Chapter 3

Non-invasive Stimulation of the Cerebellum in Health and Disease

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Abstract

The cerebellum is linked to motor, cognitive and affective functions. Anatomically, the cerebellum is part of an interconnected network including a wide range of other brain structures. This chapter reviews ways in which non-invasive stimulation has been used to activate or inhibit these circuits and how this has contributed to our understanding of cerebellar function in both motor and non-motor domains. The utility of non-invasive stimulation of the cerebellum in the treatment of neurological and psychiatric diseases (Parkinson's disease, cerebellar ataxia, stroke, depression and schizophrenia) is discussed. The chapter concludes with consideration of the challenges that must be overcome if non-invasive cerebellar stimulation is to be adopted in a wider clinical setting.

Keywords: cerebellum, tDCS, tACS, TMS, motor learning, emotion and cognition

1. Introduction

The mammalian cerebellum is a highly folded structure at the back of the brain, which contains the majority of all neurones within the central nervous system (approximately 80% in humans and other species [1]). It has long been known to play a key role in movement control, regulating a range of motor functions (both reflexive and voluntary) [2, 3].

There is now also growing evidence that cerebellar contributions to behaviour are not restricted to motor control but also extend to the cognitive domain (for a review, see [4]). There is a high degree of interconnectivity between the cerebellum and almost all other brain regions, with connections from cerebrum to the cerebellum primarily through the pontocerebellar tract, and reciprocal connections to the cerebral hemispheres primarily from the lateral

cerebellum via the dentato-thalamo-cortical tract [5]. Other cerebellar output pathways originate from its paravermal and vermal compartments and these are known to play significant roles in motor and non-motor functions [6, 7].

Given the interconnectivity between the cerebellum and other structures such as hippocampus [8, 9], and prefrontal cortex [10–12], a role in higher order information processing is perhaps unsurprising. Indeed, there is now a substantial literature based on functional imaging and reports of cerebellar patients linking the cerebellum with cognitive functions such as verbal working memory, attention and emotion [13–18].

However, a comprehensive understanding of the way the cerebellum makes its contribution to behaviour (motor and non-motor) remains unresolved. Two major classes of theory dominate current thinking. On the one hand are those that suggest that the cerebellum acts to learn associations between stimuli (learning hypotheses), and on the other, those that suggest the cerebellum acts as a timing device (timing hypotheses).

Learning hypotheses stem from Marr's original theoretical proposal [19] and typically centre on the plasticity of synaptic inputs to the principal neurones of the cerebellar cortex—the Purkinje cells (for a review of cerebellar anatomy, see [3]). The numerous synaptic inputs to each Purkinje cell, via the mossy fibre-granule cell pathway, are thought to transmit sensorimotor information during movement. When a behavioural error occurs (thought to be a mismatch in the sensory consequences of the predicted movement) this is signalled to the Purkinje cells, via their powerful synaptic input from climbing fibres (originating from the inferior olive). This teaching signal induces plasticity mechanisms in the mossy fibre-granule cell synaptic connections to the same Purkinje cells, modifying synaptic weights and thereby adjusting the pattern of sensorimotor integration performed by Purkinje cells [20].

By contrast, timing hypotheses generally propose that the olivocerebellar circuit (made up of a feedback loop between inferior olive neurones, cerebellar cortical Purkinje cells and the output of the cerebellum, the cerebellar nuclei) is able to generate rhythmic and synchronised activity, to drive timing and spatial organisation of motor sequences [21], and other functions [22].

While studies of the cerebellum have generally considered its function in the context of either learning or timing hypotheses, they have been discussed together with the view that the two hypotheses are not mutually exclusive [23].

