Non-invasive brain stimulation as a tool to study cerebellar-M1 interactions in humans

Sara Tremblay*, Duncan Austin, Ricci Hannah and John C. Rothwell

Abstract

The recent development of non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) has allowed the non-invasive assessment of cerebellar function in humans. Early studies showed that cerebellar activity, as reflected in the excitability of the dentate-thalamo-cortical pathway, can be assessed with paired stimulation of the cerebellum and the primary motor cortex (M1) (cerebellar inhibition of motor cortex, CBI). Following this, many attempts have been made, using techniques such as repetitive TMS and transcranial electrical stimulation (TES), to modulate the activity of the cerebellum and the dentate-thalamo-cortical output, and measure their impact on M1 activity. The present article reviews literature concerned with the impact of non-invasive stimulation of cerebellum on M1 measures of excitability and “plasticity” in both healthy and clinical populations. The main conclusion from the 27 reviewed articles is that the effects of cerebellar “plasticity” protocols on M1 activity are generally inconsistent. Nevertheless, two measurements showed relatively reproducible effects in healthy individuals: reduced response of M1 to sensorimotor “plasticity” (paired-associative stimulation, PAS) and reduced CBI following repetitive TMS and TES. We discuss current challenges, such as the low power of reviewed studies, variability in stimulation parameters employed and lack of understanding of physiological mechanisms underlying CBI.

Keywords: Cerebellum, Non-invasive brain stimulation, Paired-associative stimulation, Primary motor cortex, Theta burst stimulation, Transcranial direct current stimulation, Transcranial magnetic stimulation

Background

The cerebellum plays a fundamental role in the production and control of skilled movements [1, 2] via its outputs to both cortical and brainstem structures. Here we consider the evidence that it is possible to stimulate and influence the excitability of the cerebellum non-invasively through the scalp in conscious volunteers.

The main evidence that transcranial stimulation can activate neurones in the cerebellum comes from the work of Ugawa and colleagues who studied the specific connection between cerebellum and primary motor cortex (M1). Classically this pathway is comprised of the disynaptic dentate-thalamo-cortical (DTC) connection [3, 4] which exerts a facilitatory effect on the motor cortex. It originates from the dorsal region of the dentate nucleus and receives inhibitory input from likely targets of transcranial stimulation, the Purkinje cells in lobules VII and VIII of cerebellar cortex [2, 5]. Ugawa et al. showed that stimuli delivered by either high intensity electrical pulses applied across the mastoid processes or transcranial magnetic pulses around the inion reduced the excitability of corticospinal outputs from the M1 contralateral to the site of cerebellar stimulation if tested 5–6 ms later [6, 7]. This was termed cerebellar inhibition of motor cortex (CBI). They postulated that stimulation activated Purkinje cells which then inhibited ongoing excitatory output from dentate nucleus and removed facilitation from M1. The delay of 5–6 ms before suppression could be detected at M1 and was considered to be compatible with the estimated time for conduction and synaptic delays. This conclusion was supported by later findings showing that the effect was suppressed in patients with pathology affecting the cerebellar cortex or cerebellar output pathway [8]. It was also consistent with the finding that deep brain stimulation of the ventrolateral thalamus in patients with essential tremor could modulate CBI [9]. In addition to effects on corticospinal
excitability, stimulation of cerebellum was also found to interact with other local circuits in M1 that were involved in short interval intracortical inhibition (SICI), long interval intracortical inhibition (LICI) and intracortical facilitation (ICF) [10].

These early experiments also highlighted a number of other factors that could overlap with this effect and confound the simple interpretation that all the effects were caused by stimulation of cerebellum. Because the surface of the cerebellum is some distance from the scalp, relatively strong stimuli have to be applied to suppress M1. This activates sensory afferents in the neck which themselves can suppress M1 excitability. Luckily the latency of this effect occurs later (7–8 ms), meaning that a relatively pure cerebellar effect can only be guaranteed by testing with cerebellum-M1 intervals of 5–6 ms [11]. A second consequence of the high stimulus intensities is that the stimulation can spread deeper into the brainstem and activate the corticospinal tract at the pyramidal decussation. This can be avoided by carefully finding the threshold for corticospinal activation and then reducing the intensity below this by 10 % [6]. Given the potential for activation of corticospinal fibres, it remains an open question as to whether there could also be activation of sensory afferents in the medial lemniscus. This would lead to a short latency suppression of M1 excitability analogous to short latency afferent inhibition (SAI) usually evoked by direct stimulation of peripheral nerve.

A final unknown concerns the idea that CBI is due to withdrawal of ongoing facilitation. We know that facilitatory effects can have a rapid onset, which is consistent with the known duration of the rising phase of a cortical (extrastriate and thalamocortical) excitatory post-synaptic potentials (EPSP, 1–2 ms: [12–14]). There are no comparable ways to estimate how rapidly removal of ongoing facilitation could take effect. If we imagine instantaneous halting of all ongoing EPSPs, then the time taken for activity to fall should equal the total duration of the last set of EPSPs that arrived, which is at least 5–7 ms [13]. This is much slower than the very rapid onset of CBI (1–2 ms). The situation is unclear and needs to be resolved. Nevertheless, given these caveats, cerebellar inhibition of M1 is a useful tool for testing connectivity in the dentato-thalamo-cortical pathway.

More recently, a number of other methods have been introduced in an attempt to produce long lasting, “plasticity-inducing” changes in cerebellar function. These employ repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS). The rationale is that when these are applied directly to M1, they change the excitability of corticospinal output for the following 30–60 min by mechanisms that involve early stages of synaptic plasticity in cortical neurones. The assumption is that similar effects might be seen over cerebellum since animal studies have shown that cerebellar Purkinje cells exhibit unique features of synaptic plasticity, involving both long-term depression and long-term potentiation [15].

The aim of this article is to review relevant literature concerned with the impact of cerebellar “plasticity” protocols on M1 measures of excitability and plasticity in both healthy and clinical populations. Results will be discussed with regards to the specific aspect of M1 neurophysiology that was assessed following cerebellar stimulation in healthy individuals. This will be followed by a short summary of the impact of cerebellar stimulation in clinical populations.

When reviewing the evidence, we have borne in mind the evolutionary aspects of the much larger body of work in which the same or similar methods were applied to M1. In this case, early descriptions in small cohorts of volunteers appeared to be consistent with simple rules such as “high frequencies of rTMS increase and low frequencies decrease M1 excitability”, or “anodal TDCS excites whereas cathodal suppresses M1 excitability”. Later work, however, in larger populations has shown that the methods are highly variable, often with only 50 % of people responding in the “expected” way. The reasons for this are complex and probably multifactorial. Nevertheless, they probably explain a number of puzzles such as some of the failures to reproduce results and apparent contradictions in the literature. They might also be a factor that limits therapeutic potential.

Review
A systematic review of the literature was performed using the following databases: PubMed (2000 to Mar 2016) and Medline (2000 to Mar 2016). The following search keywords were selected: “TDCS”, “transcranial direct current stimulation”, “theta burst stimulation”, “TBS”, “repetitive transcranial magnetic stimulation”, “rTMS”, “primary motor cortex”, “cerebellum”. Initially, 70 articles corresponded to our search criteria. After carefully reviewing the abstracts we identified 23 articles that specifically investigated the effects of cerebellar stimulation on primary motor cortex neurophysiology (hand muscles) in clinical populations and healthy individuals. We excluded studies that assessed the effect of cerebellar stimulation using only behavioural measures or imaging methods other than TMS. Subsequently, we read the full texts of the final sample and searched references for additional articles, which led to the inclusion of five additional papers. Studies were only included if they were published in English and described thoroughly their methodology. Our final sample comprised 28 publications.
Primary motor cortex changes following cerebellar stimulation in healthy individuals

Three different types of plasticity protocols have been applied to the cerebellum: low and high frequency rTMS; intermittent and continuous theta burst stimulation (iTBS, cTBS); and TDCS or transcranial alternating current stimulation (TACS). The effects of these protocols when applied over M1 are considered to be well established, although they exhibit wide inter-individual variability (see [16–18] for methodological reviews). For instance, low frequency rTMS (≤1Hz) and cTBS are known to reduce M1 excitability presumably via modification of synaptic plasticity similar to long term depression, while high frequency rTMS (5–20 Hz) and iTBS are associated to increases in M1 excitability via long term potentiation-like mechanisms. TDCS is thought to induce similar bidirectional modifications of cortical excitability, i.e. decrease with cathodal stimulation and increase with anodal stimulation, presumably via changes in resting membrane potentials. Transcranial alternating current stimulation (TACS) can increase neuronal excitability through entrainment of desired neuronal firing frequency. When applied over the cerebellum, studies have generally employed the same stimulation parameters (e.g. duration, intensity) as for plasticity protocols over M1. A separate group of plasticity paradigms involves cerebellar-M1 paired-associative stimulation (CB-M1 PAS) [19]. This paradigm is thought to induce spike-timing dependent plasticity (STDP), by repeatedly pairing (120 pairs at a frequency of 0.25 Hz) a cerebellar afferent input with M1 suprathreshold TMS at different intervals (2, 6 and 10 ms).

The effects of these forms of cerebellar stimulation have been assessed on a range of outcome measures involving M1. Table 1 provides a description of each protocol. These include: 1) corticospinal excitability measured in terms of resting motor threshold (RMT); motor evoked potential (MEP) amplitude to standard suprathreshold TMS pulse and MEP recruitment curve (MEP<sub>RC</sub>); 2) intracortical excitability measures such as SICI ([20, 21]), LICI [22], cortical silent period (CSP: [23]), ICF [20], short interval intracortical facilitation (SICF: [24]), SA1 [25] and long latency afferent inhibition (LAI [26]); and 3) M1 plasticity assessed via PAS [27, 28] and TBS.

