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NON-INVASIVE CEREBELLAR STIMULATION – A CONSENSUS PAPER

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Abstract

The cerebellum processes motor, cognitive and affective information. The field of neurostimulation of the cerebellum either with transcranial magnetic stimulation (TMS; single pulse or repetitive rTMS) or transcranial direct current stimulation (tDCS; anodal or cathodal) is gaining popularity in the scientific community, in particular because these stimulation techniques are non invasive and provide novel information on cerebellar function. There is a consensus amongst the panel of experts that both TMS and tDCS can effectively influence cerebellar functions, not only in the motor domain but also for the cognitive and affective operations handled by the cerebellar circuits. Both TMS and tDCS modulate the connectivity between the cerebellum and the primary motor cortex, tuning cerebellar excitability. Cerebellar TMS is an effective and valuable method to evaluate the cerebello-thalamo-cortical loop functions. DCS induces a polarity-dependent site-specific modulation of cerebellar activity. However, several important issues still remain unsolved and require further studies. In particular, the role of TMS in promoting cerebellar plasticity is not established. Moreover, the exact positioning of electrode stimulation or the duration of the after effects of tDCS remain unclear. The long-term neural consequences of non-invasive cerebellar modulation are unclear. There is an agreement that the clinical applications in cerebellar disorders are likely numerous, but rigorous clinical trials are missing. Further studies should clarify the role of using non-invasive neurostimulation techniques over the cerebellum in motor, cognitive and psychiatric rehabilitation strategies.

Keywords: Cerebellum, transcranial magnetic stimulation, direct current stimulation, anodal, cathodal, motor adaptation, excitability, cerebellar inhibition, paired associative stimulation, vision, language, predictions, motor surround inhibition, working memory, semantic associations, ataxia.

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Introduction

Non-invasive cerebellar neuromodulation has recently increased its attractiveness in both the neuroscience and neurorehabilitation communities. This Consensus Paper aims to present current views on transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS; anodal or cathodal) in studies devoted to cerebellar functions. The panel of experts provides lines of consensus and identifies unclear points requiring further studies.

Cerebellar Neurostimulation. What did we learn from TMS studies?

Cerebellar Inhibition

The cerebellum is well known to play important roles in movement execution and motor control by modulation of the primary motor cortex (M1) through cerebello-thalamo-cortical connections [1]. The cerebellum receives inputs from the cortex mainly through the middle cerebellar peduncle in terms of the cortico-ponto-cerebellar pathway or through the inferior cerebellar peduncle via climbing fibers from the olive in terms of the cortico-rubro-olivo-cerebellar pathway [2]. The cerebellar efferent pathway consists of projections from the cerebellum to the motor cortex through the di-synaptic dentato-thalamo-cortical pathway [3]. Fibers from the dentate nucleus connect to the ventrolateral motor thalamus via the superior cerebellar peduncle. The motor thalamic cells project further to areas 4 and 6. The dentato-thalamo-cortical pathway itself is facilitatory. However, Purkinje cells of the cerebellar cortex inhibit the dentate nucleus. Therefore activation of Purkinje cells results in disfacilitation of the motor cortex.

Physiological studies of cerebellar functions in humans were methodologically limited for a long time. However, the introduction of transcranial electric stimulation (TES) and transcranic magnetic stimulation (TMS) techniques allowed us to investigate neural networks by stimulating neural structures in humans non-invasively. The motor evoked potential (MEP) to single pulse TMS

of M1 is used to measure the motor cortical excitability. A conditioning stimulus over the cerebellum preceding a test stimulus over the contralateral M1 enables us to study the cerebellar regulatory effects on M1. In healthy subjects, cerebellar conditioning TMS inhibits the amplitude of the test MEP, when it precedes the test stimulus by 5 to 7 ms [4,5]. This inhibition is mediated through the pathway between cerebellum and M1 and has therefore been termed cerebellar brain inhibition (CBI). It is likely that cerebellar TMS activates Purkinje cells of the cerebellar cortex, leading to an increased inhibition of the di-synaptic dentate-thalamo-cortical facilitatory connection, and then finally resulting in the observed inhibition of M1 [6,7,8].

Recently, it has been shown, that CBI can effectively be modulated by transcranic direct current stimulation (tDCS), another non-invasive brain stimulation technique. The application of cathodal tDCS, which reduces cortical excitability, leads to a lasting inhibition of CBI for up to 30 minutes after stimulation. On the other hand, anodal tDCS, which increases cortical excitability, increases the magnitude of CBI, when applied over the cerebellum. This suggests that cerebellar tDCS leads to a sustained and polarity dependent bidirectional modulation of cerebellar excitability by changing tonic Purkinje cell activity [9].

Cerebellar TMS as a diagnostic tool

The neurological examination alone does not allow the determination of the exact localization of a lesion in ataxic patients, since cerebellar ataxia may be caused by a lesion anywhere within the fronto-pontine-cerebello-thalamo-cortical loop. This loop consists of the cerebellar afferent pathways and the cerebellar efferent pathways including cerebellar output fibers (Figure 1). As described above, cerebellar TMS is supposed to reflect functions of the cerebellar efferent pathways and may therefore be useful to clinically differentiate cerebellar efferent ataxia from cerebellar afferent ataxia [7].

Patients with diseases affecting the cerebellar cortex, e.g. cerebellar cortical atrophy, spinocerebellar ataxia, multiple system atrophy (cerebellar type), or cerebellar stroke, showed impaired CBI [10,11]. Involvement of the dentate nucleus, such as dentatorubral-pallidoluysian atrophy or Wilson's disease, reduced CBI as well [10,11]. In contrast, ataxic patients with involvement of cerebellar afferent pathways, such as pontine infarction or middle cerebellar peduncular affection, had normal CBI. Moreover, patients without cerebellar involvement, e.g. Parkinson's disease, motor neuron disease or peripheral neuropathy, show normal CBI [10,11].

Patients with progressive supranuclear palsy (PSP) had significantly reduced CBI without clinically detectable cerebellar signs [12]. This is consistent with pathological and radiological findings of PSP revealing an involvement of the cerebellar dentate nucleus and superior cerebellar peduncle. It indicates that cerebellar TMS revealed masked cerebellar dysfunction in PSP.

Ataxic hemiparesis is a lacunar syndrome with ataxia accompanying ipsilateral corticospinal tract impairment. In such patients, ataxia may result from a small lesion anywhere within the fronto-pontine-cerebello-thalamo-cortical loop. In those patients, cerebellar TMS differentiated cerebellar efferent ataxia from cerebellar afferent ataxia. Their results are consistent with the well-known anatomical knowledge of the cerebellar circuits [13].

Limitation

Suprathreshold cerebellar stimulation may induce antidromic pyramidal tract co-activation, which can affect cerebellar stimulation experiments [4,14]. However, when the stimulation threshold is carefully defined using rectified electromyography and current direction and stimulation site are accurately and appropriately chosen [15], cerebellar TMS has been proven to be a powerful and reliable method to investigate cerebellar function in humans non-invasively [14].

