Send Orders for Reprints to reprints@benthamscience.ae

14 *Current Neuropharmacology*, **2019**, *17*, **14-20**

REVIEW ARTICLE

Noninvasive Cerebellar Stimulation as a Complement Tool to Pharmacotherapy

Roberta Ferrucci[a,b,c,*], Tommaso Bocci[b,d], Francesca Cortese[b,e,f], Fabiana Ruggiero[b] and Alberto Priori[a,b,c]

[a]*Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan Medical School, Milan, Italy;* [b]*Ca' Granda IRCCS Foundation Hospital, Milan, Italy;* [c]*III Neurological Clinic San Paolo Hospital Milan, Italy;* [d]*Department of Clinical and Experimental Medicine, Cisanello Neurology Unit, Pisa University Medical School, Pisa, Italy;* [e]*Fracastoro Hospital, San Bonifacio, Verona, Italy;* [f]*Department of Medico-Surgical Science and Biotechnologies, Sapienza University of Rome, Latina, Italy*

ARTICLE HISTORY

Received: June 20, 2017
Revised: October 09, 2017
Accepted: November 06, 2017

DOI:
10.2174/1570159X15666171114142422

Abstract: ***Background*:** Cerebellar ataxias represent a wide and heterogeneous group of diseases characterized by balance and coordination disturbance, dysarthria, dyssynergia and adyadococinesia, caused by a dysfunction in the cerebellum. In recent years there has been growing interest in discovering therapeutical strategy for specific forms of cerebellar ataxia. Together with pharmacological studies, there has been growing interest in non-invasive cerebellar stimulation techniques to improve ataxia and limb coordination. Both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are non-invasive techniques to modulate cerebro and cerebellar cortex excitability using magnetic or electric fields.

***Methods*:** Here we aim to review the most relevant studies regarding the application of TMS and tDCS for the treatment of cerebellar ataxia.

***Conclusion*:** As pharmacological strategies were shown to be effective in specific forms of cerebellar ataxia and are not devoid of collateral effects, non-invasive stimulation may represent a promising strategy to improve residual cerebellar circuits functioning and a complement tool to pharmacotherapy.

Keywords: tDCS, cerebellar tDCS, cerebellar TMS, ataxia, non invasive neuromodulation, cerebellum.

1. INTRODUCTION

Cerebellar ataxias represent a wide and heterogeneous group of diseases defined by a collection of signs and symptoms in combination, such as balance and coordination disturbance, dysarthria, dyssynergia and adyadococinesia, caused by a dysfunction in the cerebellum. Cerebellar ataxia may occur as an isolated syndrome or in association with the involvement of other neurological systems (*i.e*. in multiple sclerosis, multiple system atrophy, vasculitis) and arises from very different causes.

Depending on the aetiologies, the primary distinction is between acquired and genetic ataxias. Acquired cerebellar ataxias include different forms: autoimmune, paraneoplastic, toxic (*i.e*. alcoolism), infectious, vascular, and associated to vitamin deficiency (*i.e* vitamin E) or to primary or metastatic brain tumors. Hereditary cerebellar ataxias represent a group of rare genetic diseases characterized by slow progression of cerebellar symptoms (ataxia, incoordination of extremities and eye movements and dysartria) and often associated to cerebellar atrophy [1]. Depending on the inheritance mode, genetic ataxias may be subdivided into autosomal dominant forms (including spinocerebellar ataxias, episodic ataxias, DRPLA, SPAX1), autosomal recessive forms, with Friedreich ataxia, ataxia-telangiectasia, and ataxia oculomotor apraxia being most common, mitochondrial forms (*i.e*. MELAS, MERRF, NARP and others) and X-linked forms (fragile X tremor ataxia syndrome).

Management of ataxia requires a multidisciplinary approach through rehabilitation techniques, occupational therapy and speech therapy.

Pharmacological therapy is for most forms only supportive and aimed to the treatment of comorbidities (*i.e*. spasticity, diabetes, epilepsy *etc*).

In recent years there has been growing interest in discovering therapeutical strategy for specific forms of cerebellar ataxia. 4-aminopyridine (4-AP) was shown to improve cerebellar gait ataxia and also to be effective in reducing the

*Address correspondence to this author at the Aldo Ravelli" Research Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan Medical School, Milan, Italy;
E-mail: roberta.ferrucci@policlinico.mi.it

1570-159X/19 $58.00+.00

number of attacks of ataxia, ameliorating the quality of life in patients affected by episodic ataxia type 2; observational studies also evidenced the effectiveness of the modified amino-acid acetyl-DL-leucine in cerebellar ataxia [2]. A recent Cochrane systematic review [3] did not identify clear evidence supporting the use of antioxidants to improve neurological status in patients affected by Friedreich ataxia, even though idebenone was shown to induce a decrease in left ventricular mass (whose clinical significance still needs to be clarified). Gene replacement strategies [4], iron chelators [5], erythropoietin [6], immune modulators [7] as well as iRNAs are under investigation [8] in patients and animal models of Friedreich ataxia. Vitamin E replacement is useful for ataxia with vitamin E deficiency (AVED). Steroids, plasmapheresis and/or intravenous immunoglobulin (IVIG) are used for immune-mediated cerebellar ataxia (gluten ataxia, paraneoplastic cerebellar degeneration, GAD antibody associated cerebellar ataxia, and Hashimoto's encephalopathy), after the removal of autoimmune triggering factors [9, 10].

Together with pharmacological studies, there has been growing interest in non-invasive cerebellar stimulation techniques to improve ataxia and limb coordination [11-13]. Both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are non-invasive techniques to modulate cerebro and cerebellar cortex excitability using magnetic or electric fields [14].

Here we aim to review the most relevant studies regarding the application of TMS (Table **1**) and tDCS (Table **2**) for the treatment of cerebellar ataxia. As pharmacological strategies were shown to be effective in specific forms of cerebellar ataxia and are not devoid of collateral effects, non-invasive stimulation may represent a promising strategy to improve residual cerebellar circuits functioning and a complement tool to pharmacotherapy.

1.1. Non Invasive Neuromodulation for the Treatment of Spinocerebellar Ataxias: An Overview

A growing body of literature has highlighted the impairment of corticospinal pathways in ataxias, by using single and paired pulse TMS, exploring the floating border between Hereditary Spastic Paraplegias (HSP) and Spinocerebellar Ataxias (SCAs); TMS revealed a high motor threshold in SCA1, accompanied by prolonged peripheral and central motor conduction times, whereas a reduced intracortical facilitation (ICF) has been reported both in SCA2 and SCA3 [12, 15-17]. More recently, a reduced intracortical inhibition (SICI) has been described in SCA14, clinically characterized by slowly progressive ataxia associated with mild dystonia and myoclonus [18].

Conversely, only few papers have investigated to date the role of repetitive TMS (rTMS) for therapeutic purposes. rTMS has been evaluated in primary neurodegenerative, as well as in sporadic and secondary ataxias, and clinical improvement has been reported following either low-frequency rTMS or theta-burst stimulation [19-21].

More studies have investigated the effects of DCS for the treatment of spinocerebellar ataxias, showing a significant improvement in clinical scores and neurophysiological parameters following anodal tDCS [22-26].

Despite the encouraging outcome, these preliminary results have some critical limitations, ranging from the different protocols used to the clinical and pathophysiological heterogeneity of patients enrolled. Moreover, the site of stimulation is highly variable among different studies.

1.1.1. Methods

We searched articles published through July 2017 on Medline (PubMed) using the terms ‘ataxia’, in combination with ‘cerebellar tDCS’ OR ‘TMS’ OR repetitive transcranial magnetic stimulation ‘rTMS’ AND the stimulation site ‘cerebellum’.

Published reports examining clinical motor improvements of cerebellar ataxias after neuromodulation interventions were included.

The types of NIBS included were TMS, rTMS, anodal-tDCS, and cathodal-tDCS. Furthermore, we included a single case and articles examining the clinical improvement and safety of cerebellar non-invasive brain stimulation in patients with cerebellar disorders.

1.1.2. Clinical rTMS Studies

Shimizu [27] first reported a beneficial effect of low-frequency rTMS in patients with spinocerebellar degeneration, as proved by a reduction in the time required for a 10m walk and by a concurrent increase in the number of feasible steps in tandem gait [27]. Few years later, Shiga and colleagues [21] showed a significant improvement after rTMS treatment in truncal ataxia in patients with SCAs, comprising spinocerebellar (SCA6) and olivopontocerebellar types (sporadic OPCA, SCA1 and SCA3), paralleled by significant changes in the regional cerebral blood flow (rBF) [21]; they used a particular kind of cerebellar stimulation, with the coil placed over the scalp and centred on the inion, 4 cm lateral to the right of the inion, and 4 cm lateral to the left of the inion. For each location, ten pulses (five clockwise and five counter clockwise) were delivered at an interstimulus interval of about 6 seconds, once a day and for three consecutive weeks. By using a similar protocol, Ihara and co-workers confirmed the efficacy of low-frequency rTMS for the treatment of ataxia, possibly through changes in regional blood flow and oxidative stress biomarkers [28]. However, in both studies, no causal relationship was clearly established between rBF changes and clinical outcome. Furthermore, the extent of functional improvement was not reported and quantitative assessment of gait and physical function was not performed.

More recently, using the same protocol, Farzan and colleagues [19] have quantified the improvement in functional mobility, standing postural control and gait kinematics in a patient with a probable diagnosis of idiopathic late-onset cerebellar ataxia [19]: rTMS likely dampens the cerebellar cortex inhibitory control over dentate nucleus, ultimately interfering with the cerebellar-brain inhibition (CBI). The Authors also reported a clear improvement in non-motor functions, possibly modulating connectivity between deep cerebellar nuclei and prefrontal areas.

Recently, other studies have highlighted the role of rTMS in stroke patients with ataxias [29]. In particular, cerebellar theta burst stimulation seems to modulate the functional

Table 1. rTMS studies.

Author & Year	Sample	Trial Type	Method of Stimulation	Target Location	Outcome	Results
Cerebellar Ataxia/ Spinocerebellar Degeneration and Stroke Ataxia						
Shimizu *et al*. (1999)	N= 4 (mean age 49.25 ± 23.59)	A	Single session cerebellar rTMS, 9 cm circular coil, 100% maximal output, 10 stimuli of 0.1 millisecond each for 21 days	4 cm later to the right and left of the inion	10 m walk, Gravicometer AS10, EEG, ECG, blood examination	A rTMS decreased: time by about 19% and the number of steps by about 15% and total length of tracing body balance by about 23%; TMS increased: the number of feasible steps by about 3% and the blood flow of the cerebellar hemisphere, putamen and pons.
Shiga *et al*. (2002)	N= 74 (mean age 57. 5 ± 1.7)	A/S	Single session cerebellar rTMS, 14 cm circular coil, 100% maximal output, 10 stimuli of 0.1 millisecond each for 21 days	(1) coil centered 4cm lateral to the right of the inion, (2) coil centered on the inion, and (3) coil centered 4cm lateral to the left of the inion, tangentially (active stimulation) or vertically (sham stimulation)	10 m walk, 10 m steps, standing capacities	A rTMS improved: 10 m Time by about 31%, 10 m steps by about 18%, tandem Steps by about 5%, standing capacities by about 30%.
Ihara *et al*. (2005)	N= 20 (mean age 51. 8 ± 10.9)	A	Single session cerebellar rTMS, 7 cm eight-shaped coil, 100% maximal output. Ten stimuli of 0.2 Hz delivered at each of the three points on Monday, Wednesday, and Friday for 8 weeks	coil placed tangentially over the inion and at points 4 cm laterally, to both the right and the left	CHBF, AFR, superoxide dismutase protein, superoxide scavenging activity, 8-OHdG in cerebrospinal fluid	A rTMS improved CHBF and reduced oxidative stress biomarkers.
Farzan *et al*. (2013)	N= 1 (61 years)	A	Single session cerebellar rTMS, 14 cm circular coil, 100% maximal output, 10 stimuli of 0.1 millisecond each for 21 days	(1) coil centered 4cm lateral to the right of the inion, (2) coil centered on the inion, and (3) coil centered 4cm lateral to the left of the inion	Timed up-and-go test, quantitative gait assessment, CBI	A rTMS improved: Timed up-and-go test by 9%, the average speed and area of postural sway by about 24% and 31 respectively; In the normal and cognitive dual task conditions, respectively, gait speed increased 15 and 33 %, stride duration variability decreased 21 and 26 %, and double support time decreased 43 and 47 %.
Kim *et al*. (2014)	N= 32 (mean age 66. 7 ± 9.5)	A/S	Single session cerebellar rTMS, 75 mm coil, 100% maximal output, 1 Hz, for 5 days	2 cm below the inion and 2 cm lateral to the midline on the cerebellar hemisphere ipsilateral to the ataxic side, with the handle pointing superiorly, targeting the posterior cerebellar lobe	10 m walk, BBS	A rTMS improved: time and steps in 10 m walk by 16 and 8%, respectively, and BBs by 46%.

Abbreviations: Legend: A: active; AFR: Ascorbate free radical; BBS: Berg Balance Scale; CBI: Cerebellar-brain inhibition; Cm: centimeters; CHBF: Cerebellar hemispheric blood flow; ECG: Electrocardiography; EEG: Electroencephalogy; Hz: Hertz; Min: minutes; Mm: millimeters; rTMS: repetitive transcranial magnetic stimulation; S: sham; TMS: transcranial magnetic stimulation; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; 10 MW: 10-Meter Walking Time.

Table 2. tDCS studies.

Author & Year	Sample	Trial Type	Polarity and Number of Sessions	Stimulation Electrode Position	Reference Electrode Position	Current Strength and Duration	Outcome	Results
Cerebellar Ataxia								
Grimaldi *et al*. (2013)	N= 9 (mean age 51.3 ± 14)	Single blind, sham-controlled;	A/S	Right cerebellar cortex, vermis	Contralateral supra-orbital area	1 mA	SR, MCT, Computerized Posturography	A tCDCS reduced the amplitudes of long-latency stretch reflexes
Grimaldi *et al*. (2014)	N=2 (mean age 46 ± 4.24)	Single blind, sham-controlled;	A/S	Right cerebellar cortex, Left M1	Contralateral supra-orbital area, right supra-orbital area	1 mA, 20 + 20 min	SARA, Upper limb tremor (postural and action tremor), dysmetria	A tCCDCS reduced: the PSD peak by 38.63 and 41.42% in both patients, the magnitude of low frequency oscillations by 46.9 and 62.3% respectively, and the the onset latency of the hypermetria by about 41 and 45%.
Benussi *et al*. (2015)	N= 19 (mean age 53.8 ± 18.4)	Randomized, double blind, cross-over; sham-controlled;	A/S	Cerebellar cortex	Right deltoid muscle	2 mA, 20 min	SARA, ICARS, 9HPT, 8MW	A tCDCS improved: SARA by about 10%, ICARS by 12%, 9HPT by 11%, 8MW by 11%.
Benussi *et al*. (2017)	N= 20 (mean age not reported)	Randomized, double blind, sham-controlled;	A/S 10 daily tDCS	Cerebellar cortex	Right deltoid muscle	2 mA, 20 min	SARA, ICARS,9HPT, 8MW, CBI assessment	A tCDCS improves: SARA by about 3%, ICARS by 12%, CBI by about 18%.
Bodranghien *et al*. (2017)	N= 1 ANO10 mutation (33-year-old female)	Single blind, sham-controlled;	A/S	Right cerebellar cortex	Contralateral motor cortex	1,5 mA, 20 min	SARA, Traces of accelerometry, Spectral parameters of postural tremor	A tCCDCS improved the power spectral density to 26.12% of basal values.

Abbreviations: A:anodal tDCS; CBI: cerebellar brain inhibition; ICARS: International Cooperative Ataxia Rating Scale; M1: motor cortex; mA: milliampere; MCT: Mechanical Counter Test; Min: minutes; Offline: the subject receives stimulation before and after executing the task; Online: the subject receives stimulation during the task; S: sham tDCS; SARA: scale for the Assessment and Rating of Ataxia; SR: Stretch reflexes; tCDCS: transcranial cerebellar direct current stimulation; tCCDCS: transcranial cerebello-cerebral direct current stimulation; 9HPT: Nine-Hole Peg Test; 8MW: 8-Meter Walking Time.

cerebellar-brain connectivity, thus improving postural control and ataxic gait [20, 30] these changes are coupled with neurophysiological modifications, as proved by the modulation of glutamatergic intracortical networks. Also low-frequency rTMS is effective for the treatment of ataxia following cerebellar unilateral infarction [31].

Nonetheless, samples were too small and heterogeneous in terms of the affected cerebellar hemisphere; moreover, only few clinical scales were assessed, which may not be sufficient to detect all the complex clinical aspects of cerebellar dysfunction in stroke patients.

1.1.3. Clinical tDCS Studies

There is a growing evidence that cerebellar tDCS appears to be a new tool to study the modulation of long latency stretch reflexes (LLSR) response by the cerebellar cortex. Grimaldi and colleagues (2013) [25] examined the effects of anodal cerebellar tDCS in nine ataxic patients. The protocol provided the administration of the SR recorder in the upper limbs and upper limb dexterity and coordination using a mechanical counter test (MCT), before and after tDCS over the right cerebellar hemisphere. Their results showed that anodal tDCS over the right cerebellar hemisphere reduced the amplitude of the long latency SR (LLSR), but did not affect the short latency SR response or the MCT score compared to the baseline and sham group. After sham or active stimulation of the region in front of the vermis, the postural parameters remained unchanged.

The results obtained may suggest that anodal tDCS applied over the cerebellum reinforces the inhibitory activity exerted by the cerebellar cortex over cerebellar nuclei.

Grimaldi and colleagues (2014) [26] performed a second experiment on upper limb tremor and dysmetria in two patients with dominant spinocerebellar ataxia. tDCS was administer over the cerebellum for 20 minutes immediately followed by tDCS applied over the contralateral motor cortex (tCCDCS: transcranial cerebello-cerebral DC stimulation).

For the postural tremor, quadratic power spectral density (PSD) revealed that tCCDCS induced a reduction in the amplitude of the oscillations at the level of the index in both patients. For action tremors, tCCDCS also had a positive effect as observed by the drop in the magnitude of low-frequency oscillations from 62.3% to 46.9% of the baseline values in patient 1 and 2, respectively.

In both patients following tCCDCS, hypermetria occurred along with a reduction of the onset latency of the antagonist electromyography (EMG) activity. Despite the small sample these results are highly encouraging to study the therapeutic effects of tDCS on upper limb tremor.

Bodranghien and colleagues (2017) [24] conducted a single case study in a patient with ANO10 mutation (ARCA3). They delivered anodal tCCDCS over the cerebellum with a return electrode on the contralateral motor cortex. Clinical rating, accelerometry studies, and recordings of voluntary movements were recorded at baseline, after sham, and after active tCCDCS.

Results revealed that there was an improvement on postural tremor after tCCDCS, with a major drop of the power spectral density to 26.12% of basal values. The combination of tDCS of the cerebellum with tDCS of the motor/premotor cortex demonstrated that this technique may be considered a symptomatic therapeutic strategy to reduce tremor in disabling cerebellar ataxia.

Benussi and colleagues (2015) [23] explored the effect of a single session of cerebellar anodal and sham tDCS in nine patients with ataxia. They found a positive effect of anodal cerebellar tDCS on functional clinical scores, as observed with the Scale for the Assessment and Rating of Ataxia (SARA), on the International Cooperative Ataxia Rating Scale (ICARS), and in motor task measurement with the nine-hole peg test (9HPT) and 8-Meter Walking Time (8MW) assessment within the entire cohort of patients.

Particularly, a significant improvement was observed in the posture, gait and limb coordination ICARS subscores. Authors conducted a single-group analysis in the SCA (spinocerebellar ataxia) and the cerebellar variant of MSA (multiple system atrophy, MSA-C) cohorts demonstrating a significant effect from anodal cerebellar tDCS on SARA, ICARS, and 9HPT testing.

Only in the SCA group there was a significant difference in the 8MW testing. No significant difference in the MSA-C group was reported. The findings obtained *via* a single stimulation session applied to the cerebellar cortex suggests that tDCS can temporarily improve symptoms in patients with ataxia and might have therapeutic potential in these patients, but more powerful stimulation may be needed.

To evaluate whether a two-weeks' treatment with cerebellar anodal tDCS could affect cerebello-motor connectivity, in a subsequent study the same group [22] assessed symptoms in twenty patients with neurodegenerative cerebellar ataxia at short and long term (3 months).

In a double-blind, randomized, sham controlled trial with cerebellar tDCS (5 days/ week for 2 weeks) they conducted a clinical evaluation pre- and post-anodal tDCS or sham stimulation. Cerebello-motor connectivity was evaluated using TMS at baseline and at follow-up. Results reported that a two-weeks' treatment with anodal cerebellar tDCS improves symptoms in patients with ataxia and restores physiological cerebellar brain inhibition pathways compared to patients who underwent sham stimulation.

Given that patients which were less affected clinically and functionally demonstrated a greater improvement, which outlasted the stimulation interval for at least three months, authors highlight that repetitive sessions of tDCS do not necessarily induce a linearly cumulative result and, actually, the optimal repetition rate and inter-stimulation interval has still to be determined.

In the light of these studies, treatment with cerebellar tDCS could be considered a potentially promising tool for future therapeutic and rehabilitative approaches in patients with ataxia.

1.2. Putative Mechanisms of Action

Despite the promising outcome, the exact mechanisms of action still remain unknown. Probably, low frequency TMS mediates its therapeutic effects by dampening the inhibitory tone exerted by Purkinje cells over the dentate nucleus, thus leading to a reduced cerebellar-brain inhibition. By analogy, both anodal tDCS and high frequency rTMS likely lead to an increase in CBI. However, cerebellar-brain connections are both excitatory and inhibitory and, consequently, different mechanisms should be carefully considered. In particular, a reduced inhibitory control from Purkinje cells may also enhance the activation of the vestibular nuclei, resulting in postural balance improvement [32]. The Purkinje axons from the vestibular-cerebellum end primarily in the area of the vestibular nuclei sending ascending fibers to the external ocular muscles through the medial longitudinal fasciculus, thus dynamically modulating the position of the body within extra- and peripersonal space [33, 34]. Although the cellular and molecular targets at a cerebellar level have not been clarified so far, the efficacy of rTMS/tDCS for the treatment of ataxias may depend on changes both in ascending and descending pathways.

The use of TMS/tDCS as therapeutic tools complementary to pharmacological interventions may also depend on the time of intervention, especially in stroke patients [31]. In fact, cerebellar infarctions result in acutely increased contralateral inhibition of the primary motor cortex, likely reflecting the increase in intracortical inhibition related to the loss of dentate-cortical facilitatory projections [35]. Conversely, as time passes, the intracortical inhibition within the contralesional M1 progressively decreases, leading to an impaired interhemispheric balance in cortical excitability [36]. Moreover, as short and long-term effects of cerebellar tDCS likely arise from the depolarization of Purkinje and Golgi cells respectively, plasticity changes induced by either

anodal or cathodal polarization become strictly time-dependent [37]. Overall, these mechanisms could explain the paradox that the inhibitory low-frequency rTMS and the excitatory anodal tDCS, applied over the cerebellar cortex, both lead to a clinical improvement in patients with spinocerebellar ataxias.

CONCLUSION

We found that a total of 282 patients were involved in 10 studies (7 had blinded designs and 3 were open label). Inclusion criteria varied greatly among the studies, but all patients had a diagnosis of cerebellar ataxia. There was a great variability regarding the duration of the intervention. All trials used non invasive neuromodulation techniques (rTMS or tDCS) targeting the posterior fossa. Besides motor outcomes, 5 studies also analyzed neurophysiological parameters. 5 used TMS stimulation, 5 used tDCS stimulation. All studies reported favorable clinical outcomes. No study reported major side effects.

Overall, low-frequency rTMS and theta-burst stimulation and tDCS seem to be effective for the treatment of cerebellar ataxias; future studies should be focused on a better definition of molecular and cellular targets, in order to clarify the specific timeline of intervention among sporadic, neurodegenerative and vascular diseases. This review suggests that cerebellar non invasive neuromodulation could be an interesting therapeutic option relieving some symptoms in specific cerebellar ataxia disorder.

LIST OF ABBREVIATIONS

8MW	=	8-Meter Walking Time
9HPT	=	Nine-hole Peg Test
CBI	=	Cerebellar-Brain Inhibition
EMG	=	Electromyography
HSP	=	Hereditary Spastic Paraplegias
ICARS	=	International Cooperative Ataxia Rating Scale
ICF	=	Intracortical Facilitation
LLSR	=	Long Latency Stretch Reflexes Response
M1	=	Primary Motor Cortex
rBF	=	Regional Blood Flow
rTMS	=	Repetitive Transcranial Magnetic Stimulation
SARA	=	Scale for the Assessment and Rating of Ataxia
SCAs	=	Spinocerebellar Ataxias
SICI	=	Intracortical Inhibition
SLSR	=	Short Latency Stretch Reflexes Response
SR	=	Stretch Reflexes
tCCDCS	=	Transcranial Cerebello-Cerebral DC Stimulation
tDCS	=	Transcranial Direct Current Stimulation
TMS	=	Transcranial Magnetic Stimulation

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Alberto Priori and Roberta Ferrucci are stakeholders in Newronika s.r.l., a spin-off company formed by the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Università degli Studi di Milano. This study received no specific funding and was supported from the Italian Ministry of Health (Ricerca Corrente IRCCS RC-2017).

ACKNOWLEDGEMENTS

Design/conception: Roberta Ferrucci and Alberto Priori. Literature and database search: Roberta Ferrucci, Francesca Cortese, Tommaso Bocci and Fabiana Ruggiero. Data extraction: Roberta Ferrucci, Francesca Cortese, Tommaso Bocci and Fabiana Ruggiero. The initial draft of the manuscript is written by Roberta Ferrucci, Francesca Cortese, Tommaso Bocci, Fabiana Ruggiero and Alberto Priori. All authors critically revised and approved the final manuscript.

REFERENCES

[1] Bird, T.D. Hereditary Ataxia Overview., **1993**. [Epub a head of print].

[2] Feil, K.; Bremova, T.; Muth, C.; Schniepp, R.; Teufel, J.; Strupp, M. Update on the pharmacotherapy of cerebellar ataxia and nystagmus. *Cerebellum*, **2016**, *15*(1), 38-42. [http://dx.doi.org/10.1007/s12311-015-0733-1] [PMID: 26519380]

[3] Kearney, M.; Orrell, R.W.; Fahey, M.; Pandolfo, M. Antioxidants and other pharmacological treatments for Friedreich ataxia. Cochrane *Database Syst. Rev*., **2012**, *18*(4), CD007791. [PMID: 22513953]

[4] Li, Y.; Polak, U.; Bhalla, A.D.; Rozwadowska, N.; Butler, J.S.; Lynch, D.R.; Dent, S.Y.R.; Napierala, M. Excision of expanded GAA repeats alleviates the molecular phenotype of Friedreich's *Ataxia. Mol. Ther.,* **2015**, *23*(6), 1055-1065. [http://dx.doi.org/10.1038/mt.2015.41] [PMID: 25758173]

[5] Elincx-Benizri, S.; Glik, A.; Merkel, D.; Arad, M.; Freimark, D.; Kozlova, E.; Cabantchik, I.; Hassin-Baer, S. Clinical experience with deferiprone treatment for Friedreich ataxia. *J. Child Neurol*., **2016**, *31*(8), 1036-1040. [http://dx.doi.org/10.1177/0883073816636087] [PMID: 27029487]

[6] Saccà, F.; Puorro, G.; Marsili, A.; Antenora, A.; Pane, C.; Casali, C.; Marcotulli, C.; Defazio, G.; Liuzzi, D.; Tatillo, C.; Cambriglia, D.M.; Schiano di Cola, G.; Giuliani, L.; Guardasole, V.; Salzano, A.; Ruvolo, A.; De Rosa, A.; Cittadini, A.; De Michele, G.; Filla, A. Long-term effect of epoetin alfa on clinical and biochemical markers in friedreich ataxia. *Mov. Disord*., **2016**, *31*(5), 734-741. [http://dx.doi.org/10.1002/mds.26552] [PMID: 26879839]

[7] Calap-Quintana, P.; Soriano, S.; Llorens, J.V.; Al-Ramahi, I.; Botas, J.; Moltó, M.D.; Martínez-Sebastián, M.J. TORC1 inhibition by rapamycin promotes antioxidant defences in a Drosophila model of Friedreich's Ataxia. *PLoS One*, **2015**, *10*(7), e0132376. [http://dx.doi.org/10.1371/journal.pone.0132376] [PMID: 26158631]

[8] Bürk, K. Friedreich Ataxia: current status and future prospects. *Cerebellum Ataxias*, **2017**, *4,* 4. [http://dx.doi.org/10.1186/s40673-017-0062-x] [PMID: 28405347]

[9] Mitoma, H.; Hadjivassiliou, M.; Honnorat, J. Guidelines for treatment of immune-mediated cerebellar ataxias. *Cerebellum Ataxias*, **2015**, *2*, 14. [http://dx.doi.org/10.1186/s40673-015-0034-y] [PMID: 26561527]

[10] Gungor, S.; Kilic, B.; Arslan, M.; Ozgen, U. Hodgkin's lymphoma associated with paraneoplastic cerebellar degeneration in children: a case report and review of the literature. *Childs Nerv. Syst*., **2017**,

33(3), 509-512. [http://dx.doi.org/10.1007/s00381-016-3284-y] [PMID: 27796550]

[11] Ferrucci, R.; Bocci, T.; Cortese, F.; Ruggiero, F.; Priori, A. Cerebellar transcranial direct current stimulation in neurological disease. *Cerebellum Ataxias*, **2016**, *3*(1), 16. [http://dx.doi.org/10.1186/s40673-016-0054-2] [PMID: 27595007]

[12] Groiss, S.J.; Ugawa, Y. Cerebellar stimulation in ataxia. Cerebellum, **2012**, 11(2), 440-442. [http://dx.doi.org/10.1007/s12311-011-0329-3] [PMID: 22116658]

[13] Pope, P.A.; Miall, R.C. Restoring cognitive functions using non-invasive brain stimulation techniques in patients with cerebellar disorders. *Front. Psychiatry*, **2014**, *5,* 33. [http://dx.doi.org/10.3389/fpsyt.2014.00033] [PMID: 24765079]

[14] Grimaldi, G.; Argyropoulos, G.P.; Boehringer, A.; Celnik, P.; Edwards, M.J.; Ferrucci, R.; Galea, J.M.; Groiss, S.J.; Hiraoka, K.; Kassavetis, P.; Lesage, E.; Manto, M.; Miall, R.C.; Priori, A.; Sadnicka, A.; Ugawa, Y.; Ziemann, U. Non-invasive cerebellar stimulation--a consensus paper. *Cerebellum*, **2014**, *13*(1), 121-138. [http://dx.doi.org/10.1007/s12311-013-0514-7] [PMID: 23943521]

[15] Abele, M.; Bürk, K.; Andres, F.; Topka, H.; Laccone, F.; Bösch, S.; Brice, A.; Cancel, G.; Dichgans, J.; Klockgether, T. Autosomal dominant cerebellar ataxia type I. Nerve conduction and evoked potential studies in families with SCA1, SCA2 and SCA3. *Brain*, **1997**, *120*(Pt 12), 2141-2148. [http://dx.doi.org/10.1093/brain/120.12.2141] [PMID: 9448569]

[16] Schöls, L.; Amoiridis, G.; Büttner, T.; Przuntek, H.; Epplen, J.T.; Riess, O. Autosomal dominant cerebellar ataxia: phenotypic differences in genetically defined subtypes? *Ann. Neurol.*, **1997**, *42*(6), 924-932. [http://dx.doi.org/10.1002/ana.410420615] [PMID: 9403486]

[17] Schwenkreis, P.; Tegenthoff, M.; Witscher, K.; Börnke, C.; Przuntek, H.; Malin, J.P.; Schöls, L. Motor cortex activation by transcranial magnetic stimulation in ataxia patients depends on the genetic defect. *Brain,* **2002**, *125*(Pt 2), 301-309. [http://dx.doi.org/10.1093/brain/awf023] [PMID: 11844730]

[18] Ganos, C.; Zittel, S.; Minnerop, M.; Schunke, O.; Heinbokel, C.; Gerloff, C.; Zühlke, C.; Bauer, P.; Klockgether, T.; Münchau, A.; Bäumer, T. Clinical and neurophysiological profile of four German families with spinocerebellar ataxia type 14. *Cerebellum,* **2014**, *13*(1), 89-96. [http://dx.doi.org/10.1007/s12311-013-0522-7] [PMID: 24030789]

[19] Farzan, F.; Wu, Y.; Manor, B.; Anastasio, E.M.; Lough, M.; Novak, V.; Greenstein, P.E.; Pascual-Leone, A. Cerebellar TMS in treatment of a patient with cerebellar ataxia: evidence from clinical, biomechanics and neurophysiological assessments. *Cerebellum*, **2013**, *12*(5), 707-712. [http://dx.doi.org/10.1007/s12311-013-0485-8] [PMID: 23625327]

[20] Koch, G.; D'Angelo, E. Magnetic stimulation of the cerebellum. Moving towards the clinic. *Funct. Neurol.*, **2014**, *29*(1), 5. [PMID: 25014043]

[21] Shiga, Y.; Tsuda, T.; Itoyama, Y.; Shimizu, H.; Miyazawa, K.I.; Jin, K.; Yamazaki, T. Transcranial magnetic stimulation alleviates truncal ataxia in spinocerebellar degeneration. *J. Neurol. Neurosurg. Psychiatry,* **2002**, *72*(1), 124-126. [http://dx.doi.org/10.1136/jnnp.72.1.124] [PMID: 11784843]

[22] Benussi, A.; Dell'Era, V.; Cotelli, M.S.; Turla, M.; Casali, C.; Padovani, A.; Borroni, B. Long term clinical and neurophysiological effects of cerebellar transcranial direct current stimulation in patients with neurodegenerative ataxia. *Brain Stimul.,* **2017**, *10*(2), 242-250. [http://dx.doi.org/10.1016/j.brs.2016.11.001] [PMID: 27838276]

[23] Benussi, A.; Koch, G.; Cotelli, M.; Padovani, A.; Borroni, B. Cerebellar transcranial direct current stimulation in patients with ataxia: A double-blind, randomized, sham-controlled study. *Mov. Disord.,* **2015**, *30*(12), 1701-1705. [http://dx.doi.org/10.1002/mds.26356] [PMID: 26274840]

[24] Bodranghien, F.; Oulad Ben Taib, N.; Van Maldergem, L.; Manto, M. A postural tremor highly responsive to transcranial cerebellocerebral DCS in ARCA3. *Front. Neurol.,* **2017**, *8*(71), 71. [PMID: 28316589]

[25] Grimaldi, G.; Manto, M. Anodal transcranial direct current stimulation (tDCS) decreases the amplitudes of long-latency stretch reflexes in cerebellar ataxia. *Ann. Biomed. Eng.*, **2013**, *41*(11), 2437-2447. [http://dx.doi.org/10.1007/s10439-013-0846-y] [PMID: 23780473]

[26] Grimaldi, G.; Oulad Ben Taib, N.; Manto, M.; Bodranghien, F. Marked reduction of cerebellar deficits in upper limbs following transcranial cerebello-cerebral DC stimulation: tremor reduction and re-programming of the timing of antagonist commands. *Front. Syst. Neurosci.,* **2014**, *8,* 9. [http://dx.doi.org/10.3389/fnsys.2014.00009] [PMID: 24523678]

[27] Shimizu, H.; Tsuda, T.; Shiga, Y.; Miyazawa, K.; Onodera, Y.; Matsuzaki, M.; Nakashima, I.; Furukawa, K.; Aoki, M.; Kato, H.; Yamazaki, T.; Itoyama, Y. Therapeutic efficacy of transcranial magnetic stimulation for hereditary spinocerebellar degeneration. Tohoku. *J. Exp. Med.,* **1999**, 189(3), 203-211. [http://dx.doi.org/10.1620/tjem.189.203] [PMID: 10674722]

[28] Ihara, Y.; Takata, H.; Tanabe, Y.; Nobukuni, K.; Hayabara, T. Influence of repetitive transcranial magnetic stimulation on disease severity and oxidative stress markers in the cerebrospinal fluid of patients with spinocerebellar degeneration. *Neurol. Res.,* **2005**, *27*(3), 310-313. [http://dx.doi.org/10.1179/016164105X39897] [PMID: 15845214]

[29] Kim, W-S.; Jung, S.H.; Oh, M.K.; Min, Y.S.; Lim, J.Y.; Paik, N.J. Effect of repetitive transcranial magnetic stimulation over the cerebellum on patients with ataxia after posterior circulation stroke: A pilot study. *J. Rehabil. Med.,* **2014**, 46(5), 418-423. [http://dx.doi.org/10.2340/16501977-1802] [PMID: 24658396]

[30] Bonnì, S.; Ponzo, V.; Caltagirone, C.; Koch, G. Cerebellar theta burst stimulation in stroke patients with ataxia. *Funct. Neurol.,* **2014**, *29*(1), 41-45. [PMID: 25014048]

[31] Cury, R.G.; Teixeira, M.J.; Galhardoni, R.; Barboza, V.R.; Alho, E.; Seixas, C.M.; Lepski, G.; Ciampi de Andrade, D. Neuronavigation-guided transcranial magnetic stimulation of the dentate nucleus improves cerebellar ataxia: A sham-controlled, double-blind n = 1 study. *Parkinsonism Relat. Disord.*, **2015**, *21*(8), 999-1001. [http://dx.doi.org/10.1016/j.parkreldis.2015.05.010] [PMID: 26022755]

[32] Rüb, U.; de Vos, R.A.; Schultz, C.; Brunt, E.R.; Paulson, H.; Braak, H. Spinocerebellar ataxia type 3 (Machado-Joseph disease): severe destruction of the lateral reticular nucleus. *Brain,* **2002**, *125*(Pt 9), 2115-2124. [http://dx.doi.org/10.1093/brain/awf208] [PMID: 12183356]

[33] Zee, D.S.; Yamazaki, A.; Butler, P.H.; Gücer, G. Effects of ablation of flocculus and paraflocculus of eye movements in primate. *J. Neurophysiol.,* **1981**, *46*(4), 878-899. [http://dx.doi.org/10.1152/jn.1981.46.4.878] [PMID: 7288469]

[34] Shin, M.; Moghadam, S.H.; Sekirnjak, C.; Bagnall, M.W.; Kolkman, K.E.; Jacobs, R.; Faulstich, M.; du Lac, S. Multiple types of cerebellar target neurons and their circuitry in the vestibulo-ocular reflex. *J. Neurosci.,* **2011**, *31*(30), 10776-10786. [http://dx.doi.org/10.1523/JNEUROSCI.0768-11.2011] [PMID: 21795530]

[35] Sönmezoğlu, K.; Sperling, B.; Henriksen, T.; Tfelt-Hansen, P.; Lassen, N.A. Reduced contralateral hemispheric flow measured by SPECT in cerebellar lesions: crossed cerebral diaschisis. *Acta Neurol. Scand.,* **1993**, *87*(4), 275-280. [http://dx.doi.org/10.1111/j.1600-0404.1993.tb05507.x] [PMID: 8503255]

[36] Farias da Guarda, S.N.; Cohen, L.G.; da Cunha Pinho, M.; Yamamoto, F.I.; Marchiori, P.E.; Scaff, M.; Conforto, A.B. Interhemispheric asymmetry of corticomotor excitability after chronic cerebellar infarcts. *Cerebellum,* **2010**, *9*(3), 398-404. [http://dx.doi.org/10.1007/s12311-010-0176-7] [PMID: 20461489]

[37] Priori, A.; Ciocca, M.; Parazzini, M.; Vergari, M.; Ferrucci, R. Transcranial cerebellar direct current stimulation and transcutaneous spinal cord direct current stimulation as innovative tools for neuroscientists. *J. Physiol.,* **2014**, *592*(16), 3345-3369. [http://dx.doi.org/10.1113/jphysiol.2013.270280] [PMID: 24907311]