None of the types of cerebellar stimulation have been applied at an intensity sufficient to activate directly the dentate-thalamo-cortical connection. Thus any effects on M1 seem unlikely to be due to repeated application of CBI. They are more likely to involve persisting local changes in the cerebellum itself. A comprehensive description of the methodology and results is shown in Table 2 (rTMS and TBS), Table 3 (TDCS and TACS) and Table 4 (CB-M1 PAS). Table 5 gives a complete description of results for each outcome measure.

Effect of cerebellar stimulation on corticospinal excitability

None of the studies reports an effect of cerebellar “plasticity” paradigms on RMT. In contrast, MEPs evoked by a standard suprathreshold TMS pulse (usually set to produce a baseline average MEP of 1 mV peak-to-peak amplitude) may change. The effect is seen in M1 contralateral to the side of cerebellar stimulation and hence is appropriate for a cerebellar-induced effect.

However, the findings are variable and sometimes contradictory. Thus, cerebellar 1Hz rTMS (rTMS<sub>CB</sub>) has been investigated in four studies. Gerschlager et al. [29] were the first to assess the effect of rTMS<sub>CB</sub> on M1 MEP amplitude and found a significant increase that lasted up to 30 min after stimulation. This was substantiated by two studies [30, 31], although a more recent study found no significant change [32]. Cerebellar cTBS (cTBS<sub>CB</sub>), which like 1 Hz rTMS is usually claimed to have an inhibitory effect on M1 excitability, appears to have an opposite effect on cerebellum: cTBS<sub>CB</sub> reduced MEP amplitudes in 7 studies (and in 2 of them it also reduced the slope of the MEP recruitment curve) [33–39], but had no effect in two others [32, 40]. Cerebellar iTBS (iTBS<sub>CB</sub>) was reported to increase MEPs in one study [34] but there was no effect in two studies [32, 39].

Cerebellar TDCS (TDCS<sub>CB</sub>) has never been reported to have any effect on MEP amplitude or MEP<sub>RC</sub> following either anodal or cathodal stimulation [41–43]. In contrast to the usual “offline” study (i.e. where MEPs are evaluated before and after TDCS), Hamada et al. [44] noted an effect on MEPs if they were assessed during TDCS<sub>CB</sub>. However, the effect could only be observed if MEPs were evoked by low intensity stimuli in actively contracting muscle using an antero-posterior induced current in M1. It is therefore possible that the effect of TDCS<sub>CB</sub> on M1 excitability may be masked when MEPs are assessed with a suprathreshold stimulus applied using the standard posterior-anterior current direction.

Two further sets of observations have been reported but not yet replicated. In one of them 50 Hz TACS increased MEP amplitudes [45]. The other used a novel cerebellar-M1 paired-associative protocol in an attempt to engage STDP mechanisms [19]. One hundred and twenty pairs of cerebellum/M1 TMS pulses applied with an interstimulus interval of 2 ms increased MEPs whereas ISIs of 6 and 10 ms decreased MEPs.

Effect of cerebellar NIBS on CBI

Only 5 articles have reported effects on CBI. Most of them report reductions in the effectiveness of CBI: this occurs after 1 Hz rTMS<sub>CB</sub> or cTBS<sub>CB</sub> [32]; after TACS<sub>CB</sub>
As with SICI, only a few studies provide evidence that cerebellar “plasticity” protocols have an effect on ICF. No effects were observed after cTBS\textsubscript{CB} [34, 36, 40, 49], TDCS\textsubscript{CB} [41], 10 Hz rTMS\textsubscript{CB} [47] and CB-M1 PAS [19]. Reduced ICF was reported following iTBS\textsubscript{CB} [34]. Two studies reported that 1 Hz rTMS\textsubscript{CB} increased ICF levels [30, 47] and a third [31] observed a trend towards an increase of ICF using a 15 ms ISI and a significant decrease at an ISI of 10 ms.

**Other protocols**

There is very little data available for other protocols. LICI was reported to be unchanged by TACS\textsubscript{CB} [45], increased by cTBS\textsubscript{CB} [34, 49], and decreased by iTBS\textsubscript{CB} [34]. No change in the CSP was seen after 1 Hz rTMS\textsubscript{CB} [30], and both iTBS and cTBS [39]. SICF was unaffected by continuous or intermittent TBS\textsubscript{CB} [34], whilst no effects were observed after anodal TDCS\textsubscript{CB} [42, 46], cathodal TDCS\textsubscript{CB} [42], or cTBS\textsubscript{CB} [40, 49] for SAI. LAI was unchanged following cTBS\textsubscript{CB} [49].

### Cerebellar interactions with M1 plasticity

Most studies have focused on the impact of cerebellar modulation on motor cortex paired-associative stimulation (PAS). PAS entails pairing an afferent sensory input (usually median nerve stimulation) with a suprathreshold TMS pulse applied to motor cortex after a short interval. Adjusting this interstimulus interval varies the effect of the protocol in a way that mirrors the effect seen with animal models of spike-timing dependent plasticity. It is generally agreed that ISIs of 21.5 – 25 ms are facilitatory. In the reviewed articles, 5 out of 6 studies report significant interactions, and suggest that the effects are mediated by an effect of cerebellar activity on transmission of sensory input from median nerve to M1.

Popa et al. [50] found that cerebellar cTBS increased the amplitude, duration and spatial extent of the response to PAS25 (i.e. PAS with a 25 ms interval between median nerve stimulation and M1 TMS), whereas...
| Authors                  | Sample size | Stimulation target(s) | Protocol            | Parameters                  | Target muscle | Coil size                  | Timing of measurements | Findings                  |
|--------------------------|-------------|-----------------------|---------------------|-----------------------------|---------------|-----------------------------|------------------------|---------------------------|
| Gerschlager et al. (2002) [29] | 8 HC        | Right CRB             | 1 Hz rTMS           | 500 pulses 40 % MSO Biphasic | Right and left FDI | CRB: double-cone (110 mm) M1: figure-of-eight (90 mm) | Pre/Post N1 (0, 5, 10, 15 min), Post N2 (20, 25, 30 min) | CRB and control target: ↑ MEP only in Left FDI |
|                          | 5 HC        |                      |                     |                             |               | Neck: figure-of-eight (90 mm) |                        | As above                  |
| Oliveri et al. (2005) [30] | 10 HC       | Left CRB (main experiment) | 1 Hz rTMS       | 600 pulses 90 % RMT         | Left FDI      | M1 and CRB: figure-of-eight (70 mm) | Pre (3 blocks)/Post 0, 5, 10 min | ↑ MEP, ICF ↔ SICI, CSP |
|                          | 6 HC        | Left CRB (time course) | As above            |                             | As above      | As above                    | Pre (3 blocks)/Post 0, 30, 60 min | ↑ ICF (0–30 min) |
| Fierro et al (2007) [31]  | 8 HC        | Right lateral CRB (main experiment) | 1 Hz rTMS  | 900 pulses 90 % RMT (inion) | Right FDI      | M1 and CRB: figure-of-eight (70 mm) | Pre (2 blocks)/Post 0, 10 min | ↔ SICI, MEP ↓ ICF |
|                          | 4 HC        | Right posterior neck (control) | As above            |                             | As above      | As above                    | As above               | As above                  |
|                          | 4 HC        | Right lateral CRB (time course) | As above            |                             | As above      | As above                    | Pre/Post 5, 10, 15, 20 min | ↑ MEP (15–20 min) |
|                          | 8 HC        | Right lateral CRB (time course) | As above            |                             | As above      | Right FDI                   | Pre/Post 0, 10, 20 min | ↓ ICF (0–20 min) |
| Langguth et al. (2008) [48] | 10 HC       | Medial CRB Right lateral CRB | 1 Hz rTMS        | 1000 pulses 120 % RMT 4 randomized crossover | Right ADM      | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 0 | 1 Hz: ↑ SICI, ICF, ↔ RMT |
|                          | 10 HC       | Medial CRB Right lateral CRB | 10 Hz rTMS       | 600 pulses 80 % AMT 20 subjects randomly assigned to 7 exp. | Left and Right FDI | M1 and CRB: figure-of-eight (90 mm) | Pre/Post 0, 15, 30, 60 min | ↓ MEP, SICI |
| Koch et al. (2008) [34]  | 12 HC       | Left lateral CRB      | cTBS               | 600 pulses 80 % AMT         | As above      | As above                    | As above               | ↑ LICI; ↔ SICF |
|                          | 6 HC        | Left cervical root (control) | As above            |                             | As above      | As above                    | Pre/Post 0, 15, 30, 60 min | ↑ MEP, SICI, LICI |
|                          | 10 HC       | Left lateral CRB      | iTBS                | 600 pulses 80 % AMT         | As above      | As above                    | Pre/Post 0, 15, 30, 60 min | ↑ MEP, SICI; ↑ LICI |
| Koch et al. (2009) [48]  | 10 PD with LID | Left lateral CRB      | cTBS                | 600 pulses 80 % AMT         | As above      | As above                    | Pre/Post 0, 15, 30, 60 min | ↑ LICI; ↔ SICF |
|                          | 10 HC       |                      | As above            |                             | As above      | As above                    | Pre/Post 0, 15, 30, 60 min | ↓ LICI; ↔ SICF |
|                          |             |                      |                    |                             |               |                             |                        | Active (vs sham): ↓ SICI; ↑ LICI |
Table 2: Effect of cerebellar rTMS and TBS on primary motor cortex excitability (Continued)