Conclusion

Taken together, these results suggest that cerebellar TMS is an effective and valuable method to evaluate the cerebello-thalamo-cortical loop function in humans and may be useful for pathophysiological analysis of ataxia.

Dynamic modulation of cerebellar excitability

Dynamic modulation of cerebellar excitability by non-invasive stimulation is a relatively new concept. However, the development of such procedures is of significant interest to further the understanding of cerebellar functions and as a potential rehabilitation tool. As there is no direct way in which cerebellar excitability can be assessed in humans, research in this field has relied on the inhibitory tone the cerebellar cortex exerts over the contralateral M1 via the thalamus [16]. Initial studies applied rTMS over the cerebellar cortex, producing a 'virtual lesion' which is thought to decrease cerebellar output. The subsequent neurophysiological effects of this 'virtual lesion' were then determined indirectly by testing M1-excitability with TMS. One would predict that this should result in an increase in M1 excitability, yet the findings were inconsistent. Some studies described an increase in intracortical M1 excitability [17,18] but others a decrease [19,20]. The reasons for these differences remain elusive however the application of different rTMS protocols and measures of M1 excitability among the various studies makes a direct comparisons difficult.

Rather than measuring M1 excitability, assessing CBI [16,21] allows to probe the current excitability level of the cerebellum (see previous section). Galea et al. [9] applied anodal, cathodal or sham tDCS to the cerebellar cortex. Following 25 minutes of stimulation, it was found that cathodal tDCS resulted in a clear decrease of CBI suggesting reduced cerebellar excitability, whereas anodal increased it. Similar decreases in CBI have been found with inhibitory rTMS protocols [22]. However, unlike rTMS, the tDCS effects were specific to the cerebellum as no changes were observed in isolated measures of M1 excitability. These results suggest that tDCS and rTMS can modulate cerebellar excitability with the changes lasting up to 30 minutes after

stimulation has ended [9,22], but also indicate that there are subtle differences in how rTMS and tDCS may act on the cerebellum and its cortical connections.

Despite these dissimilarities, recent work has shown that rTMS and tDCS can lead to similar results of cerebellar modulation. Hamada et al. [23], and Popa et al. [24], used tDCS and rTMS respectively to induce changes in cerebellar excitability during M1 paired associative stimulation (PAS), a protocol to induce long-term potentiation-like plasticity in M1. Both studies found that protocols which are thought to increase cerebellar excitability lead to abolition of PAS-induced M1 plasticity. This demonstrates a key role of the cerebellum in priming M1 plasticity possibly through the processing of sensory information [23-25]. These results could have interesting clinical implications for dystonia patients, a disease where hyper-plasticity in M1 leads to pathological co-contraction and abnormal postures [23].

At present, the clinical applications of non-invasively modulating cerebellar excitability have mainly been applied to Parkinson's disease patients who suffer from levodopa-induced dyskinesias, a symptom proposed to be, in part, due to over excitation between the cerebellum and cortex. Koch et al. [26], showed that a 2-week inhibitory rTMS protocol over the cerebellum lead to a reduction in these clinical symptoms. This was associated with decreased activity of the pathway that connects the cerebellar cortex with the deep cerebellar nuclei, measured with positron emission tomography imaging [26,27]. Crucially, this provides evidence that non-invasive stimulation can produce plasticity changes in the cerebellum which are clinically relevant and that are observable weeks after stimulation has ended.

Although the aforementioned research highlights that rTMS and tDCS can dynamically modulate the excitability of the human cerebellum there are many unresolved questions. First, animal work is required that directly investigates how non-invasive stimulation modulates the cerebellum and in particular which cells are receptive to such plasticity protocols. Second, with the emerging field of concurrent TMS/tDCS and functional magnetic resonance imaging (fMRI) it should be possible to

better understand the neural consequences of non-invasive cerebellar modulation. Although it is known that cerebellar stimulation alters M1 excitability, the cerebellum has reciprocal connections with many areas of the cortex and basal ganglia [28]. Therefore, it will be interesting in the future to investigate whether dynamic modulation of the cerebellum leads to activity changes in other connected areas of the brain.

tDCS of the cerebellum: from rodent studies to cerebellar ataxias

The interest of tDCS as a research technique to promote neuroplasticity and as a therapeutic tool is growing [29,30]. tDCS is now considered a potentially valuable clinical tool for neurorehabilitation interventions [31]. Research applications are gaining extensions to emerging fields such as brain-computer interfaces (BCIs), widening considerably the future applications (Wei et al., 2013). In the vast group of neurological disorders, cerebellar ataxias are amongst the most disabling [33]. Still, no cure exists for most degenerative forms of cerebellar ataxias [33].

Rodents are commonly used to assess novel therapeutic strategies and to identify mechanisms of action of therapies under development. In particular, there is a great need for novel animal models to test the effects of DCS in order to improve our understanding of complex cerebral processes [34].

Studies in rats confirm that anodal DCS induces a polarity-dependent site-specific modulation of brain activity [35]. Cerebellum is known to receive numerous sensory inputs, to participate in sensory processing and plays a critical role in the modulation of motor cortex excitability following peripheral sensory stimulation, allowing both the maintenance and the fine tuning of corticomotor discharges. Nevertheless, the exact mechanisms by which cerebellum interacts with motor cortex are a matter of debate. Acute cerebellar lesions cause a depression in the excitability of contralateral motor cortex [36,37]. Enhanced inhibition within the motor cortex has

been reported in several studies [38,39]. Hypoexcitability of both the motor cortex and the anterior horn of the spinal cord are two major defects associated with acute cerebellar lesions, especially when the lesion involves cerebellar nuclei or is extensive such as in hemicerebellar ablation. These changes are involved in the pathogenesis of the deficits of skilled movements in cerebellar patients. The analysis of the effects of anodal/cathodal DCS applied epidurally over the cerebellum, in rats, shows that anodal DCS of the cerebellum reduces the excitability of the motor cortex, as confirmed by the analysis of the recruitment curves of corticomotor responses and the analysis of the amplitudes of corticomotor responses [40]. Interestingly, it reshapes the representation of agonist/antagonist muscles in the motor cortex. Moreover, it decreases the excitability of the anterior horn of the spinal cord. Cathodal DCS of the cerebellum, on the other hand, exerts partially reversed effects. Results obtained with anodal DCS can be interpreted in terms of disfacilitation of the dentatothalamocortical pathway: anodal DCS increases the inhibition exerted by Purkinje neurons over cerebellar nuclei, thus removing the facilitatory cerebellofugal drive exerted by cerebellar nuclei on extra-cerebellar structures such as thalamic nuclei [40].

One of the neurophysiological findings in cerebellar disorders associated with degeneration of the cerebellar cortex is the enhancement of long-latency stretch reflexes, as a consequence of a disinhibition of cerebellar nuclei [41]. Anodal cerebellar tDCS reduces the magnitude of long-latency responses in the upper limbs of patients who do not exhibit deficits of force [42], confirming that this form of DCS restores, at least partially, the inhibitory activity exerted by Purkinje neurons over cerebellar nuclei. The effects are not likely to be the consequence of a direct action on extra-cerebellar targets, such as a direct stimulation of brainstem nuclei. Indeed, the studies by Jayaram et al. [43] and Galea et al. [9,44] have shown no effect of cerebellar DCS on the excitability of brainstem nuclei such as vestibular or trigeminal nuclei.

The tDCS-induced modulation of motor cortex discharges and cerebellar activity opens the road for tDCS applications in human cerebellar ataxias, including for wearable applications during daily life since gait and posture are commonly impaired in cerebellar ataxias. tDCS applied over the

cerebellum in humans modulates locomotor training in neurological patients with gait impairments [43] and speeds up learning of reaching [44,45]. Cerebellar tDCS also finds application in the study of the so-called cognitive cerebellar functions. Cerebellum is deeply involved in numerous aspects of behavior. tDCS over the cerebellum tunes attention, verbal working memory, and might affect the processing of facial expressions [46-49].

Use of cerebellar stimulation to tune motor function is not a novel idea [50]. For instance, Cooper observed that cerebellar stimulation reduces the amplitudes of somatosensory evoked responses. Spasticity and epilepsy have been considered as disorders which could be improved by cerebellar stimulation. Overall, the large group of neurological disorders in which a manipulation of cortical excitability might be beneficial -for instance to stimulate the plastic changes underlying learning and the process of recovery- are potential therapeutic targets for DCS [40]. Future studies are required to better define how DCS affects individual cerebellar symptoms, given the topographical organization of cerebellar symptoms. One possible future direction in the emerging field of cerebellar neuromodulation is to combine DCS of the cerebellum with DCS of the extra-cerebellar structures critically involved in motor control such as motor/premotor cortex.

Paired associative stimulation of human cerebellum and primary motor cortex

PAS is a now broadly used TMS protocol that allows induction of bidirectional spike-timing dependent plasticity (STDP)-like changes in corticospinal excitability and/or effective connectivity of the stimulated pathway [51]. Depending on the interstimulus interval between an afferent input into the M1 and action potential generation in M1 corticospinal neurons by suprathreshold TMS, long-term depression(LTD)-like or long-term potentiation (LTP)-like plasticity of corticospinal neurons occurs. These effects are akin to STDP as studied in single cells in brain slices or neuronal cultures [52]. At the systems level of human M1, bidirectional STDP-like plasticity has been shown

after repeated pairing of TMS of M1 with afferent input into M1 from peripheral nerves [53-55], ipsilateral ventral premotor cortex [56], and supplementary motor area [57].

In a recent study we tested the possibility to induce STDP-like plasticity along the cerebellar-dentato-thalamo-M1 connection by cerebellum-to-M1 (CB→M1) PAS in healthy subjects [25]. Conditioning stimulation over the right lateral cerebellum preceded focal TMS of the left M1 hand area by 2ms (CB→M1 PAS_{2ms}), 6ms (CB→M1 PAS_{6ms}) or 10ms (CB→M1 PAS_{10ms}) or randomly alternating intervals of 2 and 10ms (CB→M1 $PAS_{Control}$). TMS of the left M1 was performed with a 70mm figure-of-eight coil, TMS of the right lateral cerebellum with a 110mm double-cone coil. MEP were recorded in the first dorsal interosseous muscle (FDI) of the right hand as readout for changes in corticospinal excitability. In addition, cerebellar-motor cortex inhibition (CBI; see section "cerebellar inhibition") was measured as an index for effective connectivity of the stimulated cerebello-dentato-thalamo-cortical pathway according to an established protocol [7].

We found that CB→M1 PAS_{2ms} resulted in MEP potentiation, CB→M1 PAS_{6ms} and CB→M1 PAS_{10ms} in MEP depression, and CB→M1 $PAS_{Control}$ in no change (Figure 2). The MEP changes lasted for 30-60 min after PAS. CBI decreased non-specifically after all PAS protocols.

Findings indicate that PAS of the cerebello-dentato-thalamo-M1 pathway can induce bidirectional long-term (> 30 min) STDP-like plasticity of corticospinal excitability, extending previous studies that showed bidirectional STDP-like plasticity of corticospinal excitability when M1 stimulation was paired with associative stimulation of other input pathways [55-57].

It is thought that TMS over the lateral cerebellum activates Purkinje cells, i.e. the major inhibitory neurons of the cerebellum [5]. The Purkinje cells inhibit deep cerebellar nuclei, which provide tonic facilitation to the contralateral M1 through the dentato-thalamo-M1 pathway [2]. Therefore, activation of the Purkinje cells leads to M1 disfacilitation. The observed CB→M1 PAS-induced changes in MEP amplitude may be then explained as follows: rTMS of M1 at a time when

lateral cerebellum conditioning stimulation has inhibited this tonically active pathway should lead to Hebbian LTD-like MEP decrease, similar to LTD induced in hippocampal slices when a high-frequency conditioning input was negatively correlated in time with a test input [58]. Given a CBI onset latency of 5-6ms [7], CB→M1 PAS intervals of ≥ 6ms should lead to LTD-like plasticity and this is what was found (Figure 2). The LTP-like MEP increase after CB→M1 PAS_{2ms} implies a reversal of the order of these events, i.e. action potential generation in M1 corticospinal cells regularly occurred at a time when the tonic excitatory dentato-thalamo-M1 input was active above average.

Our data are in agreement with two 1 Hz rTMS studies of the lateral cerebellum, which demonstrated an increase in MEP amplitude [17,19]. Low-frequency rTMS leads to excitability depression of the stimulated brain area [59]. Therefore, the putative depression of Purkinje cell excitability would lead to reduced inhibitory regulation of the dentate-thalamo-M1 pathway and consequently to increased tonic excitatory input to M1.

Our experiments did not reveal a differential effect of CB→M1 PAS on CBI but rather a non-specific decrease independent of CB→M1 PAS interval. Other recent studies demonstrated a significant CBI increase after anodal versus a CBI decrease after cathodal transcranial direct current stimulation of the lateral cerebellum [9], and a CBI decrease after 1 Hz rTMS or continuous theta-burst stimulation [60], without changes in MEP amplitude. While the reasons for these differences need further exploration, together these findings indicate that the modifications of corticospinal excitability (indexed by MEP amplitude) and CBI are often dissociated.

The bidirectional modification of M1 excitability induced by CB→M1 PAS may prove useful for correcting abnormal M1 excitability caused by cerebellar disease. Future studies may investigate the behavioral significance of this plasticity, in particular with respect to motor skill performance and motor adaptation.

