Repetitive transcranial magnetic stimulation: a tool for human cerebellar plasticity

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Abstract

Non-invasive brain stimulation methods, such as repetitive transcranial magnetic stimulation (rTMS), are currently used to modulate the excitability of the cerebral cortex, providing important insights into mechanisms of cortical plasticity. Used to create long-lasting changes in the excitability of synapses, rTMS has been intensively investigated as a therapeutic tool in several neurological and psychiatric conditions and given some promising results. Recent studies have shown that rTMS of cerebellar structures is capable of inducing long-lasting changes in the excitability of cerebello-thalamo-cortical pathways. Thus, this novel approach may be important for investigating the functions of cerebellar plasticity. Indeed, cerebellar rTMS has been shown to modulate motor control, cognitive functions, emotion and mood. Moreover, recent studies seem to indicate that long-lasting modifications of cerebellar pathways could be usefully exploited in the treatment of several pathological conditions characterized by altered cortical excitability, such as Parkinson's disease, stroke, depression and schizophrenia. The high potential of cerebellar rTMS as a therapeutic tool in neurology could depend on the possibility of modulating several interconnected remote areas, through the activation of different systems, such as the cerebello-thalamo-cortical and limbic-thalamo-cortical networks.

KEY WORDS: cerebellum, depression, Parkinson, stroke, theta burst stimulation, TMS

Introduction

The cerebellum plays a role in several motor functions through its influence on the contralateral motor cortex and corticospinal outputs (1,2). Purkinje cells (PCs), the output neurons of the cerebellar cortex, have inhibitory connections with the deep cerebellar nuclei (DCN), which have a disynaptic excitatory pathway through the ventral thalamus to the motor cortex (3). Inhibitory PC output results in a reduction of excitatory output from DCN to the motor cortex, which leads to modification of motor control.

Furthermore, cerebellar PCs exhibit unique features of synaptic plasticity. In animal models, when two inputs, one from a climbing fiber and the other from a set of granule cell axons, are repeatedly associated in PCs, the input efficacy of the granule cell axons in exciting the PCs is persistently reduced (2). On the other hand, granule cell excitation may be persistently enhanced following theta burst or prolonged high frequency (100 Hz) electrical stimulation of the mossy fibers, indicating the occurrence of glutamatergic long-term potentiation (LTP) (4-6). These mechanisms are crucial for the spatial distribution of plasticity, local network activity and long-range modulation of different neural sites.

In humans, dysfunction of the cerebellum is classically associated with specific motor symptoms. Cerebellar ataxia is a clinical condition that is caused by lesions in the cerebellum or in the parts of the brain that connect with it, such as the cerebellar peduncles, the pons and the red nucleus. Since the cerebellum is responsible for synchronizing voluntary muscle movement throughout the body, cerebellar ataxia can result in uncoordinated walking (gait ataxia), reduced control of range of movement such as over- or under-shooting of targets (dysmetria), inability to maintain a steady posture (hypotonia), inability to maintain a steady rhythm (dysdiadochokinesia), intention tremor, dysarthria and nystagmus.

Patients with cerebellar damage often present with this cerebellar motor syndrome, yet cerebellar lesions can also result in the cerebellar cognitive affective syndrome, which includes executive, visuo-spatial, linguistic impairments, and affective dysregulation. The cerebellar motor syndrome arises when lesions involve mainly the anterior lobe and parts of lobule VI, interrupting cerebellar communication with cerebral and spinal motor systems. Cognitive impairments occur when posterior lobe lesions affect lobules VI and VII (including Crus I, Crus II, and lobule VIIB), disrupting cerebellar modulation of cognitive loops with cerebral association cortices. Neuropsychiatric disorders are manifested when vermis lesions deprive cerebro-cerebellar-limbic loops of cerebellar input (7).

In recent years, non-invasive brain stimulation methods have opened up the possibility of inducing plastic changes of the cerebral cortex in healthy subjects and in patients with neuropsychiatric disorders (8). Early studies focused on the primary motor cortex (M1), given that single-pulse transcranial magnetic stimulation (TMS) of M1 evokes a small twitch in contralateral hand muscles that can be measured with surface electromyography. When repetitive trains of TMS (rTMS) are applied over M1 at different intensities and frequencies, this response may be persistently increased or inhibited, implying the activation of cortical plastic mechanisms.