| Study Reference | Participants | Side | CRB | Stimulation Type | Total Pulses | Intensity (%) | AMT | Crossover | Pre/Post | CBI Effect | MEP Effect | Other Effects |
|-----------------|--------------|------|-----|-----------------|--------------|--------------|-----|-----------|----------|-------------|-------------|---------------|
| Tab. 2          |              |      |     |                 |              |              |     |           |          |             |             |               |
| Popa et al. (2010) [32] | 10 HC | Right | CRB | 1 Hz rTMS | 900 pulses | 90% | Adj.RMT | Randomized crossover | Right FDI | CRB: double-cone (110 mm) | Pre/Post 1–10 min, Post 10–20 min | Right CRB (FDI + ADM); ↓ CBI ↔ MEP; ↔ CBI, MEP |
|                 | 6 HC | Right cervical root (control) | As above | As above | As above | As above | As above | As above | Cervical roots (FDI, ADM): ↔ CBI, MEP |
|                 | 6 HC | Left CRB | As above | As above | As above | As above | As above | As above | Left CRB: ↓ CBI (FDI), 10 min only; ↔ MEP (FDI, ADM) |
|                 | 10 HC | Right CRB | cTBS | iTBS | 600 pulses | 80% | Adj.AMT | | Right FDI | CRB: figure-of-eight (70 mm) | Pre/Post 0, 20, 40 min | cTBS: ↓ CBI (FDI) ↔ MEP; iTBS: ↔ CBI, MEP |
| Carrillo et al. (2013) [36] | 16 HC | Right CRB | cTBS | 600 pulses | 80% | AMT | | | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre/Post | HC: ↓ MEP, SICI |
|                 | 13 PD |                  | As above | 2 (On vs Off) | | | | | PD: ↔ MEP, SICI |
| Di Lorenzo et al. (2013) [40] | 12 HC | Right lateral CRB | cTBS | 600 pulses | 80% | AMT | | | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre/Post | HC: ↔ MEP, SICI, ICF, SLAI |
|                 | 12 AD | | | | | | | | AD: ↔ MEP, SICI, ICF; ↑ SLAI |
|                 | 8 HC | Right lateral CRB (control) | As above | As above | As above | As above | As above | As above | ↔ SAIC |
|                 | 8 HC | Right OC (control) | As above | As above | As above | 1 | | As above | ↔ MEP, SICI, ICF, SLAI |
| Popa et al. (2013) [50] | 14 HC | Right lateral CRB (Lobule VIII) | iTBSCiff → PAS25 → iTBSciff | 600 pulses | 80% | AMT | 3, pseudo-randomized | Right APB | Right ADM | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 0, 5, 10, 15, 25, 45 min | ↓ PAS25 (APB only); ↑ PAS25 (APB and ADM); ↔ iTBSAM1 |
| Hubsch et al. (2013) [49] | 9 HC | As above | cTBSciff → iTBSAM1 | As above | As above | As above | As above | As above | ↔ iTBSAM1 |
|                 | 25 HC | Lobule VIII CRB | cTBSciff → PAS25 → iTBSciff → PAS25 | 600 pulses | 80% | AMT | 3 randomized | Right APB | Right ADM | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 10, 15, 20, 25, 30 min | HC: ↓ PAS25; iTBS: ↑ PAS25; All conditions: ↔ SICI, ICF, LI, SAI, LAI |
|                 | 21 WD | | | | | | | | WD: cTBSciff ↔ PAS25; iTBSciff ↔ PAS25; All conditions: ↔ SICI, ICF, LI, SAI, LAI |
### Table 2  Effect of cerebellar rTMS and TBS on primary motor cortex excitability (Continued)

| Study             | Patient Group | CRB Location | Intervention | Control | Polarities | Pre/Post | Active (vs. sham) | Notes |
|-------------------|---------------|--------------|--------------|---------|------------|----------|------------------|-------|
| Kishore et al. (2014) [51] | 16 PD with LIDs | CRB ipsi to affected side (Lobule VIII) | cTBS$_{cb}$ → PAS$_{55}$ | Sham$_{rb}$ → PAS$_{55}$ | 600 pulses 80 % AMT | 2 randomized | Contra. APB | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 5, 15, 30 min | ↑ PAS$_{25}$ ↔ RMT, SICI, LIC, SLI, LAI |
|                   |               |              |              |         |            |          | Right APB        | As above | As above | ↔ PAS$_{25}$ |
|                   | 16 HC         | Right lateral CRB | As above | As above | 2 randomized | Contra. APB | M1 and CRB: figure-of-eight (70 mm) | Pre/week 2, 4, 8 post | ↑ PAS$_{25}$ |
|                   |               |              |              |         |            |          | Right APB        | As above | As above | ↔ iTBS$_{M1}$ |
| Bonni et al. (2014) [58] | 6 PCS | Damaged lateral CRB | iTBS | 600 pulses 80 % AMT | 10 (2 weeks) | 2 randomized | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre/Post | ↓ CBI; ↑ ICF; ↓ SICI |
| Brusa et al. (2014) [59] | 10 PSP | Left and right lateral CRB (2 min pause in between) | iTBS | 600 pulses 80 % AMT | 10 (2 weeks) | 2 randomized | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 2-week intervention (no further information) | ↑ CB; ↔ MEP, SICI, ICF, SAI |
| Koch et al. (2014) [57] | 10 CD | Bilateral CRB | iTBS | 600 pulses 80 % AMT | 10 (2 weeks) | 2 randomized | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre (Friday before the start of the 2-weeks treatment) Post (Monday after the end of the 2-weeks treatment) | Active (vs. sham): ↓ CB; ↔ ICF, SICI, CSP |
|                   | 10 CD         | Sham (coil angled 90°) | As above | As above | As above | As above | As above | As above | ↓ symptoms |
| Li Voti et al. (2014) [35] | 12 HC | Right lateral CRB | cTBS | 600 pulses 80 % AMT | 1 | 2 randomized | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 15, 30, 60 min | ↓ MEP |
| Di Biasio et al. (2014) [33] | 10 PD OFF | Ipsi. Damaged CRB (neck muscles) | cTBS | 600 pulses 80 % AMT | 2 randomized | Contra. FDI | M1 and CRB: figure-of-eight (90 mm) | Pre/Post 5, 25 min | ↑ MEP |
|                   | 11 HC         | Right CRB (neck muscles) | cTBS | 600 pulses 80 % AMT | 2 randomized | Right FDI | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 5, 45 min | ↓ MEP$_{PC}$; ET: ↔ MEP$_{PC}$ |
|                   | 13 RT         | Ipsi. CRB to tremor hand (neck muscles) | cTBS | 600 pulses 80 % AMT | 2 randomized | FDI (tremor hand) | M1 and CRB: figure-of-eight (70 mm) | Pre/Post 5, 45 min | ↓ MEP$_{PC}$ |
|                   | 13 HC         | Right CRB | cTBS | 600 pulses 80 % AMT | 3 randomized | cTBS | M1 and CRB: figure-of-eight (70 mm) | Pre/Post | ↔ MEPS |

AD Alzheimer’s disease, AMT active motor threshold, APB abductor pollicis brevis, CRB cerebellar brain inhibition, CBIRC cerebellar brain inhibition recruitment curve, CRB cerebellum, Contra contralateral, CSP cortical silent period, ET essential tremor, FDI first dorsal interosseus, HC healthy controls, ICF intracortical facilitation, Ipsilateral, LIC long interval intracortical inhibition, M1 primary motor cortex, MEP motor evoked potential, MEPS$_{PC}$ motor evoked potential recruitment curve, MSO maximal stimulator output, PAS paired-associative stimulation, PCS posterior circulation stroke, PD Parkinson’s disease, PSP progressive supranuclear palsy, SLI short latency afferent inhibition, SAI$_{PC}$ short latency afferent inhibition recruitment curve, SICI short interval intracortical inhibition, SICF short interval intracortical facilitation, WD writing dystonia
| Authors                      | Sample size | Electrode position                                      | Polarity       | Parameters       | Sessions | Target muscle | Coil size                      | Timing of measurements | Findings                                      |
|----------------------------|-------------|---------------------------------------------------------|----------------|------------------|----------|---------------|---------------------------------|------------------------|-----------------------------------------------|
| Galea et al. (2009) [41]    | 8 HC        | Right CRB (25 cm²)                                      | Anodal TDCS    | 2 mA 25 min      | 3        | FDI           | M1: figure-of-eight (70 mm)     | Pre/Post 0 min          | Cathodal cDCS (vs sham): ↓ CBI                |
|                            |             | Right buccinator muscle (25 cm²)                        | Cathodal TDCS  |                  |          |               | CRB: double-cone (110 mm)      |                        | ↔ MEP, SICI, ICF Anodal cDCS (vs sham): ↔ CBI, MEP, MT, SICI, ICF |
|                            | 8 HC        | As above                                                | Anodal TDCS    | As above 1 mA 25 min | 1        | As above      |                                |                        | Up CBR                                   |
|                            | 6 HC        | As above                                                | Cathodal TDCS  | 2 mA 25 min      | 2        | As above      |                                |                        |                                |
| Hamada et al. (2012) [42]   | 12 HC       | Right CRB (25 cm²)                                      | Anodal TDCS-PAS25 | 2 mA 15 min    | 3        | APB           | M1: figure-of-eight (70 mm)     | Pre/Post 0, 30 min      | Anodal and cathodal (vs sham): ↓ PAS25, ↔ SAI, MEPRC |
|                            |             | Right buccinator muscle (25 cm²)                        | Cathodal TDCS-PAS25 |                  |          |               |                                |                        |                                |
|                            | 8 HC        | As above                                                | Anodal TDCS-PAS21.5 | As above 2 mA 15 min | 2        | As above      |                                |                        | Anodal (vs sham): ↔ PAS21.5                  |
| Hamada et al. (2014) [44]   | 17 HC       | Right lateral CRB (25 cm²)                              | Sham TDCS-PAS21.5 | 2 mA 15 min    | 4        | APB           | M1: figure-of-eight (70 mm)     | Pre/Post 0, 15, 30 min | Anodal (vs sham): ↓ PAS25, ↔ PAS21.5          |
|                            |             | Right buccinator muscle (25 cm²)                        | Sham TDCS-PAS25 |                  |          |               |                                |                        |                                |
|                            | 10 HC       | As above                                                | Sham TDCS      | 2 mA 25 min      | 2        | As above      |                                | Online (5 min after onset of stimulation) |                                |
| Sadnicka et al. (2014) [56] | 10 WD       | Right CRB (25 cm²)                                      | Anodal TDCS-PAS25 | 2 mA 15 min    | 2        | APB           | M1: figure-of-eight (70 mm)     | Pre/Post 0, 30 min      | Anodal (vs sham): ↔ PAS25, CSP, MEPRC        |
|                            |             | Right buccinator muscle (25 cm²)                        | Sham TDCS-PAS25 |                  |          |               |                                |                        |                                |
| Strigaro et al. (2014) [52] | 8 HC        | Right CRB (25 cm²)                                      | Anodal TDCS-PASvar360p | 2 mA 30 min | 2        | APB           | M1: figure-of-eight (70 mm)     | Pre/Post 0 min          | Anodal (vs sham): ↑ PASvar360p          |
Table 3 Effect of cerebellar transcranial electrical stimulation on primary motor cortex excitability (Continued)