The cerebellum and visually-guided tracking tasks

TMS over the cerebellum induces long latency electromyographic (EMG) response in the soleus muscle in stance [61,62]. Peak latency of this response is as long as 100ms. Recently, another study found that cerebellar TMS induces long latency fluctuation of index finger movement with an onset latency of 90ms, and long latency EMG response in the FDI muscle with an onset latency of 70ms during a visually-guided manual tracking task [63]. In order to evoke these responses, TMS was delivered over the site 3cm right to and 1cm below to the inion, at which the right cerebellar cortex is efficiently stimulated. Interestingly, the probability of the response induced by cerebellar TMS was higher than that induced by sham TMS during the visually-guided manual tracking task, but this difference was absent when maintaining the finger at a stationary target. Accordingly, it has been assumed that this response may partially reflect task-dependent cerebellar activity.

A concern about these findings was that the long latency finger fluctuation induced by cerebellar TMS may have been caused by motion artifacts in the neck. Thus, a subsequent study was conducted in order to rule out this possibility [64]. The probability of long latency index finger fluctuation induced by cerebellar TMS was not significantly different from that induced by magnetic stimulation over the neck. Accordingly, a hypothesis that long latency finger fluctuation induced by cerebellar TMS is partially due to the TMS-evoked neck twitch was not ruled out in this study.

Task dependency of long latency EMG responses in the FDI muscle induced by cerebellar TMS was investigated in the same study [64]. It was expected that the long latency EMG response would preferentially appear during the visually-guided manual tracking task if the response reflects cerebellar activity, because cerebellar activity is enhanced during visually-guided manual tracking task [65]. As expected, the probability of long latency EMG responses induced by cerebellar TMS was significantly higher than that induced by TMS over the neck or than that induced by sham TMS

during continuous visually-guided manual tracking task, but these significant differences were not present during the other motor tasks; a discrete visually-guided manual tracking task, a phasic movement task, and a tonic contraction task. Accordingly, it was concluded that the long latency EMG responses in the FDI muscle induced by cerebellar TMS are not due to neck twitch, and preferentially appears during a continuous visually-guided manual tracking task.

The cerebellum is involved in visually-guided manual tracking. The latency of eye movements and the frequency of corrective saccades increase, and the correlation between eye and hand movement decreases during visually-guided manual tracking task in baboons with lesion of the dentate nucleus ipsilateral to the hand tested [66]. Accordingly, long latency EMG responses, which preferentially appears during continuous visually-guided manual task, may be a useful probe for investigating particular cerebellar activity during a visually-guided manual tracking task.

What are the pathways mediating long latency EMG responses induced by cerebellar TMS? The pathways mediating this response may partially share common pathways with those controlling visually-guided manual tracking tasks, because this response preferentially appears during visually-guided manual tracking. The pathways mediating long latency EMG response in the FDI muscle must be polysynaptic, because of its long latency. Because the long latency EMG response is a motor response, this response partially reflects activity of the efferent motor pathways. However, it is also apparent that this response does not reflect direct stimulation of the spinal cord, because of the different latencies. On the other hand, the long latency EMG response is not likely to be mediated by dentatothalamocortical pathway, as CBI might suggest [5,6,67] (see section “Cerebellar inhibition”), because the response appears with an onset latency of 70ms [63,64]. A previous study using optokinetic stimulation suggests that the vestibulospinal tract mediates long latency EMG response induced by cerebellar TMS in the soleus muscle in stance [62]. In spite of that, it is not certain that long latency EMG response in the FDI muscle is mediated by this

pathway. In order to identify the pathways mediating long latency EMG response induced by cerebellar TMS, further investigations are needed.

The cerebellum and motor surround inhibition

Surround (or lateral) inhibition is a term usually used to describe a key property of the sensory system in which activation of a central receptive field causes direct inhibition of the surroundings. Within the motor system, it was first explored conceptually as a mechanism by which basal ganglia circuits might selectively execute desired motor programs [68]. Later, a potential neurophysiological measure of motor surround inhibition (mSI) was demonstrated; by stimulating the motor cortex using TMS at the onset of movement of the index finger, suppression in the size of responses of non-synergistic surround muscles was seen [69] (Figure 3A). The potential clinical importance of mSI is supported by several electrophysiological studies in dystonic patients, which reveal that the involuntary co-contraction of hand muscles that occurs in this condition is associated with a disruption of mSI [72].

It is not known which structures within the central nervous system are important for the generation of mSI. Some authors favour a neocortical mechanism, mainly because mSI has only been demonstrated after cortical stimulation. Electrophysiological studies [69,72] of spinal excitability (H-reflex, F-wave) at the onset of a voluntary movement failed to show topographic-specific modulation of excitability at the spinal level. Further studies on the dependency of mSI on intrinsic primary motor cortical inhibitory networks (SICI, LICI, cSP) or premotor- motor cortex interactions have failed to associate specific neuronal networks with the generation of mSI [69,72-74].

Some characteristics of cerebellar function make it a suitable candidate to contribute to the generation of mSI. Most obvious, is the cerebellum's role in the coordination of movement. Deficiencies in hand control and timing of individual finger movements are seen in patients with cerebellar disease [75]. Furthermore, it has been shown that the cerebellum has a net inhibitory

effect on the cerebral cortex via the cerebello dentato-thalamo-cortical pathway, an inhibitory pathway that could potentially mediate mSI [5,76].

Two electrophysiological studies have explored the role of the cerebellum in the generation of mSI. These studies explored CBI in active and surround muscles of the hand at movement onset when mSI is most prominent [69,72]. CBI was found to be reduced in both active and surround muscles at the onset of movement. However muscle-specific modulation of CBI at onset of movement in parallel with mSI was not confirmed and thus the study did not provide evidence of a functional link between CBI and mSI (Figure 3B) [70].

CBI relies on a powerful (and fairly painful) phasic non-topographically specific magnetic stimulation of the cerebellum that might not reveal subtle cerebellar contributions to mSI. A further study therefore explored the effect of cerebellar tDCS on mSI [71]. tDCS is a technique that enhances (anodal) or decreases (cathodal) cerebellar excitability [9]. The cerebellum is stimulated for 15 minutes, and changes in excitability are seen for at least 30 minutes after the stimulation [9]. The effect of this stimulation has been confirmed neurophysiologically (measuring CBI) and behaviorally (measuring rates of adaptation to sensory perturbations, a cerebellar-dependent learning task) [9,44]. mSI was tested before and after both anodal and cathodal cerebellar tDCS to investigate if the magnitude of mSI was modulated. Here the hypothesis was that anodal tDCS would enhance mSI and cathodal tDCS would impair mSI. However this study found no evidence that modulating the excitability of the cerebellum changed the magnitude of mSI (Figure 3C).

In the computational motor control literature, the cerebellum is commonly considered to play a role in integrating predictions of the sensory consequences of movement with sensory feedback using an internal model of movement dynamics [77]. This process is essential for adaptation of future motor commands when sensory prediction errors are generated. The hypothesis that mSI is also capable of adaptation in response to sensory prediction error was explored in a study where vibration was used to generate sensory prediction error in a surround muscle [78].

Repetition of the movement with altered sensory feedback in a surrounding muscle lead to increases in the strength of mSI confirming that mSI is indeed subject to adaptation. In addition this study suggested that motor commands are not spatially limited to active muscles and that mSI may represent an electrophysiological correlate of the part of motor command responsible for controlling the non-active surround muscles. It remains an open question whether cerebellar stimulation applied during the training session may affect the adaptation process shown in this study.

Thus, the role of the cerebellum in the generation and regulation of mSI is currently uncertain. There does not seem to be a direct relationship between CBI and mSI. Nor does modifying the activity of the cerebellum by tDCS change any characteristics of mSI. It may be that mSI is a fundamental inhibitory mechanism within the nervous system, and subtle alteration of the activity of one of the nodes within the mSI network does not allow a meaningful change in mSI to be observed. Alternatively, the genesis of mSI may reside within other areas such as the basal ganglia nuclei or local networks within the motor cortex itself. The adaptation of mSI in response to sensory feedback does suggest that the cerebellum may have a regulatory role over adaptation of mSI. Studies investigating the underlying physiology of mSI and the disruption of mSI in disease states are on-going and are likely to provide further information on this topic in the future.

The cerebellum Stimulation and Motor Adaptation

One of the fundamental abilities of the central nervous system is to learn new motor behaviors. This ubiquitous capacity has been extensively investigated in humans and animals. Motor learning, broadly defined as the ability to acquire a new motor behavior that can be stored and expressed at a later time, involves different forms of learning with likely different neuronal mechanisms. One type is motor adaptation, typically defined as a short-term form of learning (minutes to hours) that is driven by sensory prediction errors [79,80]. This form of learning is commonly used to return baseline levels of performance in the presence of a perturbation, for example, when manipulating an

object with unknown or suddenly different characteristics (such as when learning to appropriately use a new tool or computer mouse). Another form is success-based learning, a slower process that is reinforced by successful goal completion [81,82]. For example, when learning a novel motor skill where new muscle activation patterns lead to new abilities (i.e. learning a new sport, playing a musical instrument or a videogame).

The cerebellum has been recognized as a crucial structure involved in motor learning, in particular in relation to motor adaptation forms of learning [83]. This knowledge comes from testing patients with cerebellar damage who typically experience a reduced capacity to adapt to novel environmental demands [84-86]. Similarly, neurophysiological studies in animals have indicated that motor adaptation may be mediated by LTD processes in cerebellar Purkinje cells [87,88]. Until recently motor adaptation processes have been mostly investigated using imaging techniques and/or employing patients with cerebellar damage. However, more recent developments in non-invasive brain stimulation techniques have permitted studying the role of the cerebellum in motor adaptation.

Taking advantage of the CBI measure and of the possibity to indirectly infer the level of excitability of the cerebellum if M1 excitability is not changing or if these changes are accounted for [9], our recent series of experiments has assessed the role of the cerebellum in different forms of motor adaptation. One study has investigated the potential physiological substrates underlying locomotor adaptation. This type of motor adaptation has been extensively studied using a split-belt paradigm [89]. Here participants' gait is assessed before, during, and after being exposed to walking on a treadmill where one belt (and therefore one leg) moves two to three times faster than the other belt. When this happens people experience a gait asymmetry or a limp. However, this can be corrected for within 10 to 15 minutes of walking at different belt speeds. In this paradigm it is evident that the individual learns to correct for the perturbation because sudden removal of the perturbation elicits a behavioral aftereffect characterized by a limp in the opposite direction. Using this task we showed that the magnitude of CBI is reduced proportionally to the amount of locomotor adaptation. This

correlation was present using two independent measures of learning and these effects were absent in control groups where learning did not occur. Importantly, M1 excitability did not change in association to this form of locomotor adaptation [89]. A second study investigating adaptation to a visual perturbation during reaching movements found similar results. Here subjects performed fast reaching movements to move a computer screen cursor to different targets. After a baseline period, an unexpected 30-degree visual rotation (perturbation) was applied to the cursor causing errors that could be adapted for by adjusting the reaching movements. Using this paradigm we found that CBI, but not M1 excitability, is reduced early on when subjects are correcting for the visual perturbation, followed by a return to baseline CBI levels once the perturbation is accounted for. Importantly, changes in CBI were not driven by the mere presence of errors that could not be corrected (i.e. random perturbations), suggesting that the cerebellum is crucially engaged during the successful reduction of large errors [90].

Altogether these studies indicated that CB-M1 connectivity changes are cerebellar dependent, rather than originating from M1, and are specifically linked to motor adaptation. Interestingly, the direction of CBI changes associated with learning seems consistent with the concept of LTD formation in cerebellar Purkinje cells [89,90].

The crucial role of the cerebellum in motor learning processes has been corroborated in another line of studies using tDCS, known to modulate the excitability of the cerebellum [9]. Applying anodal tDCS (the excitatory form of stimulation) over the cerebellum during visuomotor reaching [44,91] or locomotor adaptation [89] sped up the adaptation process resulting in faster error reduction. Importantly, when the inhibitory form of tDCS (cathodal) was applied over the cerebellum the locomotor adaptation rate was reduced, indicating a polarity specific effect of tDCS on the cerebellum [89].

In sum, it is possible to assess neurophysiological changes occurring in the cerebellum during adaptive motor learning and possibly other motor behaviors. Interestingly, this first series of studies

emphasize the role of the cerebellum during motor adaptation and indicate specific connectivity changes that can be targeted to augment behavioral processes. Indeed, applying tDCS to increase cerebellar excitability resulted in faster adaptation in reaching and locomotor tasks. These findings suggest that cerebellar stimulation has the potential to become a useful neurorehabilitation strategy to improve motor function in patients with neurological conditions.

Cerebellar tDCS and learning

Neuroimaging and clinical studies [92,93] show that besides motor functions, the human cerebellum processes cognitive and affective information, and plays a pivotal role in learning [94]. Thanks to research over the past years the cerebellar involvement in learning can be "observed" during several tasks. A further fascinating development now allows researchers to manipulate functions in the human cerebellum–- a "switch" for learning–– with cerebellar tDCS [95]. This simple, painless neuromodulatory technique entails delivering a direct current on the scalp over the cerebellum for minutes. Preliminary modeling studies showed that the electric field generated during cerebellar DCS [45] effectively reaches the cerebellum (Figure 4).