In order to further our understanding of cerebellar function, non-invasive methods of neurostimulation have been used to manipulate cerebellar function in humans. This chapter will focus on studies of non-invasive techniques to alter cerebellar activity in both health and disease—however it is by no means an exhaustive account of current literature. We will begin by outlining basic research involving direct (invasive) stimulation of the cerebellum, and highlight how manipulation of cerebellar activity can lead to changes in a wide variety of behaviours. Research using the two major forms of non-invasive stimulation (transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)) will then be discussed, including possible mechanisms of action. We will then discuss the use of these techniques as potential therapeutic methods to treat neurological and psychiatric conditions, including both motor and affective disorders. The chapter will conclude with a consideration of the challenges facing the use of non-invasive stimulation of the cerebellum.

2. Basic research

2.1. Direct cerebellar stimulation

Neurophysiological investigations of the cerebellum have long utilised manipulation of neuronal activity to explore its function. Of interest to this review is the use of direct cerebellar stimulation to alter behaviour.

Direct electrical stimulation of fastigial nucleus afferents and cerebellar nuclei have been shown to activate groups of muscles leading to multi-joint movements [24–26], suggesting that the cerebellum is able to directly shape complex movements. Stimulation of the cerebellar nuclei has also been shown to affect autonomic physiology such as cardiovascular and respiratory control and gut motility, but also integrated responses related to emotional behaviour (reviewed in [6, 27]).

Clinically, chronic stimulation of cerebellar cortex in epileptic patients was observed to improve not only motor symptoms, but cognitive and affective symptoms (increased alertness, attention, and suppression of rage reactions) [28]. However, whether the latter effects were due to the direct cerebellar stimulation or were a secondary effect of relief from the epileptic seizures and debilitating motor symptoms remains unclear.

Recent findings in mice have also shown that electrical stimulation of the cerebellar cortex and dentate nucleus are able to moderate dopamine release in the prefrontal cortex, consistent with a cerebellar role in cognition [29]. In addition, optogenetic stimulation of cerebellothalamic projections in a mouse model of frontal schizophrenia has been shown to rescue timing performance deficits in an interval timing task [30]. In relation to epilepsy, optogenetic stimulation of a subtype of Purkinje cells in a mouse model of temporal lobe epilepsy led to the suppression of either seizure duration, or seizure occurrence, depending on specific cerebellar target [31]. Overall, a growing body of evidence therefore points toward the cerebellum playing an important role in a myriad of physiological and pathophysiological processes, with direct stimulation of the cerebellum capable of manipulating these processes.

In contrast to animal studies, direct stimulation of neural tissue in humans is restricted by the availability of patients with implanted electrodes, especially in the cerebellum. The advent of non-invasive methods has therefore provided a valuable alternative approach to manipulate cerebellar activity in humans, in both healthy and disease states.

2.2. Non-invasive stimulation of the cerebellum

Typically, transcranial electrical stimulation (direct or alternating current) of the cerebellum is achieved with an active electrode, usually a 20–35 cm^2 saline soaked sponge, placed over the back of the skull approximately 2–3 cm left or right of inion for activating the cerebellar hemisphere of interest. Note that the cerebellum exhibits mainly ipsilateral control for motor related tasks. The opposing polarity electrode (often referred to as the 'return' electrode) is usually placed over a deltoid/buccinator muscle or at a frontal-supraorbital location. Such an arrangement is thought to help draw current flow primarily through the cerebellar cortex and away from other structures so that any observed effects are due mainly to manipulations of cerebellar

activity. Magnetic stimulation methods do not have the same issue, however careful consideration of coil geometry is needed as this affects the targetability of the induced fields [32].

Modelling studies for both electric and magnetic stimulation show that it is possible to target predominantly cerebellar tissue, albeit with some spread of stimulation into occipital areas [33–36]. However, selective sub-cerebellar structure targeting (vermis versus hemispheres) has so far not been clearly demonstrated. As such, although some reports in the literature suggest the targeting of certain cerebellar areas, without further validation of electrical currents via either direct measurement or modelling techniques, this should be taken with caution. It is likely that future advances in our understanding of stimulation parameters and electrode montages/geometries, will lead to further specificity of stimulation. However, it is generally accepted that it may be possible to selectively target the cerebellum with non-invasive stimulation techniques when careful attention is given to stimulation parameters and electrode placement.