| Study                      | Participants | Cortical Site | Technique/Parameters | Anodal Duration | Sham Duration | Pre/Post Time Points | Anodal (vs sham): |
|----------------------------|--------------|---------------|----------------------|-----------------|---------------|----------------------|-------------------|
| Doeltgen et al. (2015)     | 14 HC        | Right lateral CRB | Anodal TDCS          | 2 mA            | 20 min        | FDI M1: figure-of-eight (70 mm) | ↓ CBI ↔ SAI       |
|                            |              | Right buccinator muscle | Sham              |                 |               | CRB: figure-of-eight |                   |
| Naro et al. (2016)         | 25 HC        | Right CRB (25 cm²) | 10 Hz TACS          | 2 mA            | 30 min        | Right and left APB M1: figure-of-eight CRB: double-cone | Pre/Post 0 min |
|                            |              | Right buccinator muscle (25 cm²) | 50 Hz TACS 300 Hz TACS | 4 randomized crossover | 3000 cycles |                         | 50Hz TACS: ↓ CBI, ↑ MEP, ↔ LICI |
|                            |              |                | 300 Hz TACS Sham TACS |                 |               |                      | ↑ CBI, ↔ MEP, LICI |

AP anterior-posterior, APB abductor pollicis brevis, CBI cerebellar brain inhibition, CBIRC cerebellar brain inhibition recruitment curve, CRB cerebellum, CSP cortical silent period, TACS transcranial alternating current stimulation, TDCS cerebellar transcranial direct current stimulation, FDI first dorsal interosseous, HC healthy controls, ICF intracortical facilitation, M1 primary motor cortex, MEP motor evoked potential, MEPRec motor evoked potential recruitment curve, PA posterior-anterior, PAS paired-associative stimulation, SAI short latency afferent inhibition, SICI short interval intracortical inhibition, WD writing dystonia.
cerebellar iTBS blocked the effect of PAS25. Similar results were reported by Hubsch et al. [49], while no effect of cTBS_CB on PAS25 was found by Kishore et al. [51]. In contrast, neither form of cerebellar TBS affected the response to motor cortex iTBS, consistent with the cerebellum being involved in the afferent arm of the PAS protocol.

Rather than examining the offline effects of cerebellar interventions, a series of studies reported the effects of online TDCS_CB. Hamada et al. [42] found that both anodal and cathodal TDCS_CB blocked the effect of PAS25. However, they found that anodal TDCS_CB had no effect on the response to PAS21.5. They argued that this was compatible with the idea that PAS21.5 and PAS25 have different mechanisms. One possibility was that PAS25 utilised an afferent pathway from median nerve to M1 that traversed cerebellar pathways, whereas PAS21.5 represented an interaction with more direct lemniscal inputs. Results compatible with this hypothesis were reported by Strigaro et al. [52].

### Primary motor cortex changes following cerebellar stimulation in clinical populations

The current systematic review identified 12 studies involving six different neurological disorders. Interestingly, 11 out of the 12 studies investigated the effect of intermittent or continuous TBS_CB. One study assessed the effect of TDCS_CB, whereas CB-M1 PAS and low- or high-frequency rTMS have not been investigated. Main findings for each clinical population will be briefly described below. See Table 6 for a complete description of results for each M1 outcome measure.

**Parkinson’s disease**

Although Parkinson’s disease (PD) is primarily associated with degeneration of the dopaminergic nigrostriatal pathways, recent studies have suggested that cerebellar circuits could be a potential therapeutic target [53]. For example, there is evidence for the presence of cerebellar hyperactivity in PD patients, which could either be compensating or contributing to motor deficits [54]. If the latter is true, then reducing cerebellar activity could restore normal interactions between M1 and the cerebellum [36], and have a positive impact on symptoms. The effect of a single (5 studies) and multiple (1 study) session(s) of cTBS_CB were assessed in this population.

In detail, in PD patients displaying levodopa-induced dyskinesia (LID), results from Koch et al. [48] show that a single session of cTBS_CB can modify M1 intracortical circuits (decreased SICI and increased LICI). While Kishore and colleagues [51] did not replicate this result, they show that both a single session as well as 10 sessions of cTBS_CB increase the effect of PAS25 applied over M1 and reduced symptoms of dyskinesia. In PD patients off dopaminergic therapy, decreased M1 cortical excitability was induced by a single session of cTBS_CB in two studies [33, 55], although only one of those was paralleled by functional changes, i.e. improvements in somatosensory temporal discrimination in PD patients off therapy [33]. In contrast, in PD patients displaying probable abnormal DTC pathway activity at baseline (reduced CBI levels), cTBS_CB did not modulate M1 cortical excitability and inhibition [36]. CBI levels were not reassessed following theta burst stimulation. Although current evidence remains limited, these studies suggest that the cerebellum may be involved in specific aspects of the pathophysiology of PD, such as levodopa-induced dyskinesias and altered sensory discrimination.

**Dystonia**

Dystonia is a movement disorder characterised by excessive involuntary muscle contraction. In the context of the present review, focal dystonia, i.e. cervical and writer’s dystonia, has been studied (three studies in total). In writer’s dystonia patients, Hubsch et al. [49] assessed the impact of cTBS_CB, iTBS_CB and sham TBS_CB on subsequent PAS applied to M1. As opposed to

---

**Table 4 Effect of cerebellar-M1 paired-associative stimulation on primary motor cortex excitability**

| Authors | Sample size | Stimulation target(s) | Protocol | Parameters | Sessions | Target muscle | Coil size | Timing of measurements | Findings |
|---------|-------------|-----------------------|----------|------------|----------|---------------|-----------|------------------------|----------|
| Lu et al. (2012) [19] | 13 HC | Right lateral CRB | CRB – M1 (PAS210ms) | CS: 90 % AMT 120 pairs 0.25 Hz | 1 | Left FDI | CRB: double-cone (110 mm) M1: figure-of-eight (90 mm) | Pre/Post 0, 30, 60 min | ↑ MEP, ↓ SICI CBI, ↔ ICF |
| 6 HC | As above | CRB – M1 (PAS210ms) | As above | 1 | As above | As above | As above | ↓ MEP, ↓ SICI CBI, ↔ ICF |
| 13 HC | As above | CRB – M1 (PAS210ms) | As above | 1 | As above | As above | As above | ↓ MEP, ↓ SICI CBI, ↔ ICF |
| 9 HC | As above | CRB – M1 (PAS210ms) | As above | 1 | As above | As above | As above | ↔ MEP, SICI, CBI, ICF |