The first demonstration that cerebellar DCS could effectively influence cerebellar function came from a study from our laboratory describing its effects on proficiency in a working memory task in a group of healthy subjects [46]. Our experiments showed that cerebellar DCS blocked the practice-dependent increase in task proficiency. Evidence that tDCS over the dorsolateral prefrontal cortex increased task proficiency showed that the effect was specific, and given that cerebellar DCS left visual evoked potentials unchanged ruled out possible non-specific effects arising from visual cortex stimulation. Hence, cerebellar DCS somehow inhibited the *learning of learning*. This observation opened the way to experiments exploring how cerebellar stimulation and the cerebellum itself influence several other types of learning.

Extending cerebellar learning research, Jayaram et al. [43] conducted experiments on motor learning. They found that anodal cerebellar tDCS applied during walking improved locomotor adaptation, whereas cathodal tDCS worsened it, without affecting the rate of de-adaptation to the new locomotor pattern. The results suggested that cerebellar tDCS could be used as a tool to modulate *locomotor learning* and training in patients with neurological disorders with gait impairments.

In a series of experiments conducted in healthy subjects, Galea et al. [44] found that cerebellar tDCS enhanced the acquisition process during adaptive motor learning, further supporting the idea that cerebellar modulation by DCS affects visuomotor learning and demonstrated that the cerebellum and primary motor cortex have distinct functional roles in the processes of acquisition and retention during adaptive *motor learning*.

A final major advance comes from further experiments conducted in our laboratory concerning cerebellar DCS-induced changes in human *procedural learning*: i.e. learning involving a set of automatic, non conscious, and unintentional processes important in structuring skills, perceptions, and behavior [45]. We designed these experiments to investigate whether cerebellar tDCS influences procedural learning as measured by the serial reaction time task (SRTT) and hence whether this structure intervenes directly in procedural learning. Healthy young participants performed the SRTT, a mood and fatigue visual analogue scale (VAS) and a visual attention task, before and after receiving anodal and sham cerebellar tDCS. The main finding in this study is that anodal cerebellar tDCS improved procedural learning as indexed by the SRTT in healthy subjects. Because scores in mood and fatigue VAS and visual attention task remained unchanged, the cerebellar tDCS-induced changes in SRTT performance did not reflect changes in arousal or alertness. Hence, the learning benefits provided by anodal cerebellar DCS may have promising implications for designing motor learning protocols in patients with cerebellar disorders undergoing

neurorehabilitation and, possibly, for developing novel treatment strategies for deficits in procedural learning in conditions such as dyslexia and schizophrenia.

In conclusion, even though several important issues remain unresolved (i.e. the electric field geometry, the optimal stimulating electrode positioning, lack of polarity specificity in some behavioral tasks but not in others, the duration of the after effects, and off-line/on-line stimulation) and studies on larger sample sizes are needed, available data suggest that cerebellar tDCS can be a valuable tool to manipulate the cerebellar "cockpit" for the various learning processes.

The cerebellum and verbal working memory

Non-motor functions of the cerebellum have intensively been studied in the context of verbal working memory (VWM), the ability to maintain and manipulate (verbal) information that has just been experienced, but no longer exists in the external environment [96]. This essential cognitive faculty has been linked to a network of cerebral brain regions including prefrontal, parietal, and temporal cortices [96]. Converging evidence from numerous neuroimaging, clinical, and brain stimulation studies however suggests that not only cerebral regions, but also the cerebellum contributes to VWM [97,98].

VWM has been conceptualized as a multi-component system, consisting of a phonological store, which holds verbal information for a short delay, and an articulatory control process, which allows for refreshing information maintained within the phonological store by sub-vocal rehearsal [99]. Brain activity related to these VWM components has systematically been studied using item recognition paradigms such as the Sternberg task [100]. During the Sternberg task, participants see or hear a sequence of letters or digits ("encoding phase") which they have to maintain during a delay period ("maintenance phase"). Afterwards, they are asked to decide if a probe item matches one of the previously presented items ("retrieval phase"). Neuroimaging studies show that the

superior cerebellum, including lobule VI and Crus I, is activated during the encoding of newly presented items and co-activates with lateral prefrontal regions involved in speech processing. It has therefore been suggested that the superior cerebellum is involved in generating an articulatory trajectory required to initiate articulatory rehearsal [101,102]. In contrast, the right inferior posterior cerebellar lobules VIIb and VIII show task-related activity when items are maintained in mind over a delay and co-activate with inferior parietal regions implicated in storage-related processing. These findings led to the assumption that the inferior cerebellum contributes to phonological storage [101,102].

Although neuroimaging studies clearly identified cerebellar activation during different VWM phases, these activations do not necessarily relate to cognitive processes, but may also reflect task-related motor demands. Clinical studies in patients with cerebellar lesions, however, support the view that the cerebellum contributes to the cognitive demands of VWM [103]. A standard clinical test to capture VWM capacity is the Wechsler Memory Scale forward and backward digit-span test [104]. During this test, sequences of digits of increasing lengths are presented at a rate of one item per second, and participants are asked to recall the sequences in forward or backward order. Patients with focal cerebellar lesions, due to stroke or tumor resection, presented shorter forward and backward digit-spans, clearly confirming a cerebellar role in the cognitive processes involved [97,105]. These deficits are most evident in patients with lesions involving the posterior lobe of the cerebellum [97], which agrees with neuroimaging data [98] and known anatomical connections between the posterior cerebellum and prefrontal cortical regions involved in higher-order cognitive function [106].

Another way to study the causal role of the cerebellum in VWM is to use non-invasive brain stimulation techniques to alter the excitability of cerebellar neurons. As compared to patient studies, this approach offers the opportunity to study the cerebellar involvement in cognitive processes in healthy subjects without confounding factors such as pharmacological treatment, concomitant

damage to other cerebral brain regions, or compensatory plastic processes in cerebral regions due to cerebellar damage. A recent study applied tDCS over the right cerebellum in healthy subjects to investigate its effects on digit-spans [47]. Confirming a cerebellar role in VWM, the authors found shorter forward digit-spans after cathodal stimulation [47], which is known to decrease neuronal excitability in the motor cortex and cerebellar-M1 connectivity [9].

Another study administered single-pulses TMS over the right superior cerebellum during the encoding phase of the Sternberg task [107]. Due to TMS pulses, reaction times during memory retrieval substantially increased confirming the causal role of the right superior cerebellum in VWM.

A role of the cerebellum even in cognitive practicing was suggested by a study investigating the influence of cerebellar tDCS on the practice-dependent increase in proficiency in the Sternberg task [46]. The authors found that cathodal as well as anodal cerebellar tDCS impair the known practice-dependent increase in reaction times in this task. This finding is in line with recent models of cerebellar involvement in higher-order cognitive functions, which assume that the cerebellum automatizes cognitive processes originally taking place in other cerebral regions [108].

While the brain stimulation studies cited above found impairing effects of tDCS and TMS over the cerebellum on VWM, a recent tDCS study indicates that cerebellar stimulation can also enhance working memory performance [48]. In this study, participants were aurally presented with sequences of numbers and had to subtract a number heard from the number immediately before it. The authors found improved performance after cathodal tDCS as compared to anodal or sham tDCS. The crucial difference between Pope and Miall's task and the digit-span task as well as the Sternberg task is the higher degree of executive processing involved, suggesting that the effects of cerebellar stimulation differentially interact with different levels of executive demand. Future studies will have to prove whether the direction of tDCS effects is a matter of the degree of executive demand.

In sum, growing evidence from neuroimaging studies and clinical observations founded the theory that the cerebellum contributes to cognitive processes involved in VWM. Recent non-invasive brain stimulation techniques confirmed this theory and proved a causal role of the cerebellum in different sub-processes of this essential cognitive faculty.

Cerebellum and semantic associations

Cerebellum and Associative Processing: Introduction

The cytoarchitectural homogeneity of the cerebellum and its closed parallel loop-like connectivity with cerebrocortical areas ground the view that it applies its algorithms in a uniform fashion to its inputs [108]. These algorithms are well established to instantiate state estimation and feedforward control, fundamental for acquiring associations between and generating predictions about temporally contiguous events in sensory, motor, emotional and cognitive domains [109]. However, cerebellar contributions to semantic associations remain under-researched, while methodological issues with patient and imaging studies compromise the replication and interpretation of the few yet promising findings. Neurostimulation offers the potential of conducting methodologically robust experimentation capable of establishing direct cerebellar contributions to semantic associations.

‘Semantic Associations’, ‘Phrasal Associations’, and ‘Semantic Relations’

The terms ‘semantic’ and ‘associative’ are used in the literature so vaguely to the extent of denoting different cognitive processes. While semantic associations are admittedly not restricted to the linguistic domain, or, a fortiori, to inter-lexical relations, lexical priming studies help us establish a fundamental distinction of semantic associations from semantic categorical relations and phrasal associations: *semantic associations* reflect the association of concepts based on world knowledge, as in ‘instrument-action’ pairs (‘broom-sweep’), ‘script relations’ (‘theatre-play’), ‘locative relations’ (‘beach-house’), ‘compositional relations’ (‘brick-house’). On the contrary,

semantic categorical relations rely on featural similarities and taxonomic relations between units, as in paradigmatic co-exemplars within a category (‘pig-horse’), or in subordinate-superordinate pairs (‘storm-weather’). Finally, *phrasal associations* rely on the temporal contiguity of the particular units in processing, reflecting use rather than meaning, as in idioms (‘gift-horse’, ‘skeletons-closet’) [110].

Cerebellar Contributions to Processing Semantic Associations

The emergent picture suggests that the cerebellum contributes to processing semantic and possibly phrasal associations, but not semantic categorical relations. The patient examined by Fiez and colleagues generated inappropriate, yet categorically related responses in word-generation tasks (e.g. ‘small’, instead of ‘take’ or ‘swallow’, in response to ‘pill’). This could not be attributed to overall cognitive impairment, as their performance on tests of memory, intelligence, ‘frontal function’, and language skills was excellent, suggesting that cerebellar damage leaves semantic networks intact [111]. In another study [112], patients performed poorly in generating verbs for nouns, but selected the correct verb for a noun from a list of alternative responses, suggesting that semantic/syntactic representations were preserved. They also produceed appropriate subordinate term-responses to superordinate terms, suggesting that ‘‘[t]he right posterolateral cerebellum may be more involved in associative semantics than in categorical semantics’’ [112]. Non-motor-related cerebellar activations for verb-to-noun generation have also been shown in PET [113] and fMRI studies [114].

In a recent TMS study [115], noun-primes preceding verb-targets that could be categorically (e.g. ‘theft’-‘stealing’) or associatively related (e.g. ‘chef’-cooking’) were used in a lexical decision task. Stimulation of a lateral cerebellar site selectively boosted associative priming, while no effects were found after medial cerebellar stimulation or no stimulation at all. Moreover, neocerebellar TMS has been shown to also affect phrasal associative but not semantic categorical priming [116], as well as the acceleration of lexical decisions performed on previously encountered pairs of letter

strings [117]. These findings are in line with patient [118] and TMS [119] studies showing that cerebellar lesions impair verbal fluency by affecting phonemic rule-based word production, yet sparing semantic categorical rule-based performance.

Finally, evidence supports cerebellar involvement in semantic associations at the sentential level: In a TMS study, right lateral cerebellar stimulation selectively delayed participants' eye fixations to target objects predicted by the content of the sentences they were aurally presented with, while no effect was seen on fixations in sentences without predictable content [120]. Moreover, in a study employing a card-sequencing task, patients with left lesions performed poorly, selectively on script sequences based on pictorial material, while patients with right lesions only on script sequences requiring verbal elaboration [121].

Cerebellar Neurostimulation in Studies of Semantic Associations

The majority of evidence for cerebellar involvement in semantic associations comes from fMRI and patient studies. Methodological difficulties make the replication and interpretation of these findings problematic: cerebellar activation may be owed to sensorimotor and not cognitive task aspects. For instance, the lateral cerebellar activations yielded by Frings and colleagues were also found as a measure of noun reading in inner speech [112]. Similarly, the restricted subject pool of selective non-extra-cerebellar lesions, along with the great heterogeneity of the larger non-restrictive ones make the replication of findings such as verb generation impairments problematic [122].

Neurostimulation offers outstanding methodological advantages, allowing for larger subject pools and within-subjects repetition. It is conducted acutely, since time is insufficient for functional reorganization. Moreover, its sensorimotor effects are far from compromising the ability of subjects to participate in behavioral tasks or from inducing global cognitive impairments [123].

Above all, systematically comparing the effects of stimulation on cerebellar lobules and their cerebral cortical targets would offer the possibility to assess in a causal fashion whether cerebellar contributions to semantic associations are direct or modulatory.

The cerebellum and language. rTMS and predictive language processing

Over the last decades, a considerable body of evidence has implicated the cerebellum in language processing. This evidence includes neuropsychological data from cerebellar patients, anatomical and functional evidence for connectivity between cortical language areas and the cerebellum, neuroimaging studies in healthy participants, and crossover evidence from dyslexia studies [124]. The striking cytoarchitectonic homogeneity of the cerebellar cortex strongly suggests that it performs a uniform computation, whereby the cerebellum performs similar operations on different input signals and information is sent to different output targets [125]. Hence, it seems sensible to test the hypothesis that, in analogy to its predictive role in motor control [126], the cerebellum's contribution to linguistic function would also be characterised by short-term prediction and feedforward control.

Cerebellar patients may present with problems with lexical access and syntax, and with speech production deficits [124]. These deficits are interpreted as a failure of a cortico-cerebellar system comprised of frontal language areas and the lateral cerebellum. Indeed, posterolateral cerebellar areas are reciprocally connected to prefrontal cognitive areas in a closed-loop fashion [127]. Evidence from resting state functional connectivity studies demonstrates connections between the lateral cerebellum and frontal, parietal, and temporal language regions [128]. Moreover, patients with right cerebellar lesions show selective hypo-perfusion in Broca's area [124] and a recent fMRI study reported strong bidirectional effective connectivity between the right cerebellum and both left inferior frontal gyrus and left middle temporal gyrus [129]. Dyslexia has been linked to cerebellar deficits, and structural volumetric differences between dyslexics and

controls have been found in the right cerebellum [130]. Right cerebellar activity is often found in functional imaging of language tasks [98,131], and language localiser tasks can identify activity in the right cerebellum on an individual participant basis [132]. Thus there is good reason to expect that TMS-induced disruption of right cerebellar cortex will affect language, and that this disruption may be specific to feedforward prediction processes.

However, to date, there have been few studies of the impact on language processing of TMS targeted at the cerebellum, although there are studies on related cognitive aspects such as verbal working memory [107].

Argyropoulos [116] was the first to use TMS to depress cerebellar activity in a linguistic task. By applying continuous theta burst stimulation (cTBS) to the medial and lateral cerebellum in a lexical priming task, he reported a selective drop in accuracy of lexical decisions for medial stimulation, which was seen only in the first of two test sessions. The medial site and the temporary effect of the manipulation leave some open questions about whether this was a genuine impairment of lexical priming. Argyropoulos also reports that there is some overlap with oculomotor areas that might confound his results. However, in 2012, Argyropoulos and Muggleton [115] used cTBS over lateral cerebellum, and reported a 4-way interaction effect of selective enhancement of semantic associative noun-to-verb priming post-stimulation. This enhancement might reflect neocortical disinhibition [17,48], but it is also possible that their effect was in fact a reduction of the practice-induced improvement in response times in one condition, as such improvement was seen in other groups including no-stimulation controls. Arasanz et al. [119] have also used cTBS and reported reduced category switching (reduced phonemic and semantic fluency) after right cerebellar stimulation/depression.

Finally, Lesage et al. [120] applied rTMS over the right cerebellar hemisphere (directed towards Crus II) in a linguistic prediction task and monitored the latency of eye movements made towards pictures of target items referred to in spoken sentences. In the baseline, before application

of rTMS, there was a 350ms advantage in saccadic response times (Figure 5), if the verb predicted a single target object later in the sentence (as in “The man will sail the … boat/mountain/bird/car”), compared to non-selective verbs (“The man will watch the … boat/mountain/bird/car”). Following 10 minutes of 1 Hz rTMS, this advantage was reduced by 100ms. Importantly, there was no change in saccadic latencies in the non-predictive sentences, ruling out a general effect on language processing. There was also no change in eye movement kinematics, ruling out latency effects due to impaired oculomotor control. This evidence therefore implies that the predictive role previously ascribed to the cerebellum, based on motor studies [126], can be extrapolated to language.

Conclusion

The field of neurostimulation of the cerebellum with TMS and tDCS is gaining in popularity in the scientific community. Both techniques influence effectively cerebellar functions in the motor and non-motor domain. Several important technical issues remain unsolved, such as the exact positioning of electrode stimulation or the duration of the after effects, and require further studies. Besides the huge potential in terms of physiological studies of the cerebellar, the clinical applications in cerebellar disorders are likely numerous. Rigorous clinical trials should be encouraged to clarify whether these techniques might have a therapeutic role and how they might be included in the list of validated therapies.

Abbreviations

ADM: abductor digiti minimi

BCIs: brain-computer interfaces

CB: cerebellum

CBI: cerebellar-brain inhibition

cSP: cortical silent period

cTBS: continuous theta burst stimulation

DCS: direct current stimulation

EMG: electromyographic

FDI: first dorsal interosseous

fMRI: functional magnetic resonance imaging

LICI: long interval intracortical inhibition

LTD: long term-depression

LTP: long-term potentiation

M1: primary motor cortex

MEP: motor evoked potential

mSI: motor surround inhibition

PAS: paired associative stimulation

PET: positron emission tomography

PSP: progressive supranuclear palsy

rTMS: repetitive transcranial magnetic stimulation

SICI: short interval intracortical inhibition

SRTT: serial reaction time task

STDP: spike-timing dependent plasticity

tDCS: transcranial direct current stimulation

TES: transcranial electric stimulation

TMS: transcranial magnetic stimulation, single shock

VAS: visual analogue scale

VWM : verbal working memory

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Legends

Figure 1. Simplified scheme of the fronto-pontine-cerebello-thalamo-cortical loop. Solid lines indicate the cerebellar efferent pathways and dotted lines the cerebellar afferent pathways (from Groiss et Ugawa [8], with permission).

Figure 2. Means (± SEM) of MEP amplitude (in mV) are depicted at baseline (B0), immediately (P0), 30 min (P30) and 60 min (P60) after CB→M1 PAS (rhomboids: CB→M1 PAS_{10ms}; triangles: CB→M1 PAS_{6ms}; squares: CB→M1 PAS_{2ms}; crosses: CB→M1 $PAS_{Control}$). Filled symbols denote significant differences in MEP amplitude after CB→M1 PAS compared to B0. Note significant MEP suppression at P0 and P30 after CB→M1 PAS_{10ms} and at P0 – P60 after CB→M1 PAS_{6ms} but MEP potentiation at P0 – P60 after CB→M1 PAS_{2ms}. In contrast, MEP amplitude remained unchanged after CB→M1 $PAS_{Control}$.

Figure 3. A. mSI in the surround ADM muscle at the onset of an index finger flexion (FDI synergist). **B.** Non-toporaphic specific modulation of CBI at the onset of finger flexion (FDI synergist muscle, ADM surround muscle). **C.** Non significant change in mSI in ADM muscle 0minutes (T0) and 20minutes (T20) after cerebellar TDCS (intensity 2mAmps, duration 15minutes) (modified from Kassavetis et al. [70] and Sadnicka et al. [71]).

Figure 4. This preliminary modeling study shows that the active electrode over the cerebellum with an extra-cephalic reference generates the maximum electric field density in the cerebellum. Back and lateral views of the E field distributions on the cortex and cerebellum with the reference color scale for intensity (modified from Ferrucci et al. [45], with permission).

Figure 5. (a) Example of a scene in the Visual World paradigm.. In the Prediction condition the direct object of the sentence can be predicted from the verb whereas in the Control condition such prediction is not possible. (b) Target fixation latencies before and after rTMS to the right lateral

cerebellum. rTMS significantly reduced the advantage for the Prediction condition (solid line), while fixation latency in the Control condition (dashed line) was unaffected (modified from Lesage et al. [120], with permission).