2.2.1. Motor-learning

Since the original demonstrations that transcranial direct stimulation (tDCS) over the motor cortex was able to elicit motor evoked potentials, investigations of motor learning in humans have relied extensively on non-invasive stimulation methods [37, 38].

Typically, TMS and tDCS have been used in combination to show a dissociation in temporal involvement of the cerebellum and primary motor cortex during motor learning. Such studies infer an effect of non-invasive stimulation on cerebellar activity of functional connectivity by measuring changes to the amplitude of motor evoked potentials elicited by a TMS pulse delivered to the motor cortex after TMS stimulation of the cerebellum (cerebellar brain inhibition, CBI). It has recently been shown that CBI is reduced during early phases of motor skill acquisition, whereas motor cortex plasticity may be restricted to later learning phases [39]. A significant reduction of CBI was restricted to early learning (returning to baseline levels during later test sessions), and the magnitude of these changes were proportional to the level of individual skill acquisition. Conversely, measurements of plasticity states in the primary motor cortex revealed that plasticity in the primary motor cortex was occurring in later, but not early learning phases, and was proportional to skill retention on subsequent days, suggesting a role in consolidation of a newly learned motor memory. In a separate study, reduction in CBI was also shown during sensorimotor adaptation in early stages of an abruptly imposed perturbation, but not in either later stages, or when the perturbation was introduced gradually [40], further suggesting that the cerebellum is involved in the early stages of in motor learning.

tDCS has also been used to show a similar dissociation between the cerebellum and motor cortex [41]. Anodal stimulation over the cerebellum increased the rate of reduction of behavioural errors when a rotation transformation was imposed onto a computer based reaching task (visuomotor adaptation—see [42]), whereas motor cortical stimulation led to improved retention of the previously learned rotation on repeated exposure, with no effect on the learning rate.

In summary, studies using non-invasive stimulation methods provide evidence that the cerebellum is involved in the initial phases of motor learning (when behavioural errors are large).

This involvement declines when this initial adaptive period is complete. Further research is needed to investigate whether the temporal dissociation of the cerebellum and motor cortex in motor adaptation represents either different learning mechanisms, or a transfer of information from the cerebellum to the motor cortex about the new relationship between motor programs and sensory consequences for long term storage and use. The picture is, however, by no means clear cut. As will be discussed in the final section of this chapter, there are conflicting reports of effectiveness of non-invasive stimulation of the cerebellum to affect motor behaviours.

2.2.2. Cognition and emotion

Non-invasive stimulation methods have also contributed to our understanding of cerebellar involvement in higher order functions. For example, cathodal tDCS stimulation to the right cerebellum in healthy participants improved performance during two cognitive tasks of varying difficulty (Paced Auditory Serial Addition Task and Paced Auditory Serial Subtraction Task) [43]. Improvements in attention and working memory performance following cerebellar stimulation were proposed to result from task dependent dis-inhibition of prefrontal circuitry, with greater disinhibition during the more difficult task.

EEG based studies determined that theta-burst cerebellar TMS modulates oscillatory activity in both M1 and posterior parietal cortex (PPC), further demonstrating the widespread effect of cerebellar stimulation [44]. Modulatory effects in both time and frequency domains were dependent on the stimulation protocol. Specifically, continuous theta burst TMS (three 50 Hz pulse bursts repeated every 200 ms, for 600 total pulses) over the cerebellum increased the magnitude of TMS induced evoked potentials (~100–200 ms post stimulation) over both M1 and PPC at 10 minutes after the TMS protocol. Conversely, intermittent theta-burst TMS (2 s trains of pulses, repeated 20 times, every 10 s for a total of 600 pulses) decreased the magnitude of TMS evoked potentials in these frontal areas.