CBI cerebellar brain inhibition, CRB cerebellum, FDI first dorsal interosseous, HC healthy controls, ICF intracortical facilitation, M1 primary motor cortex, MEP motor evoked potential, PAS paired-associative stimulation, SICI short interval intracortical inhibition
| Outcome measure | Plasticity protocol | Authors | Parameters | Findings |
|-----------------|---------------------|---------|------------|----------|
| 1. Corticospinal excitability |                      |         |            |          |
| Resting motor threshold | Anodal TDCS | Galea et al. (2009) [41] |             | ↔        |
|                        | Cathodal TDCS   | Galea et al. (2009) [41] |             | ↔        |
|                        | 1 Hz rTMS      | Langguth et al. (2008) [47] |             | ↔        |
|                        | 10 Hz rTMS     | Langguth et al. (2008) [47] |             | ↔        |
|                        | cTBS           | Di Lorenzo et al. (2013) [40] |             | ↔        |
|                        |                | Koch et al. (2008) [34] |             | ↔        |
|                        |                | Harrington et al. (2015) [39] |             | ↔        |
|                        | iTBS           | Koch et al. (2008) [34] |             | ↔        |
|                        |                | Harrington et al. (2015) [39] |             | ↔        |
| MEP amplitude          | Anodal TDCS    | Galea et al. (2009) [41] | 1 mV        | ↔        |
|                        | Cathodal TDCS  | Galea et al. (2009) [41] | 1 mV        | ↔        |
|                        | TACS           | Naro et al. (2016) [45] | 120 % RMT  | ↑ contralateral up to 15 min (50 Hz) |
|                        | 1 Hz rTMS      | Gerschler et al. (2002) [29] | 1–1.5 mV  | ↑ up to 30 min |
|                        |                | Oliveri et al. (2005) [30] | 1 mV       | ↑ contralateral up to 15 min ↔ ipsilateral |
|                        |                | Fierro et al. (2007) [31] | 120 % RMT  | ↔ 5–10 min ↑ 15–20 min |
|                        |                | Popa et al. (2010) [32] | 120 % RMT  | ↔        |
|                        | cTBS           | Koch et al. (2008) [34] | 1 mV       | ↓ up to 15 min |
|                        |                | Popa et al. (2010) [32] | 120 % RMT  | ↔        |
|                        |                | Di Lorenzo et al. (2013) [40] | 1 mV       | ↔        |
|                        |                | Li Voti et al. (2014) [35] | 1 mV       | ↓ up to 30 min |
|                        |                | Di Blasio et al. (2014) [33] | 120 % RMT  | ↓        |
|                        |                | Carrillo et al. (2013) [36] | 0.5–1 mV  | ↓ up to 40 min |
|                        |                | Harrington et al. (2015) [39] | 110 % RMT | ↓ (rest) ↔ (active) |
|                        | iTBS           | Koch et al. (2008) [34] | 1 mV       | ↑ up to 15 min |
|                        |                | Popa et al. (2010) [32] | 120 % RMT  | ↔        |
|                        |                | Harrington et al. (2015) [39] | 110 % RMT | ↔ (rest and active) |
|                        | CB-M1 PAS      | Lu et al. (2012) [19] | 1 mV       | ↑ (PAS2ms) ↓ (PAS6ms PAS10ms) |
### Table 5 Effect of cerebellum modulation on M1 neurophysiology assessed with TMS in healthy individuals (Continued)

| MEP recruitment curve | Anodal TDCS | Hamada et al. (2012) [42] | 100, 120 and 140 % RMT | ↔ | PA rest (online)  
| | Hamada et al. (2014) [44] | 100, 120, 140 and 160 % RMT | ↔ | AP rest (online)  
| | Cathodal TDCS | Galea et al. (2009) [41] | 100, 110, 120 and 140 % RMT | ↔ | PA active (online)  
| | Hamada et al. (2012) [42] | 100, 120 and 140 % RMT | ↔ | AP active (online)  
| | cTBS | Bologna et al. (2015) [38] | 100 to 150 % RMT | ↓ | 5 min, return to baseline 45 min  
| | | Bologna et al. (2015b) [37] | 100 to 140 % RMT | ↓ | up to 45 min  

2. Cerebellum brain inhibition

| CBI | Anodal TDCS | Galea et al. (2009) [41] | ISI: 5 ms  
| | | | CS: 5 % below bsAMT, and 5, 10, 15, 20, 25 % below bsAMT  
| | | | TS: 1 mV (adjusted post)  
| | Doeltgen et al. (2015) [46] | ISI: 5 ms  
| | | | CS: 100 % RMT (FDI)  
| | | | TS: 50 % MEPMAX  
| | Cathodal TDCS | Galea et al. (2009) [41] | ISI: 3 and 5 ms  
| | | | CS: 5 % below bsAMT  
| | | | TS: 1 mV (adjusted post)  
| | TACS | Naro et al. (2016) [45] | ISI: 7 ms  
| | | | CS: 90 % AMT  
| | | | TS: 120 % RMT  
| | 1 Hz rTMS | Popa et al. (2010) [32] | ISI: 5 ms  
| | | | CS: 90 % adjusted-RMT  
| | | | TS: 120 % RMT  
| | cTBS | Popa et al. (2010) [32] | ISI: 5 ms  
| | | | CS: 90 % adjusted-RMT  
| | | | TS: 120 % RMT  
| | iTBS | Popa et al. (2010) [32] | ISI: 5 ms  
| | | | CS: 90 % adjusted-RMT  
| | | | TS: 120 % RMT  
| | CB-M1 PAS | Lu et al. (2012) [19] | ISI: 7 ms  
| | | | CS: 95 % AMT (ionion)  
| | | | TS: 0.6–0.8 mV (FDI)  

4. Intracortical inhibition

| SICI | Anodal TDCS | Galea et al. (2009) [41] | ISI: 2 ms  
| | | | CS: 80 % RMT  
| | | | TS: 1 mV (adjusted post)  
| | Cathodal TDCS | Galea et al. (2009) [41] | ISI: 2 ms  
| | | | CS: 80 % RMT  
| | | | TS: 1 mV (adjusted post)  

↑ CBI recruitment curve at 20–25 % below bsAMT  
↓ (2 mA only, until 30 min post-TDCS)  
↑ (50 Hz: up to 15 min post-TACS)  
↑ (300 Hz: only 0 min post-TACS)  
↓ (contralateral only, until 30 min post)
| Procedure | Study (Year) | ISI | CS | TS |
|-----------|-------------|-----|----|----|
| 1 Hz rTMS | Oliveri et al. (2005) [30] | 1 and 3 ms | 70 % RMT | 1 mV (adjusted post) |
|           | Fierro et al. (2007) [31] | 2 and 4 ms | 80 % RMT | 120 % RMT (adjusted post) |
|           | Langguth et al. (2008) [47] | 2, 3, 4 and 5 ms | 90 % AMT, TS: 1 mV | ↔ |
|           | Langguth et al. (2008) [47] | 2, 3, 4 and 5 ms | 90 % AMT, TS: 1 mV | ↑ (averaged ISIs) |
|           | Carrillo et al. (2013) [36] | 1, 2, 3, 4 and 5 ms | 80 % AMT | ↓ (3 ms, contralateral only) |
|           | Di Lorenzo et al. (2013) [40] | 1, 2, 3, 4 and 5 ms | 80 % AMT | ↓ (2 and 3 ms, 0–20 min) |
|           | Hubsch et al. (2013) [49] | 2.5 ms | 70 % RMT | 130 % RMT (adjusted post) |
|           | iTBS Koch et al. (2008) [34] | 1, 2, 3, 4 and 5 ms | 80 % AMT | ↓ (100 ms) |
|           | CB-M1 PAS Lu et al. (2012) [19] | 2 ms | 70 to 90 % AMT (50 % inh.) | ↓ (all PAS ISIs) |
| LICI      | Naro et al. (2016) [45] | 50 ms | 120 % RMT | 120 % RMT |
|           | cTBS Koch et al. (2008) [34] | 100 and 150 ms | 120 % RMT | ↑ (100 ms) |
|           | Hubsch et al. (2013) [49] | 100 ms | 120 % RMT | 130 % RMT (adjusted post) |
|           | iTBS Koch et al. (2008) [34] | 100 and 150 ms | 120 % RMT | ↓ (100 ms) |
| CSP       | Oliveri et al. (2005) [30] | 30 % maximal force | 1 mV | ↔ |
|           | cTBS Harrington et al. (2015) [39] | 20 Newton force | 110 % RMT | ↔ |
| Technique   | Study                          | Parameters                                                                 |
|------------|--------------------------------|---------------------------------------------------------------------------|
| iTBS       | Harrington et al. (2015) [39]   | 20 Newton force, TS: 110% RMT                                            |
|            |                                | **↔**                                                                     |
| **5. Intracortical facilitation**                         |                                                                            |
| ICF        | Anodal TDCS Galea et al. (2009) [41] | ISI: 10 ms, CS: 80% RMT, TS: 1 mV (adjusted post)                        |
|            | Cathodal TDCS Galea et al. (2009) [41] | ISI: 10 ms, CS: 80% RMT, TS: 1 mV (adjusted post)                        |
|            | 1 Hz rTMS Oliveri et al. (2005) [30] | ISI: 7, 10 and 15 ms, CS: 70% RMT, TS: 1 mV (adjusted post)            |
|            | Fierro et al. (2007) [31]       | ISI: 7, 10 and 15 ms, CS: 80% RMT, TS: 120% RMT                          |
|            | Langguth et al. (2008) [47]     | ISI: 7, 8, 10, 15 and 20 ms, CS: 90% AMT, TS: 1 mV                      |
|            | 10 Hz rTMS Langguth et al. (2008) [47] | ISI: 7, 8, 10, 15 and 20 ms, CS: 90% AMT, TS: 1 mV                  |
|            | iTBS Koch et al. (2008) [34]    | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV                            |
|            | cTBS Koch et al. (2008) [34]    | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV                            |
|            | Carrillo et al. (2013) [36]     | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV                            |
|            | Di Lorenzo et al. (2013) [40]   | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV                            |
|            | Hubsch et al. (2013) [48]       | ISI: 15 ms, CS: 70% RMT, TS: 130% RMT (adjusted post)                  |
|            | CB-M1 PAS Lu et al. (2012) [19] | ISI: 10 ms, CS: 70 to 95% AMT                                           |
| SICF       | cTBS Koch et al. (2008) [34]    | ISI: 1.0, 1.3, 2.1, 2.5, 3.3, 4.1 ms, CS: 90% RMT, TS: 130% RMT       |

Table 5: Effect of cerebellum modulation on M1 neurophysiology assessed with TMS in healthy individuals (Continued)
Table 5: Effect of cerebellum modulation on M1 neurophysiology assessed with TMS in healthy individuals (Continued)

6. Afferent inhibition

| Modulation Type | Technique | Study Details | ISI | CS | TS |
|-----------------|-----------|---------------|-----|----|----|
| iTBS            | Anodal TDCS | Hamada et al. (2012) [42] | 15, 20 and 25 ms | 90 % RMT | 1 mV |
|                 | Cathodal TDCS | Hamada et al. (2012) [42] | 15, 20 and 25 ms | 90 % sensory threshold | 1 mV |
| cTBS            | Anodal TDCS | Hamada et al. (2012) [42] | N20 – 4 ms to N20 + 8 ms | 130 % sensory threshold | 1 mV |
|                 | Cathodal TDCS | Hamada et al. (2012) [42] | N20 – 4 ms to N20 + 8 ms | 130 % sensory threshold | 1 mV |

