of the central and peripheral nervous system, leading to both motor and non-motor manifestations along the disease course[1,2]. Surgical treatments for PD, specifically stereotactic ablations (conventional thalamotomy and pallidotomy), were developed before the introduction of levodopa, and reemerged later as a means to overcome difficulties in the medical management of motor complications, due to the dopaminergic therapy in patients with advanced PD[1].

Deep brain stimulation (DBS) has been shown to have several advantages compared to traditional lesions, including adaptability, reversibility, and the possibility to be performed bilaterally in the same surgical session[3]. The subthalamic nucleus (STN) is the preferred target among centers and is an established and effective form of treatment that improves motor fluctuations, dyskinesia, and quality of life in well-selected patients with PD[4,5].

The success of deep brain stimulation does not rely only on the surgery itself, but also on a whole process, that encompasses several preoperative and postoperative issues. There are key factors in the success of the therapy, starting with the rigorous and standardized selection of patients and meticulous surgical planning to optimize the placement of electrodes. After the procedure, electrode programming strategies and medical management, in both the early and the long-term follow-up, are crucial, given that an unbalancing between them can compromise motor and non-motor functions over time[2,4].

Medical management is not straightforward, because the phenotype of patients undergoing surgery is variable[6]. Some patients have more dyskinesia, tremor, or motor fluctuations, or a combination thereof. Additionally, the range of non-motor symptoms varies among candidates, and this may influence how medications are managed[2]. Therefore, the way we change the medication after surgery should be tailored to the individual characteristics of each patient.

In view of the importance of standardized medical management after surgery, the present study aims to:

- Evaluate literature data on acute medical management after DBS in PD.
- Propose a clinical algorithm on medical management focused on the patient's phenotypic profile at the perioperative period.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified by searches on PubMed, published up to August 2019, and references from relevant articles. We searched for the terms "hyperdopaminergic syndrome", "hypodopaminergic syndrome", "apathy", "cognition", "dementia", "depression", "dopamine agonist", "impulse control disorders", "psychosis", "dyskinesia", "medication", "levodopa" and "non-motor symptoms" in combination with the terms "deep brain stimulation" and "Parkinson's disease". There were no language restrictions. The final reference list was generated based on the relevance to the topics covered in this article.

WHO ARE THE PATIENTS REFERRED FOR DBS?

Patient eligibility for DBS is determined by standardized evaluation in specialized movement disorder centers, using a comprehensive selection process, including a levodopa challenge test, brain imaging, and assessment of neuropsychological and psychiatric functions, with the purpose of achieving the best clinical results and minimizing side effects and complications[6-8]. Parkinsonian motor signs, such as OFF symptoms, dyskinesias, and tremor are the major complaints of the patients refereed for DBS surgery[6-8]. Pre-operative levodopa-responsiveness has been universally accepted as the single best outcome predictor for response to DBS; with the exception of levodopa-unresponsive tremor, all motor signs that improve with levodopa prior to surgery are expected to improve postoperatively[8,9].

Besides the impairment in motor functions, patients undergoing DBS often present a range of non-motor symptoms. In a large cohort of PD patients referred to DBS, half of them fulfilled diagnostic criteria for hyperdopaminergic behavioral disorders, encompassing dopamine dysregulation syndrome and impulse control disorders[10,11]. Patients undergoing DBS present bothersome disease-related symptoms (motor and non-motor symptoms) associated with high doses of dopaminergic drugs (total levodopa equivalent daily dose - LEDD-greater than 1000 mg), frequently including a dopamine agonist[11,12]. As detailed below, when we "add" the STN stimulation to patients who are already under high doses of dopaminergic drugs, there is an over-inhibition of the STN activity[13]. This inhibition, in turn, may 'release the horses' and culminates in a worsening of dyskinesias and increases the risk of hyperdopaminergic syndrome, such as impulse control disorders during the short-term period after surgery[1-14]. Thus, a careful and individualized medical management strategy is needed to 'hold the horses'.