Low-frequency (~1Hz) stimulation reduces neural activity (9), whereas stimulation at higher frequencies – usually over 5Hz – increases cortical excitability (10). Moreover, a recently developed protocol, termed theta-burst stimulation (TBS), uses brief trains of higher frequencies (up to 50 Hz) and lower intensities of stimulation compared to other rTMS protocols, to induce focal long-lasting changes in cortical excitability (11), in analogy with the well-known protocols able to induce LTP or long-term depression (LTD) in animal brain slices (12). Used to create long-lasting (plastic) changes in the excitability of synapses within the motor system, rTMS has been intensively investigated as a therapeutic tool in the specialist area of movement disorders and in post-stroke rehabilitation, showing some promising results (8). Therefore, rTMS is currently emerging as a promising therapeutic tool for treating refractory neuropsychiatric diseases on the basis of neural network modulations, and can be considered a modern, non-invasive and non-painful alternative to electrical stimulation (13). Within this framework, in recent years several studies have investigated the potential impact of cerebellar rTMS as a means of studying mechanisms of cerebellar plasticity and its implications for various neurological and psychiatric disorders.

Mechanisms of cerebellar stimulation

The physiology of the cerebello-thalamo-cortical pathway activated by magnetic stimulation has recently been clarified. It has been proposed that cerebellar TMS activates the PCs of the superior cerebellum, this activation resulting in inhibition of the dentate nucleus, which is known to exert a background tonic facilitatory drive onto the contralateral M1 through a synaptic relay in the ventral lateral thalamus (14). This in turn leads to inhibition of the contralateral M1, due to a reduction of the dentato-thalamo-cortical facilitatory drive (15,16). A single TMS pulse applied over the lateral cerebellum 5-7 ms before magnetic stimulation of M1 causes inhibition of the motor-evoked potential (MEP) produced by motor cortical stimulation (cerebellar inhibition, CBI) (15,16). A recent study used magnetic cerebellar stimulation to investigate connections between the cerebellum and intracortical circuits within the contralateral M1 tested with paired pulse TMS protocols. Daskalakis and coworkers (17) reported that cerebellar stimulation is able to modulate both inhibitory and excitatory neurons in the human motor cortex, since magnetic stimulation of the cerebellum at different intensities changed the activity of short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) (18,19), and long-interval intracortical inhibition (LICI) (20) in the contralateral M1. Such intracortical circuits are thought to reflect the activity of distinct GABAergic and glutamatergic interneurons (19). Indeed, recent investigations showed that when rTMS is applied over the cerebellum at low frequency (1 Hz), long-lasting changes occur in the excitability of the contralateral M1. Following 600 pulses of cerebellar rTMS at 1 Hz, MEPs were enhanced up to 30 minutes and ICF was concurrently modified (21,22). Indeed, the same procedure interfered with the execution of cognitive tasks, presumably modulating cerebello-thalamo-cortical circuits targeting different cortical areas, such as the contralateral prefrontal and parietal cortices (23-26).

Recently, considering previous animal studies showing the existence of both LTP- and LTD-like mechanisms in the cerebellum (27-29), Koch and colleagues (30) demonstrated that the TBS protocols are able to induce bidirectional and long-lasting changes in the excitability of the cerebello-thalamo-cortical circuits in humans, and therefore to activate different mechanisms of synaptic plasticity when applied over the cerebellum. In healthy subjects, when different TBS protocols are applied over the lateral cerebellum, they exert profound changes in the excitability of the contralateral M1 (30) (Fig. 1).

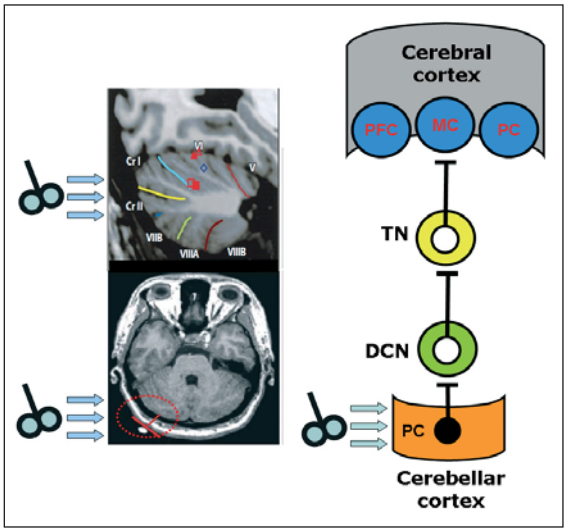

Figure 1 - Schematic representation of the pathways that are activated by repetitive stimulation of the cerebellum.
When the coil is positioned over the lateral cerebellum, the magnetic field reaches the posterior and superior lobules (left panel). rTMS likely induces changes in the excitability of the cerebellar cortex, leading to modifications in the excitability of the PC, which in turn modifies the excitatory disynaptic pathway of deep cerebellar (DCN) and thalamic nuclei (TN) cortical projections. Note that different cerebello-thalamo-cortical circuits project to different portions of the cerebral cortex.