7. Motor cortex plasticity

| Modulation Type | Technique | Study Details | ISI | CS | TS |
|-----------------|-----------|---------------|-----|----|----|
| PAS             | Anodal TDCS | Hamada et al. (2012) [42] | 21.5 and 25 ms | 130 % sensory threshold | 1 mV |
|                 | Cathodal TDCS | Hamada et al. (2012) [42] | 21.5 and 25 ms | 130 % sensory threshold | 1 mV |
|                 | cTBS | Popa et al. (2013) [50] | 25 ms | 130 % RMT (adjusted post) | 1 mV |
|                 | iTBS | Popa et al. (2013) [50] | 25 ms | 130 % RMT (adjusted post) | 1 mV |
Table 5  Effect of cerebellum modulation on M1 neurophysiology assessed with TMS in healthy individuals (Continued)

| Group   | Modulation | Reference                  | Protocol Details                  | Note |
|---------|------------|----------------------------|-----------------------------------|------|
| CTBS    | iTBS       | Popa et al. (2013)         | 80% AMT, 600 pulses               | ↔    |
| iTBS    | iTBS       | Popa et al. (2013)         | 80% AMT, 600 pulses               | ↔    |

AMT: active motor threshold, CBI: cerebellar brain inhibition, CS: conditioning stimulus, Contra: contralateral, CSP: cortical silent period, HC: healthy controls, ICF: intracortical facilitation, Ipsi: ipsilateral, ISI: inter-stimulus interval, LAI: long latency afferent inhibition, LICI: long interval intracortical inhibition, MEP: motor evoked potential, PAS: paired-associative stimulation, SAI: short latency afferent inhibition, SICI: short interval intracortical inhibition, SICF: short interval intracortical facilitation, TS: test stimulus
| Outcome measure                        | Plasticity protocol | Authors                        | Population | Parameters | Findings                  |
|----------------------------------------|---------------------|--------------------------------|------------|------------|---------------------------|
| 1. Corticospinal excitability          |                     |                                |            |            |                           |
| Resting motor threshold                | cTBS                | Di Lorenzo et al. (2013) [40]  | AD         |            | ↔ (HC)                    |
|                                        | cTBS                | Kishore et al. (2014) [51]     | PD with LIDs|            |                           |
| MEP amplitude                          | cTBS                | Di Lorenzo et al. (2013) [40]  | AD         | 1 mV       | ↔ (HC)                    |
|                                        | Di Biasio et al. (2015) [33] | PD                        |            | 120 % RMT  | ↓ Off medication (HC)     |
|                                        | iTBS                | Carrillo et al. (2013) [36]    | PD         | 0.5–1 mV   | ↔ On or Off medication (HC)|
|                                        | Brusa et al. (2014) [59] | PSP                          |            | 1 mV       | ↔ (HC)                    |
| MEP recruitment curve                  | cTBS                | Bologna et al. (2015) [38]     | ET         | 100 to 150 % RMT | ↔ (HC) |
|                                        | Bologna et al. (2015b) [37] | RT (PD)                    |            | 100 to 140 % RMT | ↓ up to 45 min (HC) |
|                                        | Sadnicka et al. (2014) [56] | WD                          |            | 100 to 140 % RMT | ↔ (HC) |
| 2. Cerebellum brain inhibition         |                     |                                |            |            |                           |
| CBI                                    | cTBS                | Koch et al. (2014) [57]        | CD         |            | ↓ ISI 10 ms               |
|                                        | iTBS                | Bonni et al. (2014) [58]       | PCS        |            | ↓ all ISIs                |
|                                        | Brusa et al. (2014) [59] | PSP                          |            |            | ↑ all ISIs                |
| 3. Intracortical inhibition            |                     |                                |            |            |                           |
| SICI                                   | cTBS                | Koch et al. (2009) [48]        | PD         |            | ↓                         |
|                                        | Carrillo et al. (2013) [36] | PD                        |            |            | ↔ (HC)                    |
|                                        | Di Lorenzo et al. (2013) [40] | AD                        |            |            | ↔ (HC)                    |
|                                        | Hubsch et al. (2013) [49] | WD                          |            |            | ↔ (HC)                    |
| Table 6 Effect of cerebellum modulation on M1 neurophysiology assessed with TMS in clinical populations (Continued) |
|---------------------------------------------------------------------------------------------------------------|
| Koch et al. (2014) [57] CD | ISI: 1, 2, 3, 4 and 5 ms, CS: 80% AMT, TS: 1 mV | ↔ |
| Kishore et al. (2014) [51] PD with LIDs | ISI: 2.5 ms, CS: 70% RMT, TS: 1 mV | ↔ |
| iTBS | Bonni et al. (2014) [58] PCS | ISI: 1, 2, 3, 4 and 5 ms, CS: 80% AMT, TS: 1 mV | ↔ |
| Brusa et al. (2014) [59] PSP | ISI: 1, 2, 3, 4 and 5 ms, CS: 80% AMT, TS: 1 mV | ↔ |
| LICI | cTBS | Koch et al. (2009) [48] PD with LID | ISI: 100 and 150 ms, CS: 120% RMT, TS: 1 mV | ↑100 ms |
| Hubsch et al. (2013) [49] WD | ISI: 100 ms, CS: 120% RMT (adj. post), TS: 1 mV | ↔ | HC |
| Kishore et al. (2014) [51] PD with LIDs | ISI: 100 ms, CS: 110% RMT, TS: 1 mV | ↔ |
| CSP | Anodal TDCS | Sadnicka et al. (2014) [56] WD | 20% maximal force APB, TS: 120% RMT | ↔ |
| cTBS | Koch et al. (2014) [57] CD | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV | ↔ |
| 4. Intracortical facilitation | | | |
| cTBS | Koch et al. (2009) [48] PD | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV | ↔ |
| Carrillo et al. (2013) [36] PD | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV | ↔ | HC |
| Di Lorenzo et al. (2013) [40] AD | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV | ↔ | HC |
| Hubsch et al. (2013) [49] WD | ISI: 15 ms, CS: 70% RMT (adj. post), TS: 130% RMT | ↔ | HC |
| Koch et al. (2014) [57] CD | ISI: 7, 10 and 15 ms, CS: 80% AMT, TS: 1 mV | ↔ |
| Procedure | Authors | Population | ISI/AD | TS/CS | Outcome |
|-----------|---------|------------|--------|-------|---------|
| iTBS      | Bonni et al. (2014) [58] | PCS | 7, 10 and 15 ms | 80% AMT | ↑ 15 ms |
|           | Brusa et al. (2013) [59] | PSP | 7, 10 and 15 ms | 80% AMT | ↔       |
|           | Brusa et al. (2013) [59] | PSP | 16, 20, 24 and 28 ms | 1 mV | ↔       |
|           | Hubsch et al. (2013) [49] | WD | 20 ms | 130% RMT (adj.post) | ↔ (HC) |
|           | Hubsch et al. (2013) [49] | WD | 200 ms | 130% RMT (adj.post) | ↔ (HC) |
|           | Kishore et al. (2014) [51] | PD with LIDs | 20 ms | 130% sensory threshold | ↔ |
|           | Koch et al. (2014) [57] | CD | 25 ms | ↑ (topographic specificity) | ↔ (HC) |
|           | Kishore et al. (2014) [51] | PD with LIDs | 25 ms | ↑ (topographic specificity) | ↔ (HC) |
|           | Hubsch et al. (2013) [49] | WD | 25 ms | ↔ |
|           | Kishore et al. (2014) [51] | PD with LIDs | 25 ms | ↔ |

5. Afferent inhibition

6. Motor cortex plasticity

AD Alzheimer’s disease, AMT active motor threshold, CBBI cerebellar brain inhibition, CS conditioning stimulus, Contra contralateral, CSP cortical silent period, ET essential tremor, HC healthy controls, ICF intracortical facilitation, lpsl ipsilateral, ISI inter-stimulus interval, LAI long latency afferent inhibition, LICI long interval intracortical inhibition, LIDs levodopa-induced dyskinesias, MEP motor evoked potential, PAS paired-associative stimulation, PCS posterior circulation stroke, PD Parkinson’s disease, PSP progressive supranuclear palsy, RT resting tremors, SAI short latency afferent inhibition, SICI short interval intracortical inhibition, TS test stimulus, WD writing dystonia.
healthy individuals, patients did not display modulations of PAS. Similar findings were observed in a separate study in cervical dystonia that used anodal TDCS_CB and showed no impact on subsequent PAS applied to M1 [56]. These two studies suggest that loss of cerebellar control over sensorimotor plasticity could underlie alterations of specific motor programs involved in writing. In a sham controlled trial involving 2-weeks of cTBS_CB in twenty patients with cervical dystonia, “active” stimulation resulted in reduced CBI levels, as well as increased sensorimotor topographic-specific plasticity (PAS) and clinical improvements [57]. However, no changes were observed regarding levels of M1 intracortical inhibition (SICI, CSP) and facilitation (ICF). Results from this study suggest that targeting the cerebellum could help restore normal M1-CB pathways and reduce symptoms of cervical dystonia.