THE SUBTHALAMIC NUCLEUS IN THE CONTEXT OF DEEP BRAIN STIMULATION

The STN is a small nucleus that projects fibers to the pallidum and to the substantia nigra and uses glutamate to mediate its function[15]. Deep brain stimulation interferes with the function of the STN and reduces its output, alleviating parkinsonian symptoms (orthodromic effect). In addition, DBS exerts its activity by modulating afferent terminals, including those from the cortex (antidromic effect). The stimulation of afferent

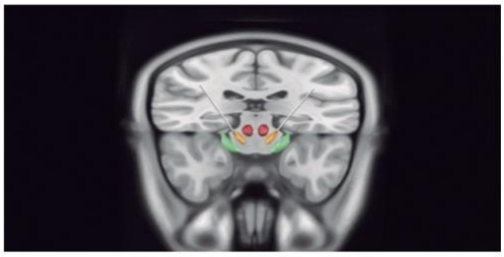
axons could antidromically activate several cortical areas in a retrograde manner, influencing distal sites[6]. Most of the cortical afferents to the STN arise from the primary motor cortex and supplementary motor area and innervate the dorsal aspects of the nucleus (motor part of STN)[16]. The limbic ventromedial portion of the STN receives fibers from the prelimbic-medial orbital areas of the pre-frontal cortex[17]. Electrode contacts used for chronic DBS in PD are supposed to target the dorsolateral part of the STN (Figure 1), but limbic spread of the current could lead to neuropsychiatry symptoms[18].

PRACTICAL RECOMMENDATIONS IN THE ACUTE PHASE FOLLOWING STN DBS

The concerns that clinicians should be aware of after surgery are:

- The *amount* of medication that should be reduced (total LEDD).
- *Which* medication, in a logical order, should be tapered.

Several studies have shown that the LEDD[19] is reduced by 30 to 50% one year after surgery[14-21] (Table 1 defines the 'total' and the 'dopamine agonist' LEDD). One study demonstrated that the major modifications in medication dosage occurred during the initial postoperative period - the first 6 months[14]. In this study, the total LEDD was reduced by 53.4% compared to baseline at 6 months and 47.9% at 3 years[14]. They evaluated 150 patients and showed that 56% of patients were on monotherapy at 6 months and 41.3% at 3 years. Furthermore, 9.3% patients were free from medication at 6 months, and 7% were free at 3 years[14]. The complete discontinuation of medication is usually avoided because the lack of dopamine in the limbic system can lead to apathy and depression[2,14]. The order of medication tapering will depend on the clinical phenotype before the surgery and the patient's profile following the surgery. Details are provided in the following sections.



Orange: STN; Red: Red Nucleus; Green: Globus Pallidus Internus[47]

Figure 1. Upper view of electrodes implanted in a patient with Parkinson's disease located in the dorsal part of subthalamic nucleus.

Dyskinesias

Levodopa-induced dyskinesia (LID) occurs in nearly all patients with PD after 10 years of chronic dopaminergic treatment, it is secondary to early treatment with high doses and chronic pulsatile stimulation of dopamine receptors[22]. In the extreme, patients can cycle between disabling dyskinesias during the "ON" state and disabling parkinsonism during the "OFF" state[23]. Risk factors for the development of dyskinesias are young-onset PD, female gender, high UPDRS part II scores at baseline, lower weight, and high dose of levodopa[23]. Striatal denervation and subsequent structural alterations of post-synaptic dopaminergic transmission are necessary for LID to develop[24].

STN DBS does not have an appreciable antidyskinetic effect and can even induce dyskinesias, which thwarts an increase in stimulation during programming[1]. In most cases, when stimulation-induced dyskinesia occurs it has been interpreted as a good prognostic sign, indicating that the optimal lead location has been achieved[25,26]. There are experiments suggesting that glutamate neurotransmitter release may underpin stimulation induced dyskinesia, but the exact mechanisms remain unknown[27].

Dyskinesia reduction has been consistently reported after STN implantation, due to the reduction of postoperative dopamine replacement therapy[1], in particular levodopa. Russmann et al. found that LID was reduced by 74% after 21 months of STN DBS, along with a reduction in antiparkinsonian medication during this time[22].

In a prospective study of 91 patients, a robust improvement in all motor signs in the OFF condition (the percentage of time with good mobility and no dyskinesia and mean dyskinesia score) was observed. Six months after DBS, 74% of patients were without dyskinesia in "ON" state compared to 27% at baseline, and 7% of patients were with dyskinesias in "ON" state compared to 23% at

Table 1 Protocol for calculating levodopa equivalent daily dose for antiparkinsonian agents.

Parkinsonian Drug	Conversion factor
Immediate release L-dopa dose	x 1
Controlled release L-dopa dose	x 0.75
Entacapone	x 0.33
Pramipexole	x 100
Ropinirole	x 20
Rotigotine	x 30
Selegiline	x 10
Rasagiline	x 100
Amantadine	x 1

Total LEDD is the sum of all drugs (Actual total daily dose x Conversion factor). Dopamine agonist (DA) LEDD represents the Pramipexole, Ropinirole or Rotigotine daily dose x Conversion factor.

baseline. The mean reduction in the LEDD was approximately 60%[28,29]. It became clear that the reduction in dyskinesia could be attributed, at least partly, to the reduction in the levodopa dosage[28]. A comprehensive meta-analysis of 921 patients who underwent STN DBS between 1993 and 2004 noted an average reduction in dyskinesia of 69.1%, with an average reduction in LEDD of 55.9%[28,30].

Vingerhoets et al. evaluated 20 patients with PD with motor fluctuations and dyskinesia, who underwent bilateral STN DBS. The medication was reduced by 79% and was completely withdrawn in 10 patients. Fluctuations and dyskinesia showed an overall reduction of 90%, disappearing completely in patients without medication[31].

In patients referred for DBS treatment due to severe dyskinesia, an initial reduction in levodopa (mainly the plasmatic peak) soon after the surgery seems to be reasonable and can be considered as the best approach. It is worth mentioning that although the DBS stimulation is usually kept turned off during the first weeks after surgery, a microlesion effect is a commonly observed phenomenon after the electrode insertion and mimics the DBS stimulation effect[32]. The microlesion effect results from a transient damage of the STN and usually lasts 3-4 weeks[32].

In patients who maintain dyskinesias, even after a reduction of levodopa following DBS, other strategies may be considered, such as: a concomitant reduction of dopaminergic agonist, introduction of amantadine and/or clozapine, and also programming techniques (not the aim of this article), such as titrating of the stimulation by small steps (0.1-0.2 volts every week), bipolar stimulation, and stimulation of the more dorsal contacts. This later approach allows the current to spread into the dorsally adjacent lenticularis fasciculus, which exerts an effect similar to that of pallidal stimulation and ultimately suppresses dyskinesia, mimicking the antidyskinetic effect of globus pallidus internus stimulation[1].

An infrequent but nonetheless potential complication of STN DBS is a permanent stimulation-induced dyskinesia following the surgery. A small subset of patients experiences troublesome dyskinesia after STN DBS, despite optimal programming and medication adjustments (called 'brittle' dyskinesia)[25]. Young onset of PD may play a role in the genesis of this post-STN DBS 'brittle' dyskinesia. Other risk factors, such as longer disease duration, longer duration of levodopa therapy, and female patients with a low body weight have been suggested, although the number of patients reported so far is small[27,28]. The emergence of this troublesome dyskinesia post-STN DBS is challenging. Rescue GPi DBS can be effective in 'brittle' dyskinesia and was previously reported[25].

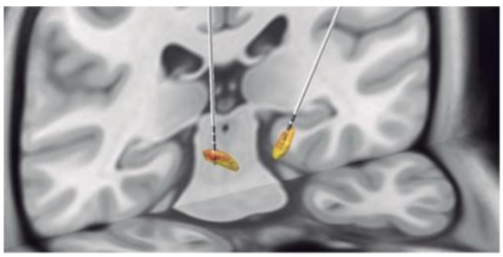
Hyperdopaminergic syndrome

During the few days immediately following surgery, patients usually experience a mild euphoria, hyperactivity, and increased motivation[32]. Overall, this "disinhibition" is overlooked by patients and their relatives, and it naturally improves within a few weeks. However, in a few patients, a more robust hyperdopaminergic syndrome may arise, and generally results from a combination of the lesioning effect of the electrode, the high frequency stimulation itself (which has an inhibitory effect over the nucleus), and a high dopaminergic load.

The STN is a key player in the inhibitory control of complex motivated behavior[2] and is directly involved in our decision making, providing a "NoGo" signal that suppresses responses[13]. Accordingly, some evidence from pre-clinical studies shows that STN lesions impair the response selection processes, and lead to premature responding in high-conflict choice selection paradigms[13]. Taken together, in the acute phase after surgery, the synergistic activity of both high frequency stimulation and the persistent effect of dopaminergic drugs over-inhibit the STN, releasing the brake and disinhibiting behavior[2].

Hyperdopaminergic syndrome following the surgery can worsen if the current spreads to the ventral-medial regions (limbic part) of the STN[34]. DBS-induced mania/hypomania appears to occur in 4% of patients[35], but this number increases to 82% with ventromedial electrode placement[36]. Therefore, slow titration of the stimulation and avoidance of the most medial and inferior contacts are recommended (Figure 2).

Reducing dopaminergic medication load might lead to an improvement in behavioral features. In patients with a high risk of hyperdopaminegic syndrome (male sex, young age at onset, previous history of ICD, and dopamine agonist LEDD over 150 mg) an initial reduction of dopaminergic agonists - even before the surgery - is recommended. The amount of reduction is not established, but a reduction of 15-30% of dopamine agonists LEDD during the first months following the surgery seems reasonable (which represents the Pramipexole, Ropinirole or Rotigotine daily dose x Conversion factor - see Table 1). An aggressive reduction (more than 70% in dopamine agonists LEDD) can be associated with severe apathy and depression and should be discouraged[37]. In those



Orange: STN sensorimotor region; Yellow: STN limbic region[47].

Figure 2. Electrode reconstruction illustrating the volume of tissue activated (circumferential red circle around the electrode) into the sensorimotor region of the STN (dorsal part). Note the yellow region (limbic region) in the anterior part of the nucleus. The spread of the current to this region could lead to neuropsychiatry symptoms.

patients not taking dopamine agonists, the initial levodopa reduction should be preferable over other drugs, because of its psychostimulant effects1[11]. A short course of clozapine or quetiapine may be necessary in some cases during the first weeks following surgery, along with neuropsychologist evaluation and cognitive behavioral therapy[2].

It is important to highlight that a dopaminergic drug decrease does not instantly lead to a reduction in the behavioral effects, because the drugs also have long-term effects[35]. In the long-term, the reduction of dopaminergic medication leads to progressive disappearance of their long-term effects and to desensitization[38].

Despite being uncommon, the presence of hyperdopaminergic syndrome after STN DBS can be reduced if a detailed preoperative assessment is performed. In our center, the neuropsychology team routinely applies the Ardouin Scale of Behavior in Parkinson's Disease (ASBPD)[15], which uses a structured, standardized interview designed to detect and quantify a wide range of neuropsychiatric symptoms in PD[15,39]. The scale assesses 'behavioral addictions' to classify repetitive behaviors found in patients with PD, including impulse control disorder, punding, and excessive hobbyism. Every item is rated on a five-point scale from 0 (absence of disorder or change compared to usual behavior) to 4 (severe behavioral disorder) by accounting for the severity and the frequency of the disorder compared to premorbid usual functioning and its psychosocial effect. When any item on the ASBPD scores 3 or 4 the patient is not referred for DBS until the symptom is compensated.

Finally, psychosis, characterized by short-lasting transient hallucinations and delusions, are described shortly after surgery. In these cases, the first medications to be generally reduced or discontinued are the anticholinergic drugs, followed by amantadine, dopaminergic agonists, catechol-O-methyltransferase inhibitor (COMTi), monoamine oxidase inhibitor (MAOi), and, lastly, levodopa. The prescription of antipsychotics for short-term use can be necessary[2].

The other side of the coin: Hypodopaminergic syndrome

Apathy and depression are common neuropsychiatric disorders in PD, with the prevalence reaching 50% for depression, and from 17 to 70% for apathy[39]. These symptoms can be observed at all stages of the disease, but are predominant at its onset or when it is undertreated[39]. Postoperatively, apathy and depression may emerge and have been attributed to direct stimulation effects of the STN for apathy or of adjacent zones for depression, but most importantly, due to inadvertent overreduction of levodopa and dopamine agonists inducing dopamine withdrawal syndromes[24-40].

Apathy

Apathy is one of the most common symptoms found in PD and is defined as a lack of motivation accompanied by reduced goal-directed cognition, behavior, and emotional involvement[11]. It may be observed at all stages of PD, in isolation or more frequently in association with dementia, depression, or anxiety[41]. Postoperative apathy is frequently associated to anxiety or depression and seems to be the tip of the iceberg of a larger spectrum of hypodopaminergic symptoms[42].

Apathy occurs after a mean of 4-7 months following DBS[1] and is associated with rapid reduction of dopaminergic therapy, which leads to a postoperative deactivation of dopaminergic receptors within the mesocortical and mesolimbic pathways[1]. Thobois and some colleagues showed that after a forceful 82% reduction of dopaminergic medication within 2 weeks after surgery, half of patients developed apathy. Furthermore, postoperative apathy has been considered in the spectrum of dopamine withdrawal syndrome (DAWS). A PET study at baseline revealed that the greater the mesocorticolimbic dopaminergic denervation, the higher the odds of developing apathy after surgery[43].

Apathy following STN DBS responds to dopamine agonist treatment[43]. Czernecki et al. showed that apathy dramatically improved with ropinirole, a D2 and D3 dopaminergic agonist, in all but one of the 8 patients who became apathetic after complete withdrawal of dopaminergic medication following STN stimulation[44]. In the present study, the average score on the Starkstein Apathy scale showed an improvement of 54% (±24%), and the improvement in mood was not correlated to the effect on apathy[44]. Thobois et al. also showed that piribedil, another D2/D3 dopaminergic agonist, significantly alleviates postoperative apathy in patients with PD after STN DBS[42].

Because of the risk of hyperdopaminergic syndrome, dopamine load should not be reduced sharply after surgery, since this could lead to patients becoming apathetic. The presence of apathy after surgery can "block" the beneficial effect of DBS on motor symptoms. Whereas clinicians are happy with the motor outcome, the patient's global impression does not change after surgery or, in some cases, it even worsens. This is why apathy should be detected after surgery and treated early on with dopaminergic drugs to prevent postoperative depression with suicidal risk[2,43]. Practical recommendations indicate that, overall, dopaminergic medications, especially dopamine agonists, should be reduced during the months following STN DBS, but a reduction of more than 70%, or a complete discontinuation, must be avoided.

Depression

In patients with bilateral chronic STN stimulation, depressive features improved, remained unchanged, or even worsened compared to the preoperative condition[20,45]. Postoperative improvement of depression might result from a psychological response to the alleviation of disabling motor symptoms or from the effects of STN stimulation on neural circuits involved in mood[20,45]. On the other hand, suicidal tendencies have been reported in

some patients with PD after STN DBS[1]. Occurrence of suicide has been linked to hypodopaminergic features secondary to acute post-surgical withdrawal of medications, which, as discussed, is a common practice in the initial phase of DBS treatment[46]. We recommend a very close follow-up and repetitive psychological assessment, if needed, throughout the first postoperative year to detect a delayed onset hypodopaminergic syndrome, which requires cautious as to the re-introduction of dopaminergic medications and antidepressant treatment[2].

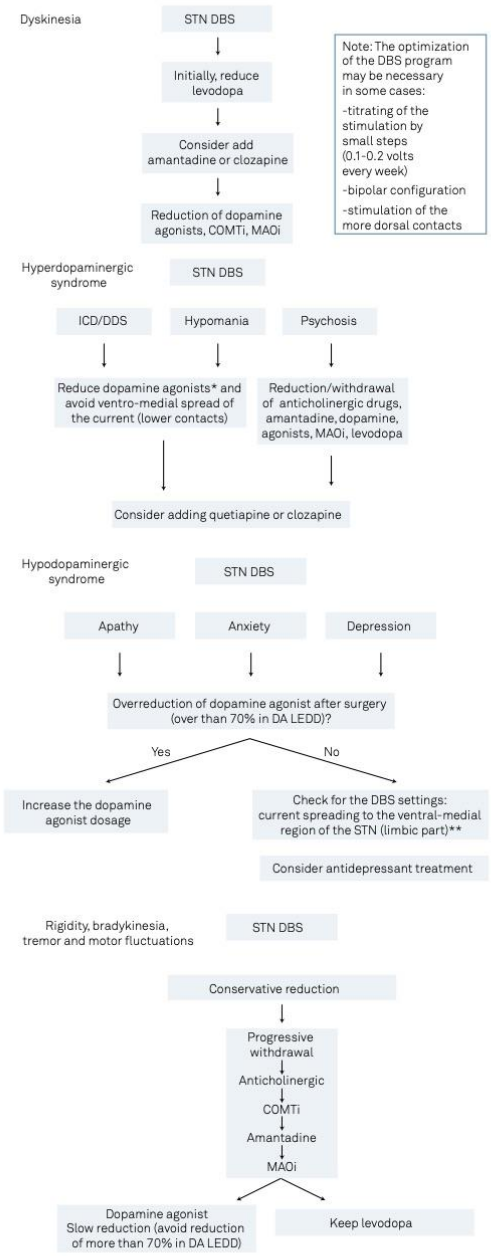
Rigidity, bradykinesia, tremor and motor fluctuations

STN DBS improves rigidity and bradykinesia by 63 and 52%, respectively, 12 months after surgery[1]. With the addition of dopaminergic replacement therapy, these improvements increased to 73 and 69%, respectively[1]. Regarding the tremor, STN stimulation may produce an improvement of 86% in the first year after surgery[1]. When the patient's phenotype before surgery is the severe parkinsonism (wearing-off) with or without tremor, the reduction of the medication can be more conservative. In such cases, the *add-on* of DBS plus medication are beneficial. Overall, we keep the levodopa unchanged and decrease the dopaminergic agonist when the DA LEDD is greater than 150 mg, due to potential neuropsychiatric side effects, as previously discussed. Sequentially, when the stimulation reaches a stable value, there is a gradual reduction in anticholinergic medications, followed by COMTi, amantadine, and MAOi[14].

FINAL REMARKS

In patients referred for DBS surgery, it is important to evaluate the patient's main phenotype at baseline, because it directly influences the drug management soon after surgery (Figure 3 summarizes the algorithm). This assessment of motor and non-motor symptoms, which predominate in each individual, allows a more individualized reduction in the amount of dopaminergic drugs and a logical sequence of reduction to minimize potential postoperative risks. Hyperdopaminergic and hypodopaminergic syndromes, together with severe dyskinesia, are the most challenges issues[31].

A multidisciplinary approach with the systematic assessment of non-motor dopamine-dependent symptoms is essential to screen for changes in motivation and mood, and to manage and prevent hypodopaminergic and hyperdopaminergic episodes[2]. The reduction in dopaminergic drugs afforded by STN DBS, and the consequent striatal desensitization, enable long term reversal, not only of dyskinesia but also of hyperdopaminergic behaviors. However, an abrupt drastic reduction in dopaminergic drugs (in case of either disabling dyskinesia or



STN DBS: Subthalamic nucleus deep brain stimulation; COMTi/: catechol-O-methyltransferase inhibitor; MAOi: monoamine oxidase inhibitor; ICD: impulse control disorder; DDS: dopamine dysregulation syndrome; DA LEDD: dopamine agonist levodopa equivalent daily dose. *Overreduction can lead to dopamine agonist withdrawal syndrome. **Although the limbic spread of the current usually leads to hyperdopaminergic syndrome, negative symptoms, such as apathy can happen and dramatically improve after DBS adjustment.

Figure 3. Algorithm for medical management in the acute phase after subthalamic stimulation, according to the most prevalent patient's phenotype.

pathologic hyperdopaminergic syndrome) may lead to complications ranging from isolated apathy up to a full-blown hypodopaminergic syndrome, highlighting apathy as the core symptom in association with anxiety, depression, and pain, in various combinations[2].

A slow, progressive, and orchestrated increase of STN DBS intensity parallel to a reduction in dopaminergic drugs according to patient's characteristics is the more logical approach. However, systematic studies addressing medical management following DBS are still needed and will contribute to the ultimate success of DBS in PD.

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