Cerebellar continuous TBS (cTBS) induces a reduction of MEP amplitude, and decreases SICI and increases LICI circuits. On the other hand, cerebellar intermittent TBS (iTBS) brings about an increase in MEP amplitude and reduces LICI circuits. These changes may reflect the long-lasting modulation of motor cortical excitability driven by activation of cerebello-thalamo-cortical pathways (30), targeting specific GABAergic interneurons. Similar bidirectional changes were obtained by stimulating the lateral cerebellum by means of transcranial direct current stimulation (tDCS), a widely used non-invasive tool for brain stimulation able to induce powerful neuromodulatory changes in the excitability of the cortex (31). Galea and colleagues observed that the strength of CBI assessed by means of bifocal TMS was either increased or decreased for several minutes after the application of excitatory or inhibitory tDCS (i.e. anodal or cathodal tDCS respectively). These results have therefore highlighted the possibility of modulating the excitability of specific cerebellar circuits bidirectionally (32). Thus, these studies pave the way for modulating the ex-

citability of cerebellar circuits *in vivo*, which has clear implications as regards study of the physiology of cerebellar plasticity and possible translational approaches to the treatment of several psychiatric and neurological disorders, as recently demonstrated in the case of Parkinson's disease (PD) (see below). Given the very low intensity of stimulation adopted with TBS protocols, it is conceivable that stimulation is relatively focal and affects mainly the superficial layers of the cerebellar cortex (33). We proposed that low-intensity cerebellar TBS induces different plastic changes in PCs or in local interneurons, mainly affecting the ones with lower thresholds of excitability. This would result in indirect changes in the excitability of the dentate nucleus, which is known to exert a background tonic facilitatory drive onto the contralateral M1, through a synaptic relay in the ventral lateral thalamus (14). One possibility is that the projections from the ventral thalamus may be activated in different ways depending on the strength of the input from the dentate nucleus, which may induce increased or decreased activity of specific interneuronal populations within the contralateral M1, or over other cortical targets such as the prefrontal and the parietal cortices. Clearly this hypothesis remains highly speculative and further investigations are needed to clarify this issue.

Modulating cerebellar plasticity: possible impact on neuropsychiatric disorders

Recent studies (Table 1) have highlighted the growing importance of cerebellar stimulation in the field of vari-

Table I - Cerebellar repetitive transcranial magnetic stimulation (rTMS) protocols tested in healthy subjects and patients

Authors (ref.)	Protocol for cerebellar rTMS	Neurophysiological changes in contralateral M1	Behavioural changes	Neurological and psychiatric disorders
Oliveri et al., 2005 (21)	Lateral cerebellum 1 Hz, 90% RMT, 900 stimuli	↑ MEPs, ↓ ICF		
Fierro et al., 2007 (22)	Lateral cerebellum 1 Hz, 90% RMT, 900 stimuli	↑ MEPs, ↓ ICF		
Koch et al., 2007 (23)	Lateral cerebellum 1 Hz, 90% RMT, 900 stimuli		Alterations of millisecond time processing	
Torriero et al., 2004 (24)	Lateral cerebellum 1 Hz, 90% RMT, 900 stimuli		Reduced procedural learning	
Del Olmo et al., 2007 (33)	Lateral cerebellum 1 Hz, 90% RMT, 900 stimuli		Alterations of externally paced rhythmic finger movements	
Miall et al., 2007 (43)	Lateral cerebellum 20 Hz, 45% MSO		Reaching errors of movements planned on the arm's previous position	
Koch et al., 2008 (30)	Lateral cerebellum Continuous TBS, 80% AMT, 600 stimuli	↓ MEPs, ↑ LICI, ↓ SICI		
Koch et al., 2008 (30)	Lateral cerebellum Intermittent TBS, 80% AMT, 600 stimuli	↑ MEPs, ↓ LICI, ↑ SICI		
Schutter et al., 2009 (38)	Medial cerebellum 5 Hz, 80% RMT, 9000 stimuli		Increases in emotional responses to happy facial expressions	
Koch et al., 2009 (34)	Lateral cerebellum Continuous TBS, 80% AMT, 1200 stimuli (20 sessions)	↑ LICI, ↓ SICI		Long-lasting reduction of L-Dopa-induced dyskinesias in Parkinson's disease
Demirtas-Tatlidede et al., 2010 (41)	Medial cerebellum Intermittent TBS, 100% AMT, 600 stimuli			Significant improvements on negative subscale for schizophrenia