EEG recordings over the prefrontal cortex of healthy participants, with TMS over the cerebellar vermis, revealed increased theta band oscillations compared to a sham stimulation protocol [45]. Frontal theta oscillations (specifically septo-hippocampal circuits) have been related to cognitive processes such as working memory maintenance and also anxiety states [46, 47], suggesting a cerebellar role in regulation of cognitive and emotional processes. Other studies have suggested that cerebellar influence on frontal theta oscillations are fundamental to temporal processing (interval timing) and synchronisation of multiple brain regions [48], which may subserve a role in working memory. Indeed, a cerebellar role in verbal working memory has been demonstrated via deficits in a task based on the Sternberg Task induced by a TMS 'virtual lesion' [49] and in a digit span task using cathodal tDCS [50].

In agreement with the wider literature on a cerebellar role in timing, TMS studies have directly tested its role in timing perception. In a series of experiments requiring subjects to discriminate whether test tones resemble a long or short template tone, repetitive TMS of the right lateral and medial cerebellum disrupted tone perception of sub-second durations, but not durations longer than one second [51]. Similar results were observed using a task requiring participants to reproduce specified stimulus durations [52]. Specifically, repetitive TMS to

the left lateral cerebellum resulted in participants overestimating the duration of short (up to 600 ms) tone durations, but had no effect on tone durations longer than 1600 ms [52]. Together these experiments provide evidence that the cerebellum plays an important role in maintaining the perception of rhythmic time intervals when such intervals are short (sub-second), but not necessarily at longer intervals. In support of this view, Purkinje cell simple spike discharge have been shown to be consistent with a predictive timing role, in relation to operation of an internal model of a target's motion, with operating ranges of at least 200–300 ms [53].

In summary, these studies demonstrate how non-invasive stimulation of the cerebellum has been utilised to investigate functional connectivity between the cerebellum and other brain structures associated with cognition, complementing anatomical and neuroimaging based studies [10, 54]. Such an approach also has the potential to be used to influence higher cognitive processing in both health and disease.

3. Clinical studies

Notwithstanding the challenges that will be discussed later, non-invasive stimulation methods promise a useful avenue for clinical therapy of many neurological and psychiatric conditions. Such an approach is attractive because of the ease of use, suitability for high-risk populations (elderly, overweight, and those who elect against surgical interventions), low cost (especially in the case of tDCS), and good safety record, with only mild, transient side effects [55, 56]. The cerebellum is well placed to be a target for treatment of a number of clinical impairments [57].

3.1. Parkinson's disease and essential tremor

A number of TMS protocols have indicated that targeting the motor cortex with non-invasive stimulation can lead to short term improvements in Parkinsonian symptoms, most commonly motor aspects, but also depression [58]. Parkinson's has classically been associated with the degeneration of the dopaminergic pathways of the basal ganglia, leading to both motor and affective symptoms. Recent studies propose however that the disease mechanism(s) may be better understood as a dysfunction of a basal ganglia-cortical-cerebellar network [59], and evidence for a role of the cerebellum has been building [60]. Indeed there are Parkinsonian symptoms (particularly resting tremor) in populations with spinocerebellar ataxia type 3 [61], which support a cerebellar link in such symptoms.

Compared to a sham protocol, low frequency repetitive TMS over the cerebellum in early stage Parkinson's patients has been shown to improve gross upper limb motor function (around a 10% improvement), but a non-significant decrease in fine finger control [62]. Significant decreases in fine motor control have also been noted in healthy participants [63]. The beneficial effect on gross motor function is thought to be mediated by a reduction in the tonic inhibitory influence of the cerebellum on the motor cortex, however the opposing effects on fine motor control remain unexplained. Since it may be undesirable to modestly improve gross motor functions at the detriment of fine motor control, further studies are needed to

resolve the mixed results of this TMS protocol before it can be considered a reliable clinical intervention for early stage Parkinson's.

Cerebellar targeted theta burst repetitive TMS over a 2-week period in Parkinson's patients who had developed levodopa-induced dyskinesia, resulted in improvements in dyskinesia symptoms up to 4-weeks after the stimulation period [64]. By contrast, a 15 minute, 1 Hz repetitive TMS stimulation over the supplementary motor cortex has been reported to have no long term effect [65]. A recent report revealed that cerebellar (as well as motor cortical) tDCS may also provide positive therapeutic outcomes in levodopa-induced dyskinesia [66]. The mechanisms of action remain poorly defined, but one possibility is the overall increase in CBI (see above). Overall, the cerebellum may therefore provide a promising target for manipulating network activity underlying motor symptoms of Parkinson's disease.

3.2. Cerebellar ataxia

Studies utilising TMS over motor cortex have shown abnormal motor cortex excitability in cerebellar ataxic patients, attributed both to direct cerebellar influence [67], and compensatory motor cortical mechanisms [68]. The heterogeneous origins of individual ataxias (with degeneration possible in both cortical, and peduncle locations) likely means that this is not strictly the case for all patients [69]. Indeed, cerebellar ataxia may not be explained solely by disruption to motor cortical excitability, but disruption of the cerebellum's role in co-ordinating multiple muscle groups to produce smooth, accurate movements [70].

Despite the limited literature on the use of therapeutic non-invasive cerebellar stimulation in patients [71], cerebellar TMS has shown the potential for therapeutic use, successfully alleviating ataxic symptoms [72, 73] through facilitation of motor cortex excitability [74]. Conversely, a study testing the effects of anodal cerebellar tDCS on grip force in both ataxic patients and healthy controls did not reveal any effects in either group [75]. Regardless of the unresolved, and probably heterogeneous causes of motor disability in ataxic patients, cerebellar TMS stimulation may be well placed to rescue cerebellar function in cases of partial cerebellar degeneration, but is unlikely to benefit those with substantial dysfunction of cerebellar structures.

3.3. Cerebral stroke

Cerebral stroke can affect motor, cognitive, and/or emotional abilities depending on the size and location of the insult. Non-invasive stimulation procedures over the motor cortex have been investigated, however the effectiveness of targeting the motor cortex has been questioned [76]. As detailed above, cerebellar stimulation can modulate a wide range of behaviours in healthy subjects, and so has the potential to influence symptoms suffered by stroke patients. Certainly, a few small scale studies have shown success in improving post-stroke symptoms, such as greater recovery of language and spelling abilities with multiple sessions of cerebellar tDCS combined with spelling therapy compared to therapy alone [77].

A prevalent outcome of stroke is the development of depression [78]. Repetitive TMS of frontal sites has been shown to have some beneficial effect, although questions still remain over the longer term success [79]. Direct stimulation of the cerebellar fastigial nucleus alleviates

some depression-like symptoms in rat, including weight loss, reduced sucrose preference, and reduced locomotor activities [80]. However, translating these results to non-invasive human stimulation will be challenging; particularly as non-invasive techniques have so far been limited to modulating cerebellar cortex.

Another common consequence of cerebellar stroke is the inability to swallow effectively (post-stroke dysphagia) [81]. Although the precise mechanisms leading to dysphagia are unresolved, non-invasive brain stimulation techniques have been explored as potential tools for the management of dysphagia [81]. The cerebellum has been implicated in effective swallowing [6], and repetitive TMS of the cerebellum has been shown to improve swallowing mechanisms (reviewed in [82]), as measured by an increase in pharyngeal motor evoked potential following stimulation.

Taken together these findings therefore suggest that non-invasive stimulation of the cerebellum may be a useful method for the treatment of a range of post stroke symptoms.

3.4. Major depression and schizophrenia

The majority of interest in using non-invasive brain stimulation methods to treat psychiatric disorders has focussed on cerebral targets [83]. However, in a rodent model of schizophrenic deficits in interval timing tasks, optogenetic stimulation of cerebellar projections at 2 Hz resulted in a return of control level performance in an interval timing task, which correlated with a return of medial-frontal delta (1–4 Hz) oscillations, not observed in unstimulated animals [30]. In addition, a study in schizophrenic patients has shown the potential utility of non-invasive cerebellar stimulation to alleviate some of the symptoms of the disorder; such as reduced depression (measured on the Calgary Depression Scale), and fewer omissions in working memory tasks [84]. Given the growing understanding of the brain-wide networks involved in these types of disorder, the cerebellum is clearly a potential target for further investigation [57].

4. Challenges and the future of non-invasive cerebellar stimulation

Since the revival of interest in non-invasive stimulation techniques about 2–3 decades ago, there have been clear advances made in both their use as research tools—advancing our knowledge about neurophysiological processes—and as therapeutic interventions. However, the literature is still awash with many uncertainties about the efficacy of the techniques, and there is typically a high degree of variability in the results. For example, a recent attempt to replicate an experiment dissociating the roles of the cerebellum and M1 in motor adaptation [41] was unsuccessful in a like-for-like experiment [85]. The study went further and pooled data across several experiments (varying some parameters of the design). The pooled data re-captured the effects of the original experiment, however the effect size was reduced. The authors concluded that some publications may be overestimating the effects of tDCS, possibly because of underpowered experiments.

Although changing, many studies assume that the electrical fields induced in the underlying brain tissue are uniform—or at least quasi-uniform—and so the stimulation delivered to the

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local circuitry of the target area can be considered homogenous. However, it is now recognised that this is almost certainly an oversimplification. Even in the localised space of a single cerebral cortical gyrus or cerebellar folium, neurones can be hyperpolarised or depolarised by the same field because of differences in the orientation of the cellular compartments (see **Figure 1**), and differences in the geometry of current flow [86–88]. Consequently, small inter-individual variations in brain morphology, or inaccurate electrode/coil placements could lead to significant differences in the polarisation of the target tissue. Given the much greater level of cortical folding in cerebellar folia compared to cerebral areas, this is likely of greater influence on cerebellar circuitry than cerebral circuitry. Certainly, data collected from cerebral tissue may not accurately reflect patterns of polarisation in cerebellar tissue.

Such issues can be investigated directly in animal models which allow investigation of neurophysiological mechanisms at the cellular level. Different compartments of individual neurones (dendritic vs. somatic) have been shown to exhibit opposing polarities in an electric field in *ex vivo* preparations of rodent cerebral tissue [89–91], and turtle cerebellar tissue [92]. How such effects translate to the whole living brain remains an open question, and further *in vivo* studies are needed in animals [93–96].

