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CONSENSUS PAPER

Consensus Paper: Novel Directions and Next Steps of Non-invasive Brain Stimulation of the Cerebellum in Health and Disease

Mario Manto[1,2] · Georgios P. D. Argyropoulos[3] · Tommaso Bocci[4,5] · Pablo A. Celnik[6] · Louise A. Corben[7] · Matteo Guidetti[4,8] · Giacomo Koch[9] · Alberto Priori[4,5] · John C. Rothwell[10] · Anna Sadnicka[11,12] · Danny Spampinato[9] · Yoshikazu Ugawa[13] · Maximilian J. Wessel[14,15] · Roberta Ferrucci[4,5]

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Abstract

The cerebellum is involved in multiple closed-loops circuitry which connect the cerebellar modules with the motor cortex, prefrontal, temporal, and parietal cortical areas, and contribute to motor control, cognitive processes, emotional processing, and behavior. Among them, the cerebello-thalamo-cortical pathway represents the anatomical substratum of cerebellum-motor cortex inhibition (CBI). However, the cerebellum is also connected with basal ganglia by disynaptic pathways, and cerebellar involvement in disorders commonly associated with basal ganglia dysfunction (e.g., Parkinson's disease and dystonia) has been suggested. Lately, cerebellar activity has been targeted by non-invasive brain stimulation (NIBS) techniques including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) to indirectly affect and tune dysfunctional circuitry in the brain. Although the results are promising, several questions remain still unsolved. Here, a panel of experts from different specialties (neurophysiology, neurology, neurosurgery, neuropsychology) reviews the current results on cerebellar NIBS with the aim to derive the future steps and directions needed. We discuss the effects of TMS in the field of cerebellar neurophysiology, the potentials of cerebellar tDCS, the role of animal models in cerebellar NIBS applications, and the possible application of cerebellar NIBS in motor learning, stroke recovery, speech and language functions, neuropsychiatric and movement disorders.

Keywords Cerebellum · Neuromodulation · Non-invasive · tDCS · TMS

Introduction

The cerebellum represents 10% of total brain volume, but it contains more than 50% of total brain neurons, reflecting the complex cellular architecture connecting this subcortical structure to other parts of the brain. Traditionally, researchers have focused on the role of the cerebellum in the control and coordination of movement [1], since the motor cortex is one of the main targets of cerebellar projections. Besides sending inputs through the cortico-ponto-cerebellar and cortico-rubro-olivo-cerebellar pathway [2], the motor cortex receives inhibitory projections resulting in cerebellum-motor cortex inhibition (CBI) [3]: Purkinje cells inhibit the dentate nucleus [4], which reduce excitatory input on the motor cortex from the dentato-thalamo-cortical pathway [5, 6]. However, the cerebellum contributes to numerous other functions, such as learning, cognition, emotions, and behavior, as disclosed by several findings [7, 8]. Multiple closed-loop circuits working in parallel connect the cerebellum and cerebral cortex, allowing the cerebellum to influence, among many other targets, prefrontal, temporal, and parietal cortical areas [7, 9]. Recently, for example, studies combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG), a combination that allows to precisely record the neuronal responses as result of TMS [10], have suggested that cerebellar stimulation strongly affects the activity of different cortical areas forming part of the parieto-frontal network [11, 12], for example those involved in motor learning [12].

Moreover, several studies have shown a strict relation between the cerebellum and basal ganglia, disclosing neural projections from the dentate nucleus and cerebellar cortex to the striatum and subthalamic nucleus, respectively [13]. This may be one way in which the cerebellum

✉ Roberta Ferrucci
roberta.ferrucci@unimi.it

Extended author information available on the last page of the article

can influence symptoms in disorders commonly associated with basal ganglia dysfunction (for example, Parkinson's disease and dystonia) [14, 15].

These data suggest that cerebellar function, physiology, and pathophysiology need to be further explored, and non-invasive brain stimulation (NIBS) techniques applied to cerebellum have fostered such knowledge [16]. TMS and transcranial direct current stimulation (tDCS) studies, indeed, allow for non-invasive investigation of neural networks [16]. For example, cerebellar TMS applied in 1995 by Ugawa et al. [6] revealed the physiologic mechanisms of CBI, further extensively explored in later studies. More recently, it has been shown that CBI could be modulated by tDCS, although with controversial results. While Galea et al. [17] showed that anodal tDCS increased CBI – suggesting an excitatory effect on Purkinje cells activity, Doeltgen et al. [18] observed opposite results, suggesting an excitatory effect on superficial inhibitory interneurons or on cerebello-thalamo-cortical projections targeting inhibitory interneurons within the primary motor cortex (M1).

The unraveling of the therapeutic mechanisms of NIBS requires the understanding of the effects of NIBS on (1) the cerebellar cortex, (2) cerebellar nuclei, and (3) the inferior olivary complex, three major structures of the cerebellar circuitry engaged in functional units of the cerebellum. Neurons of the cerebellar nuclei convey the cerebellar output signals to the spinal cord, brainstem nuclei (including red nuclei and reticular nuclei), basal ganglia, thalamic nuclei and cerebral cortex. Cerebellar nuclei are under the profound inhibition of Purkinje neurons, whose activity depends on mossy fibers, climbing fibers and interneurons of the cerebellar cortex, and mossy fibers, which transmit sensory and cortical information to granule cells via excitatory synaptic connections; small granule axons project up into the molecular layer of the cerebellar cortex, bifurcating and forming excitatory synapses onto Purkinje cell dendrites [19]. Meanwhile, parallel fibers also activate stellate cells and basket cells, which form inhibitory synapses with Purkinje cells, establishing a stereotypical feed-forward-inhibition circuit [19]. Reducing the inhibitory effect of Purkinje cells upon dentate/interpositus/fastigial neurons will increase the excitatory discharges exerted by cerebellar nuclei upon extra-cerebellar targets [20]. In other words, cerebellar cortex sculpts cerebellar output by tuning the firing rates and patterns of nuclear neurons [21]. NIBS likely tunes the inhibitory discharges of the cerebellar cortex, especially the posterior and inferior parts of the cerebellum (i.e., lobules VI-VIII) which seem particularly susceptible and accessible to neuromodulation in human [22]. Current views hypothesize that cerebellar NIBS is mediated by both electrical and non-electrical (vascular, metabolic) effects on the cerebellar cortex [22]. Spectroscopy (MRS) suggests that, in humans, anodal tDCS reduces GABA locally, whereas cathodal stimulation decreases glutamatergic neuronal activity [23].

In this review, we report the advances made on the use of cerebellar NIBS and reach a consensus on the future steps to moving forward. For each topic covered, we present the current evidences and underline the implications for future research. The following specific topics will be discussed: the use of TMS to explore cerebellar neurophysiology; the current knowledge on cerebello-cerebellar tDCS; the role of animal models in cerebellar NIBS applications; the clinical application of cerebellar NIBS (motor learning, stroke recovery, speech and language functions, neuropsychiatric and movement disorders, and pain syndromes).

TMS of the Cerebellum: Some Lessons for the Application of tDCS

The first demonstration of cerebellar stimulation was performed using transcranial high-voltage electrical stimulation (TES); this was quickly followed by attempts using TMS. TES and TMS directly initiate action potentials in central neurons unlike the mild polarization of neural membranes produced by tDCS. However, the early experiences with TES and TMS illustrate some of the potential complexities of cerebellar stimulation was well as the difficulties involved in interpreting the outcome of experimental interventions that are equally relevant to tDCS and related paradigms. As we will show, using the example of CBI, these include problems such as (1) distinguishing between effects that are attributable to stimulation of cerebellum and those due to stimulation of skin and scalp or to stimulation of other neural structures in the brainstem; (2) choosing the optimal coil geometry and stimulus intensity to maximize cerebellar effects; (3) interpreting which structures in the cerebellum are the primary targets of stimulation.

First Description of CBI

Ugawa et al. [3, 5] were the first to attempt to stimulate structures in the posterior fossa using TES. They found that TES via electrodes placed on left and right mastoid processes could activate the corticospinal tract (CST) at the level of the pyramidal decussation in the brainstem [3]. Given the distance of the site of activation from the scalp surface, they reasoned that it should be possible to use a similar electrode configuration to activate more superficial structures such as the cerebellum. A later paper [5] provided evidence in support of this possibility by describing the physiology of what would be termed CBI. Using a conditioning-test design, they showed that TES at an intensity below the threshold for corticospinal activation suppressed the response of the contralateral motor cortex to a subsequent TMS pulse given

5–15 ms later. Since responses of the motor cortex to TES were not affected by cerebellar stimulation, it was postulated that a cerebello-thalamo-cortical pathway was involved. The effect was not due to head movement produced by TES-induced contraction of neck muscles since movement did not start until at least 11 ms after TES.

However, even in this early study, it was clear that the effect was not as simple as it first appeared. Indeed, (1) locating the TES electrodes superiorly/inferiorly to the optimal site abolished the early effect at 5–8 ms, but had little effect on the later inhibition; (2) the early suppression was maximal when the anode of the TES was contralateral to the target M1 but the later suppression was equally prominent whether the anode was ipsilateral or contralateral; (3) early suppression was unaffected if the experiment was performed in relaxed or active muscle, whereas the late suppression was more effective during voluntary contraction than at rest. The conclusion was that two different effects were intermixed. The later period of CBI was thought to be a "non-specific" effect that was the result of strong peripheral sensation caused by TES. In contrast, CBI at 5–8 ms was assumed to be due to stimulation of the cerebellum. It was proposed that the TES pulse activated Purkinje cells of the cerebellar cortex which then inhibited deep cerebellar nuclei, withdrawing any tonic facilitation from the nuclei to motor cortex via thalamus. The following year, Amassian et al. [24] used TMS over the cerebellum and tried to record the evoked-EEG response from central scalp areas that they thought would accompany inhibition or withdrawal of facilitation of the motor cortex.

The Mechanism of CBI

At this stage in the development of cerebellar stimulation, it is important to recall that there was no direct evidence that the cerebellum was involved in CBI. For example, it remained a possibility that the transmastoid stimulus had activated sensory fibers in the medial leminiscus and that the inhibition was, in fact, short-latency afferent inhibition which had been described some years earlier. There was even less certainty about the postulated mechanism, involving stimulation of Purkinje cells and CBI.

The best evidence we have that CBI depends on the cerebellum and its projections comes from a series of studies on patients. The first studies [25, 26] were performed with electrical stimulation, but many more followed after the demonstration that CBI could be produced using TMS with a large double cone coil over the cerebellum, with less discomfort than the electrical technique [6]. Diseases mainly or selectively affecting the cerebellar cortex consist of spinocerebellar ataxias (SCAs; SCA 6 or SCA 31), cerebellar cortical atrophy (CCA), cerebellar-type multiple system atrophy (MSA-C), cerebellar stroke, cerebellitis, paraneoplastic CCA, and intoxication from antiepileptic drugs. All these conditions had impaired CBI [25, 27]. The involvement of the dentate nucleus or superior cerebellar peduncle in dentatorubral–pallidoluysian atrophy (DRPLA) and Wilson's disease also lead to reduced CBI [27]. In contrast, ataxic patients with lesions in cerebellar afferent pathways (pontine or middle cerebellar peduncular lesions, shown by blue arrows in Fig. 1) had normal CBI, even though the patients showed definite clinical cerebellar ataxia [27]. Similarly, CBI was present in patients with non-cerebellar ataxia, such as sensory ataxia, Miller-Fisher syndrome, and hypothyroidism [25, 27]. Taken together, these studies are strong evidence that CBI involves activation of structures in the cerebellar cortex and conduction to motor cortex via the superior cerebellar peduncle, and presumably the deep cerebellar nuclei. Following these initial studies, CBI has been investigated in healthy subjects performing behavioral tasks which are known to involve the cerebellum. It was shown that during a locomotion adaptation task, for example, CBI was reduced during the learning of a new locomotor pattern, but not during the actual performance. Moreover, the subjects who experienced the best adaptation, had the largest reduction of CBI [28]. Corroborating the concept that CBI can be rapidly modulated in contextual specific manner, another study showed that CBI was clearly reduced prior to movement onset [29]. CBI has been also used to investigate cerebellar involvement in disorders in which there is

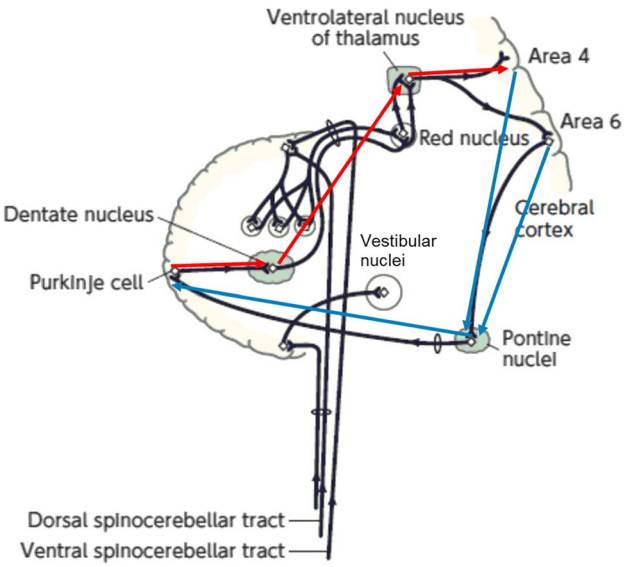

Fig. 1 Postulated anatomical pathway (red arrows) responsible for CBI. TMS is hypothesized to activate Purkinje neurons in the cerebellar cortex, which inhibit neurons in the dentate nucleus. This withdraws any ongoing facilitation from dentate via thalamus to area 4, resulting in reduced excitability of motor cortex. The blue arrows indicate the reciprocal connection from area 4 to cerebellum via the pons

no primary pathology of cerebellum. In progressive supranuclear palsy (PSP), CBI revealed cerebellar involvement in patients whose cerebellar clinical ataxic signs were masked by rigidity due to basal ganglia pathology [30]. CBI and prism adaptation task studies showed cerebellar impairment in patients with essential tremor [31].

Open Questions About CBI

TMS over the basal scalp using a large double cone coil activates many structures. Anyone who has taken part in a CBI study will testify that stimulation activates sensory afferents in the skin and peripheral motor fibers innervating neck muscles; and given the potential of the double cone coil to activate corticospinal fibers in the pyramidal decussation, cerebellar stimulation could also activate many other structures in the brainstem. So how certain can we be that CBI is what we think it is?

Contamination of CBI by Non-cerebellar Inhibition

As noted in the original experiments, later timings of CBI appear to be contaminated by effects that do not originate in the cerebellum. Meyer et al. [32] observed CBI in a patient with a cerebellar defect, but only with an interstimulus interval of 8–9 ms between cerebellum and M1. The authors proposed that this was caused by activation of peripheral structures at the neck level. This conclusion was reinforced by Werhahn et al. [33] who found that inhibition at longer inter-stimulus intervals (ISIs) (> 7 ms) may be produced by peripheral nerve activation. A recent review article also concluded that CBI involves a cerebellar inhibitory (or disfacilitatory) effect on M1, but does not always reflect a purely cerebellar effect [34]. As a result of such studies, it is usually recommended to evaluate CBI at an ISI of 5 ms.

Another very important source of contamination is direct stimulation of the CST by the conditioning stimulus [3, 35, 36]. Sometimes this can be detected because it causes peripheral muscle activity (technically a CMEP: a cervico-medullary motor evoked potential), but intensities below motor threshold may still activate the CST, although the orthodromic volley is insufficient to bring spinal motoneurons to threshold. There can be two consequences of this subthreshold effect: (1) in addition to orthodromic activity to the spinal cord, there will also be antidromic action potentials to the cortex. These can collide with orthodromic activation from M1 stimulation and suppress motor evoked potentials (MEPs) at short ISIs of 3–4 ms, rather than 5–7 ms for CBI; (2) the orthodromic volley will increase excitability of spinal motoneurons even if it fails to reach discharge threshold. This could cancel out any CBI, even at 5–7 ms, and lead to the erroneous conclusion that CBI was reduced or absent. Thus, the intensity of cerebellar stimulation should always be adjusted relative to CST activation. It has been recommended that this should be 5 -10% below the threshold for evoking a CMEP in preactivated muscle [36].

Does CBI Involve Activation of Purkinje Cells?

Figure 1 (red arrows) shows the hypothesized anatomical pathways activated in CBI. Purkinje cell stimulation inhibits ongoing facilitation from the dentate nucleus, withdrawing facilitation from motor cortex. However, given that CBI is usually evaluated at rest, can we be sure that there is any ongoing facilitation that can be withdrawn? And if facilitation is withdrawn would we not expect that the onset of CBI would be less abrupt than it appears to be? CBI is absent with a 4 ms interval between cerebellar and cortical stimulation but is present and often maximum if the interval is 5 ms, which implies a very synchronous and powerful onset. In contrast, withdrawal of facilitation should be slower and, in the absence of other factors, depend on the duration of the last excitatory postsynaptic potentials (EPSPs) that occur before facilitation was withdrawn.

Although there is no information about resting dentate discharge in humans, studies in primates show a sustained resting level of discharge [37, 38] which could presumably be suppressed by activity of Purkinje cells. In addition, direct electrical stimulation of the superior cerebellar peduncle leads to activation of neurons in motor and premotor cortex [39], indicating an excitatory effect. However, facilitation was terminated after only a few ms by a longer lasting and dominant inhibition, so that the net effect of any ongoing dentate discharge on cortical excitability is unclear.

Given the dominant inhibitory effect of peduncular stimulation, is it possible that CBI is produced by direct stimulation of cerebellar outflow? This is difficult to dismiss completely. The timing seems appropriate since peduncular stimulation in primates causes initial facilitation of cortex 4 ms later. If inhibition began shortly after that, then it would be appropriate to account for the onset latency of CBI at ISI = 5 ms. However, since there is no sign of facilitation prior to the onset of CBI, this seems unlikely in human. In addition, the duration of CBI is short compared with the duration of inhibition seen after direct stimulation. However, since the late component of CBI is contaminated by activation of peripheral afferents, some uncertainty remains.

Finally, these experiments [39] may provide a way to explain how CBI can produce suppression with such an abrupt onset. As noted above, initial cortical facilitation is quickly followed by inhibition which the authors suggested was probably due to feedforward inhibition. Such an organization would mean that each EPSP produced by activation of a thalamo-cortical axon is terminated by a disynaptic inhibitory postsynaptic potentials (IPSP): rather than lasting (e.g.,

15 ms), the EPSP may only last 1–2 ms. Thus, withdrawal of facilitation by Purkinje suppression of dentate, as postulated for CBI, would result in rapid disfacilitation of the cortex because the duration of the last EPSPs to arrive at the cortical level is so short.

Importance of Coil Geometry for Evoking CBI

The initial experiments [6] used a large angled figure-of-eight coil to explore CBI; smaller flat coils that are usually employed to activate M1 could not reliably produce CBI at 5–7 ms even though they always evoked clear suppression at 8 ms or longer [33]. Hardwick et al. [40] reassessed the problem and again found that CBI could only be evoked reliably with large coils and not with the conventional flat figure-of-eight coils, a fact confirmed by later studies [41]. They also calculated the distance from the scalp to lobules V and VII, which would be the supposed location of projections to M1. They found that the distance of the nearest region of cerebellar surface was about 1.5 times as far from the scalp as the surface of M1. However, the distance to lobules V and VII was even further, being 3–3.5 cm. This additional distance is presumably why CBI is difficult to obtain using coils conventionally employed to activate the M1 hand area. It should be noted however that such coils may be able to activate regions of the cerebellum closer to the scalp, as demonstrated, for example by Hashimoto & Ohtsuka [42], who used a flat figure-of-eight coil at localized scalp sites to stimulate vermal regions of the cerebellum and interact with voluntary saccadic eye movements.

Finally, it should be recalled that the cerebellar surface is highly convoluted such that alignment of the Purkinje cells (if these are the target of TMS) can be at all angles respective to the direction of the induced currents in the cerebellum. Those that are parallel to the induced current will have a low threshold for stimulation whereas those that are perpendicular to the current will have a high threshold. Thus, TMS may activate very particular populations of Purkinje neurons which may differ between individuals, and which will vary according to the orientation of the coil on the scalp.

Implications for Future Research

The early experiences with TMS of the cerebellum should alert us to three unresolved questions about cerebellar tDCS. Indeed, it is important to know (1) which effects of tDCS are due to modulation of the cerebellum itself and what could be caused by the influence of tDCS on other structures both centrally and in the periphery; (2) what is the optimal tDCS montage to achieve modulation of a specific target region of the cerebellum, and how will this be affected by the orientation of the Purkinje neurons of the cerebellar cortex; (3) what specific mechanism mediates the overall effects of tDCS.

Cerebello-Cerebellar tDCS: What We Know

The interest of the scientific community in tDCS of the cerebellum keeps growing. This is illustrated by the number of articles published on the topic these last years (Fig. 2). Given (1) the anatomical connectivity between the cerebellum and the spinal cord, brainstem, basal ganglia, and cerebral cortex, and (2) the multiple roles played by cerebellar circuitry in motor control, cognitive operations and emotional processing, the potential applications of cerebellar tDCS are huge.

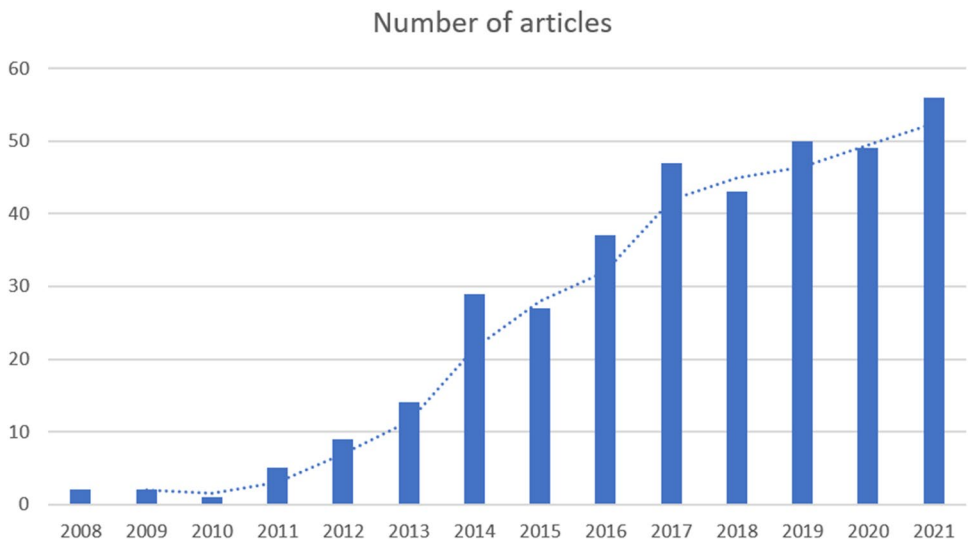

Fig. 2 Number of articles published per year between 2008 and 2021, listed in PubMed (search strategy: cerebell* AND (transcranial direct current stimulation OR tDCS)). A number of 371 articles are found between 2008 and 2021, of which half (198) were published in the past 4 years

tDCS and Cerebellar Plasticity

One of the main objectives of this cerebellar NIBS technique is to enhance neural plasticity, which is thought to underlie neuronal excitability and learning in vivo, including semantic prediction, word generation and verbal working memory [43–46]. In particular, the cerebellum seems to be engaged in the early acquisition of new motor and non-motor skills, whereas the primary motor cortex is likely involved in retention and consolidation of memory traces [47–49]. From a mechanistic standpoint, cerebellar circuitry operates as a forward controller learning to predict the precise timing of events [50]. Signals entering the cerebellum via the mossy fibers are processed in the granular layer, transmitted to Purkinje cells via parallel fibers through complex signals mediated by local interneurons, with a copy relayed in cerebellar nuclei. Purkinje cells inhibit nuclei via GABA. In other words, the cerebellar cortex orchestrates a side loop blocking or unblocking cerebellar nuclei [50]. Sites of synaptic plasticity are multiple in the granular layer, the molecular layer and at the level of cerebellar nuclei. Therefore, the concept of a single form of synaptic plasticity between parallel fibers and Purkinje neurons under the unique control of climbing fibers originating in the inferior olive is no longer valid [50]. This makes of the cerebellum a highly complex neuronal machine characterized by an unparalleled degree of flexibility. Furthermore, Purkinje cells are chemically heterogeneous, and the mossy fiber system itself is a critical actor in cerebellar plasticity [51]. Coordination is currently explained by accurate regulation of timing and gain in the different cerebellar modules composing the cerebellum [51]. Cerebellum is viewed as a timing machine in whom interactions within the cerebellar cortex support sub-second timing, with supra-second timing requiring cortical and basal ganglia networks [52]. In this scenario, the mechanisms by which cerebellar polarization may improve learning in humans remain largely unknown, possibly involving both cortical and subcortical routes. A recent fMRI paper has shown that anodal cerebellar tDCS dampens putamen-cerebellar connectivity, reducing cerebellar inhibition and enhancing sequence learning in the serial reaction time task [53]. However, this observation does not explain the increased learning-related BOLD activity in M1, nor the effect of parallel and climbing fibers on synapses with Purkinje cells in deep cerebellar nuclei (DCN), also considered to play a key role in cerebellar-dependent learning [54].

Variability in the Outcome of cerebellar tDCS

Converging evidence suggests that CBI could be modulated by tDCS, although results are still unclear. The first neurophysiological evidence was by Galea et al. [17], who showed in healthy subjects that cathodal cerebellar tDCS decreased CBI, anodal cerebellar tDCS increased it, and sham stimulation induced no changes. Other results were reached by a later study [18], in which anodal cerebellar tDCS reduced CBI. Although controversial, such results clearly suggest that cerebellar tDCS can modulate cerebellar control over the motor cortex. Studies combining functional MRI with cerebellar tDCS have shown that cerebellar tDCS has a polarity-specific effect on the BOLD activity of the dentate nuclei and on functional connectivity [55, 56]. Unfortunately, these are isolated findings. More systematic studies combining different imaging techniques are crucially needed to gain more insight into the underlying mechanisms of cerebellar tDCS and the possible impact it can have at neurophysiological level. Such fundamental studies are necessary, especially since the behavioral results of studies using cerebellar tDCS are divergent [57]. The variability in the outcome of cerebellar tDCS might be explained by recent modeling studies that have shown that different placements of the reference electrode (e.g., on the buccinator muscle or on the contralateral supraorbital area) can have a significant effect on the electric field distribution and orientation inside the cerebellum [58]. In addition, significant inter-individual differences in electric field distribution even when using the same sponge electrode montage have been shown [59]. Since both the distribution and the orientation of the electric field inside the cerebellum are critical to predict the behavioral effect of cerebellar stimulation future studies should consider modeling the electric field on an individual level, taking into account the areas and types of neurons (e.g., synapses between parallel fibers and dendritic trees of Purkinje cells, or Purkinje cell responsiveness) which are targeted [58]. High-definition (HD)–tDCS might provide more opportunities concerning targeted stimulation, but more research is needed to address its limitations—such as the lower electric field strengths due to the smaller electrode–skin interface—and to determine the optimal electrode configuration [58].

Cerebello-Cerebellar tDCS: an Entire Field to Discover

At this stage of research, the approach of neuromodulation of cerebellar circuitry by application of tDCS targeting only the cerebellum remains totally open. We are missing data showing whether the tuning of a given portion of the cerebellar cortex with respect to another portion might impact on motor, cognitive or emotional processing. In theory, cerebello-cerebellar tDCS paradigms would enhance the excitability of a given area (area under the anode) and simultaneously reduce the excitability of the second area (area under the cathode), keeping in mind that the most accessible portion of the cerebellar cortex below the skull belongs to the posterior lobe (lobules VI-VII-VIII-IX). Typical applications

would be the treatment of defects of the intra-cerebellar distribution of activity as observed in dyslexia [60] or modulation of aberrant networks as observed in schizophrenia [61]. The length of parallel fibers in humans extends beyond several millimeters (mm), an anatomical parameter that needs to be considered for neuromodulation of the cerebellar cortex.

Cerebello-Cerebral tDCS

Cerebello-cerebral tDCS has been shown to be effective in very small samples of patients [62]. The technique can reduce postural tremor, action tremor and motor dysmetria. Both tremor and dysmetria are landmarks of cerebellar dysfunction. Tremor is particularly responsive in rare genetic ataxias related to calcium-activated chloride channel involved in neuronal excitation [63]. The improvement of motor dysmetria is associated with a favorable effect on the onset latency of the antagonist electromyographic (EMG) activity, a neurophysiological marker of the defect in programming of timing of motor commands. Again, there is a major need to address the following points: (1) which patients respond to this technique of stimulation? (2) what is the duration of the effect? (3) how does the technique impact on the plasticity occurring in the cerebellum? (4) is there a link with the functional level of the cerebellar reserve, defined as the capacity of the cerebellum to compensate for tissue damage or loss of function [64]? At a molecular level, the mechanisms of action include the modulation of ionic gradients in the extracellular space, regulation of channels and pumps as well as modulation of receptors/neurotransmitters [22]. All these elements are critical for neuronal plasticity.

Transcranial Alternating Current (tACS) and the Cerebellum

Besides tDCS, the use of other transcranial electrical stimulation methods to stimulate the cerebellum is also increasing. tACS has been suggested as a promising stimulation method due to the intrinsic cerebellar oscillations. Naro et al. [44] already showed that tACS over the cerebellum is safe, and that certain frequencies can influence CBI and, consequently, motor adaptation. Other studies have investigated tACS but used a dual site approach to study the phase specificity of the stimulation [65, 66]. By targeting the cerebellum and M1 at the same time, either in phase or anti-phase, it has been demonstrated that intercortical functional synchronization is an important feature of motor performance improvement, irrespective of current intensity [65, 66].

Implications for Future Research

Physiological and clinical effects of cerebello-cerebellar tDCS, in terms of changes in motor, cognitive and emotional behaviors, are still missing. However, this represents a scientific field to be further explored, in lights of its potentialities. Besides direct current (DC) and alternating current (AC) applications, several other stimulation methods have been sporadically used to manipulate the oscillatory activity and connectivity of the cerebellum, such as transcranial pulsed current stimulation (tPCS) [67] and oscillatory transcranial direct current stimulation (otDCS) [68], with promising effects on cognition and awareness. However, more research is needed to confirm the effectiveness of these methods and understand how they impact on the various forms of cerebellar plasticity.

Animal Models of cerebellar NIBS

NIBS is expected to become an accepted tool to promote neural plasticity in a wide range of disabling disorders affecting the human brain, allowing symptomatic alleviation [69]. This is particularly relevant for cerebellar disorders, from pure cerebellar disorders to disorders affecting both cerebellar and extra-cerebellar circuits [70]. Cerebellar NIBS also contributes to the discovery of cerebellar functions [69]. The demonstration of the detailed network/cellular/molecular mechanisms of action of cerebellar NIBS will benefit from the analysis of both animal and human studies, provided the animal models are used in a translational perspective. Historically, disorders of basal ganglia such as Parkinson's disease have attracted the attention of scientists interested in noninvasive and invasive neuromodulation techniques, but other nodes of the motor circuitry are gaining in interest [69, 71]. The recent discovery of anatomical connectivity between the cerebellum and basal ganglia (subthalamic nucleus and striatum) has contributed to a reconsideration of the cerebellum as a potential target to manage movement disorders [72]. Modulation of basal ganglia might influence cerebellar circuitry and vice-versa [69].

Animal Studies Assessing NIBS of the Motor Cortex

We will not review here the details of the invasive approaches such as deep brain stimulation with implanted electrodes in animal models (including recent genetic approaches such as the Cre/LoxP model to silence selective tracts or the optogenetic stimulation instead of electrical stimulation) which have been discussed recently in details in another Consensus Paper [69]. The effects of TMS/tDCS/tACS of the cerebellum or the motor cortex have been explored mainly in rodents, but also in other species such as turtles or rabbits [73, 74]. In TMS research, application of 4 weeks of low-intensity repetitive TMS (LI-rTMS) to the mouse cerebellum alters Purkinje cell dendritic and spine morphology [75]. Furthermore, LI-rTMS induces climbing

fiber reinnervation to a denervated hemicerebellum. High-frequency stimulation increases intra-cellular calcium by releasing the ions from intracellular stores. tDCS of the motor cortex restores the excitability of the motor cortex which is observed contralaterally to a hemicerebellar ablation [76], and modulates CBI, as observed in humans [77]. Using extra-cellular recordings, it has been demonstrated in rats that the simple spike activity of Purkinje cells is particularly entrained by AC fields, with clear evidence that these neurons represent the primary cell type affected by electrical stimulation thanks to their connectivity and the morphology of their dendritic trees [78]. It has also been shown in rats, using optogenetic techniques that delta frequency optogenetic stimulation of thalamic synaptic terminals of lateral cerebellar projection neurons improve timing performances in a model of schizophrenia-related frontal dysfunction [79]. In mouse, anodal stimulation of the cerebellum has an acute post-stimulation effect on baseline gain reduction of the vestibulo-ocular reflex (VOR), a mechanism related to long-term potentiation (LTP) and intrinsic plasticity pathways of Purkinje neurons [80]. tACS entrains endogenous neural oscillations in the cerebellar cortex: (1) during the negative phase of a sinusoidal electric current applied over the cerebellar cortex, the firing rates augments in cerebellar cortex; (2) during the positive phase of tACS, the neural activity is suppressed [73]. The orientation of neurons with respect to the direction of the current administered is particularly relevant, given the highly folded structure of the cerebellar cortex. This is particularly relevant for neuromodulation due to the major role played by brain oscillations in sensorimotor and cognitive processes. Within the cerebellar cortex, complex spike activity causes low frequency oscillations in the 1–4 Hz range, whereas simple spikes lead to high frequencies in the 160–260 Hz range, as shown using tetrode and multisite recording [81]. In vivo electrophysiological measurements in adult rat brain slices have confirmed marked resonance at 200 Hz in Purkinje neurons, as a result of the morphology of the Purkinje cell, interacting with a simple spiking mechanism and dendritic fluctuations [82]. Nevertheless, other studies have found a wide range of frequencies. Overall, it is assumed that NIBS tunes the patterns and timing of discharges within the cerebellar cortex.

Implications for Future Research

There is a clear need to develop standardized animal experiments to elucidate the mechanisms of action of cerebellar NIBS in humans, in order to optimize/maximize the efficiency of cerebello-cerebral commands for a large list of brain disorders. Invasive approaches such as deep brain stimulation of the cerebellar cortex or cerebellar nuclei allow the fine characterization of the effects upon cerebello-cerebral networks and provide complementary data to the results obtained by cerebellar NIBS techniques [69]. The community has accepted the safety profile of NIBS but is expecting clear-cut demonstrations on both its mechanisms of action and its effectiveness in selected disorders. Animal models are needed, for example, to explore the hypothesis that targeting the cerebellum might improve motor and cognitive deficits occurring after supra-tentorial stroke, given its massive connectivity with the cerebral cortex and its high degree of plasticity (see Sect. 6—Cerebellar Stimulation: a new Approach for Stroke Recovery). Moreover, cerebellar NIBS might complement the pharmacological approach, since pharmacological therapies are effective in specific forms of cerebellar ataxias, but many progressive cerebellar disorders still lack active drugs (see Sect. 9—cerebellar tDCS in individuals with hereditary cerebellar ataxia). Therefore, potential complementary effects of cerebellar NIBS and drugs should be investigated [83]. Animal models provide the opportunity to do so, and might contribute to the understanding of long-term neural consequences of cerebellar NIBS, a question which still lacks a consensus [16]. Finally, animal models are also required to better understand how cerebellar NIBS acts upon cerebello-spinal projections, given the discovery that cerebello-spinal NIBS reduces symptoms in ataxic patients [84].

Effects of Cerebellar NIBS on Motor Learning in Healthy and Disease

Learning new motor skills is vital for carrying out the daily life activities we perform. Our ability to learn new motor patterns or to adjust previously learned ones requires the engagement of several behavioral and plasticity mechanisms that span across a network of cortical and subcortical brain regions. A key node of the learning network is the cerebellum, which plays a particularly important role in acquiring new motor patterns when responding to new environmental demands and in re-learning motor skills after injury [85]. Given the cerebellum's rich neuroplasticity potential, its modulation through cerebellar NIBS, like tDCS and theta-burst stimulation (TBS), has received increasing attention, with the aim to enhance performance during motor tasks.

To understand how targeting the cerebellum with stimulation can influence motor learning, it is critical to distinguish the different types of learning tasks studied in a laboratory setting. This is because motor learning encompasses multiple processes, which range from an implicit error-driven mechanism for maintaining calibration of our movements to complex, high-level cognitive strategies to respond to novel environments [29, 45]. Here, we will cover how cerebellar stimulation affects distinct task categories: motor adaptation and de-novo skill learning.

Motor adaptation is the short-term reshaping of a well-practiced action in the face of dynamic perturbations (e.g., visuomotor rotation, force-field). In these tasks, participants learn to quickly reduce movement errors that are imposed by the perturbation by generating an internal model that predicts the consequences of efferent motor commands during movement. The cerebellum is widely believed to calibrate this model since patients with cerebellar lesions are impaired at adjusting their movements to novel environments [86]. This is supported by recent evidence showing that Purkinje cells appear to encode the outcomes of kinematic predictions rather than motor commands [87].

Animal studies have shown that adaptation is mediated through synaptic mechanisms of long-term depression (LTD) in Purkinje cells [88]. Similarly, studies in healthy individuals have shown a link between changes in cerebellar excitability and motor adaptation [12, 28]. Bearing this in mind, along with the notion that anodal tDCS likely increases Purkinje cell activity, Galea et al. [48] investigated how applying this technique to distinct brain regions (cerebellum, M1, primary visual cortex—V1) influenced learning of a visuomotor rotation [48]. Cerebellar tDCS was found to specifically speed-up the error reduction process, whereas M1 stimulation enhanced the retention of the newly learned rotation. No changes were found when stimulating V1, suggesting that modulating the cerebellum improves acquisition in reaching. Similar effects of cerebellar tDCS have been found for force-field tasks [89] and locomotor adaptation [90]; however, the effects appear limited to the trained cerebellar hemisphere [91]. Interestingly, applying distinct cerebellar TBS protocols before a visuomotor rotation produces bidirectional effects on learning [12]. Intermittent TBS (iTBS), a protocol thought to increase cerebellar excitability by activating LTP of parallel fiber-Purkinje cell synapses, was found to accelerate adaptation in healthy subjects [12] and stroke patients [92]. For example, Bonnì et al. [92] reported that cerebellar iTBS increased in the performance of 8 chronic stroke patients during a visuomotor adaptation task (i.e., during both the learning and re-adaptation phase of the task). On the other hand, continuous TBS (cTBS) produced an opposite effect by decreasing the learning rate [12]. Overall, these investigations indicate that cerebellar stimulation modulates motor behavior by enhancing cerebellar-dependent, error-based learning mechanisms.

Unlike motor adaptation, motor skill learning refers to an improvement in both movement speed and accuracy of a novel motor pattern that goes beyond baseline levels. Indeed, skill learning requires one to develop movement patterns from scratch, which become automatized through repeated practice and fine-tuned by cerebellar-dependent learning mechanisms [47]. For example, successfully performing a tennis forehand swing requires one to learn how to control the tennis-racket (i.e., develop an internal model) while performing a fluid sequence of movements. Thus, it is likely that skill learning can also benefit from excitatory cerebellar stimulation. The sequential-visuomotor isometric pinch force task (SVIPT) is a well-characterized task to mimic this kind of learning since it requires individuals to simultaneously learn how to control a new device in a novel environment, along with performing a sequence of isometric movements. Interestingly, when anodal cerebellar tDCS was administered during SVIPT performance, healthy individuals showed enhanced motor skill acquisition [93]. Specifically, skill improvement was marked by reduced errors rather than movement times. This finding suggests that tDCS may enhance cerebellar-dependent error-based learning, which likely plays a role in developing an internal representation of skill task dynamics.

It should be noted that skill learning also requires the involvement of cognitive strategies (e.g., tennis players will aim to place the ball at a location away from the opponent). Given the accumulating evidence that the cerebellum plays an important role in cognition and its vast connections to prefrontal areas [85], tDCS may also enhance the implementation of strategies. Supporting this notion, inhibitory repetitive TMS (rTMS) over the cerebellum disrupts cognitive functions like procedural learning, as measured by the serial reaction time task (SRTT), where individuals must learn to respond as quickly as possible to stimuli that cue a specific keyboard button response [94]. On the other hand, anodal cerebellar tDCS applied during SRTT performance was found to reduce error rates [95] and reaction time responses [96], indicating that stimulation can also improve cognitive components that are embedded in motor skills.

The work highlighted above importantly demonstrates that the cerebellum has a role in various motor and cognitive activities, which suggests that applying neuromodulatory strategies to this brain region may be particularly effective for improving patient recovery. Indeed, a recent clinical trial found that combing cerebellar iTBS with physical therapy to patients with stroke leads to improved gait and balance recovery by enhancing motor relearning and promoting cerebello-cortical reorganization [97]. While the effects of anodal tDCS on motor function in stroke remain unclear, recent work has shown that cerebellar stimulation enhanced the effects of behavioral aphasia [98]. Finally, applying a single-session of anodal cerebellar tDCS improved the symptoms of patients with ataxia [99], providing preliminary evidence for the efficacy of tDCS, to be further explored in future rehabilitative approaches.

Implications for Future Research

Recent evidence demonstrates how modulating cerebellar excitability with NIBS can enhance motor learning. As the effects of stimulation in healthy individuals primarily

enhances the acquisition of new motor patterns, these interventions have the potential to augment physical therapy and speed up rehabilitation processes. Given the role the cerebellum plays in numerous learning paradigms, stimulation over this region might support patient recovery in both motor and cognitive functions. Further studies are needed with larger sample sizes, homogenous populations, as well as optimized study designs and stimulation protocols.

Cerebellar Stimulation: a New Approach for Stroke Recovery

Stroke is a major cause for mortality, disability, and resulting economic costs for health care systems worldwide [100]. Further optimization of post-stroke care, including the development of novel treatment strategies, is of great importance. One promising novel strategy is the combination of cerebellar NIBS with behavioral training.

Stroke and Cerebellar Neurophysiology

Stroke often results in brain network disturbances, frequently impacting the cortico-cerebellar system. For instance, one pathophysiological consequence frequently described is cerebellar diaschisis—a reduction of cerebral blood flow and metabolism in the contralateral cerebellar hemisphere following a supratentorial ischemic stroke [101]. Furthermore, vascular lesions of the cerebellar cortex, thalamus, or posterior limb of the internal capsule have shown to result in disbalanced cerebellar cortical output, including aberrant CBI [102]. These processes have been associated with functional impairment, making them a potential mechanistic target to develop and test novel cerebellar NIBS protocols. Additionally, cerebellar NIBS could be used to support intrinsic learning processes with the aim of augmenting the reacquisition of lost abilities [103]. Of note, this treatment strategy may be applicable to various syndromes following stroke. For example, frequent target impairments are hand motor deficits, balance and gait disturbance, or cognitive abnormalities—affecting ~ 85%, ~ 50%, ~ 60% of stroke survivors respectively [104]. Table 1 summarizes a series of investigations testing the use of cerebellar NIBS to treat different impairments in stroke survivors.

Cerebellar NIBS Studies Targeting Balance and Gait

The largest proportion of research was conducted assessing potential effects on balance and gait functions. For instance, Zandvliet et al. [106] studied the effect of ipsi- and contralesional anodal cerebellar tDCS in combination with training of a balance tracking task in 15 chronic stroke patients. Their study followed a randomized, single-blind, sham-controlled, cross-over design. Active contralesional stimulation led to an improved tandem stance performance at the post-stimulation evaluation, when compared to sham. This pioneering work is important as it documents the potential of improving balance function in stroke using cerebellar tDCS, in a task, which has considerable similarity to everyday life activities. Complementary to this work, Koch et al. [97] provided important evidence that multi-session iTBS of the contralesional cerebellar hemisphere applied in combination with physiotherapy for a duration of 3 weeks can lead to an improvement in gait and balance function as quantified with the Berg Balance Scale (BBS) [112]. Picelli et al. [107] extended the described approach by testing a multi-site stimulation strategy in 20 chronic stroke patients. In their first pilot trial, the authors compared a group receiving cathodal contralesional cerebellar tDCS plus cathodal spinal tDCS (S-tDCS) with a group receiving anodal tDCS to the ipsilesional primary motor cortex (M1-tDCS) plus cathodal S-tDCS. The stimulation protocols were applied for 20 min over 10 sessions while patients performed robot-assisted gait training (RAGT). The cerebellar-spinal stimulation group reached a larger improvement in the primary outcome (6-min walk test—6MWT) [113], when compared to the M1-spinal group. In a follow-up study, Picelli et al. [108] compared cathodal cerebellar-spinal stimulation protocol targeting the contralesional cerebellar hemisphere to an ipsilesional cerebellar hemisphere stimulation group, while the patients underwent RAGT. No significant group differences in the primary outcome (6MWT), were found. The work from Picelli et al. [108] is of particular relevance, since it tested an innovative multi-site stimulation approach and documented the feasibility of combining cerebellar tDCS with a neurotechnology-based intervention (RAGT). Cerebellar NIBS has been also used to target balance and gait functions in patients with posterior circulation stroke including cerebellar lesions, for example the studies from Bonni or Kim et al. [110, 111]. These studies applied different TMS protocols (iTBS and 1 Hz conventional rTMS) in different patient cohorts (chronic versus acute stroke) and demonstrated an improvement in balance and gait function.

Cerebellar NIBS Studies Targeting Cognitive Deficits

Other studies have assessed the effects of cerebellar NIBS in stroke patients with cognitive abnormalities, in particular in the language domain. In their pioneering work, Sebastian et al. [98] applied anodal tDCS to the right cerebellum in a double-blind, sham-controlled, within-subject cross-over case design studying a mute chronic, stroke patient with bilateral lesions in the middle cerebral artery territory. The stimulation protocol was applied over 15 sessions concurrently to a behavioral spelling treatment. Active stimulation improved spelling to dictation performance, when compared

Table 1 Cerebellar NIBS studies conducted in the stroke cohort

Author	Year	Domain	Cohort (n)	Protocol	Task / therapy	Main finding
tDCS						
Sebastian et al. [98]	2017	Cognition (language)	Chronic bilateral MCA infarct (1, case report)	Randomized, double-blind, sham-controlled, cross-over design; anodal ctDCS (I: 2 mA, T: 20 min (active) or 30 s (sham) consecutive to 2×15 training sessions, A: 25 cm^2, E1: right cerebellum 1 cm below and 4 cm lateral to the inion, E2: over right deltoid muscle)	Behavior spelling treatment	Greater improvement in word spelling to dictation; generalization to written picture naming after active stimulation
Marangolo et al. [105]	2018	Cognition (language)	Chronic left-hemispheric stroke (12)	Randomized, double-blind, sham-controlled, cross-over design; cathodal ctDCS (I: 2 mA, T: 20 min (active) or 30 s (sham) over 5 consecutive daily sessions, A: 5×7 cm, E1: right cerebellum 1 cm below and 4 cm lateral to the inion, E2: over right deltoid muscle)	Verb generation and verb naming task	Active stimulation led to greater improvement in a verb generation task when compared to sham; no effect on verb naming task
Zandvliet et al. [106]	2018	Standing balance	Chronic stroke (15), exclusion of patients with cerebellar lesions	Randomized, single-blinded, sham-controlled, cross-over design; anodal tDCS to contra- or ipsilesional cerebellum partially overlapping with performance of a tracking task (I: 1.5 mA, T: 20 min (active) or 2×30 s (sham), A: 3.14 cm^2, E1: 3 cm lateral to the inion, E2/3: over ipsilateral buccinator muscle)	Postural tracking task	Contralesional cerebellar tDCS improved standing balance performance (tandem position)
Picelli et al. [107]	2018	Gait	Chronic stroke patients (20) with unilateral lesions in the anterior circulation	Randomized, single-blind, parallel design; cathodal contralesional ctDCS + cathodal S-tDCS or anodal ipsilesional M1-tDCS + cathodal S-tDCS concurrently to 10 sessions of 20 min RAGT (I: 2 mA, T: 20 min, A: circular 4 cm diameter, E1: 10–20 EEG position O1 or O2, E2: over ipsilateral buccinator muscle)	RAGT, outcome: 6MWT	ctDCS + S-tDCS stimulation group showed greater improvement in 6MWT at 1st post-treatment assessment when compared to the M1-tDCS + S-tDCS group

Table 1 (continued)

Author	Year	Domain	Cohort (n)	Protocol	Task / therapy	Main finding
Picelli et al. [108]	2019	Gait	Chronic first-ever unilateral supratentorial stroke (40) with lesions in the anterior circulation	Randomized, single-blind, parallel design; cathodal contralesional ctDCS + cathodal S-tDCS or cathodal ipsilesional ctDCS + cathodal S-tDCS concurrently to 10 sessions of 20 min RAGT (I: 2 mA, T: 20 min, A: circular 4 cm diameter, E1: 10–20 EEG position O1 or O2, E2: over ipsilateral buccinator muscle)	RAGT, outcome: 6MWT	No significant differences between stimulation groups (contra versus ipsilesional cerebellar hemisphere) at post-treatment assessments
Sebastian et al. [109]	2020	Cognition (language)	Chronic left-hemispheric stroke patients (24)	Randomized, double-blind, sham-controlled, within-subject cross-over design, 2 phases of 15 treatment sessions starting with anodal or cathodal ctDCS followed by sham or opposite order (I: 2 mA, T: 20 min (active) or 45 s (sham), A: 5 × 5 cm, E1: over the right cerebellum (1 cm under and 4 cm lateral to the inion), E2: over right shoulder	Computerized aphasia therapy	Repetitive ctDCS in combination with computerized aphasia treatment improved picture naming
rTMS / TBS						
Bonni et al. [110]	2014	Gait	Chronic cerebellar stroke (6)	Non-controlled interventional study; iTBS over lesioned cerebellum applied over 10 sessions (C: 1 cm below and 3 cm lateral to the inion, P: 3 pulses at 50 Hz repeated at 5 Hz, 20 trains of 10 burst delivered at 8 s intervals, 600 pulses, 80% of AMT)	Standard physical therapy	Improvement in posture and gait subscale of MICARS
Kim et al. [111]	2014	Balance and gait	Acute posterior circulation stroke (32)	Randomized, double-blind, sham-controlled, 2-to-1 ratio design; 1 Hz rTMS ipsilesional cerebellar hemisphere over 5 sessions (C: 2 cm below and 2 cm lateral to the inion, P: 900 pulses at 1 Hz at 100% RMT, sham coil was placed perpendicular to the scalp)	Conventional rehabilitation therapy	Active stimulation resulted in greater improvement in BBS and 10MWT

Table 1 (continued)

Author	Year	Domain	Cohort (n)	Protocol	Task / therapy	Main finding
Koch et al. [97]	2019	Balance and gait	Chronic stroke patients (36) with lesions in the MCA territory	Randomized, double-blind, sham-controlled, parallel design; iTBS to contralesional cerebellar hemisphere over 3 weeks of daily sessions (C: over lateral cerebellum as guided by a neuronavigation system, P: iTBS, 1200 pulses (delivered in 2 runs), 80% of AMT normalized to scalp-to-cortex distance)	Conventional physiotherapy	Active stimulation resulted in an improved BBS score at the immediate post intervention assessment, the effect persisted at a 3-weeks post intervention follow-up

Table depicts the summary of identified studies testing cerebellar NIBS interventions in the stroke cohort assessing effects on cognitive and balance/gait functions. Abbreviations: tDCS transcranial direct current stimulation; ctDCS cerebellar tDCS; S-tDCS spinal tDCS; M1 primary motor cortex; MCA middle cerebral artery; I current strength; T stimulation duration; A electrode size; E1 position stimulation electrode; E2 position return electrode; RAGT robot-assisted gait training; 6MWT 6-min walk test; rTMS repetitive transcranial magnetic stimulation; iTBS intermittent theta burst stimulation; C TMS coil position: P description of TMS protocol; AMT active motor threshold; RMT resting motor threshold; MICARS Modified International Cooperative Ataxia Rating Scale; BBS Berg Balance Scale; 10MWT 10-m walk test

to sham. This case study is important as it provides preliminary evidence for the feasibility of repetitive application of cerebellar tDCS to target language abnormalities following stroke. Of note, the combined behavioral and cerebellar tDCS treatment induced improvements beyond the trained task, indicating transfer effects to related activities (written picture naming). Similarly, Marangolo et al. [105] extended this approach by studying the effects of cathodal tDCS applied to the right cerebellum concurrently to a language training. Their study cohort consisted of 12 chronic stroke patients with left-hemispheric lesions and resulting mild non-fluent aphasia. Active stimulation resulted in greater improvement in a verb generation task, when compared to sham. This proof-of-principle work was crucial as is indicates the effectiveness of cerebellar tDCS to augment language training in a small cohort of mildly affected stroke patients. Indeed, in a recent follow-up investigation, Sebastian et al. [109] performed a randomized, double-blind, sham-controlled, within-subject cross-over study design, where participants received anodal cerebellar tDCS ($N=12$) or cathodal cerebellar tDCS ($N=12$) plus computerized aphasia therapy as well as sham plus computerized aphasia therapy. The authors found that tDCS was more effective than sham in the immediate post-treatment phase for participants who received "tDCS first"; a significant effect of tDCS for untrained naming was also observed immediately and 2 months post-treatment. These interesting findings corroborate the concept that cerebellar stimulation might be an optimal target site for aphasia rehabilitation solving the concerns over stimulation of a lesioned brain area.

Other Applications

Cerebellar tDCS may also be useful to improve hand motor function following stroke. This novel approach is supported indirectly by a growing body of evidence documenting beneficial effects of cerebellar tDCS on different motor learning hand skill tasks in young healthy volunteers [93, 114]. Yet, to the best of our knowledge, evidence favoring this treatment approach in the stroke cohort is lacking.

Implications for Future Research

Cerebellar NIBS is a promising alternative approach to reduce a variety of impairments in stroke survivors. However, to help establish cerebellar NIBS in clinical practice additional research is needed: (1) to determine the role of the cerebellum in recovery processes; (2) to investigate the effects of different stimulation protocols, e.g., effect of stimulation polarity, focality, and duration; (3) to assess interactions between task-specific training and cerebellar NIBS; (4) to identify predictors of clinical response; (5) to confirm

cerebellar NIBS efficacy in regular clinical settings by performing larger randomized controlled trials.

Cerebellar NIBS in Relation to Speech and Language

Clinical and neuroimaging studies have implicated the cerebellum in the regulation of speech and language, and cerebellar NIBS may offer substantial advantages in establishing a causal role in these functions [115]. This section provides a brief overview of cerebellar NIBS studies examining such a role in healthy adults, along with those that have used cerebellar NIBS as a neurorehabilitation method.

Verbal Working Memory

Cerebellar pathology has been often associated with impairment in verbal working memory, and functional neuroimaging has disclosed task-related cerebellar activation in verbal working memory tasks [115]. Consistent with these findings, cerebellar NIBS effects on Sternberg task performance have been reported, with single-pulse TMS (right HVI/HVIIa Crus I) increasing response latencies [116], and with cTBS (right posterolateral cerebellum) impairing accuracy [117]. Further evidence has been provided by cerebellar tDCS studies. In Ferrucci et al. [118], both anodal and cathodal bilateral posterolateral cerebellar tDCS compromised the practice-dependent reduction in response latencies; in Boehringer et al. [119], cathodal cerebellar tDCS (right posterolateral cerebellum) decreased forward digit spans and impaired the practice-induced increase in backward digit spans. In Macher et al. [120], impaired recognition of items of medium difficulty (memory load) was reported following anodal cerebellar tDCS (right cerebellum), with no effect on items of low or high difficulty. These results suggest that task difficulty may interact with stimulation effects. Such interactions were also reported in another study [121], where cathodal cerebellar tDCS (right posterolateral cerebellum) increased response speed on the (difficult) Paced Auditory Serial Subtraction Task [122], but not on the (easier) Paced Auditory Serial Addition Task [121]. In conditions of high executive demand and memory load, depression of the cerebellar cortex may release cognitive resources by disinhibiting the contralateral prefrontal cortex and enhancing performance [121].

Verbal Fluency

Likewise, functional neuroimaging and clinical studies have been corroborated by neurostimulation research in establishing a cerebellar role in verbal fluency [115]. In Arasanz et al. [123], two groups completed phonemic and semantic fluency tasks pre- and post-cTBS: one received stimulation over the right posterolateral cerebellum and the other on the left. Right cerebellar NIBS induced lower switching (i.e., exhaustion of a phonemic or semantic cluster and shift to another) scores in the first 15 s of phonemic fluency performance, without affecting semantic fluency (but see Rami et al. [124]). In a tDCS study, facilitatory effects were reported following cathodal cerebellar tDCS (right posterolateral cerebellum) on the rate and consistency of participants' responses in a verb-generation task [121]. In another study [56], anodal cerebellar tDCS (right posterolateral cerebellum) improved phonemic fluency (trend in the same direction was observed for cathodal stimulation).

Predictive Language Processing

The cerebellum might optimize language processing by supporting predictive mechanisms, as it does on motor control [125]. Noun-to-noun (forward) phrasal associative priming (but not semantic categorical priming) was enhanced following right posteromedial cerebellar cTBS [126]. Moreover, noun-to-verb (forward) semantic associative priming (but not semantic categorical priming) was enhanced following right posterolateral cerebellar cTBS [127]. In Allen-Walker et al. [128], cTBS of the left posterolateral cerebellum increased backward associative priming (and no changes for forward priming). Furthermore, 1-Hz rTMS (right posterolateral cerebellum) slowed participants' predictions of the final noun in sentences presented verbally [129]. In Miall et al. [130], cathodal cerebellar ctDCS (right posterolateral cerebellum) decreased and anodal cerebellar tDCS increased the speed advantage for the predictable sentence items, without changing performance for the unpredictable ones. In Gatti et al. [131], participants judged whether noun-adjective pairs were semantically related, while online neuronavigated TMS was administered over a control site or a right posterolateral cerebellar site implicated in semantic prediction. Cerebellar NIBS caused a selective decrease in accuracy for related pairs relative to unrelated ones, consistent with theories extending the cerebellar predictive role to semantic processing. In Dave et al. [132], neuronavigated offline rTMS (beta stimulation) of a right posterior HVIIa Crus I region (vs. a control site) influenced the N400 ERP component during semantic prediction in sentence comprehension.

Grammar

Cerebellar pathology has also been associated with grammatical deficits [115]. An rTMS study [133] has disclosed evidence of cerebellar involvement in processing spatial–temporal associations in verb tenses. Participants

indicated whether a verb was past or future tense with right and left response buttons. Faster and more accurate responses were produced if the left button was associated with the past and the right with the future tense. Stimulation over both cerebellar hemispheres decreased such accuracy for identifying future (right) and past (left) tense. Right cerebellar NIBS selectively increased response latencies to the future tense of action verbs. These findings were interpreted as reflecting a cerebellar role in processing grammatical rules for verb conjugation, and in anticipating future events based on past experiences.

Speech Motor Programming

NIBS may also help to establish whether the cerebellum supports speech production above and beyond articulatory execution [115]. A low-frequency rTMS study [134] investigated the possibility of a causal role of the right posterior cerebellum (right or left HVIIa Crus I and II) in speech motor programming, especially the self-monitoring of speech errors. Performance in a speech production task was impaired after right cerebellar NIBS, suggesting that the cerebellum may support internal models of upcoming speech via verbal working memory processes.

Effects on Cerebro-Cerebellar Networks

Further studies have combined NIBS with functional neuroimaging to investigate the effects of cerebellar NIBS on the interaction between the cerebrum and the cerebellum within the context of speech and language processing. In Cho et al. [135], 1-Hz rTMS (left posterolateral cerebellum) was followed by increased glucose metabolism (fludeoxyglucose PET—FDG PET) in cognition- and language-related areas, including Wernicke's and Broca's areas, interpreted as reflecting compensatory neural activity. In Macher et al. [136], anodal cerebellar tDCS (right cerebellum) was followed by impaired digit recognition performance (modified Sternberg task). Attenuated signal (fMRI) was reported in right HVIIb, along with decreased functional connectivity between HVIIb and the posterior parietal cortex in the late encoding phase. In another study [56], however, anodal cerebellar tDCS (right posterolateral cerebellum) modulated resting-state functional connectivity in language networks, increased the functional connectivity between the cerebellum and language and speech-motor regions, and improved verbal fluency. In D'Mello et al. [55], anodal cerebellar tDCS (right posterolateral cerebellum) increased activation in right HVIIa Crus I/II during semantic prediction and enhanced resting-state functional connectivity between hubs of the reading/language networks; cerebellar tDCS effects were focal to language-associated regions of the cerebellum and cerebral cortex.

Neurorehabilitatory Potential

Given the functional and anatomical connectivity of the (right) cerebellar hemisphere with core language regions in the (left) cerebral hemisphere, cerebellar NIBS has also been employed in studies of speech and language rehabilitation [115]. Some studies have employed inhibitory cerebellar NIBS protocols. Their facilitatory effects are often attributed to a reduction of CBI over the motor and nonmotor cerebral areas targeted by the cerebellar nuclei. In Marangolo et al. [105], cerebellar tDCS was combined with language treatment in 12 aphasic patients. Each patient underwent cerebellar tDCS in four conditions (right posterolateral cathodal vs. sham stimulation; verb naming vs. generation), run in five consecutive daily sessions over 4 weeks. Improvement was only noted for verb generation following cathodal stimulation, suggesting that cerebellar tDCS is efficacious in tasks requiring the additional employment of nonlinguistic strategies. These effects dovetail with those noted following cathodal cerebellar tDCS on the rate and consistency of responses in verb generation in healthy adults [121]. In Sebastian et al. [109], 24 patients with chronic aphasia received anodal or cathodal cerebellar tDCS and computerized aphasia therapy followed by sham stimulation and computerized aphasia therapy, or the opposite order. While there was no significant effect of treatment (cerebellar tDCS vs. sham) for trained naming, cerebellar tDCS was more effective than sham when it followed treatment immediately. For untrained naming, there was significant improvement immediately post-treatment, which persisted for 2 months. The enhancement was larger following cathodal cerebellar tDCS for both trained and untrained naming.

Inhibitory cerebellar NIBS protocols have also been employed in cerebellar pathology. In [137], a low-frequency rTMS protocol (right posterolateral cerebellum; 21 days of stimulation) was applied on a patient with idiopathic late-onset cerebellar atrophy that presented with scanning speech dysarthria. Improvements were noted for limb coordination and gait, but also for speech (louder and clearer voice), and naming in dual-task conditions, consistent with the enhancement noted in healthy adults following inhibitory cerebellar NIBS protocols [121]. In Lin et al. [138], 19 SCA patients underwent neuronavigated cTBS (right cerebellum vs. sham stimulation) and were then instructed to produce sustained vowels while perceiving their voice pitch-shifted. Relative to sham, cerebellar cTBS led to smaller magnitudes of vocal compensations for pitch perturbations, showing that cerebellar NIBS can modulate the abnormal auditory-vocal integration in SCA.

In other studies, the application of excitatory protocols was accompanied by increased CBI and facilitatory effects. In Brusa et al. [139], daily sessions of bilateral posterolateral iTBS for 2 weeks in 10 PSP patients were followed

by increased CBI, bilaterally increased BOLD signal in the caudate nuclei, and alleviation of dysarthria. In Sebastian et al. [98], cerebellar tDCS (anodal vs. sham) was combined with spelling therapy in a patient with aphasia and anarthria due to large bilateral chronic strokes. There was greater improvement with cerebellar tDCS relative to sham, especially for untrained words, with generalization to written picture naming only seen during cerebellar tDCS. These improvements were accompanied by increased resting-state cerebro-cerebellar functional connectivity. However, in a study of 24 patients with chronic post-stroke aphasia, anodal cerebellar tDCS (right cerebellum) did not enhance language processing, either immediately following treatment or after 3 months [140].

Implications for Future Research

The above findings highlight the need for a better understanding of the effects of different cerebellar NIBS protocols on performance in different tasks, as well as how and why these vary between healthy adults and patients, but also among different types of patients. Methodological improvements are required, including preregistered, sham-controlled, double-blind studies using larger sample sizes and neuronavigated localization of the stimulation site.

Cerebellar tDCS Evidence in Neuropsychiatric Disorders

The cerebellum has been found to have a functional role in psychiatric disorders, such as attention deficit hyperactivity disorder, autism spectrum disorders, schizophrenia, bipolar disorder (BD), major depressive disorder, and anxiety disorders [141]. This is not surprising, given the intricate connections between the cerebellum and other cerebral structures, for example those cortical areas responsible for cognitive and emotional processes through the cortico-ponto-cerebellar and cerebello-thalamo-cortical pathways [141]. In this context, cerebellar tDCS has both a clinical and neurophysiological aim, since it might provide a beneficial approach for psychiatric conditions and a tool to explore pathophysiological processes, similarly to other clinical conditions [22, 142]. Indeed, although this field is still in its infancy, some studies have indicated the effect of cerebellar tDCS in psychiatric diseases.

Available Clinical Evidence

Since tDCS has been suggested as a valuable tool for the treatment of neuropsychiatric conditions such as depression, schizophrenia, addiction and chronic pain [143, 144], and cognitive improvement has been observed in some patients undergoing tDCS [145], montages involving stimulation over the cerebellum have been tested in several studies. For example, Ho et al. [146] compared mood and neuropsychological functions (memory and frontal lobe functions) in two groups of depressed participants ($N = 14$) treated with cortical tDCS and cerebellar tDCS. Two montages were considered: Fronto-Occipital (F-O) and Fronto-Cerebellar (F–C), both with intensity set at 2 mA for 20 min/day for 3 consecutive weeks. No significant neuropsychological changes were found, but mood improved under the F-O condition, with lesser improvement in the F–C condition. Clearly, the small sample size and the absence of a sham control group affected this open label pilot study. The same year, Minichino et al. [147] used prefronto-cerebellar tDCS in 25 euthymic outpatients with a diagnosis of BD Type I or II to improve sleep quality, as assessed by the Pittsburgh Sleep Quality Index (PSQI) [148]. The authors demonstrated that the stimulation (2 mA for 20 min/day for 3 consecutive weeks) delivered through a cathodal electrode over the right cerebellar cortex and anode over the left dorsolateral prefrontal cortex (DLPFC) significantly improved PSQI total score and all PSQI sub domains. The same protocol was repeated [149] to test neuropsychological changes of 25 euthymic patients with BD. The Rey Complex Figure Test [150] delayed recall and copy, as well as the Neurological Examination Scale were used as outcomes, suggesting that such stimulation might increase visuospatial memory and executive functioning in euthymic BD patients. Analogously to the previous study, the small sample size and the absence of a sham control group might have influenced these findings.

More recently, cerebellar stimulation was tested in patients with obsessive–compulsive disorder (OCD). Indeed, an open-label pilot study [151] applied right anodal cerebellar tDCS (with cathode over left orbitofrontal cortex) to 8 patients with treatment-resistant OCD (2 mA, twice a day for 5 days). The study was the first to demonstrate the clinical relevance of cerebellar tDCS in combination with selective serotonin reuptake inhibitors (SSRIs) in patients with treatment-resistant OCD. Indeed, although depressive symptoms were not improved as assessed by the Montgomery and Asberg Depression Rating Scale (MADRS) [152], the Yale–Brown Obsessive and Compulsive Scale score (Y-BOCS) [153] decreased by more than 25%, with beneficial effect on the severity of obsessive and compulsive symptoms lasting for 3 months. Clearly, more knowledge needs to be gathered to confirm these results.

Implications for Future Research

Current findings provide preliminary support for the safety, feasibility and beneficial effect of cerebellar tDCS for psychiatric conditions. However, such restorative potential must be confirmed through controlled and methodologically uniform clinical research. Indeed, future works should investigate several unclear points, such as the characteristics of

the patients, the pathological stages or the type and site of stimulation to reach an optimal response.

Cerebellar tDCS in Individuals with Hereditary Cerebellar Ataxia

Hereditary cerebellar ataxia (HCA) encompasses a heterogeneous group of autosomal recessive, autosomal dominant, X-linked and mitochondrial ataxias [154]. The autosomal dominant cerebellar ataxias (ADCA) are classified into more than 40 subtypes of SCA [154], whilst Friedreich ataxia (FRDA) is the most common of the autosomal recessive cerebellar ataxias (ARCA) [155]. The most common group of the ADCAs, the SCAs, arise from trinucleotide expansions, in particular CAG trinucleotide expansions (SCA1, SCA2, SCA3, SCA6, SCA17, and DRPLA) [155]. The incidence of SCA in the general population is about three affected people per 100,000 [156]. FRDA, arising in 96% of cases due to homozygosity for a GAA expansion, affects one in 29,000 people [157]. Clinically, these conditions are typified to varying degrees by incoordination of gait, limb, ocular movement, and speech. Some HCAs have associated features such as neuropathy, spasticity, cardiac dysfunction and behavioral/cognitive impairment [156]. Age of disease onset is variable but most often in adulthood, the exception being FRDA, in which the average age at disease onset is 10 years [157]. Although clinical presentation and progression are variable, a universal feature is progressive deterioration of motor and cognitive function. To date no specific therapies have been identified that can alter the course of these devastating, life-threatening diseases. The challenge for clinical researchers is to establish effective non-pharmacological interventions that can modify the unremitting, declining trajectory towards functional dependency which typifies this group of diseases. Optimum motor and cognitive function for people with HCA is critical to all aspects of daily function.

Available Clinical Evidence

There is now increasing evidence that cerebellar NIBS such as tDCS can produce changes in neural plasticity that last beyond the period of stimulation and are clinically relevant [16]. Notably the capacity of cerebellar tDCS to modulate neuronal excitability suggests that it may have a therapeutic benefit in HCA [16]. Indeed, the capacity to influence the excitability of the cerebello-thalamo-cortical pathway by stimulation of the cerebellar cortex alone, or combined with stimulation to the contralateral motor cortex, has been the focus of many tDCS studies in individuals with HCA [62, 158–160]. Reflecting the burgeoning interest in this area several systematic literature reviews appraising the efficacy of cerebellar tDCS on motor control in the HCAs have been published [161–164]. Three recent reviews report the findings of various open-label, single and double-blind studies examining the efficacy of tDCS on improving motor control in individuals with HCA [161–163]. Two of these publications reviewed the same eight studies ($N=81$) determining the application of tDCS in improving motor outcomes, particularly in those with less clinical severity [163, 164]. In addition, Benussi et al. [162] reviewed 10 published studies ($N=116$), confirming the favorable effect of tDCS on a range of motor domains including gait, balance and upper limb function [162]. Extending the scope of a systematic review, Chen et al. [161] conducted a meta-analysis on five randomized controlled trials ($N=72$) examining safety and the effect of tDCS on hand and gait function in individuals with HCA [161]. This meta-analysis verified the safety and specificity of active (versus sham) tDCS, as demonstrated by a 26.1% ($p=0.003$) improvement in gait ataxia (as measured by the 8 Minute Walk Test), and a 28.2% improvement in function after three months ($p=0.04$) of treatment. In contrast there were no significant differences in hand function (as measured by the Nine Hole Peg Test) [165] following tDCS [161]. Likewise, a study by Hulst et al. [166] did not find the application of tDCS effective in improving adaptation in a force field reaching task in a group of 20 individuals with principally dominant HCA, compared to control participants [166]. Similarly John et al. [167] did not find the application of tDCS effective on improving grip force in 14 individuals with cerebellar degeneration [167]. The findings in both these studies give credence to the premise of Chen et al. [161] that the efficacy of tDCS may be depend on specific tasks, parameters, or outcome measures.

Open Questions About cerebellar tDCS in HCA

While it would appear that the application of tDCS holds promise as a motor intervention for individuals with HCA, it is crucial to understand the source of these divergent results particularly in order to inform the design of future studies. Possible reasons for such variation include 1) a small and heterogeneous sample, 2) diversity of primary and secondary outcome measures, 3) varying stimulation parameters, and 4) inconsistent application of randomization, sham and/or blinding conditions [162]. Further work is required to establish a consensus regarding tDCS as an effective therapeutic intervention for individuals with HCA [168].

Neurophysiological Mechanisms of cerebellar tDCS

Further elucidations of the neural mechanisms underlying brain reorganization necessary for mitigating the effects of disease on motor function is warranted either prior to, or in conjunction with efficacy studies [161]. In particular,

interrogation of CBI and measures of intracortical inhibition/excitation such as long-interval cortical inhibition (LICI) and short-interval cortical inhibition (SICI) will provide tangible information about the integrity of cerebellocerebral connectivity necessary for optimum motor control [34, 103]. Some studies have recognized the utility of CBI in highlighting the possible neurophysiological mechanism underlying improvement in motor control [162, 169], incorporating CBI as an outcome measures alongside neurological and functional measures. However, further studies are required specifically examining inhibition in targeted HCAs (for example, those with significant dentate nuclei pathology such as FRDA, DRPLA and SCA3, as opposed to those with significant loss of function in Purkinje cells such as SCA6, SCA31, SCA2 and early-onset ataxia with ocular motor apraxia) [170].

Heterogeneity (and Rarity) of Clinical Phenotypes

Accordingly, the issue of heterogeneity of etiology in HCA warrants consideration in studies of cerebellar tDCS in individuals with HCA. Given the rarity of the sub-types of the HCA, it is unsurprising, but potentially problematic, that most studies include participants with a mix of dominant, recessive, and sporadic ataxias in order to achieve sufficient statistical power. Mixed response to cerebellar tDCS may reflect the heterogeneity of the HCAs in regard to both neuropathology and clinical phenotype. Whilst the cerebellum is a unifying site of pathology across the disorders, associated spinocerebellar tract, dorsal column, inferior olive, pontine nucleus, red nucleus, ventrolateral thalamus, vestibular nucleus or peripheral nerve pathology may also be present to varying degrees [170]. Based on neurodegeneration in cerebellar circuitry, Tada et al. [170] postulated a classification of individuals with HCA according to the four primary loci of neuropathology that is, the Purkinje cells, the cortico-ponto-cerebellar system, the spinocerebellar system and the cerebellar deep nuclei [170]. Understanding the variability of response to tDCS in the context of HCA neuropathology is crucial to designing targeted cerebellar tDCS efficacy studies (see the study by Grimaldi et al. [62]) considering disease severity as a reflection of cerebellar integrity. A number of studies suggest that cerebellar tDCS may be most beneficial for patients with lesser clinical severity (see Chen et al. [161] for a review). Stratification of the cohort according to clinical severity may assist in sub-group analysis of tDCS efficacy. Participants with milder symptoms, perhaps reflecting greater cerebellar volume, may be more suited to cerebellar tDCS aimed at facilitating neural compensation for evolving cerebellar deficiencies than those later in the disease trajectory [164].

Sensitivity of the Outcomes

While the most common outcome measures for cerebellar tDCS trials have been neurological rating scales such as the International Cooperative Ataxia Rating Scale (ICARS) [171] or Scale for the Assessment and Rating of Ataxia (SARA) [160], there have also been an assortment of other measures of gait, balance and upper limb function [161–164]. Returning to the issue of heterogeneity of neuropathology and clinical phenotype, it is possible that some of these outcome measures may not entirely reflect targeted cerebellar structures and as such may not capture the benefits of tDCS on specific aspects of motor control [162].

Implications for Future Research

Despite the growing of evidence supporting the use of tDCS to improve clinical symptoms related to HCA, further work is needed to verify the ability of tDCS to modulate cerebello-thalamo-cortical connectivity and, in so doing, deliver a much-anticipated therapeutic intervention not only for motor deficits, but also for cognitive impairment. Indeed, it should be noted that cerebellar tDCS to ameliorate cognitive impairment related to HCA has received little attention.

Cerebellar tDCS provides a relatively simple, effective and non-invasive treatment option, and the repertoire of applications continues to expand to settings beyond the clinic [172], and as an adjunct to traditional interventions such as intensive physiotherapy [172, 173]. Therefore, this approach represents a non-pharmacological intervention capable of bridging the gap between pathophysiology and the development of new treatment approach.

Cerebellar Stimulation in Other Movement Disorders

Cerebellar NIBS in Dystonia

Dystonia is a movement disorder characterized by abnormal postures and/or repetitive movements with many subtypes [174]. Historically, dystonia was conceptualized as a basal ganglia disorder, however recent evidence that a wider neuronal network is involved has established the cerebellum as a key node within pathophysiological networks [175]. Cerebellar NIBS is an attractive therapeutic strategy for dystonia. As a hyperkinetic movement disorder, characterized by hyperexcitability of M1 and reduced markers of inhibition, NIBS may offer the opportunity to retune inhibitory influences exerted by the cerebellum or more directly modify cerebellar dysfunction.

Table 2 Cerebellar NIBS studies conducted in the dystonia cohort

Data, author	Cerebellar stimulation (*inhibitory*; facilitatory)	Clinical response	Biomarker response	Main result
Cervical dystonia				
2019, Odorfer et al. [176]	Bilateral ***cTBS***, single session 16 patients		MEP, CSP, fMRI	Increased finger-tapping related cerebellar activation on fMRI in dystonia which was more pronounced after cerebellar stimulation
72018, Popa et al. [177]	sham, **iTBS** and ***cTBS*** Three sessions 22 patients 23 controls	TWSTRS	PAS	Cerebellar inhibition suppressed PAS and excitation enhanced PAS (opposite to controls). Turning the head or providing proprioceptive perturbation to neck muscles in healthy controls inverted cerebellar modulation of plasticity
2016, Bradnam et al. [178]	sham or bilateral **iTBS** 10 sessions/days 8 patients in each group	TWSTRS, CDQ-24 QoL, hand dexterity	MEP CSP	Clinical markers improved favourably in iTBS group. No change of neurophysiology
2014, Bradnam et al. [179]	Single patient. 20 varied **a-tDCS** cerebellar stimulations over 10 weeks	TWSTRS, CDQ-24, CDIP-58	M1 excitability	Stimulation is safe with concurrent botulinum toxin injections
2014, Koch et al. [180]	sham or bilateral ***cTBS*** 10 sessions over 2 weeks	TWSTRS, BFMDRS	CBI, SICI, ICF, CSP, PAS	Small 15% improvement in TWSTRS for one week post intervention. Stimulation modified CBI and reduced heterotopic PAS potentiation
2013, Hoffland et al. [181]	***cTBS***, single session, 11 patients		EBCC	cTBS normalised deficit in eyeblink classical conditioning acquisition. In keeping with a functional and reversible disruption of the cerebellum in dystonia
Task-specific dystonia/focal hand dystonia				
2015, Bradnam et al. [182]	sham, **a-tDCS** and ***ctDCS*.** Each single session. 8 patients	WCRS, ADDS, kinematic	CBI	a-tDCS improved kinematics of handwriting and circle drawing tasks but did not reveal clear neurophysiological mechanism (CBI within normal limits)
2015, Lissen et al. [183]	sham or ***cTBS*.** Each single session 10 patients	Writing kinematics		No significant change in writing kinematics
2014, Sadnicka et al. [184]	**a-tDCS** single session. 10 patients	WCRS	RMT, AMT, CSP, PAS, RC	Anodal stimulation reduced the magnitude of plasticity response (whether they facilitated or inhibited). High variability of PAS response noted. No change in clinical score
2013, Hubsch et al. [185]	sham, **iTBS** and ***cTBS*.** Each single session. 21 writer's cramp 25 controls		PAS, SICI/LICI	Cerebellar cortex excitation and inhibition were ineffective in modulating cortical sensorimotor plasticity (in contrast to controls)

Table 2 (continued)

Data, author	Cerebellar stimulation (*inhibitory*; facilitatory)	Clinical response	Biomarker response	Main result
Mixed group				
2016, Bologna et al. [186]	Two sessions: sham and ***cTBS*** 13 focal hand dystonia, 13 cervical dystonia, 13 controls	Arm and neck kinematics	M1 excitability	cTBS reduced the excitability of contralateral primary motor cortex in healthy subjects and cervical dystonia but not patient with focal hand dystonia. No change in clinical scores
Secondary dystonia				
2019, Shin et al. [187]	Single case. Five sessions of low frequency TMS	BFMDRS		Leg dystonia secondary to cerebellar infarction. Stimulation applied to side of lesions. Improved dystonia at rest, no change to dystonia during gait

Table depicts the summary of identified studies testing cerebellar NIBS interventions in the dystonia cohort assessing effects on clinical and neurophysiological functions. Abbreviations: *ADDS* Arm Dystonia Disability Scale; *AMT* active motor threshold; *a-tDCS* anodal transcranial direct current stimulation; *BFMDRS* Burke-Fahn-Marsden Dystonia Rating Scale; *CBI* cerebellar brain inhibition; *CDIP-58* Cervical Dystonia Impact Profile; *CDQ-24 QoL* Cranio-cervical Dystonia Questionnaire Quality of Life; *CSP* cortical silent period; *cTBS* continuous theta burst stimulation; *c-DCS* cathodal transcranial direct current stimulation; *EBCC* eyeblink classical conditioning; *fMRI* functional magnetic resonance imaging; *ICF* intracortical facilitation; *iTBS* intermittent theta burst stimulation; *LICI* long-interval intracortical inhibition; *MEP* motor evoked potential; *PAS* paired associative stimulation; *RC* recruitment curve; *RMT* resting motor threshold; *SICI* short-interval intracortical inhibition; *TWSTRS* Toronto Western Spasmodic Rating Scale; *WCRS* writer's cramp rating scale

Available Clinical Evidence

The major studies that have used cerebellar stimulation to investigate dystonia are summarized in Table 2. The large majority have examined patients with either cervical dystonia and/or task-specific dystonia of the hand (in which dystonia occurs during an isolated task such as writing or playing in musical instrument). Two major types of outcome measure can be identified; studies that have tried to improve clinical markers of dystonia (e.g., severity scores) and/or those that have attempted to modulate dystonic biomarkers (e.g., neurophysiological markers, learning deficits).

In cervical dystonia, several studies have reported clinical improvement when stimulation is performed for more than a single session (see Table 2). Both cerebellar stimulation that is considered to inhibit and stimulation that is considered to facilitate cerebellar activity have been found to be beneficial. This may be because cerebellar stimulation itself does not have a clear bidirectional effect and/or that any non-specific disruption of cerebellar activity is beneficial within dystonic networks. Either alternative is encouraging, as future therapeutic interventions such as non-invasive or invasive stimulation targets are considered. Clinically cervical dystonia is characterized by its mobile nature responsive to additional sensory input (worse when eyes closed, sensory trick phenomena) suggesting a dynamic functional disturbance that may be particularly sensitive to such techniques.

Overall, studies evaluating clinical improvements in task-specific dystonia have been negative (except Bradnam et al. [182]). In task-specific dystonia individuals present with a highly stereotyped motor impairment, which at the time of diagnosis has often been symptomatic for many months or even years. It is likely that such a motor impairment will have been consolidated within encoded network thousands of times, rendering a single isolated session of stimulation unlikely to produce significant effects. Recognizing an increased influence of environmental factors in task-specific dystonia may also be important as retraining therapies can be highly effective [188]. Pairing retraining therapy with stimulation is therefore an attractive future area of study [189].

Several studies have examined the effect of cerebellar stimulation on M1 plasticity/excitability, with the rationale that modulating the excessive excitability that characterizes dystonia neurophysiology could translate into a therapeutic effect. In task-specific dystonia, Sadnicka et al. [184] found retained ability of facilitatory cerebellar stimulation (anodal cerebellar tDCS) to dampen plasticity responses of the motor cortex (similar to controls). However, the marked variability of plasticity response within the patient group undermined any theoretical benefit. This contrasted another study [185] in which both excitatory (iTBS) or inhibitory (cTBS) failed to modulate the plastic responsiveness of the hand in M1, in patients with task-specific dystonia. However, the same

group also tested a similar study design [177] in cervical dystonia, finding that cTBS suppressed paired associative stimulation (PAS) responses and excitation enhanced PAS responses (the opposite to controls). Interestingly, in healthy controls [177], mimicking some of the conditions of cervical dystonia by turning the head or perturbing proprioceptive feedback inverted cerebellar modulation of plasticity in line to that cervical dystonia. Most recently, Bologna et al. [186] have shown that cTBS modulates excitability of M1 in cervical dystonia (and healthy controls) but not patients with task-specific dystonia. Other studies [176, 181] have looked at cerebellar learning paradigms (eye blink conditioning) and motor tasks which activate the cerebellum (see Table 2). Collectively, these studies identify differences between the different subtypes of dystonia. They also appear to identify the ability of cerebellar stimulation to shift markers of cerebellar function and/or dystonic dysfunction.

Open Questions About cerebellar tDCS in Dystonia

While studying biomarkers for dystonia remains enticing as it attempts a more mechanistic and specific mode of study, some commonly made assumptions and challenges of this literature can be highlighted. For example, given the unclear and still debated efficacy and mechanism of the different types of cerebellar stimulation [57, 171, 190], it is not clear if we can reproducibly and bidirectionally modulate cerebellar activity in healthy controls. Any clinical studies using these techniques with their heterogenous patient populations need careful consideration (particularly if bidirectional effects are reported within dystonia). It is also problematic that there are no reproducible biomarkers for dystonia. For example, neurophysiological plasticity responses of M1 are often used as a biomarker for dystonia. However such responses are notoriously variable, non-specifically abnormal across a range of diseases, and cannot reliably segregate a dystonic patient group from controls [191]. Similarly, we have little ability to quantitively track hypothesized cerebellar involvement in dystonia. For example, CBI was initially thought to be reduced in a pilot study in eight individuals with task-specific dystonia and promoted as a possible marker of dystonic cerebellar dysfunction [192]. However, the deficit in CBI was not observed in a more recent publication in the same patient group [182].

Cerebellar NIBS in Parkinson's Disease (PD)

In recent years, growing attention has been focused on the treatment of Parkinson's Disease through NIBS techniques. Nonetheless, only few papers have investigated the role of cerebellar stimulation for the treatment of the three cardinal signs of the disease (i.e., bradykinesia, rigidity and tremor), as well as for the control of levodopa-induced dyskinesias (LIDs). Despite the variability in techniques, stimulation settings and protocols' design, current evidence seems to suggest that 1) cerebellar TBS represents the best protocol to interfere with cerebellar functions in vivo; 2) NIBS (cerebellar TBS) are effective for the control of both resting tremor and LIDs, with a very limited impact on rigidity and bradykinesia; 3) cerebellar stimulation does not improve speech disturbances, neither axial dysfunctions (e.g., the freezing of gait, FOG). Here, we encompass the current knowledge about cerebellar NIBS, also discussing potential mechanisms of action and rationale for the use of cerebellar stimulation in PD.

Potential Mechanism of Action

The cerebellar role in PD pathophysiology has recently gained increasing attention. In particular, the cerebellum may interfere with the basal ganglia network at three different levels: 1) it down-regulates the striatal D1 receptors as a part of a disynaptic pathway to the dorsolateral putamen and the external globus pallidus (GPe), passing through the intralaminar nuclei of the thalamus [13, 193]; 2) it expresses all types of dopamine receptors receiving inputs from the Substantia Nigra pars compacta (SNc) that terminate in the granule and Purkinje cell layers, thus sharing similar properties with the striatal dopaminergic system [194–196]; 3) the cerebellum plays an overall inhibitory effect on motor and non-motor areas (CBI). In particular, CBI is reduced in degenerative disorders, also comprising PD patients, where it could either be compensating or contributing to motor deficits [8, 15]. Although current evidence remains limited, all these studies seem to suggest that the cerebellum may be engaged in specific aspects of the pathophysiology of PD, such as levodopa-induced dyskinesias and altered sensory discrimination [197]. Moreover, as concerns tremor in PD, there is increasing evidence that the basal ganglia network triggers the onset of tremor, whereas the cerebellar network is responsible for its amplitude and maintenance [198].

Clinical Evidence

Eleven papers have been published to date about the use of cerebellar NIBS for the treatment of PD. Among these, there are only three works on tDCS. In particular, Málly et al. [199] provided the longest experiment with cerebellar tDCS, showing that anodal stimulation, delivered for one week every six months for 2 years, improved all Unified Parkinson's Disease Rating Scale UPDRS-III scores (UPDRS-III) [200]. Ferrucci et al. [201] showed that tDCS, applied either over the cerebellum or the M1, had similar effects on fluctuations and dyskinesias. Workmann et al. [202] provided the first evidence that cerebellar polarization may also

improve gait and balance, when delivered at high intensities bilaterally (4 mA).

Despite the variability in stimulation settings, protocol design, and clinical outcomes of tDCS studies, cerebellar TMS has demonstrated a high reproducibility among different papers when delivered as cTBS [203–206]. TBS significantly improves LIDs, as confirmed both by the reduction of glucose (F-FDG) uptake in the dentate nucleus [207] and the restoration of sensorimotor plasticity of M1 [208]. This improvement may be due to a cTBS-induced modulation of CBI [209], as confirmed in mice by the induction of LTD between Purkinje cell and the deep cerebellar nuclei [210]. Nonetheless, to date there still is a substantial lack of understanding about physiological mechanisms underlying TBS. Also, low-frequency rTMS (1 Hz) seems to dampen CBI, thus improving LIDs, although current evidence is based on two papers only, and further confirmation is needed [211, 212].

Cerebellar NIBS in Essential Tremor (ET)

Essential tremor (ET) presents as a postural and kinetic tremor, commonly involving both arms, and it is strictly related to cerebellar dysfunction. In particular, both the cerebello-thalamo-cortical and the inferior olive-cerebellar networks are impaired [198]. MRS showed diminished N-acetylaspartate (NAA) [213], while voxel based morphometry (VBM) studies have recently revealed a mild degree of cerebellar atrophy [214]. Nonetheless, only three published studies have explored the effects of cerebellar tDCS in patients with ET to date. In the first one [215], patients underwent ten consecutive sessions of cathodal cerebellar tDCS (2.0 mA, 20 min) without any acute or long-lasting benefits on motor scores and daily living activities. Conversely, in a second paper [216], cathodal cerebellar tDCS improved both Essential Tremor Rating Assessment Scale (TETRAS) [217] and Activities of Daily Living (ADL); the authors applied tDCS to the DLPFC (the anode) and to the inion (the cathode; 2 mA for 20 min in 10 consecutive sessions with a 2-days break between the first and the second 5-days sessions). Different from Gironell et al. [215], five more tDCS sessions were administered in an every-other-day manner, one month after the initial course of therapy, possibly accounting for the beneficial effects observed in the long-term period. More recently, a third work [218] showed that ET is suppressed via electrical stimulation of the cerebellum phase-locked to the tremor.

Cerebellar NIBS in Huntington's Disease (HD) and Multiple Sclerosis (MS)

Although a key cerebellar involvement has been suggested in the pathogenesis of Huntington's Disease (HD), both for motor and psychiatric features [219, 220], only one study has explored to date the putative role of cerebellar NIBS to date [221]. The authors showed that 5-days anodal cerebellar tDCS improved motor scores in HD, when compared to sham stimulation, with effects lasting for about four weeks after protocol completion. In Multiple Sclerosis, recent evidence suggests iTBS, applied over the cerebellum, improves both gait and balance, when combined with vestibular rehabilitation [222], likely modulating the activity of vestibule-cerebellar pathways.

Implications for Future Research

Converging evidence points to the fact that cervical dystonia may be an attractive candidate for treatment via stimulation of the cerebellum and/or its outflow tracts with a modest literature suggesting that targeted cerebellar NIBS may be beneficial for clinical markers. Studies point to the need for repeated stimulation sessions in order for cerebellar NIBS to meaningfully interact with the dystonic network. Also, the application of cerebellar NIBS to PD, ET, HD and MS has shown limited but promising results in terms of motor outcomes. Future works should investigate the safety of high intensity tDCS (> 4 mA), as well as the possibility to simultaneously combine different targets in order to optimize tDCS effectiveness (e.g., M1 and the cerebellum; the spinal cord and the cerebellum). Further studies are needed to confirm the preliminary data in larger cohorts and in a longer follow-up period. Finally, there is a growing interest for the assessment of a "deep cerebellar tDCS", possibly via temporally interfering electric fields [223, 224], as recently provided for the subthalamic NIBS [225].

Pain and the Cerebellum

During the past 15–20 years, there has been growing interest to define the cerebellar role in pain processing and perception [226–229]. Studies in humans have demonstrated that the cerebellum is critically involved both in visceral pain [230] and migraine progression and persistence [231]. Along this view, changes in structural volume and functional connectivity of the cerebellum seem to predict chronicization, as well as long-term disability in migraine [231, 232]. Moreover, functional neuroimaging has demonstrated that the posterior cerebellum plays a key role in pain-related adaptations for motor control [233, 234]. To date, however,

a critical review about the role of cerebellar NIBS for pain treatment is still lacking.

Putative Mechanisms of Action of cerebellar tDCS for Pain Treatment

It has been demonstrated that the cerebellum interferes with nociceptive processing following a CBI-like mechanism [235]. Consequently, anodal cerebellar tDCS may reduce pain perception by increasing the inhibitory tone exerted by the cerebellum on different brain targets, whereas cathodal cerebellar tDCS could elicit opposite effects by inducing hyperalgesia. This tentative model has been recently confirmed by a clinical study of Ruscheweyh et al. [236], showing that patients with cerebellar infarctions have reduced pain thresholds.

Apart from non-synaptic and synaptic (neuroplastic) changes, tDCS may modulate pain experience and processing through different mechanisms. In recent years, a growing body of evidence has supported the importance of tDCS after-effects on regional blood flow and immune responses. Accordingly, animal studies have proved that tDCS elicits neural stem cells activation in vivo, influencing the development and the distribution of microglia in the adult brain [237]. Finally, tDCS might also modulate the inflammatory response by regulating pro-inflammatory cytokines and increasing glutathione levels [238].

Available Clinical Evidence

In recent studies, Bocci et al. [239–241] have demonstrated that cerebellar tDCS modulates pain processing in healthy humans. In particular, cerebellar tDCS seems to exert polarity-specific effects on the amplitude of Laser Evoked Potentials (LEPs), thus modifying the perception of experimentally induced pain in young volunteers. Because tDCS is effective in modulating both N1 and N2/P2 components of LEPs, and since these responses are generated by parallel and partially segregated spinal pathways reaching different cortical targets [242], the authors argued that the cerebellum is involved in pain processing by modulating the activity of both somatosensory and cingulate cortices. Indeed, from a functional point of view, the cerebellum may be engaged in the sensory-discriminative, as well as in the emotional and cognitive dimension of pain [243, 244]. A recent paper by Pereira et al. [245] has confirmed these results, showing that anodal cerebellar tDCS reduces lower extremity pain perception in healthy humans. Another paper [234] has proved that cathodal polarization applied to the right cerebellar hemisphere modulates motor adaptation during gait, suggesting the possibility to interfere with motor withdrawal by using cerebellar tDCS.

However, in a previous study, Zunhammer et al. [246] failed to demonstrate the analgesic effects of rTMS applied over the cerebellum. The discrepancy with previous results may be due to different factors: the authors evaluated only changes in subjective pain thresholds and used a different neuromodulation technique (rTMS vs. tDCS).

The efficacy of cerebellar tDCS for pain treatment has been also recently confirmed also in patients suffering from "phantom limb pain" (PLP) [241]. Recent studies have shown that tDCS applied over the motor cortex represents a promising therapeutic tool in PLP, with effects likely arising from a transient restoration of the cortical representation of the phantom limb [247–249]. Based on this evidence, Bocci et al. [239] have recently shown that anodal cerebellar tDCS improves both paroxysmal pain and non-painful phantom limb sensations in subjects with upper limb amputations. They argued that, differently from other brain targets, cerebellar tDCS may reduce both painful and non-painful phantom limb sensations, which are induced by maladaptive changes in the sensorimotor network and posterior parietal cortex respectively [248].

Implications for Future Research

Similarly to other functions of cerebellum, the effects of cerebellar tDCS on pain are promising and clinically intriguing, but sadly still at their infancy. Moreover, approaching this topic, one needs to consider that pain is the result of different neurophysiological mechanisms, and that has different clinical manifestations. Thus, neuromodulation needs to be carefully tailored to the pain syndrome to be specifically targeted. Still, further studies are needed to expand the current knowledge.

Concluding Remarks

The density of neurons in the cerebellar cortex, the anatomical location and the geometrical organization of the cerebellum, the high degree of plasticity of the cerebellar cortex and the high degree of connectivity of the cerebellum with spinal cord, brainstem, basal ganglia and cerebral cortex all go in the direction of a great potential for cerebellar NIBS to explore cerebellar functions and modulate brain disorders involving primarily cerebellum or extra-cerebellar structures connected to the cerebellum. Based on the current knowledge here reviewed, there is a general consensus that cerebellar non-invasive stimulation represents a promising tool for therapeutic purposes, both in motor, cognitive and psychiatric pathological conditions. Available results suggest that the strategy of targeting the cerebellum to indirectly affect cortical and subcortical activities might be effective

in alleviating the symptoms of several pathologies, likewise in improve cognitive functions or motor learning in healthy subjects. However, numerous questions remain unsolved and require multi-disciplinary and large-scale efforts. There is a clear need to identify the physiological and pathophysiological effects cerebellar NIBS in the areas of motor behaviour, cognitive processes, and affect regulation, in addition to clarify its mechanisms of action. Also, short-term, middle-term and long-term effects upon the activity of the cerebellar cortex (Purkinje neurons and local interneurons), cerebellar nuclei and the inferior olivary complex should be explored. Finally, the interaction between neuromodulation protocols and pharmacological therapies is still an unexplored line of research that needs to be addressed to safeguard clinical success and credibility of cerebellar NIBS.

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Declarations

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Authors and Affiliations

Mario Manto[1,2] · Georgios P. D. Argyropoulos[3] · Tommaso Bocci[4,5] · Pablo A. Celnik[6] · Louise A. Corben[7] · Matteo Guidetti[4,8] · Giacomo Koch[9] · Alberto Priori[4,5] · John C. Rothwell[10] · Anna Sadnicka[11,12] · Danny Spampinato[9] · Yoshikazu Ugawa[13] · Maximilian J. Wessel[14,15] · Roberta Ferrucci[4,5]

1 Service de Neurologie, CHU-Charleroi, 6000 Charleroi, Belgium

2 Service Des Neurosciences, UMons, 7000 Mons, Belgium

3 Division of Psychology, Faculty of Natural Sciences, Faculty of Natural Sciences, University of Stirling, Stirling FK9 4LA, UK

4 Aldo Ravelli Research Center for Neurotechnology and Experimental Neurotherapeutics, Department of Health Sciences, University of Milan, 20142 Milan, Italy

5 ASST Santi Paolo E Carlo, Via di Rudinì, 8, 20142 Milan, Italy

6 Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore, MD, USA

7 Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Parkville. Victoria, Australia

8 Department of Electronics, Information and Bioengineering, Politecnico Di Milano, 20133 Milan, Italy

9 Fondazione Santa Lucia IRCCS, via Ardeatina 306, 00179 Rome, Italy

10 Department of Clinical and Movement Neuroscience, UCL Queen Square Institute of Neurology, London, UK

11 Motor Control and Movement Disorders Group, St George's University of London, London, UK

12 Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK

13 Department of Human Neurophysiology, Fukushima Medical University, Fukushima, Japan

14 Defitech Chair of Clinical Neuroengineering, Center for Neuroprosthetics (CNP) and Brain Mind Institute (BMI), Swiss Federal Institute of Technology (EPFL), Geneva, Switzerland

15 Defitech Chair of Clinical Neuroengineering, Center for Neuroprosthetics (CNP) and Brain Mind Institute (BMI), Swiss Federal Institute of Technology (EPFL Valais), Clinique Romande de Réadaptation, Sion, Switzerland