Abbreviations: M1=primary motor cortex; RMT=resting motor threshold; MSO=maximal stimulator output; TBS=theta burst stimulation; AMT=active motor threshold; MEP=motor evoked potentials; SICI=short intracortical inhibition; ICF=intracortical facilitation; LICI=long intracortical inhibition

ous neuropsychiatric disorders. Koch et al. (34) used the novel cTBS protocol to investigate whether modulation of cerebellar excitability may result in modification of levodopa-induced dyskinesias (LIDs) in PD patients. A group of PD patients was submitted to a two-week course of real or sham cTBS, applied bilaterally over the lateral cerebellum, to investigate the possible clinical efficacy of this procedure on LIDs. Cerebellar cTBS induced persistent clinical beneficial effects, reducing peak-dose LIDs for up to four weeks after the end of the daily stimulation period. These results were interpreted as a demonstration that cerebellar rTMS may also have an antidyskinetic effect in PD patients with LIDs, possibly due to long-lasting modulation of cerebello-thalamocortical pathways targeting the primary motor cortices (34). Moreover, given the potential role of non-invasive brain stimulation in stroke rehabilitation, cerebellar TBS could also be applied in patients suffering from cerebellar stroke.

The cerebellar vermis and fastigial nucleus that form part of the so-called limbic cerebellum (35,36) seem to be particularly involved in the regulation of emotion (7). They are connected with limbic/paralimbic regions in the frontal and temporal lobes, amygdala and hippocampus (37). In this setting, Schutter and colleagues recently showed that low-frequency rTMS applied to the medial part of the cerebellum in healthy volunteers impaired emotion regulation and augmented negative mood (38), while high frequency stimulation resulted in the enhanced implicit processing of happy facial expressions without changes in self-reported mood (39). More evidence supporting the idea that vermal TMS may modulate the activity of non-motor areas comes from combined TMS/EEG studies showing that single-pulse TMS over the vermis in healthy human volunteers induced an increased pre-frontal theta activity (40). While the lateral posterior cerebellum projects to the cortex via the dentate nucleus, the medial vermal cerebellum projects to limbic structures via the fastigial nucleus. Schutter and van Honk (40) thus proposed that vermal TMS may induce slow wave theta activity in the limbic-thalamocortical network.

Interestingly, in a recent study, ten sessions of iTBS were applied over the vermis in a small cohort of schizophrenic patients. In these patients, no serious adverse effect was observed and Calgary Depression Scale and self-report visual analog scales for Happiness and Sadness pointed to a significant mood elevation. Furthermore, certain neuropsychological examinations showed significant improvements in some memory functions (41). Therefore the improvement of negative symptoms, mood and cognition represents an encouraging initial step towards the treatment of neuropsychiatric disorders through non-invasive neuromodulation of the cerebellum.

Concluding remarks

Recent discoveries have revealed the existence of bidirectional plasticity at the level of the cerebellar synapses, with a postsynaptic form of LTP in the cerebellar parallel fiber-PC synapses providing a reversible mechanism for LTD (42). It is possible that the bidirectional effects observed with different protocols of rTMS may depend on the modulation of such described plastic changes, but clearly much work is needed to characterize the mechanisms of cerebellar plasticity in humans (43). Moreover, it has to be noted that magnetic stimulation of the posterior fossa probably induces other concomitant actions, activating not only the cerebellum but also the corticospinal tract antidromically (44). However, promising recent studies seem to indicate that long-lasting modifications of cerebellar pathways could be useful to treat several pathological conditions characterized by altered cortical excitability, such as epilepsy, PD, stroke, depression and schizophrenia. The high potential of cerebellar rTMS as a therapeutic tool in neurology could depend on the possibility of modulating several interconnected remote areas, through the activation of different systems, such as the cerebello-thalamo-cortical and the limbic-thalamo-cortical networks.

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