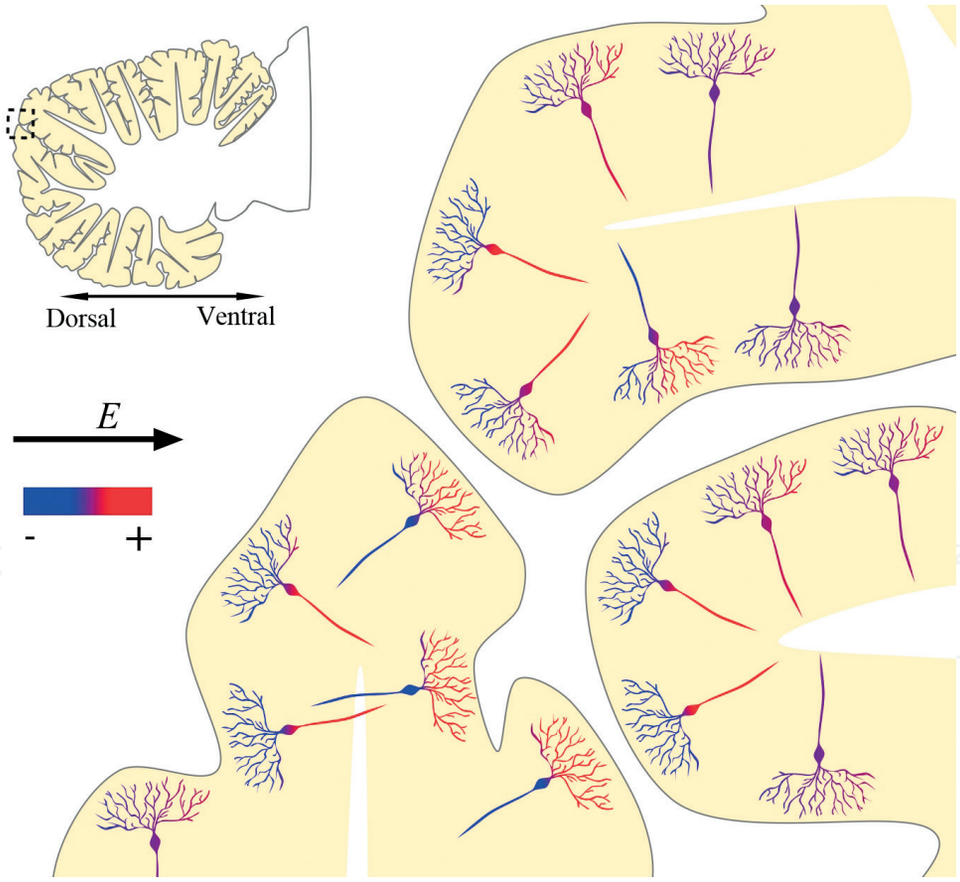

Figure 1. Representation of non-uniform Purkinje cell polarisation in a uniform electric field. Schematic showing cerebellar folia with Purkinje cells polarised in a uniform electric field. Inset shows cerebellum in sagittal plane, with location of expanded region shown in dotted box. Direction of the electric field *E* shown by arrow. This field orientation will generate hyperpolarisation (−) in dorsal cell compartments and depolarisation (+) in ventral cell compartments. Note how the orientation of Purkinje cells in different locations affects the relative polarisation of the soma and dendrites.

An additional consideration not commonly controlled for in non-invasive stimulation (particularly electrical stimulation) studies are factors such as individual skull thickness [87], gender [97], time of day [98], and brain network state [99]. With electrical stimulation, variability can also result from the specific arrangement (montage) of electrodes used—influencing the intensity, and focality of stimulation [56, 87, 100]—while for magnetic stimulation, coil geometry has been shown to alter the effectiveness of TMS [32], and positioning of the coils will clearly affect the focus of stimulation.

Stimulation intensity is also an important variable. In the case of electrical stimulation, a current of between 1 and 2 mA is typically used. The consensus is that these levels of current are well below any thresholds that will lead to neuronal damage [101, 102]. Large scale systematic studies testing the effects of increasing stimulation intensities (remaining within safety limits) would establish if there is a relationship between stimulus intensity and effect size/consistency. Advances in the use of modelling induced electric fields and the availability of individualised computational models to predict these fields would help electrode/coil placement for optimal targeting in individual subjects [86]. Furthermore, a large proportion of TMS research utilises MRI based registration methods to aid targeting. Perhaps more widespread adoption of MRI registration techniques in tDCS research to aid electrode placement might further benefit standardised targeting of tDCS. Careful choice of stimulation montages, and clear reporting of stimulus parameters would also be helpful.

In conclusion, a growing body of evidence suggests that the cerebellum is an important node in brain networks, associated with a wide range of motor and cognitive functions; and non-invasive stimulation of the cerebellum can manipulate these circuits. However, a greater understanding of the neurophysiological effects of such stimulation are needed in animal models. This could lead to more consistent approaches across human studies. As a result, the cerebellum may prove to be a useful and reliable target in altering brain activity in both health and disease.

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