Posterior circulation stroke
Cerebellar ataxia is a common impairment after posterior circulation stroke (PCS). One study [58] found that 10 sessions of iTBS_CB applied over a 2-week period increased the excitability of M1 facilitatory circuits that were found to be defective at baseline (elevated ICF prior to iTBS_CB), while SICI levels remained unchanged. As iTBS_CB also reduced CBI in patients, the authors hypothesized that changes in M1 facilitatory circuits could have been mediated by a reduction in cerebellar tonic inhibition over M1. However, generalization of the results from this study is limited by the lack of a sham condition or control group.

Progressive supranuclear palsy
Progressive supranuclear palsy (PSP) is a parkinsonian syndrome characterised by symptoms such as postural instability. Cerebellar dentate nucleus dysfunction is thought to be involved. A single study assessed the effect of 10 sessions of iTBS_CB applied over a 2-week period in 10 patients with PSP [59]. No impact was found on motor inhibitory (SICI) and facilitatory circuits (ICF) or in sensorimotor inhibition. Although iTBS_CB did not modulate CBI in the single study performed with healthy controls (see [32]), it successfully increased the abnormally low levels of CBI observed at baseline in these patients [59]. Importantly, this was paralleled by clinical improvements. Although it remains to be replicated in a sham controlled experiment, this study suggests that applying iTBS to the cerebellum can potentially modulate the cerebellar-cortical pathway and alleviate symptoms in this clinical population.

Essential tremor
Essential tremor (ET) is a common movement disorder characterized by a combination of postural and kinetic tremors. The pathophysiology of the disorder is thought to involve the cerebellor-thalamo-cortical loops and probable cerebellar hyperactivity [60]. Bologna and colleagues [38] studied the effect of a single session of active versus sham cTBS_CB in 15 patients with ET compared with 10 healthy individuals. As opposed to control subjects, cTBS_CB did not change M1 excitability in ET patients. There was no effect on clinical tremor. This study points towards the presence of probable abnormal cerebellor-thalamo-cortical connectivity or abnormal cerebellar plasticity or function in ET. However, as CBI was not assessed in these patients, this study does not allow to distinguish the involvement of either probable cerebellar hyperexcitability or abnormal connectivity with motor cortex.

Alzheimer’s disease
Alzheimer’s disease (AD) is characterized by progressive neuronal degeneration that eventually affects cortical and subcortical regions, such as the cerebellum and primary motor and sensory cortices. Di Lorenzo et al. [40] studied the effect of a single session of cTBS_CB in 12 patients with AD and 12 healthy individuals. They showed that cTBS_CB could restore the initially reduced level of SAI to healthy controls levels [40], implying that the cerebellum may have direct influence on cholinergic and GABAergic dysfunctions in AD.

Conclusions
In this systematic review of the literature, results from 27 studies which assessed the impact of cerebellar non-invasive “plasticity” protocols on TMS measures of M1 activity were reviewed. The main conclusion is that apart from CBI, produced by high intensity single pulse stimulation, all other protocols lack consistency and require further study in larger numbers of individuals. This is not surprising since most of the reviewed studies were underpowered with an average of only 11 subjects for the main experiments (ranging from 6 to 25).

Despite this rather negative conclusion, there are two relatively consistent effects. One of them is reduced CBI following cerebellar rTMS or TDCS/TACS. Facilitation of CBI was seen in one study after anodal TDCS, but this was not replicated in another study. Inhibition of CBI was found regardless of the inhibitory or excitatory impact that the same protocols might have on M1. Why this is the case is unknown. It could be that the mechanisms of cerebellar after-effects differ from those in cortex, perhaps because they target different neuronal types and pathways: alternatively it could simply reflect the well-known variability of rTMS/TDCS effects and be a chance phenomenon.

A second repeatable consequence is an effect on spike-timing dependent plasticity assessed in M1, i.e.
PAS. Cerebellar stimulation affected median nerve PAS when it was evoked with an ISI of 25 ms (PAS25) but not with an interval of 21.5 ms (PAS21.5). Hamada et al. [42] suggested that cerebellar NIBS might act by altering sensory signals reaching M1 via the cerebellum (PAS25), while more direct afferent signals may be unaltered by cerebellar stimulation (PAS21.5). A recent study conducted in patients with cerebellar degeneration also points towards the implication of the cerebellum in PAS25, without affecting PAS21.5 [61]. Of note, cerebellar NIBS did not modify M1 response to TBS which would be consistent with an effect targeting the afferent input pathway of PAS.

Changes in M1 excitability (MEP amplitude) and paired pulse measures of M1 inhibition and facilitation are inconsistent. The studies on patients are too sparse to make any definitive conclusions.

Current limitations and future directions

The main limitation in all these studies is that as yet we have no information about what is stimulated and where it is. For M1, for example, we have direct evidence in primates and in humans from pyramidal tract recordings in spinal cord that TMS activates M1 output, and that the after-effects of rTMS/TDCS protocols can modulate the response of this output to TMS. Brain imaging studies show lasting effects on metabolism and on levels of neurotransmitters, but there is no comparable data for the cerebellum. The best indirect evidence for changes in cerebellar output comes from CBI, which is thought to activate Purkinje cells of the cerebellum because of its high intensity and latency of effects. However, as noted in the Introduction, even this can be questioned. “Plasticity” protocols for the cerebellum employ stimulus intensities smaller than used for CBI and therefore evidence of their action is indirect, and probably involve synaptic inputs projecting to the Purkinje cells. Some authors have hypothesized that the effects of those protocols may be mediated by the activation of low-threshold interneurons leading to pre and post synaptic interactions at the Purkinje cell synapse which in turn modulate the output of the dentate nucleus and the DTC pathway resulting in changes in M1 excitability [34]. However, this remain highly hypothetical and further studies should investigate the effect of modifying “plasticity” paradigms to account for the anatomical characteristics of the cerebellum, e.g. use of higher stimulation intensities and longer durations or “spaced” repeated sessions for TBS.

This review also highlights a lack of consistency in parameters used for stimulation across studies. For example, some studies have used a constant stimulation intensity (40 % MSO) for repetitive TMS, while other studies based the intensity on resting or active thresholds measured over M1 or on an adjusted RMT that takes into account the distance between the coil and the cerebellum. Additionally, there is high variability in intensity (e.g. percentage of brainstem threshold, of adjusted motor threshold, of resting motor threshold and of active motor threshold) and intervals (e.g. 3 to 7 ms) used to assess CBI. This may explain some of the discrepancy among studies. For example, Galea and collaborators [41] showed that CBI is modified following anodal TDCS only at intensities of 20–25 % of brainstem threshold. These inconsistencies and the lack of a systematic assessment of those parameters may contribute to the observed lack of clear pattern of changes for M1 excitability and may significantly influence the ability to effectively modulate the lateral cerebellum. Further studies should also investigate if the same rules of M1 NIBS apply to the cerebellum, such as bidirectional changes and the effect of prior muscle contraction on the ability to induce plastic changes.

Brain imaging could in the future help to test our ideas about how these methods influence activity in cerebellum and its projections, and assess for optimal stimulation parameters. More detailed animal models of direct recordings of cell activity could also help confirm the physiological mechanisms underlying cerebellar modulation and CBI. Studies which model the distribution of electric field produced by stimulation can also give some indication of likely mechanisms of action. However, such studies are complex because of the need to integrate field calculations with individual neural geometry, and as such they only remain “models” until tested adequately with experimental methods.

Although the above-mentioned limitations currently restrict the clinical application of cerebellar modulation, results from the 12 studies involving clinical populations showed that as for healthy controls, CBI can be reliably targeted by cerebellar NIBS. Findings from clinical studies also suggest that cerebellar modulation can provide valuable information on the integrity of the DTC pathway and sensorimotor plasticity mechanisms in M1, especially in the case of Parkinson’s disease and cervical dystonia. Although this suggests that cerebellar modulation holds promise in rehabilitation of the DTC pathway and cerebellar-M1 abnormal activity, clinical studies using cerebellar NIBS remain limited. For instance, several NIBS methods studied in healthy individuals, such as low-frequency rTMS, CB-M1 PAS and TACS, lack comparative studies in clinical populations. In addition, very few studies included a control group or a sham condition, and as for healthy populations, there is a lack of consistency in parameters used for stimulation.
Abbreviations
AD: Alzheimer’s disease; CB: Cerebellar; CBl: Cerebellar brain inhibition; CSP: Cortical silent period; CTBS: Continuous theta burst stimulation; DTC: Dentate-thalamo-cortical; EPSP: Excitatory post-synaptic potentials; ET: Essential tremor; ICF: Intracortical facilitation; ITBS: Intermittent theta burst stimulation; LAI: Long latency afferent inhibition; LIG: Long interval intracortical inhibition; M1: Primary motor cortex; MEP: Motor evoked potential; MEPc: Motor evoked potential recruitment curve; PAS: Paired-associate stimulation; PCE: Posterior circulation stroke; PD: Parkinson’s disease; PSP: Progressive supranuclear palsy; RMT: Resting motor threshold; rTMS: Repetitive transcranial magnetic stimulation; SAI: Short latency afferent inhibition; SICF: Short interval intracortical facilitation; SICI: Short interval intracortical inhibition; STDP: Spike-timing dependent plasticity; TACS: Transcranial alternating current stimulation; TBS: Theta burst stimulation; TDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation

Acknowledgements
Not applicable.

Funding
ST was supported by a Canadian Institute of Health Research fellowship award. RH and JCR were supported by a Medical Research Council grant (MR/K01384X/1). DA was supported by the Stroke Association and the Wellington Hospital.

Availability of data and materials
Not applicable.

