Review

The Cerebellum and the Motor Cortex: Multiple Networks Controlling Multiple Aspects of Behavior

The Neuroscientist
1–21

DOI: 10.1177/10738584231189435
journals.sagepub.com/home/nro
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Abstract

The cerebellum and its thalamic projections to the primary motor cortex (M1) are well known to play an essential role in executing daily actions. Anatomic investigations in animals and postmortem humans have established the reciprocal connections between these regions; however, how these pathways can shape cortical activity in behavioral contexts and help promote recovery in neuropathological conditions remains not well understood. The present review aims to provide a comprehensive description of these pathways in animals and humans and discuss how novel noninvasive brain stimulation (NIBS) methods can be used to gain a deeper understanding of the cerebellar-M1 connections. In the first section, we focus on recent animal literature that details how information sent from the cerebellum and thalamus is integrated into an broad network of cortical motor neurons. We then discuss how NIBS approaches in humans can be used to reliably assess the connectivity between the cerebellum and M1. Moreover, we provide the latest perspectives on using advanced NIBS approaches to investigate and modulate multiple cerebellar-cortical networks involved in movement behavior and plasticity. Finally, we discuss how these emerging methods have been used in translation research to produce long-lasting modifications of cerebellar-thalamic-M1 to restore cortical activity and motor function in neurologic patients.

Keywords

cerebellum, motor cortex, noninvasive brain stimulation, motor learning, TMS-EEG

Introduction

The ability to perform daily motor activities, such as reaching for a cup of coffee or walking across the street, requires the coordinated activity of various brain regions that integrate spatial and temporal information about the ensuing movement. The precise timing and accurate performance of such actions involve the cerebellum (Bareš and others 2019), and its outputs are relayed to cortical motor areas. Indeed, patients with cerebellar pathology display difficulty producing well-timed and coordinated movements (e.g., ataxia and dysdiadochokinesia) and impaired ability to adjust movements to new environmental surroundings (e.g., when switching gait patterns from walking over pavement to walking). The cerebellar-thalamocortical tract is the critical pathway in which the cerebellum can sculpt cortical activity and influence the performance of various voluntary actions. Interestingly, pathways arising from the cerebellum to premotor (PM) and primary motor cortex (M1) have been selectively expanded throughout the course of evolution (Gutiérrez-Ibáñez and others 2018; Smaers and Vanier 2019), particularly when compared to the descending cerebellar control via the rubrospinal tract in nonhuman primates (ten Donkelaar 1988). These changes suggest that communication between these areas is necessary to carry the vast diversity of complex motor actions requiring precise coordination and planning. While this highlights the importance of crosstalk between the cerebellum, thalamus, and cortex, how this pathway recruits cortical neurons and modifies cortical motor activity during voluntary movements remains largely misunderstood. In the first section of this article, we focus on recent animal literature that details how information sent from the cerebellum and thalamus is integrated into an extensive network of

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cortical motor neurons. We then discuss how noninvasive brain stimulation (NIBS) in humans can be used to reliably assess this pathway's connectivity and discuss the recent advancement of these tools to investigate the multiple cerebellar-cortical networks involved in different behavioral contexts. Finally, we discuss how these emerging methods can be applied to clinical research to restore cortical activity and overcome behavioral deficits.

Dissecting Distinct Cerebellar-Cortical Pathways in Behavior: Evidence from Animal Studies

The intricacies of how the cerebellum and cortex communicate are essential to consider as they can elucidate how these brain regions' interactions can participate in various actions (Box 1). Anatomic studies have shown contralateral connections between the cerebellum and cortex through the cerebellar-thalamocortical and cortical-ponto-cerebellar pathways (Beck 1950; Kelly and Strick 2003). Notably, the cortical-ponto-cerebellar pathways provide sensory, motor, and cognitive input to different lobules of the cerebellum, which integrates this information with peripheral input to shape motor and cognitive actions (Figure 1). In turn, deep cerebellar nuclei and their thalamic targets project to various cortical areas beyond M1, including prefrontal, PM, and parietal cortices, forming multiple segregated cerebellar-cerebral loops. The arrangement of these diverse closed-loop circuits may play a role in the precise adjustment of neuronal signals, as PM-cerebellar loops and M1-cerebellar loops were respectively shown to be necessary for preparatory activity and fine motor control (Gao and others 2018; Proville and others 2014). While these data provide the basis for functionally distinct topographical regions of the cerebellum, recent work in rodents has importantly demonstrated significant convergence of mossy fibers from multiple cortical sources onto the same cerebellar area and granule cells (Henschke and Pakan 2020; Huang and others 2013; Pisano and others 2021). In other words, the same cerebellar region integrates information from various cortical areas, which suggests a more intricate interaction is at play that is likely necessary for carrying out complex motor behaviors that require high-level cognitive processes (Diedrichsen and others 2019; Stoodley and others 2012).

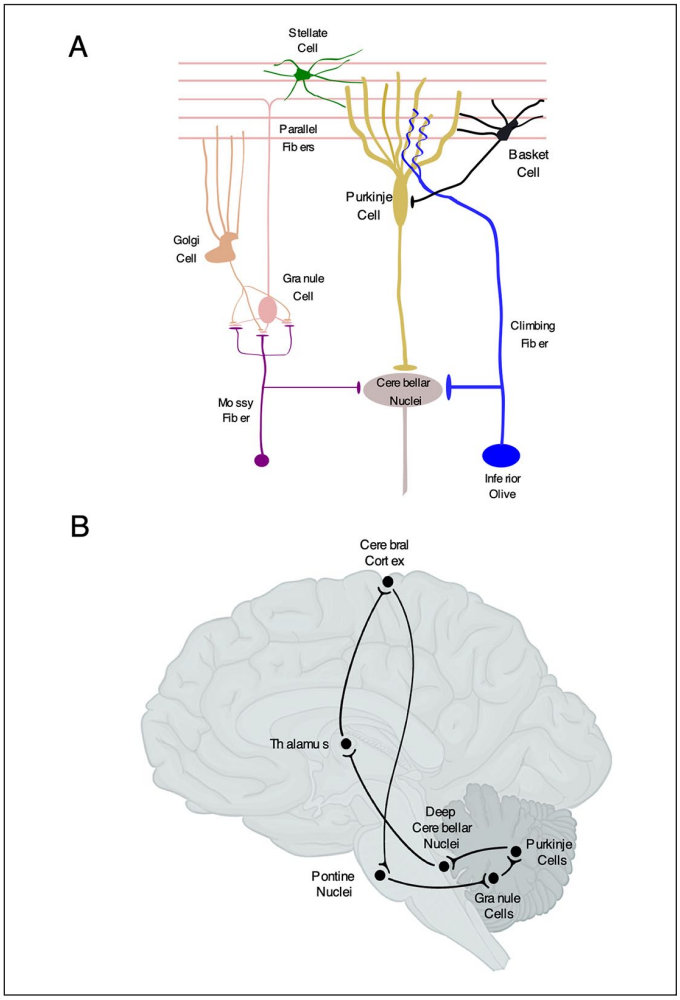
Recent human functional neuroimaging work supports this notion, showing the involvement of the cerebellum in a wide variety of behavioral tasks (King and others 2019); however, what remains obscure is how to characterize the cerebellum's functional involvement across distinct behaviors. While cerebellar inputs to the thalamus exhibit a topographic organization, projections of the cerebellar nuclei (DCN) extend to the ventral thalamus (including ventromedial, anteromedial, and ventral anterolateral subdivisions) and the intralaminar nuclei (Teune and others 2000). Thalamic relay neurons consist of two fundamentally distinct cell types: "core" neurons, which form topographically organized projections to layers of cerebral cortical, and "matrix" neurons, which send more diffuse projections to the cortices that innervate the superficial layers of multiple cortical regions, crossing receptive fields and functional boundaries (Jones 1998). Electrophysiological recordings in cats have shown that a single thalamocortical fiber receiving cerebellar input has multiple terminal patches that can spread a few millimeters along the rostrocaudal axis of M1 (Shinoda and others 1993). As the DCN project to areas of the thalamus that contain a large density of "core" (e.g., ventral, anterolateral) and "matrix" (e.g., intralaminar) neurons, this highlights how cerebellar input can affect a wide range of thalamocortical networks and functions (Figure 2).

Given how broadly these cerebellar-thalamic-cortical fibers innervate an extensive network of neurons within M1, multiple studies have proposed that these fibers play a role in coordinating the spatiotemporal dynamics of multiple muscle effectors (Berger and others 2020; Manto and others 2012). Cerebellar input triggers short-latency spiking in thalamic neurons that relay input to superficial and deep layers of M1 (Hooks and others 2013; Schäfer and others 2021), triggering responses in M1 either through layer 2/3 (Weiler and others 2008) or direct excitation of layer 5 (Sauerbrei and others 2020). These cerebellar-thalamic projections display characteristics that resemble "feedforward" driving inputs (Aumann and Horne 1996; Gornati and others 2018), contacting inhibitory and excitatory M1 cells (Nashef and others 2022), and exhibit time-locked increases in activity before movement initiation (Dacre and others 2021). Feedforward inhibition in the motor system likely serves as a principal mechanism for timing motor actions by amplifying cerebellar signals and silencing competing inputs before movement onset (Nashef and others 2022).

Cerebellar output can modulate thalamic activity and facilitate cortico-cortical communication. For instance, inhibiting cerebellar nuclei activity leads to a reduced firing rate of motor thalamic neurons (D. Popa and others 2013), decreased gamma-rhythmic coherence between M1 and somatosensory cortex (Lindeman and others 2021), and impaired ability for animals to adapt to changing sensory contexts (Proville and others 2014). These inputs are vital for producing strong transient activity at movement onset since cooling or blocking cerebellar-thalamic pathways suppresses the movement initiation (Brooks and others 1973; Dacre and others 2021; Nashef and others 2019) and induces oscillations resembling intention tremors that are characterized by erratic

Box 1. Cerebellar Circuitry and Pathways to the Cortex.

The cerebellar cortex is a highly organized brain structure with a diverse range of neurons involved in motor control and higher cognitive functions. Its stereotyped connectivity pattern compromises two input sources and a sole output channel governed exclusively by Purkinje cells, which receive input from several classes of interneurons (Box 1, Figure A). The primary input to the cerebellum is through mossy fibers that transmit information from the cerebral cortex via the pontine nuclei, the spinal cord, and brainstem structures to the cerebellar nuclei and granule cells. The axons of granule cells bifurcate in the molecular layer, where they branch transversely into parallel fibers and form excitatory synapses with up to hundreds of Purkinje cells. In contrast, climbing fibers originating from the inferior olive represent a more selective source of excitatory input: a Purkinje cell receives only one climbing fiber input. Thus, the signal arriving from climbing fibers is considerably more potent than inputs from mossy/parallel fibers.



Box 1. (A) Schematic representation of the cerebellar cytoarchitecture. The circuit comprises Purkinje cells (the output cells of the cerebellar cortex), as well as granule, Golgi, stellate, and basket cell interneurons. Purkinje cells are the sole output of the cortex, making inhibitory synaptic contact with the cerebellar nuclei. These neurons connect to a wide range of cortical and subcortical structures to control movement and cognitive processes. (B) Main connections of the cortico-cerebellar loop. Cerebellar-thalamic-cortical pathway: the deep cerebellar nuclei send its output to the thalamus, which relays information to various cortical areas (e.g., M1, prefrontal cortex, and parietal cortex). Cortico-ponto-cerebellar pathway: connects the cerebrum with the cerebellum. These pathways decussate in the pons before entering the contralateral cerebellum.

(continued)

Box 1. (continued)

Purkinje cells have inhibitory connections to the deep cerebellar nuclei: dentate, interposed, and fastigial nucleus. In particular, the dentate receives input from the lateral cerebellar cortex and projects to various areas of the cerebral cortex (e.g., motor, PM, prefrontal, and parietal regions) via the thalamus. Importantly, these connections are bidirectional, involving the cortico-cerebellar pathway through the pontine nucleus (Box 1, Figure B). These connections form "closed-loop" circuits that involve a particular network of a cerebellar region that projects to a cortical area that projects back to the same cerebellar region. These closed-loop circuits are thought necessary for adjusting neuronal signals to execute finely controlled behaviors. For example, the sensorimotor-cerebellar loop and the cortex and PM-cerebellar loop are required for fine movement control and persistent preparatory activity, respectively.

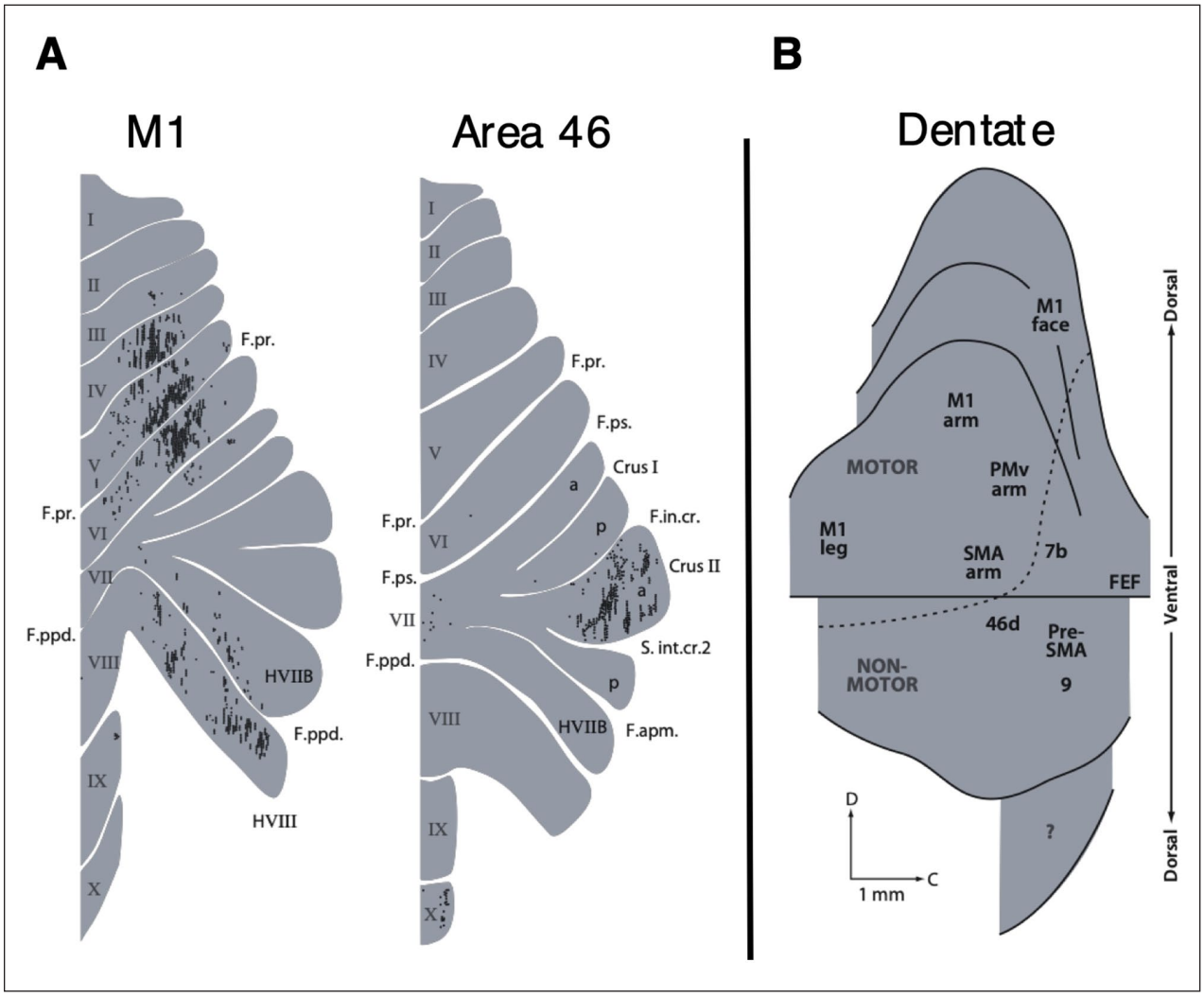


Figure 1. It is well known that the cerebellar nuclei project to multiple thalamic subdivisions, which project to various cortical areas, including prefrontal, premotor, and parietal cortices. Using both retrograde and anterograde virus injections in nonhuman primates, the seminal study by Kelly and Strick (2003) demonstrated the existence of several closed loops synaptic pathways between the cortical injection site, the pontine nuclei, and the cerebellar cortex that are both functionally and anatomically segregated. (A) Kelly and Strick (2003) demonstrated that M1 receives input from Purkinje cells primarily located in lobules IV to VI, whereas the dorsolateral prefrontal cortex (area 46) receives Purkinje cell input from Crus II. Moreover, M1 anterograde injections demonstrated that the cerebellum contains two separate somatotopic body representations (e.g., 1: lobules IV and V; 2: lobule VI), which imaging studies have confirmed. In parallel, area 46 provides inputs areas of the cerebellar cortex (Crus II) that project back to area 46, thus demonstrating the existence of multiple closed-loop circuits characterized as either sensorimotor or cognitive related. (B) Further work from tracing studies also found a rostral to the caudal organization of dentate outputs to the leg, arm, and face representations in M1. Figures adapted from Kelly and Strick (2003).

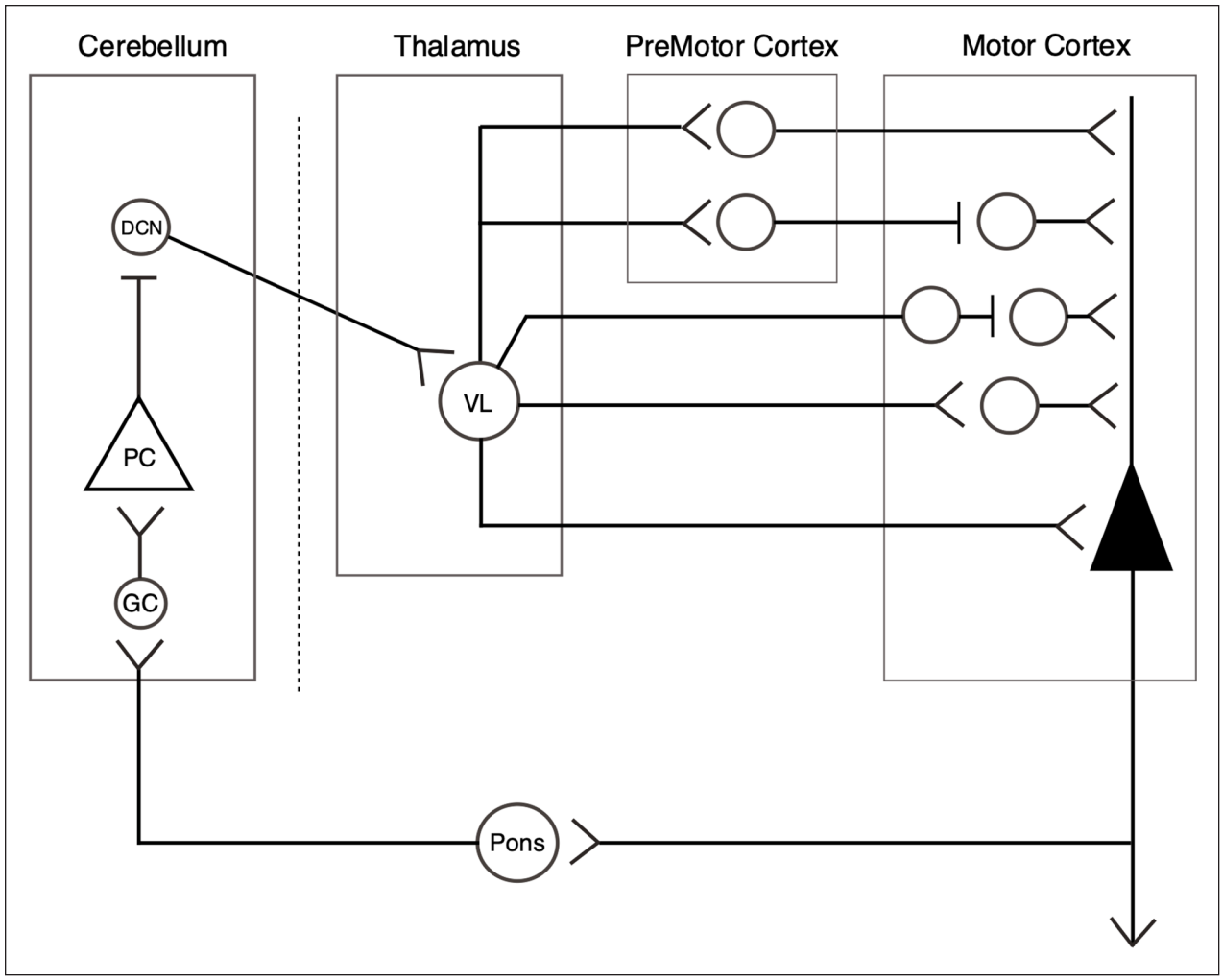


Figure 2. Schematic diagram of the cerebro-cerebellar loop. The cortical-ponto-cerebellar pathway connects the cerebrum with the cerebellum passing through the pons. Activation of the mossy fibers arriving from the pons may excite Purkinje cells (PCs) through the activation of excitatory granule cells (GCs). When a transcranial magnetic stimulation pulse is given over the cerebellum in humans, stimulation is thought to activate inhibitory PCs that synapse with the deep cerebellar nucleus (DCN), suppressing an excitatory projection to the ventrolateral thalamus (VL) and, in turn, suppressing thalamocortical projections. These projections are known to influence both excitatory and inhibitory neurons in the premotor and motor cortex.

spatiotemporal coordination of muscle patterns (Conrad and Brooks 1974; Flament and Hore 1986). Stimulation of cerebellar nuclei effectively reduces synchronicity and rhythmicity in the thalamus (Eelkman Rooda and others 2021; Kros and others 2015), providing potential therapeutic implications for conditions such as epilepsy. These findings highlight the role Purkinje cells and the deep cerebellar nuclei in the precise timing and coordination of cortical areas involved in motor functions.

Oscillatory synchronization or coherence between brain regions has been proposed as a potential indicator of information transfer within a neural network (Deco and Kringelbach 2016). In the context of movement-related behavior, both low-frequency (e.g., beta) and high-frequency (e.g., gamma) oscillations patterns have been observed in cerebellar-cortical pathways, in both healthy individuals and pathologic cases (Courtemanche and others 2003; Fischer and others 2017; Muthuraman and others 2012). Specifically, low-frequency cerebellar oscillations (4–25 Hz) is thought to play a role in the spatiotemporal organization of communication within the cerebellum and between the cerebellum and cerebral cortex (Courtemanche and others 2013). Notably, increased synchronization in this frequency range has been observed between cortical areas and the cerebellum during eyeblink conditioning (Chen and others 2013), suggesting its contribution to an associative learning process. Additionally, coherence between cortical

regions and the cerebellum in beta and gamma frequencies has also been observed during the performance of a precision grip task in monkeys (Soteropoulos and Baker 2006) and freely moving rats (D. Popa and others 2013), suggesting that synchronization may have functional importance in sensorimotor processing. In support of this, work in humans has shown coherent oscillatory activity in beta between the cerebellar thalamic targets to the sensorimotor cortex during tremor (Marsden and others 2000) and to the supplementary motor area during the preparation of self-generated movement (Paradiso and others 2004).

Using Paired Pulse Transcranial Magnetic Stimulation to Quantify Cerebellar-Cortical Strength in the Human Motor System

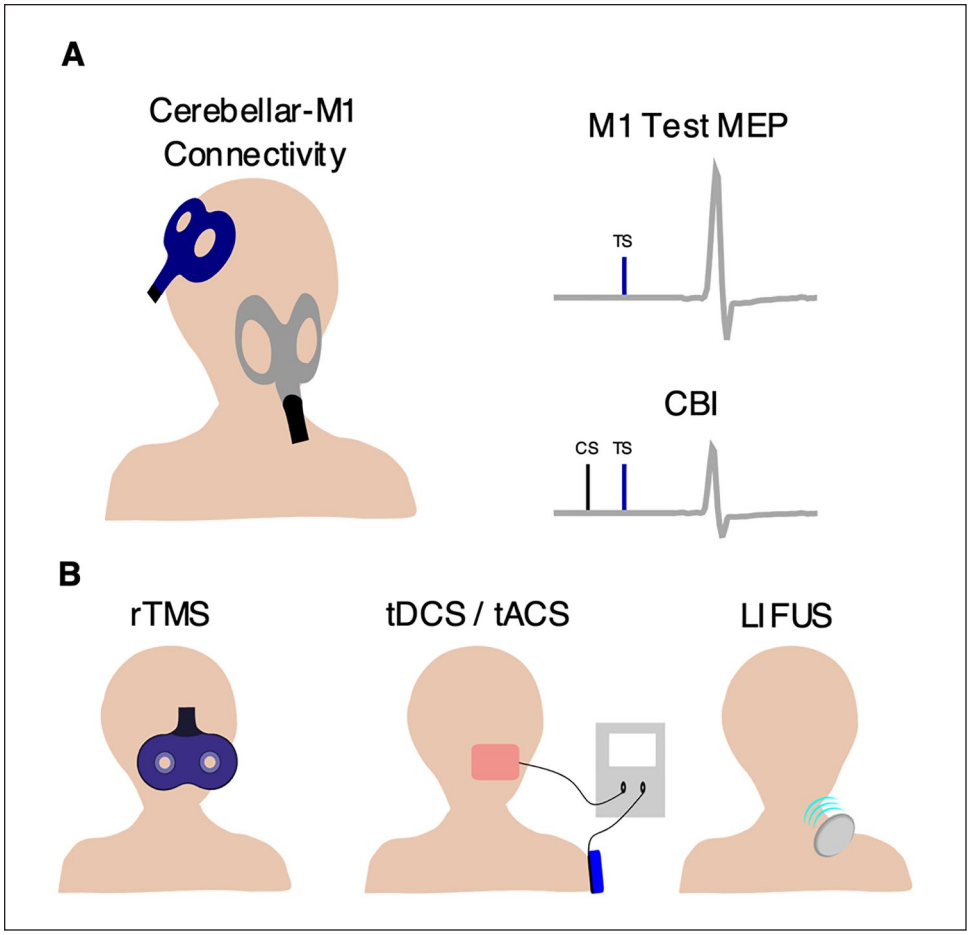
NIBS techniques have emerged as a powerful approach for investigating the physiology and function of the central nervous system (Box 2). Dual-site transcranial magnetic stimulation (TMS) offers a distinctive possibility to assess the connectivity between two brain regions (see Box 2, Figure A). In a well-documented paradigm termed cerebellar-brain inhibition (CBI), a specific coil arrangement is used to investigate the influence of the cerebellum on M1. In this paradigm, a figure-of-eight coil is placed over the left M1 to deliver a test stimulus, while typically a double-cone coil is positioned over the right cerebellum (approximately 3 cm from the inion) to deliver a conditioning stimulus. To reliably achieve CBI, the conditioning cerebellar pulse is delivered 5 to 7 ms before applying a test stimulus over M1 (Ugawa and others 1995). The quantification of CBI is based on comparing the motor-evoked potential (MEP) amplitudes conditioned by cerebellar stimulation (i.e., conditioning + test) with those produced by the test stimulus alone, with 15 pulses for each condition being the minimum for eliciting a reliable CBI measure. The result of this protocol leads to suppressed corticospinal electromyography responses evoked by TMS over contralateral M1; thus, the ratio of CBI is typically seen between values of 0.6 and 0.85 in healthy individuals. Notably, CBI can be observed across multiple muscle representations, including hand, face, and leg (Ginatempo and others 2019; Spampinato and others 2017). While the precise mechanisms underlying this phenomenon are not fully understood, it is believed that cerebellar stimulation leads to the activation of Purkinje cells via parallel fibers. These Purkinje cells subsequently inhibit the deep cerebellar nuclei, which have excitatory connections with M1 through the thalamus (Celnik 2015). Compared to other measures capable of investigating the effective connectivity between the cerebellum and cortical motor areas, such as dynamic causal modeling, TMS applied to two different sites provides distinct advantages critical for understanding the involvement of cerebellar-M1 pathways in specific behaviors. For instance, cerebellar paired-pulse TMS appears to recruit multiple cerebellar-thalamic ways that interact with different excitatory and inhibitory interneuronal populations that synapse to the corticospinal tract (Daskalakis and others 2004; Fong and others 2021; Spampinato and others 2020).

As this measure is thought to represent the strength of connectivity, CBI should be sensitive to aspects of motor control across healthy and pathologic individuals with damage across the cerebellar-thalamo-M1 tract. For example, CBI is altered in neurodegenerative diseases that involve the cerebellum, such as cerebellar ataxia, cortical myoclonus, progressive supranuclear palsy, and Parkinson's disease (Benussi and others 2019; Brusa and others 2014; Carrillo and others 2013; Ni and others 2010; Rocchi and others 2019). Across different patient populations, one may predict a gradient of CBI responses representing the degree of damage along the tract. Ugawa and others (1997) found this to be the case as individuals with mild ataxia showed reduced levels of CBI compared to healthy individuals and nearly no evidence of CBI in patients with severe cases of ataxia or patients with lesions to the motor thalamus. Recent work has also shown a relationship between CBI and motor impairment in spinocerebellar ataxia type 3, in which reduced levels of CBI were correlated with clinical scores of ataxia severity and motor skill performance (Maas and others 2021). Thus, these studies support the claim that CBI reflects the integrity of the cerebellothalamocortical tract.

Lateralization of function is an important organizational feature, with a particular limb being primarily controlled by the contralateral M1 and ipsilateral cerebellum. Studies using TMS have shown that hand preference is linked to asymmetries in activating corticospinal neurons for hand muscles. For instance, the dominant hemisphere has been found to have a more extensive cortical representation for hand muscles (Wassermann and others 1992) and a lower threshold to evoke MEPs (Triggs and others 1994), which may be in part due to the favoring of the dominant hand to perform complex tasks (Flowers 1975). Thus, hemispheric differences in the CBI response may also be expected, with the dominant cerebellar hemisphere exerting more inhibition to the cortex than the nondominant cerebellar hemisphere. Schlerf and others (2015) observed that the CBI responses recorded between the right cerebellum and left M1 in healthy right-handed individuals were more prominent than those from the left cerebellum to the right M1. Interestingly, this corroborates with an impressive large-scale study that used resting-state functional connectivity

Box 2. Studying Cerebellar-M1 Interactions in Humans.

Studies using noninvasive brain stimulation have helped to understand some of the neurophysiologic processes of cerebellar-M1 pathways, including the circuitry, dynamics, and functions underlying action execution and motor learning. Transcranial magnetic stimulation (TMS) uses an electromagnetic coil over the scalp to study the physiology of a targeted brain region and its connections (Box 2, Figure). When a TMS pulse is applied over M1, it elicits a series of waves within the corticospinal tract that summate at the spinal cord and, in turn, generate a motor-evoked potential (MEP) of a targeted muscle (Rothwell 1991). Delivering TMS pulses from two separate coils in quick succession allows experimenters to investigate the connectivity of a targeted brain region that projects to M1. In these paradigms, an initial conditioning stimulus is applied to a specific brain region (e.g., cerebellum) some milliseconds before delivering a suprathreshold stimulus over M1 that evokes an MEP recorded with EMG. Usually, a conditioning stimulus precedes the test pulse, and its effect on M1 excitability (i.e., test stimulus) can be quantified by measuring the combined stimulus MEP. In the case of assessing cerebellar-M1 connectivity, the conditioning pulse is fired between 5 and 7 ms before M1 stimulation, resulting in a smaller MEP when compared to M1 stimulation alone (Ugawa and others 1995). This decrease in MEP amplitude is theorized to be the result of cerebellar TMS activating inhibitory Purkinje cells, which would suppress the excitatory output of deep cerebellar nuclei and their disynaptic connections to the cortex (Manto and others 2021).



Box 2. (A) Cerebellar-thalamic-M1 pathways have been extensively studied with paired-pulse transcranial magnetic stimulation (TMS). If a conditioning stimulus (CS) is delivered to the cerebellum 5 to 7 ms before a test stimulus (TS) over M1, the result is a smaller motor-evoked potential (MEP). This response has been termed cerebellar-M1 inhibition (CBI) and is thought to reflect the strength of connectivity between these regions. (B) Noninvasive brain stimulation techniques that can potentially modulate the activity of cerebellar-thalamic pathways. LIFUS = low-intensity focused ultrasound stimulation; rTMS = repetitive TMS, theta-bust stimulation; tACS = transcranial alternating current stimulation; tDCS = transcranial direct current stimulation.

(continued)

Box 2. (continued)

As cerebellar-M1 connections are vital for the acquisition of new motor skills, this implies that cerebellar-dependent changes in cortical plasticity are one way these connections can influence motor output and memory formation. Targeting the cerebellum with neuromodulation can produce bidirectional and long-lasting changes in M1 plasticity, including alterations to specific excitatory and inhibitory interneurons within M1 (Hamada and others 2014; Koch and others 2008). Interestingly, studies utilizing either transcranial direct stimulation (tDCS) (Hamada and others 2014) or repetitive TMS, theta-bust stimulation (rTMS) (T. Popa and others 2013) over the cerebellum were found to abolish the effects of paired associative stimulation, a protocol to induce long-term potentiation-like plasticity in M1. These findings provide critical evidence that the cerebellum and its interactions with the thalamus are essential in controlling plastic changes in M1 through processing sensory information, overall suggesting that controlling the drive of cerebellar-thalamic connections to modulate M1 may be relevant for motor learning. Furthermore, controlling the output of this pathway with noninvasive techniques (e.g., tDCS, transcranial alternating current stimulation, rTMS, low-intensity focused ultrasound stimulation) could help manipulate M1 plasticity in conditions in which pathologic changes of M1 plasticity generate motor dysfunction.

MRI to explore the interactions between the cerebellum and M1. This study found evidence for slightly more voxels connecting the left M1 with the right cerebellum than connecting the right M1 with the left cerebellum (Buckner and others 2011). The more robust connectivity in the dominant hemisphere likely develops from the preferential use of the right hand. This would suggest that this effector has more access to sensory information and more sensitive feedback control critical for executing accurate movements (Flowers 1975). Thus, one might expect a relationship between a kinematic measure of movement precision and strength of cerebellar-M1 connectivity in healthy individuals, given the link between reduced CBI and clinical ataxia scores in cerebellar ataxic patients. Moreover, in the same study by Schlerf and others, the authors found a robust relationship between CBI and the variability of arm-reaching amplitudes, where stronger CBI was associated with greater precision (Schlerf and others 2015). While it is tempting to suggest that changes in CBI levels over the course of training may reflect alterations to an internal forward model, this was not directly tested in the study. Nevertheless, it is interesting that this relationship between precision and CBI was also observed in the corroboration of an independent data set.

Changes in CBI are also expected during motor preparation as nonhuman primates show a temporal and somatotopic specific effect of Purkinje cell activity that becomes suppressed 20 to 60 ms before movement execution (Ishikawa and others 2014). Thus, the expectation would be that CBI should reduce its inhibition over M1 (i.e., an indicator of more significant deep cerebellar activity) right before executing an action. Spampinato and others (2017) investigated this idea in humans by asking whether the preparation of a simple movement would produce changes in CBI. In this experiment, participants engaged in a simple reaction time task, performing either finger movements or foot dorsiflexion movements based on visual cues. The researchers assessed changes in CBI by applying TMS at different time intervals before movement onset, which was tuned to each subject's reaction time to respond to the cue. CBI was measured for both hand and foot muscles. The authors found that CBI was reduced only for the effector involved in motor preparation, an effect that was explicitly found around 20 to 30 ms before executing the action. This demonstrates that modulation of CBI responses in behavioral contexts follows a somatotopy-specific mechanism.

It is also clear that cerebellar-thalamo-M1 interactions play an essential role in developing and modifying motor policies during motor skill learning (Spampinato and Celnik 2021). Neurophysiologic and clinical studies consider the cerebellum as the locus for developing internal forward models (Honda and others 2018; Izawa and others 2012) or internal representations capable of predicting the future sensorimotor state given the goal of the movement, the efferent copy of the motor command, and the current state. In motor adaptation tasks, these models play an important role in modifying motor commands to achieve desired movements in novel situations by quickly reducing movement errors imposed by a perturbation. Interestingly, CBI reduces early in adapting to a perturbation when large predictable errors occur (Schlerf and others 2012; Uehara and others 2018), likely reflecting the accumulation of new neural and behavioral patterns. Reductions in CBI have also been found predominantly early on in skill-learning tasks that require individuals to control a novel tool in a complex environment (Spampinato and Celnik 2017, 2018) and in sequence learning (Spampinato and Celnik 2018; Torriero and others 2011), which is more likely to recruit an extensive brain network of areas (e.g., PM and supplementary motor areas) to optimize performance. The release of CBI after learning has been proposed to indicate long-term depression of Purkinje cells (Jayaram and others 2011), as described in models of motor learning (for review, see Spampinato and Celnik 2021). Thus, changes in CBI may reflect the physiologic contributions of the cerebellum associated with error-driven learning.

Can We Enhance Cerebellar-Cerebral Connections with NIBS?

Stimulating the cerebellum with neuromodulatory non-invasive brain stimulation techniques, like transcranial direct current stimulation (tDCS), has emerged as a strategy to enhance connectivity between the cerebellum and M1. A seminal study by Galea and others (2009) demonstrated that anodal cerebellar tDCS elicited a stronger CBI effect, whereas cathodal tDCS resulted in a reduced CBI. This polarity-specific effect of stimulation has been interpreted as tDCS influencing Purkinje cell activity, with anodal increasing and cathodal decreasing their excitability. From these results, several studies have used the logic that by modulating the activity of these cells and the connectivity between the cerebellum and M1, stimulation can potentially optimize the cerebellum's ability to integrate feedback signals involved in error correction and motor skill refinement, thus facilitating the acquisition and retention of motor skills. Moreover, recent studies have suggested that neuromodulation of the cerebellum using tDCS could represent a therapeutic strategy for the management of cerebellar disorders (Benussi and others 2015, 2017, 2018, 2021; Grimaldi and Manto 2013). However, the idea that anodal tDCS should increase CBI has not been replicated in other studies in which anodal tDCS may instead reduce the effect of CBI (Batsikadze and others 2019; Doeltgen and others 2016) or produce variable responses (Herzog and others 2022). These discrepancies may partially explain why anodal tDCS has been found to enhance learning rates of cerebellar-dependent visuomotor learning in some studies (Galea and others 2011), while in other studies, it has been observed to evoke no measurable behavioral changes (Jalali and others 2017).

The divergent physiologic and behavioral outcomes observed in studies using tDCS could be attributed to factors such as different placements of the reference electrode and individual variations in electric field distribution due to the complex anatomy of the cerebellum (e.g., brain folding, skull thickness). As such, current research has focused on increasing the efficacy of cerebellar tDCS by improving the temporal distribution of stimulation (Weightman and others 2023), focality (Reckow and others 2018), and montage setup (Gomez-Tames and others 2019), but interpreting the results of studies using neuromodulatory techniques targeting should be processed with caution. Future animal work or systematic studies using imaging techniques are needed to understand better the underlying mechanisms and neurophysiologic impact of cerebellar tDCS. For example, promising animal work using high-density neuro pixel recordings has shown that the heterogeneous effects of tDCS on Purkinje cell activity can be explained by the somatodendritic orientation of neurons relative to the electric field (Sánchez-León and others 2023). This study highlights the importance of considering neuronal orientation and morphology of Purkinje cells when using tDCS. Considering these factors is essential for improving the predictive power of computational models for tDCS and optimizing desired effects in human studies.

Progressing Our Knowledge of CB-M1 Interactions: Directional TMS, TMS-EEG, and Low-Intensity Focused Ultrasound Stimulation

Directional TMS. TMS is capable of recruiting different interneuronal networks that feed onto the corticospinal tract by applying different current directions over the scalp. At relatively low stimulus intensity, posterior-to-anterior (PA) currents over M1 predominantly elicit early indirect (I) waves in the brain, likely representing the activation of layer II and III elements that have monosynaptic and disynaptic connections to pyramidal tract neurons. On the other hand, anterior-to-posterior (AP) currents tend to recruit late I-waves that are less synchronized and smaller in size with polysynaptic origins. Modeling work has suggested that AP currents stimulate axon terminals more anterior to the crown of the precentral gyrus when compared to PA currents (Weightman and others 2023), suggesting that AP-TMS likely activates axons arriving from the PM cortex, reflecting a different population of neurons that provide inputs to corticospinal neurons. An important implication of these findings is that directional TMS allows researchers to investigate whether a specific population of neurons is sensitive to a particular behavior, as seen in simple reaction time tasks (Hannah and others 2018; Ibáñez and others 2020). This also suggests that the cerebellum likely has specific responses to these distinct cortical neuronal populations due to the extensive connectivity between the cerebellum and the PM and M1.

Hamada and others (2012) were the first to use directional TMS to investigate whether PA- and AP-MEPs showed dramatical modulation after individuals were given excitatory anodal tDCS to the cerebellum. The authors found that cerebellar tDCS specifically reduced the responses of AP-MEPs during muscle contraction, suggesting that neuronal networks recruited with AP-TMS current directions likely have some dependence on cerebellar activity (Hamada and others 2012). A follow-up study showed that repetitive stimulation to AP-sensitive neurons selectively altered participants' ability to adapt to visuomotor rotations that highly involve the cerebellum (Hamada and others 2014). While this suggests the AP network is more sensitive to cerebellar activity, these results only provide indirect evidence as connectivity (e.g., CBI) was not assessed.

This inspired recent work by Spampinato and others (2020) to conduct investigations to disentangle two separate cerebellar-cerebral pathways with cerebellar stimulation and directional M1-TMS. First, the authors demonstrated that CBI was evident with both TMS current directions, albeit at interstimulus intervals between pulses. Strong PA-CBI responses were found at 5 ms, while strong AP-CBI responses were realized at 7 ms (Figure 3A). In subsequent experiments, the authors demonstrated that these distinct cerebellar-cortical pathways were selectively modulated in response to physiologic plasticity and diverse motor learning tasks (Figure 3B,C). Specifically, PA-CBI and AP-CBI were engaged during the early and late stages of motor skill learning, respectively, which led the authors to suggest that these distinct pathways have different roles in learning. However, future experiments will need to investigate further the reliability of evoking these responses and why these two separate circuits behave differently during motor learning.

Future work should also consider assessing these pathways in both healthy older adults and individuals with pathologic conditions. Recent work has revealed age-related effects at distinct PA-CBI intervals, with older healthy adults showing stronger CBI than young adults (Mooney and others 2022). The underlying reasons for this age-related strengthening are not fully understood, but one possibility is that increased cerebellar excitability may serve as a compensatory mechanism for structural and functional decline in intraneuronal PM and M1 circuits (Seidler and others 2010). Such compensatory mechanisms may play a role in age-related deficits in motor control impairments (Mooney and others 2017). Future investigations should also explore whether similar strengthening effects are observed with AP-CBI, as these findings could hold implications for the application of directional TMS for patient studies.

Insights into Oscillatory Activity with Distinct NIBS Approaches

TMS-EEG. Although measures conducted with neuroimaging have provided tremendous insights into large-scale network connectivity, these techniques suffer from poor temporal resolution (>1 second). Thus, they cannot assess the fast cortical dynamics occurring within and between interconnected networks. On the other hand, TMS can provide valuable insights into the cerebellar-M1 circuits with high temporal resolution using MEPs. However, the main problem with this approach is that MEPs reflect the excitability of the whole corticospinal tract, including the spinal cord; thus, they cannot be considered an exclusive index of cortical activity. In addition, MEPs can be evocable only from M1 stimulation. In this context, the combined use of TMS-EEG represents a novel approach optimized to investigate how cerebellar stimulation may influence brain states and their dynamics at a network level (Figure 4). Indeed, EEG can record the postsynaptic potentials generated by the TMS-evoked neuronal depolarization, termed TEPs, which provide information on the neurophysiologic state of the stimulated area and its connections all over the cortex. This is important since, through this approach, it is possible to assess the effect of cerebellar TMS, even in nonmotor cortical areas, by analyzing the TMS-evoked EEG response in the temporal, spatial, and frequency domain. For instance, time-frequency analysis of the TMS-evoked EEG response to a single-pulse TMS over M1 reveals sustained oscillations in the beta and gamma range (Casula and others 2016, 2022; Koch and others 2020).

It is critical to note that TMS-EEG poses some critical challenges in terms of dissociating biologically relevant from stimulus artifacts. Indeed, stimulation over areas such as M1 and the cerebellum will contaminate EEG signals by direct scalp muscle activation, requiring specialized data cleaning techniques (Bertazzoli and others 2021; Hernandez-Pavon and others 2022). Moreover, TMS coils produce a high-pitched sound and cause direct activation of cutaneous fibers surrounding the target region of stimulation, illustrating the importance of integrating appropriate control methods that diminish undesirable artifacts. While auditory responses to TMS can be suppressed with noise masking (e.g., ear-defenders) and somatosensory responses tend to affect responses between 100 and 200 ms following the TMS pulse (Leodori and others 2022; Rocchi and others 2021), there is limited investigation and no consensus as to how this might influence EEG responses following cerebellar stimulation.

EEG Responses Induced by Cerebellar TMS

Recent studies have explored the integration of cerebellar TMS with EEG, with initial findings indicating the feasibility of recording TEPs and oscillatory activity following cerebellar stimulation. Fernandez and others (2021) were the first to use a control condition that used electrical stimulation to mimic the sensory effects of stimulating the cerebellum with a double-cone coil. While this study was able to find cerebellar evoked TEPs at early latencies (e.g., <50 ms) that were different from control conditions, later cerebellar TEP components showed a strong relationship with responses to somatosensory control conditions. Support for early TEP components containing cerebellar-thalamo-cortical activation was also found in a study by Gassmann and others (2022), which used a small figure-of-eight coil to stimulate the cerebellum and compared the effects of cerebellar stimulation with various control conditions. This included applying

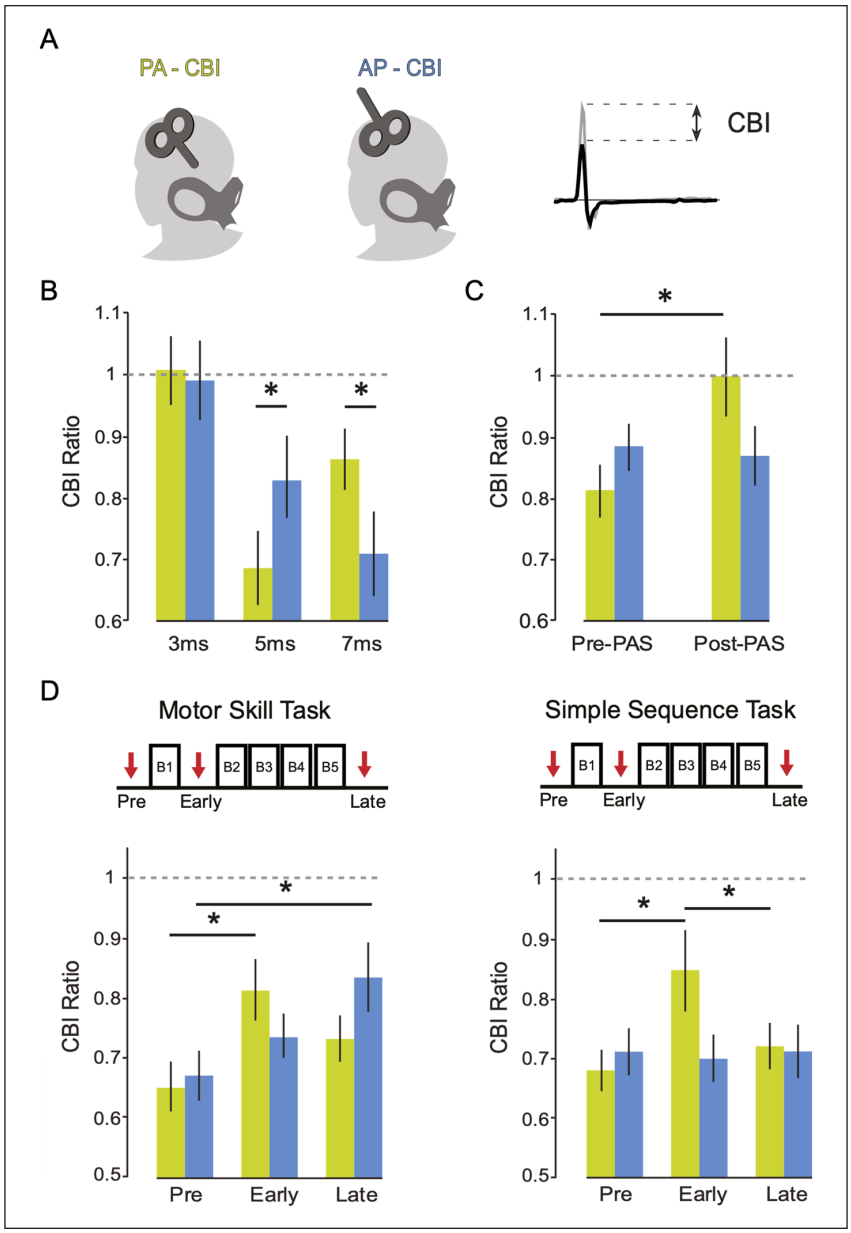


Figure 3. Different transcranial magnetic stimulation (TMS) current directions over the precentral gyrus allow an intriguing way to probe how different subsets of neurons contribute to overall cortical excitability. (A) One can combine directional TMS with cerebellar stimulation to assess how these subsets of interneurons respond to cerebellar inputs at rest and following motor actions. Cerebellar-brain inhibition (CBI) refers to the ratio of the motor-evoked potential (MEP) amplitudes that occur following the conditioned test stimulus (black MEP) that are compared to MEP amplitudes produced after an unconditioned test stimulus applied only to M1 (gray MEP). (B) In the first experiment, Spampinato and others (2020) varied the interstimulus intervals between cerebellar and cortical pulses (3, 5, 7 ms). They found that CBI elicited with posterior-to-anterior (PA) currents was strongest at an interval of 5 ms, whereas CBI with anterior-to-posterior (AP) currents produced a pronounced effect at 7 ms. The control condition of 3 ms did not elicit CBI for either direction as this interval is too short to reveal cerebellar effects on the cortex. (C) The difference in the time course of CBI produced by directional TMS could be that AP-TMS has a delayed onset in AP-MEPs, usually 2 to 3 ms later than PA-MEPs. To resolve this issue, the authors tested CBI with both current directions following paired associative stimulation of ulnar nerve stimulation and PA-TMS pulses, a protocol used to induce cortical plasticity over M1. Interestingly, this protocol reduced the PA-CBI effect but did not produce changes in CBI tested with AP currents, which argues for distinct processing of cerebellar inputs to the cortex. (D) In a final experiment, the authors measured PA- and AP-CBI at different stages of two distinct motor learning tasks: (1) motor skill learning task that involves error correction mechanisms and automatization and (2) a simple motor sequence task. Specifically, PA-CBI changed only early during motor sequence learning and a skill task where individuals had to learn a new sensorimotor mapping. On the other hand, AP-CBI changed only late in motor skill learning when individuals had significant exposure to the sensorimotor map.

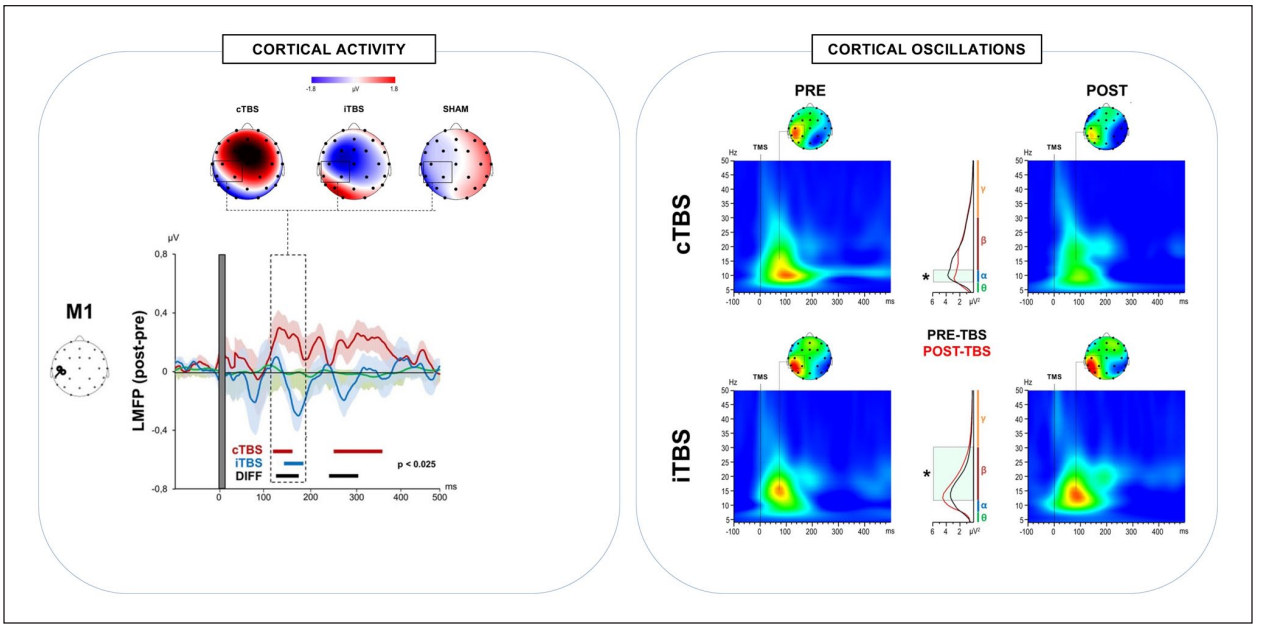


Figure 4. While motor-evoked potential (MEP) modulation can be affected by changes at a subcortical level and is limited to the study of M1, transcranial magnetic stimulation (TMS)–evoked cortical activity recorded with EEG has the potential to record data without the influence of noncortical confounds (Rocchi and others 2021; Taylor and others 2008). An advantage of the TMS-EEG is that it can be recorded from local and distant electrodes. In other words, a TMS pulse can probe the propagation of cortical signals in time and space across brain regions (Massimini and others 2009; Casula and others 2020). This may allow researchers to assess how changes in brain state (i.e., neuromodulation of the cerebellum) may affect activity affect neural activity in terms of natural cortical oscillatory patterns, cortical excitability, and cortical connectivity of a given cortical area or network (Thut and Miniussi 2009). In this figure, modified from Casula and others (2016), the authors showed how cortical activity, as measured with local mean field power (LMFP) (left panel) and cortical oscillations (right panel), changed after intermittent (iTBS) or continuous theta-burst stimulation (cTBS) over the cerebellum. Specifically, opposite effects on cortical activity (left panel) can be observable after cerebellar iTBS (blue line) and cTBS (red line), whereas sham TBS (green line) did not produce any change. Such bidirectional changes are also observable in TMS-evoked cortical oscillations (right panel).

TMS to the occipital cortex and a sham condition that combined TMS with electrical stimulation of the right shoulder (Gassmann and others 2022). Here, the authors found that cerebellar TMS increased early TEP components over prefrontal and parietal areas and increased contralateral prefrontal beta-power compared to control conditions. Late-latency TEPs (60–70 ms after the TMS pulse) of cerebellar TMS in this study also were found to overlap with control conditions, highlighting that late components of cerebellar TMS-EEG may be dominated by sensory contamination. However, in a recent study, Fong and others (2021) demonstrated evidence that late cerebellar TEP components could be distinguished from those caused by auditory and sensory artifacts. Specifically, two late TEP components (positive peak at 80 ms: P80; negative peak at 100 ms: N100) could be isolated from control conditions and were found to be reproducible across two independent groups of subjects. Of particular interest, the authors also found evidence that visuomotor learning was able to modulate the amplitude of the cerebellar TEP at P80, in which changes in P80 were found to be correlated with the amount individuals learned. However, further investigations focusing on isolating the contribution of direct cerebellar stimulation from that of sensory input are needed before any strong conclusions can be made with these findings.

Using Cortical TMS-EEG to Assess Cerebellar Neuromodulation

In a seminal study conducted by Casula and others (2016), the authors investigated whether oscillatory activity recorded in M1 and posterior parietal cortex were modulated following the application of continuous (cTBS) and intermittent theta-burst stimulation (iTBS) of the cerebellum, which has previously been shown to induce, respectively, LTD-like and LTP-like after-effects, respectively, in the contralateral M1 (Koch and others 2008). Here, the authors found that cerebellar iTBS increased beta oscillations and produced inhibitory effects on M1 cortical activation. On the other hand, cTBS decreased alpha oscillations and increased M1 cortical activity following

stimulation (Casula and others 2016). Interestingly, similar modulations of cortical activity were observable over the posterior parietal cortex (PPC), demonstrating one of the strong points of TMS-EEG: physiologic information is not restricted to M1, like the MEP, thus allowing for the comparison of responses across multiple brain regions. In a subsequent study conducted by Rocchi and colleagues (2022), the authors used both TMS-EMG (i.e., MEPs) and TMS-EEG-based measures (i.e., TEPs, TMS-evoked oscillations) to test the influence of cerebellar modulation over the contralateral M1. Here, the authors observed that cerebellar neuromodulation influences TMS-EMG and TMS-EEG–based measures; however, the latter showed higher test-retest repeatability. Moreover, previous research has demonstrated that cerebellar continuous theta-burst stimulation (cTBS) enhances long-interval cortical inhibition, associated with GABA(B)ergic activity, while cerebellar intermittent theta-burst stimulation (iTBS) reduces it (Koch and others 2008). These findings suggest that modulation of cerebellar output is likely to induce changes in the balance between excitation and inhibition within the cerebellar-thalamocortical pathway, consequently affecting the natural oscillatory frequency of M1 (Harrington and Hammond-Tooke 2015). In this regard, the TMS-EEG approach provides an additional advantage: indeed, it is known that the TMS-evoked EEG potential (i.e., TEP) reflects cortical activation related to different neurotransmitters. In specific, early components within the first 30 ms are related to local excitability of the stimulated area, whereas late components reflect more complex corticocortical interactions related to GABA(A)ergic (30–65 ms) and GABA(B)ergic (65–160 ms) neurotransmission, as revealed by pharmacologic (Cash and others 2017; Kähkönen and Wilenius 2007; Premoli and others 2014) and electrophysiologic studies (Ferreri and others 2011; Fitzgerald and others 2009).

It is also critical to consider that cerebellar TBS is applied over the posterior cerebellum (i.e., lobules VII–VIII), which are regions that constitute the anatomic substrate of both the cognitive and sensorimotor cerebellum (Stoodley and others 2012). These protocols have been used to modulate cerebellar-thalamocortical tract activity to modulate learning tasks (Arasanz and others 2012; Hoffland and others 2012; Koch and others 2020; Mirdamadi and Block 2021). Interestingly, a recent study showed that cerebellar iTBS accelerated visuomotor adaptation learning by speeding up error reduction to a novel perturbation (Koch and others 2020). The authors also demonstrated that cerebellar iTBS resulted in an increase in TMS evoked-cortical activity and a decrease in cortical oscillations in the theta and beta frequency bands when tested after the learning phase. The functional reduction in the cortical oscillations evoked by TMS has been interpreted to reflect the disengagement of nonrelevant brain activity that permits one to perform the task more efficiently. As beta oscillations have been associated with the state of motor control (Baker and others 1997; Engel and Fries 2010) and GABAergic activity (Muthuraman and others 2012), the modulation of beta with TBS may represent an essential physiologic mechanism that underlies learning via changes in cerebellar-thalamocortical tract activity. Together, these data show the utility of using TMS-EEG to investigate changes in cerebellar-cortical oscillatory activity that occur when plasticity occurs due to artificial stimulation or motor learning.

Transcranial Alternating Current Stimulation (tACS)

Another strategy to study oscillatory activity linked to cerebellar-thalamocortical connectivity has emerged by applying noninvasive transcranial alternating current stimulation (tACS) at different frequencies, with the idea that stimulation may entrain and modulate the endogenous oscillatory activity of specific cerebellar interneurons. Using an in vivo rodent model and extracellular recordings, Asan and others (2020) demonstrated that simple spike activity of Purkinje cells can be entrained by alternating current electric fields, where increasing the stimulation frequency from 2 to 40 Hz enhanced the phase-locking of Purkine cell spike timing while further increasing it to 100 Hz led to an overall increase in Purkinje cell firing frequency while maintaining the phase-locking pattern. While this study provides evidence supporting the entrainment theory during stimulation, further animal work is needed to understand whether different stimulation parameters (i.e., current intensity, stimulation time) can optimize entrainment and whether other neuronal populations in the cerebellum be selectivity entrained with different tACS frequencies. Moreover, it remains unclear whether cerebellar tACS can induce long-lasting after-effects that might depend on mechanisms independent of entrainment, like spike-timing dependent plasticity.

In humans, Naro and others (2016, 2017) first investigated the effects of short-lasting (1 minute) cerebellar tACS applied at different frequencies (10, 50, 300 Hz). The authors found that 50 Hz tACS weakened CBI, while 300 Hz tACS strengthened CBI and produced motor surround inhibition in upper limb muscles, overall demonstrating that tACS over the cerebellum is safe and can produce frequency-dependent effects on CBI. More recently, another study using a longer stimulation duration (15 minutes) also showed a frequency-dependent CBI modulation (Spampinato and others 2021). In this study, 50 Hz tACS had no effect CBI during or after stimulation, whereas 5 Hz stimulation strengthened CBI

during stimulation (online effect only). Of note, differences in the response to 50 Hz between these studies are likely due to distinct methodologic variations, such as stimulation dose (Naro, 1 mA; Spampinato, 2 mA) and duration (Naro, 1 minute; Spampinato, 15 minutes); thus, further physiologic studies testing different stimulation parameters in humans are needed to understand the effects of cerebellar tACS.

When considering how cerebellar tACS may influence behavior, thus far, gamma stimulation has been the most extensively studied. Although initial reports showed gamma tACS facilitates the performance of simple motor tasks (Miyaguchi and others 2019; Naro and others 2016), its influence on motor skill learning remains unclear, as stimulation was found in one study to impede learning (Giustiniani and others 2021) and in another had no effects (Wessel and others 2020). Moreover, a few studies have used a dual-site approach by simultaneously targeting the cerebellum and M1 with tACS (Miyaguchi and others 2018, 2019; Schubert and others 2021). In one study, simultaneous stimulation of the cerebellum and M1 at 70 Hz improved visuomotor learning more effectively than stimulating solely either the cerebellum or M1 (Miyaguchi and others 2018). Interestingly, stimulating the cerebellum and M1 in antiphase (e.g., 180-degree phase difference between the two targets) was the stimulation condition that lowered individuals' performance errors when compared to sham. Finally, a recent study used cerebellar tACS to investigate the role of alpha oscillations during a serial reaction time task. Using EEG without tACS stimulation, the authors revealed a decrease in alpha power over left PM and sensorimotor cortices and a decrease in alpha coherence between these areas and the left cerebellar crus I. In a follow-up experiment, they applied 10 Hz tACS over the left M1 and right cerebellum during task performance and found that stimulation impaired the learning rate (Schubert and others 2021). This effect was accompanied by an increase in alpha coherence in the premotor-cerebellar network and elevated alpha power in the left PM, leading the authors to suggest that functional decoupling in the alpha band within the cortico-cerebellar network may underlie motor sequence learning. Although further research using different frequencies and animal models is necessary to deepen our understanding of stimulation effects, tACS holds great potential for studying and modulating oscillatory activity related to the cerebellum and its connections to the cortex.

Cerebellar-Thalamocortical Pathways and Neurologic Disease

Stroke. Recovery from a stroke requires motor learning: either relearning to move proficiently or learning to compensate of lasting movement deficits. As mentioned previously, motor learning is a complex process that relies heavily on the cerebellum and, moreover, is often spared in cerebral stroke, presenting an opportunity to harness its capacity for motor learning to enhance functional recovery poststroke. Human imagining findings have shown the importance of the cerebellum in the functional reorganization of the motor network following stroke, where activity in the contralesional cerebellum positively correlates with recovery in stroke patients (Luft and others 2008). This is supported by animal models of stroke, which demonstrated that stimulation of deep cerebellar nucleus showed significant improvement in motor function poststoke when compared to sham stimulation (Machado and others 2013). As such, activating cerebellar-cortical circuits with noninvasive brain stimulation has also emerged as an attractive strategy to promote mechanisms of motor learning and recovery of the affected motor cortical areas.

Bonnì and others (2014) administered repetitive cerebellar iTBS in human stroke patients to facilitate cerebello-cortical inputs to the M1, thereby enhancing the cortical excitability necessary for generating proper motor output. They found evidence of cortical reorganization, as patients showed a reduced CBI and modulation of intracortical circuits in M1 following stimulation. The same authors conducted a three-week clinical trial study, which integrated cerebellar TBS with traditional physical therapy (Koch and others 2019) (Figure 5). The authors demonstrated significant improvements in gait recovery and balance control following the three-week treatment. These improvements were associated with increased cortical activity over the M1 and the PPC assessed with TMS-EEG. Specifically, patients who exhibited better gait recovery and balance control displayed stronger cortical reactivity in PPC. The authors argued that the induction of cerebellar plasticity induced changes in the neural activity of the contralateral PPC, by modulating GABAergic activity at the thalamic or cortical level. In this regard, previous work has suggested that cerebellar iTBS affects specific sets of interneurons dependent on GABAergic activity (Koch and others 2008), which plays an important role in driving mechanisms of brain plasticity during poststroke recovery (Clarkson and others 2010). Thus, the LTP-like plasticity induced by iTBS may have reinforced cerebellar-thalamo-cortical interactions cycling at a low-frequency range that facilitate spatial-motor learning, likely contributing to better clinical improvement. While these results provide an encouraging outlook for future translational research, multicenter trials involving a heterogeneous group of stroke patients with different types and severity of motor disabilities are needed to evaluate the impact of this intervention.

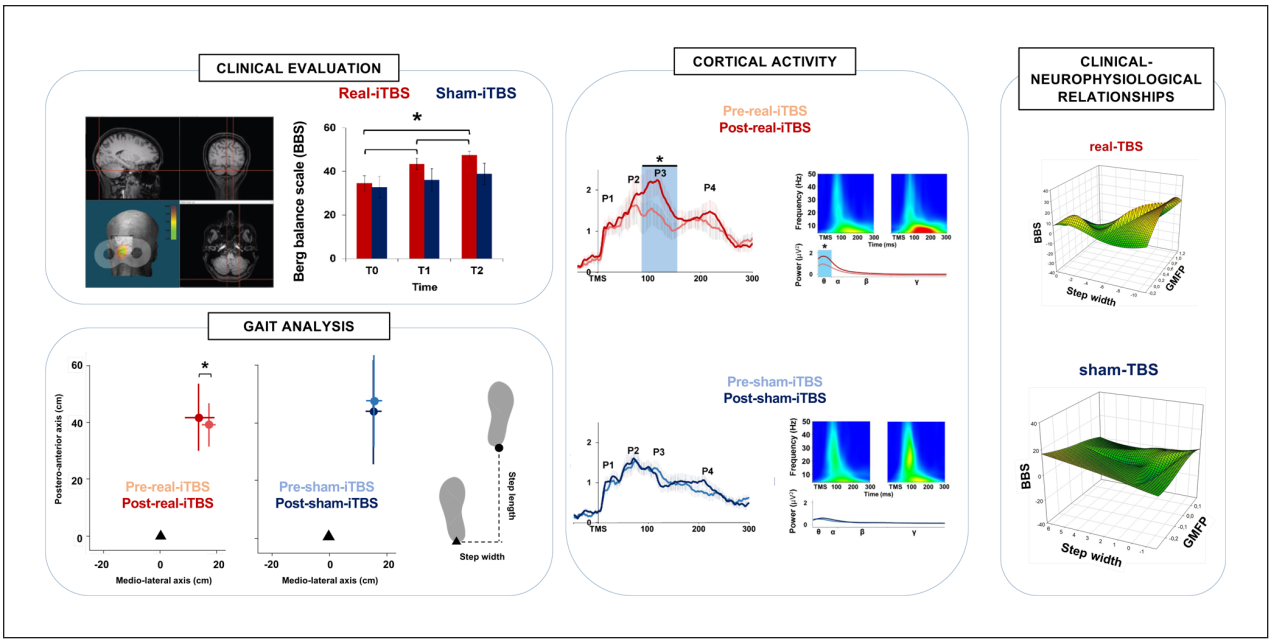


Figure 5. A study by Koch and colleagues investigated whether 3 weeks of daily cerebellar intermittent theta-burst stimulation (iTBS) combined with standard physical therapy could improve the balance and gait function of stroke patients in comparison to sham stimulation. They performed clinical evaluations, gait analysis. and transcranial magnetic stimulation (TMS)–EEG recordings at baseline (T0) and after three weeks of treatment (T1). Clinical evaluations were also performed three weeks after the end of treatment (T2). Left panel: They found that patients who received cerebellar iTBS showed significant improvements in clinical measures of balance (i.e., Berg-Balance Scale [BBS]) and reduced step widths in gait analysis measures (red). Middle panel: In their neurophysiologic measures, they found that the group that received cerebellar iTBS also showed significant increases in cortical activity, as measured with the global mean field power (GMFP) and in cortical oscillations after single-pulse TMS of the posterior-parietal cortex. No changes were observable in patients receiving sham cerebellar iTBS. Of note, the y-axis of the GMFP plots depicts the time in ms following the TMS pulse (TMS = moment TMS was delivered), and the time window of spectral analysis was averaged from 20 to 300 ms following the TMS pulse. Right panel: Correlation analysis demonstrated that patients with the highest recovery in clinical scores (i.e., BBS) were the ones who reduced their step width the most and produced a greater increase in the TMS-evoked cortical activity (i.e., GMFP).

Tremors: essential tremor and Parkinson's disease. Electrophysiologic and imaging studies have also suggested these pathways play an important role in essential tremor (ET) and Parkinson's disease (PD) tremor (Molnar and others 2005; Nicoletti and others 2015; Pinto and others 2003), with the physiologic underpinning, thought to be related to abnormal oscillatory activity in the cerebellum and downstream cerebellar-thalamocortical pathway (Pan and others 2020). Both types of tremors can be effectively suppressed by deep brain stimulation to thalamic areas that receive cerebellar input (Schuurman and others 2000), and abnormal climbing fiber-Purkinje connectivity in ET (Lin and others 2014) and PD (Louis and others 2009) has also been identified, indicating cerebellar dysfunction. Several noninvasive techniques targeting the cerebellum have been administered to patients to reduce tremor (Manto and others 2021). Particularly, cerebellar tACS holds a promising future in this regard, given its potential to interfere with ongoing oscillatory activity and modulate functional connectivity. Early evidence showed that cerebellar tACS could entrain tremors in ET and PD patients to a set stimulation frequency (Brittain and others 2013; Schreglmann and others 2020).

Interestingly, when stimulation is phase-locked to tremor movements, the tremor amplitude is dramatically reduced, a finding seen in both essential tremor patients (Schreglmann and others 2020) and dystonic patients (Nieuwhof and others 2022). While this provides causal evidence for the involvement of the cerebellar-thalamocortical circuit in rhythmic tremors, using phase-specific stimulation to improve treatment in patients will require extensive sample-sized, well-powered, personalized studies. Here, concurrent EEG or magnetoencephalography can be used to record responses to cerebellar responses to stimulation, thus providing a manner to investigate cerebellar physiology linked to tremors.

Limitations and Future Perspectives

Based on the current knowledge reviewed here, noninvasive brain stimulation targeting the cerebellum emerges as a valuable tool for assessing the excitability of cerebellar

projections to M1 and holds promise for therapeutic purposes. However, several outstanding questions require extensive interdisciplinary research efforts. Future studies should focus on elucidating the physiologic and pathophysiologic effects of cerebellar stimulation on motor and cognitive behaviors, as the underlying mechanisms remain poorly understood. A major challenge lies in precisely determining the specific neural structures stimulated by techniques like TMS and tDCS/tACS, emphasizing the need for a better understanding of their effects at the level of single neurons and cortical neural circuits. Even with the aid of neuronavigation, selectively stimulating motor regions of the cerebellum without involving cognitive areas presents difficulties (Hardwick and others 2014).

Advancements in this field will depend on refining realistic biophysical models that integrate accurate field calculations with the influence of the induced electric field on various neuronal populations. This progress should be accompanied by systematic testing and comparisons between detailed biophysical models and empirical measurements in humans. Moreover, direct validation through single-cell recordings in animal models will play a crucial role in validating and fine-tuning these models. By combining these approaches, a deeper understanding of the complex interactions among stimulation parameters, electric fields, and neural responses can be achieved, leading to more effective and targeted interventions.

One promising technique for achieving selective targeting within the cerebellum is MRI-guided cerebellar low-intensity transcranial ultrasound (LIFUS), which has shown the potential to reversibly modulate neuronal activity on the scale of millimeters to both superficial and subcortical. While early findings in rodents using LIFUS have demonstrated its ability to entrain Purkinje cell activity (Asan and others 2021), future work will need to explore whether this technique can stimulate specific cerebellar components, including the cerebellar cortex (such as Purkinje cells and interneurons), cerebellar nuclei, and the inferior olivary complex.

Last, for clinical studies exploring the therapeutic potential of cerebellar noninvasive brain stimulation, rigorous methodology is crucial. Incorporating double-blinding techniques and conducting larger randomized controlled trials will enhance the reliability and generalizability of the results. Long-term follow-up assessments using multimodal approaches such as fMRI and EEG can provide valuable insights into identifying predictors of clinical response. Monitoring TMS-EEG throughout clinical trials and follow-ups can serve as a means to assess disease progression and evaluate the effectiveness of interventions. Establishing functional target engagement and neurophysiologic biomarkers, as well as understanding interindividual variability in treatment response, is pivotal for developing personalized stimulation protocols. Overall, addressing these challenges and gaps in knowledge will pave the way for further advancements in the field of cerebellar noninvasive brain stimulation, leading to improved therapeutic strategies and a deeper understanding of cerebellar function and its modulation.

Summary

Constant crosstalk between the cerebellum and cortical areas is necessary for regulating the onset, execution, and learning of a broad range of behaviors. Here, we have summarized findings from animal and human studies that map out multiple pathways originating from the cerebellum, influencing the activity of distinct subthalamic regions and cortical circuits. Emerging technology in humans (e.g., directional TMS, TMS-EEG) has helped uncover the functional roles of these pathways in motor behaviors, providing a broader picture of the modulatory changes underlying behavior. While neuromodulatory NIBS applied to the cerebellum in healthy individuals can enhance the performance of motor tasks and learn new motor patterns, the impact on translational work is limited due to the variability of individual responses. Thus, future work should use emerging technology (e.g., tACS, LIFUS) to target specific cerebellar-cerebral pathways to improve the outlook of clinical applications for alleviating patients' symptoms.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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