Authors’ contributions
Substantial contributions to the topic and design of the review manuscript (ST, RH, DA, JCR); search of the pertinent literature (ST, RH, DA); drafting of the tables (ST, DA); drafting of the manuscript (ST, RH, DA, JCR); final approval of the version to be published (RH, LR, ST, JCR); All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Received: 1 July 2016 Accepted: 1 November 2016

Published online: 16 November 2016

References
1. Allen GJ, Tsukahara N. Cerebrocerebellar communication systems. Physiol Rev. 1974;54:957–1006.
2. Holdefer RN, Miller LE, Chen LL, Houk JC. Functional connectivity between cerebellum and primary motor cortex in the awake monkey. J Neurophysiol. 2000;84:585–90.
3. Ito M. The cerebellum and neural control. New York: Raven; 1984.
4. Hoover JE, Strick PL. The Organization of Cerebellar and Basal Ganglia Outputs to Primary Motor Cortex as Revealed by Retrograde Transneuronal Transport of Herpes Simplex Virus Type 1. J Neurosci. 1999;19:446–63.
5. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex. 2011;46:831–44.
6. Ugawa Y, Uesaka Y, Terasa Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol. 1995;37:703–13.
7. Ugawa Y, Day BL, Rothwell JC, Thompson PD, Merton P, Marsden CD. Modulation of motor cortical excitability by electrical stimulation over the cerebellum in man. J Physiol. 1991;441:57–72.
8. Di Lazzaro V, Molinari M, Restuccia D, Leggio MG, Nardone R, Fogli D, et al. Cerebro-cerebellar interactions in man: neurophysiological studies in patients with focal cerebellar lesions. Electroencephalogr Clin Neurophysiol Evoked Potentials Section. 1994;93:27–34.
9. Molnar GF, Sailer A, Gunraj CA, Lang AE, Lozano AM, Chen R. Thalamic deep brain stimulation activates the cerebellothalamiccortical pathway. Neurology. 2004;63:907–9.
10. Daskalakis ZJ, Paradiso GO, Christensen BK, Fitzgerald PB, Gunraj C, Chen R. Exploring the connectivity between the cerebellum and motor cortex in humans. J Physiol. 2004;555:589–700.
11. Werhahn KJ, Taylor J, Ridding M, Meyer BU, Rothwell JC. Effect of transcranial magnetic stimulation over the cerebellum on the excitability of human motor cortex. Electroencephalogr Clin Neurophysiol - Electromyogr Mot Control. 1996;101:58–66.
12. Irka A, Pavlides C, Keller A, Asanuma H. Long-term potentiation of thalamic input to the motor cortex induced by coactivation of thalamocortical and corticocortical afferents. J Neurophysiol. 1991;65:435–41.
13. West DC, Mercer A, Kirchhecker S, Morris OT, Thomson AM. Layer 6 cortico-thalamic pyramidal cells preferentially innervate interneurons and generate facilitating EPSPs. Cereb Cortex. 2006;16:200–11.
14. Kaneko T. Local connections of excitatory neurons in motor-associated cortical areas of the rat. Front Neural Circuits. 2013;7:75.
15. D’ Angelo E. The Organization of Plasticity in the Cerebellar Cortex: From Synapses to Control.1st ed. Prog Brain Res. Elsevier BV; 2014.
16. Nitsche MA, Paulus W. Transcranial direct current stimulation - Update 2011. Restor Neurol Neurosci. 2011;29:463–92.
17. Lewis PM, Thomson RH, Rosenfeld JJ, Fitzgerald PB. Brain Neuro modulation Techniques: A Review. Neurosci. 2016. doi:10.1177/107385816466707
18. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Ionto R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol. 2015;126:1071–107.
19. Lu MK, Tsai C-H, Ziemann U. Cerebellum to motor cortex paired associative stimulation induces bidirectional STDP-like plasticity in human motor cortex. Front Hum Neurosci. 2012;6:1–9.
20. Kujirai T, Caras M, Rothwell JC, Day BL, Thompson PD, Fernbert A, et al. Corticocortical inhibition in human motor cortex. J Physiol. 1993;471:501–19.
21. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol. 1996;496:873–81.
22. Vallés-Solé J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. Electroencephalogr Clin Neurophysiol. 1992;85:355–64.
23. Morton P, Morton H. Stimulation of the cerebral cortex in the intact human subject. Nature. 1980;285:227.
24. Tokimura H, Ridding MC, Tokimura Y, Armassian VE, Rothwell JC. Short latency facilitation between pairs of threshold magnetic stimuli applied to human motor cortex. Electroencephalogr Clin Neurophysiol - Electromyogr Mot Control. 1996;101:263–72.
25. Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Proifice P, Insola A, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol. 2000;523Pt 2:503–13.
26. Chen R, Corwell B, Hallett M. Modulation of motor cortex excitability by median nerve and digit stimulation. Exp Brain Res. 1999;129:77–86.
27. Stefan K, Kunesch E, Cohen LG, Benecke R, Claessen J. Induction of plasticity in the human motor cortex by paired associative stimulation. Brain. 2000;123Pt 3:572–84.
28. Carson RG, Kennedy NC. Modulation of human corticospinal excitability by paired associative stimulation. Front Hum Neurosci. 2013;7:823.
29. Gerschlager W, Christensen LOD, Bestmann S, Rothwell JC. rTMS over the cerebellum can increase corticospinal excitability through a spinal mechanism involving activation of peripheral nerve fibres. Clin Neurophysiol. 2002;113:1435–40.
30. Olivieri M, Koch G, Torriero S, Caltagirone C. Increased facilitation of the corticocortical afferents. J Neurophysiol. 1991;65:435–41.
31. Oliveri M, Koch G, Torriero S, Caltagirone C. Increased facilitation of the corticocortical afferents. J Neurophysiol. 1991;65:435–41.
32. Popa T, Russo M, Meunier S. Long-lasting inhibition of cerebellar output. Brain Stimul. 2010;3:161.
34. Koch G, Mori F, Marconi B, Codécé C, Pecchioli C, Salerno S, et al. Changes in intracortical circuits of the human motor cortex following theta burst stimulation of the lateral cerebellum. Clin Neurophysiol. 2008;119:2559–69.

35. Li Viet P, Conte A, Rocchi L, Bologna M, Khan N, Leodori G, et al. Cerebellar continous theta-burst stimulation affects motor learning of voluntary arm movements in humans. Eur J Neurosci. 2014;39:124–31.

36. Carillo F, Palomar FJ, Conde V, Díaz-Corales FJ, Porcacchia P, Fernández-Del Olmo M, et al. Study of cerebello-thalamocortical pathway by transcranial magnetic stimulation in Parkinson's disease. Brain Stimul. 2013;6:582–9.

37. Bologna M, Di Bisio F, Conte A, Iezzi E, Modugno N, Berardelli A. Effects of cerebellar continuous theta burst stimulation on resting tremor in Parkinson's disease. Parkin Relat Disord. 2015;21:1061–6.

38. Bologna M, Rocchi L, Leodori G, Paparella G, Conte A, Kahn N, et al. Cerebellar Continuous Theta Burst Stimulation in Essential Tremor. Cerebellum. 2015;14:133–41.

39. Harrington A, Hammond-Tooke GD. Theta burst stimulation of the cerebellum modifies the TMS-evoked N100 potential, a marker of GABA inhibition. PLoS One. 2015;10:1–5.

40. Di Lorenzo F, Martorana A, Ponzo V, Bonni S, D'Angelo E, Caltagirone C, et al. Cerebellar theta burst stimulation modulates short latency afferent inhibition in Alzheimer's disease patients. Front Aging Neurosci. 2013;5:2.

41. Galea JM, Jayaram G, Ajagbe L, Celnik P. Modulation of Cerebellar Excitability by Polarity-Specific Noninvasive Direct Current Stimulation. J Neurosci. 2009;29:9115–22.

42. Hamada M, Strigaro G, Murase N, Sadnicka A, Galea JM, Edwards MJ, et al. Cerebellar modulation of human associative plasticity. J Physiol. 2012;590:2365–74.

43. Sadnicka A, Hamada M, Bhatia KP, Rothwell JC, Edwards MJ. Cerebellar stimulation fails to modulate motor cortex plasticity in writing dystonia. Mov Disord. 2014;29:1–4.

44. Hamada M, Galea JM, Di Lazzaro V, Mazzone P, Ziemann U, Rothwell JC. Two Distinct Interneuron Circuits in Human Motor Cortex Are Linked to Different Subsets of Physiological and Behavioral Plasticity. J Neurosci. 2014;34:12837–49.

45. Naro A, Leo A, Russo M, Cannavò A, Milardi D, Bramanti P, et al. Does Transcranial Alternating Current Stimulation Induce Cerebellar Plasticity? Feasibility, Safety and Efficacy of a Novel Electrophysiological Approach. Brain Stimul. 2016;9(3):388–97.

46. Doeltgen SH, Young J, Bradnam LV. Anodal Direct Current Stimulation of the Cerebellum Reduces Cerebellar Brain Inhibition but Does Not Influence Afferent Input from the Hand or Face in Healthy Adults. Cerebellum. 2015;1:9–15.

47. Langguth B, Eichhammer P, Zowe M, Landgrebe M, Binder H, Sand P, et al. Changes in interneuron networks involved in human associative plasticity. Brain Stimul. 2014;7:658–64.

48. Ni Z, Chen R. Transcranial magnetic stimulation to understand pathophysiology and as potential treatment for neurodegenerative diseases. Transl Neurodegener. 2015;4:22.

49. Wu T, Hallett M. The cerebellum in Parkinson's disease. Brain. 2013;136:696–709.

50. Bologna M, Di Bisio F, Conte A, Iezzi E, Modugno N, Berardelli A. Effects of cerebellar continuous theta burst stimulation on resting tremor in Parkinson's disease. Parkinsonism Relat Disord. 2015;21:1–6.

Submit your next manuscript to BioMed Central
and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit