HHS Public Access

Author manuscript

Cerebellum. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Cerebellum. 2015 April ; 14(2): 171–174. doi:10.1007/s12311-014-0607-y.

Understanding and modulating motor learning with Cerebellar stimulation

Pablo Celnik, MD

Johns Hopkins University, Departments of Physical Medicine and Rehabilitation, Neurology and Neuroscience

Abstract

Non-invasive brain stimulation techniques are a powerful approach to investigate the physiology and function of the central nervous system. Recent years have seen numerous investigations delivering transcranial magnetic stimulation (TMS) and or transcranial direct current stimulation (tDCS) to the cerebellum to determine its role in motor, cognitive and emotional behaviours. Early studies have shown that it is possible to assess cerebellar-motor cortex (CB-M1) connectivity using a paired-pulse TMS paradigm called cerebellar inhibition (CBI), and indirectly infer the state of cerebellar excitability. Thus, it has been shown that CBI changes proportionally to the magnitude of locomotor learning and in association with reaching adaption tasks. In addition, CBI has been used to demonstrate at a physiological level the effects of applying TMS or tDCS to modulate, up or down, the excitability of cerebellar-M1 connectivity. These studies became the fundamental substrate to newer investigations showing that we can affect motor, cognitive and emotional behaviour when TMS or tDCS targeting the cerebellum is delivered in the context of performance. Furthermore, newer investigations are starting to report the effects of cerebellar non-invasive stimulation to treat symptoms associated with neurological conditions such as stroke and dystonia. Altogether, non-invasive cerebellar stimulation can potentially become a game changer for the management of conditions that affect the cerebellum given the scarcity of current effective therapeutic options. In this brief manuscript, some of the current evidence demonstrating the effects of cerebellar stimulation to modulate motor behaviour and its use to assess physiological processes underlying motor learning are presented.

Introduction

The cerebellum has long being recognized as a crucial structure involved in motor control and learning. Patients with cerebellar disease clearly show a vast array of impairments, where abnormal motor control and coordination (ataxia) is one of the cardinal features. Studies in patients with cerebellar lesions and degeneration have helped to characterize the role of the cerebellum in some forms of motor learning. This approach (i.e. investigations in patient populations with lesions in the CNS) however has some limitations. Specifically, the

Corresponding author: Pablo Celnik, Johns Hopkins Hospital, 707 North Broadway Ave, Room G04, Baltimore, MD 21205, Phone: (443) 923-2724 or (443) 923-2753; Lab Fax: (443) 923-2715, pcelnik@jhmi.edu.

Conflict of interest statement:
The author has not conflict of interests.

phenotypic description of what is different relative to a healthy matched control is due to the deficit plus the ability (or the lack of) of the rest of the CNS to compensate for that deficit.

Imaging studies have also helped to shape the understanding of the role of the cerebellum when alert humans perform different behaviors. This powerful technique also has some limitation such as poor temporal resolution and decreased capacity to demonstrate whether cerebellar activation changes are due to excitatory or inhibitory processes. In this context, non-invasive brain stimulation techniques, namely transcranial magnetic stimulation (TMS) and direct current stimulation (tDCS), have brought additional fundamental insight on the understanding of the physiological role of the human cerebellum in different motor, cognitive and emotional tasks.

What are some of the physiological cerebellar mechanisms associated to motor learning?

Using first transcranial electrical stimulation [1] and later TMS [2] Ugawa and colleagues demonstrated that stimulation over the cerebellum resulted in modulation of the responses to a second stimulus delivered over the primary motor cortex (M1). This group and others mapped the characteristics of this effect. Specifically they showed that delivering a TMS pulse (conditioning stimuli, CS) 5 to 7msecs over the contralateral cerebellar hemisphere prior to a second stimulus over M1 (test stimuli, TS) resulted in inhibition of the TS [3–4]. This phenomena, called cerebellar inhibition (CBI), was interpreted to be the resultant of activation of Purkinje cells by the CS leading to inhibition of the deep cerebellar nuclei which in turn has a disynaptic excitatory connection with M1. In other words, activating Purkinje cells inhibited a facilitatory pathway resulting in the temporary inhibition of M1. Importantly, these early studies explored several control conditions to ensure that the CS effects were not due to direct activation of the brachial plexus, or due to direct activation of the corticospinal track, or some other non-specific stimulation effect (i.e. startle response).

The investigations demonstrating the presence of CBI had an important implication, namely that it may be possible to assess the magnitude of inhibition the cerebellum exerts over M1 at a given point. In addition, they suggested that if one can rule out changes in M1 excitability then the modulation of CBI has to be the resultant of excitability changes in the cerebellum or in the thalamic relay. Based on this concept Jayaram et al. performed a study assessing changes in CBI before and after young healthy adults performed a locomotor adaptation task [5]. This form of learning is thought to depend on the cerebellum given that patients with cerebellar degeneration [6], but not patients with cerebral strokes [7], cannot learn the task. In addition, animal models had previously shown that this form of learning is mediated via LTD transformation in Purkinje cells [8]. Thus, assessing CBI changes after training of this task was ideal to determine whether TMS is capable of detecting changes in cerebello-M1 connectivity in the context of behaviour. Jayaram found that learning was associated with a decrease in the magnitude of CBI (the inhibitory tone the CB exerts over M1) in the absence of excitability changes in M1. In addition, the authors noted a correlation where those individuals learning the most this task experienced the largest reduction in CBI. Importantly, when the same individuals performed two different control tasks where there was no learning required they did not change the magnitude of CBI relative to baseline.

More recently Schlerf et al. replicated these results showing that healthy individuals learning to deal with a visual-hand perturbation motor task (visuomotor adaptation) also experience reduction in CBI in absence of M1 excitability changes. This effect was more prominent early in the task performance where large error reduction takes place returning towards baseline CBI levels at the end of the training session [9]. Altogether, these studies demonstrated that using TMS it is possible to assess the connectivity levels between the cerebellum and M1 in the context of behaviour.

Why adaptation learning results in reduction in CBI? Animal studies have shown that learning is mediated in part by long-term depression (LTD) in Purkinje cells [10]. It is possible then that if humans undergo a similar process when learning a task that involves LTD changes in Purkinje cells these neurons will become less excitable. Consequently, Purkinje cells will be less responsive to the conditioning TMS pulses which would in turn result in decrease modulation of the test stimuli delivered over M1 (Figure 1). In other words, the pathway tested with the CBI technique is not responsive to the conditioning TMS pulse.

Can we modulate cerebellar excitability using non-invasive brain stimulation (NIBS)?

Studies in 90's and early 2000's described the ability of TMS and tDCS to modulate excitability [11–12]. For instance, applications of repetitive TMS can elicit reduction or facilitation of cortical excitability that last beyond the period of stimulation [13–14]. Similarly, studies using tDCS showed that depending the duration of the stimulation period they can up or down regulate cortical excitability up to 1.5hrs [15] via modulation of NMDA receptor activity [16]. However, most investigations focused on affecting cerebral regions such as M1 or visual cortex. Only in the last few years research has been conducted to determine whether NIBS can also modulate the excitability of the cerebellum.

Using the paired-pulse technique to measure CBI, Galea and colleagues in 2009 showed that it is possible to up and down regulate the connectivity between the cerebellum and M1 depending on the polarity of tDCS being delivered [17]. In this study, tDCS was delivered over one cerebellar hemisphere (centred 3cm lateral to the inion) while the reference electrode was positioned ipsilaterally over the face. Cathodal stimulation, known to be inhibitory when applied over M1 [11], cancelled the inhibition that the cerebellum exerts over M1, whereas anodal tDCS, known to be excitatory [11], increased the ability of TMS to elicit CBI. Of note, multiple control experiments showed that the modulation of CBI by tDCS was not associated with changes in spinal, brainstem or motor cortex excitability. Altogether these findings suggest that the effects of tDCS appear to be circumscribed to the cerebellum, at least when delivered in the lateral montage. This notion is supported by recent human modelling studies describing the electrical field distribution of tDCS (Simulating transcranial direct current stimulation with a detailed anisotropic human head model [18]. Similar to tDCS, follow up investigations showed that application of repetitive TMS paradigms known to increase or decrease neural excitability as tested in M1, also resulted in similar modulation of CBI [19].

Importantly, the findings that CB-M1 connectivity can be modulated with TMS or tDCS have been also supported by investigations demonstrating that these interventions can affect motor, cognitive and emotional processing and behaviours (for review see Non-invasive cerebellar stimulation--a consensus paper [20]). In turn, these findings have suggested that there is potential to use cerebellar non-invasive brain stimulation as a therapeutic intervention in patients with and without cerebellar conditions.

Can we modulate motor learning with cerebellar NIBS?

As discussed in the prior section, numerous studies showed that adaptive motor learning is crucially mediated by the cerebellum (i.e. as indexed by changes in CBI) and cerebellar tDCS can change CB-M1 connectivity. With this in mind, Galea et al investigated whether anodal (excitatory) cerebellar tDCS could facilitate adaptive motor learning [21]. Participants performed a visuomotor adaptation in which fast reaching movements are performed while a 30-degree visuomotor transformation is unexpectedly introduced. During the task performance, subjects received cerebellar, M1, V1 or sham anodal tDCS. The authors found that cerebellar tDCS caused faster learning, as shown by a rapid reduction of movement errors. This effect was not present with similar modulation of visual cortex excitability, suggesting that cerebellar modulation was the driving factor behind faster adaptation. tDCS over M1 did not affect adaptation, but resulted in larger retention, consistent with other investigations [22]. Similar results were also observed in a locomotor adaptation study where anodal tDCS sped up the learning while cathodal (inhibitory) cerebellar tDCS slowed it down relative to sham stimulation [23]. Of note, other investigations showed that the facilitation in learning are also present in a force field adaptation task [24], in older adult subjects [25], and although cerebellar tDCS facilitates this form of learning it does not affect transfer of knowledge between the trained and untrained effectors [26].

Similar to the tDCS studies, other investigations using TMS have also indicated that it is possible to affect cerebellar function during different behaviours. For instance, Hoffland et al. showed that inhibitory repetitive TMS applied over the cerebellum interferes with eye blink conditioning, a task well known to be mediated by cerebellar circuitry [27].

Altogether these studies pointed to the role of the cerebellum in different motor behaviours and suggested the potential of non-invasive cerebellar stimulation as an effective strategy to enhance cerebellar function. Indeed, recently Bonni and others showed that 2 weeks of excitatory repetitive TMS over the cerebellum in patients with stroke and ataxia lead to an improvement in posture and gait [28]. Similarly, Koch et al showed that two weeks of inhibitory repetitive TMS lead to a reduction of symptoms in patients with cervical dystonia [29].

In conclusion, non-invasive cerebellar stimulation is an interesting approach that compliments studies using patient populations or neuroimaging to understand the functions of the cerebellum. TMS and tDCS are allowing us to better understand the cerebellar neurophysiological processes underlying human behaviour. In addition, they have the

potential to become therapeutic interventions to improve function in patients with neurological conditions.

Acknowledgments

Pablo Celnik receives funding from the NIH grants 1R01HD053793 and R01HD073147.

References

1. Ugawa Y, Day BL, Rothwell JC, Thompson PD, Merton PA, Marsden CD. Modulation of motor cortical excitability by electrical stimulation over the cerebellum in man. J Physiol (Lond). 1991; 441:57–72. [PubMed: 1816387]
2. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol. 1995; 37:703–713. [PubMed: 7778843]
3. Pinto AD, Chen R. Suppression of the motor cortex by magnetic stimulation of the cerebellum. Exp Brain Res. 2001; 140:505–510. [PubMed: 11685404]
4. 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. 1996; 101:58–66. [PubMed: 8625878]
5. Jayaram G, Galea JM, Bastian AJ, Celnik PA. Human locomotor adaptive ability is proportional to depression of cerebellar excitability. Cerebral Cortex. 2011; 21(8):1901–9. [PubMed: 21239392]
6. Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. J Neurosci. 2006; 26(36):9107–16. [PubMed: 16957067]
7. Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. Brain. 2007; 130(pt 7):1861–1872. [PubMed: 17405765]
8. Yanagihara D, Kondo I. Nitric oxide plays a key role in adaptive control of locomotion in cat. Proc Natl Acad Sci U S A. 1996; 93:13292–13297. [PubMed: 8917584]
9. Schlerf JE, Galea JM, Bastian AJ, Celnik P. Dynamic modulation of cerebellar excitability for abrupt, but not gradual, visuomotor adaptation. J Neurosci. 2012 Aug 22; 32(34):11610–7. [PubMed: 22915105]
10. Ito M. Cerebellar control of the vestibulo-ocular reflex—around the flocculus hypothesis. Ann Rev Neurosci. 1982; 5:275–297. [PubMed: 6803651]
11. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol (Lond). 2000; 527(Pt 3):633–639. [PubMed: 10990547]
12. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005 Jan 20; 45(2):201–6. [PubMed: 15664172]
13. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997 May; 48(5):1398–403. [PubMed: 9153480]
14. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol. 2006 Dec; 117(12):2584–96. [PubMed: 16890483]
15. Nitsche MA, Paulus W. Transcranial direct current stimulation—update 2011. Restor Neurol Neurosci. 2011; 29(6):463–92. [PubMed: 22085959]
16. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, Lu B. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learing. Neuron. 2010 Apr 29; 66(2):198–204. [PubMed: 20434997]
17. Galea JM, Jayaram G, Ajagbe L, Celnik P. Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. J Neurosci. 2009; 29(28):9115–9122. [PubMed: 19605648]
18. Rampersad SM, Janssen AM, Lucka F, Aydin U, Lanfer B, Lew S, Wolters CH, Stegeman DF, Oostendorp TF. Simulating transcranial direct current stimulation with a detailed anisotropic

human head model. IEEE Trans Neural Syst Rehabil Eng. 2014 May; 22(3):441–52. [PubMed: 24760939]

19. Popa T, Russo M, Meunier S. Long-lasting inhibition of cerebellar output. Brain Stimul. 2010 Jul; 3(3):161–9. [PubMed: 20633445]
20. Grimaldi G, Argyropoulos GP, Boehringer A, Celnik P, Edwards MJ, Ferrucci R, et al. Cerebellum. 2014 Feb; 13(1):121–38. [PubMed: 23943521]
21. Galea JM, Vazquez A, Pasricha N, Orban de Xivry JJ, Celnik P. Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. Cereb Cortex. 2011; 21:1761–1770. [PubMed: 21139077]
22. Reis J, Schambra HM, Cohen LG, Buch ER, Fritsch B, Zarahn E, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci U S A. 2009; 106(5):1590–5. [PubMed: 19164589]
23. Jayaram G, Tang B, Pallegadda R, Vasudevan EV, Celnik P, Bastian A. Modulating locomotor adaptation with cerebellar stimulation. J Neurophysiol. 2012; 107(11):2950–2957. [PubMed: 22378177]
24. Herzfeld DJ, Pastor D, Haith AM, Rossetti Y, Shadmehr R, O'Shea J. Contributions of the cerebellum and the motor cortex to acquisition and retention of motor memories. NeuroImage. 2014; 98:147–158. [PubMed: 24816533]
25. Hardwick RM, Celnik PA. Cerebellar direct current stimulation enhances motor learning in older adults. Neurobiol Aging. 2014 S0197-4580(14)00288-7.
26. Block HJ, Celnik P. Can cerebellar transcranial direct current stimulation become a valuable neurorehabilitation intervention? Expert Rev Neurother. 2012; 12:1275–77. [PubMed: 23234389]
27. Hoffland BS, Bologna M, Kassavetis P, Teo JT, Rothwell JC, Yeo CH, et al. Cerebellar theta burst stimulation impairs eyeblink classical conditioning. J Physiol. 2012 Feb 15; 590(Pt 4):887–97. Epub 2011 Dec 23. [PubMed: 22199171]
28. Bonnì S, Ponzo V, Caltagirone C, Koch G. Cerebellar theta burst stimulation in stroke patients with ataxia. Funct Neurol. 2014 Apr.7:1–5. [PubMed: 24702782]
29. Koch G, Porcacchia P, Ponzo V, Carrillo F, Cáceres-Redondo MT, Brusa L, et al. Effects of Two Weeks of Cerebellar Theta Burst Stimulation in Cervical Dystonia Patients. Brain Stimul. 2014 May 9. pii: S1935-861X(14)00172-7.

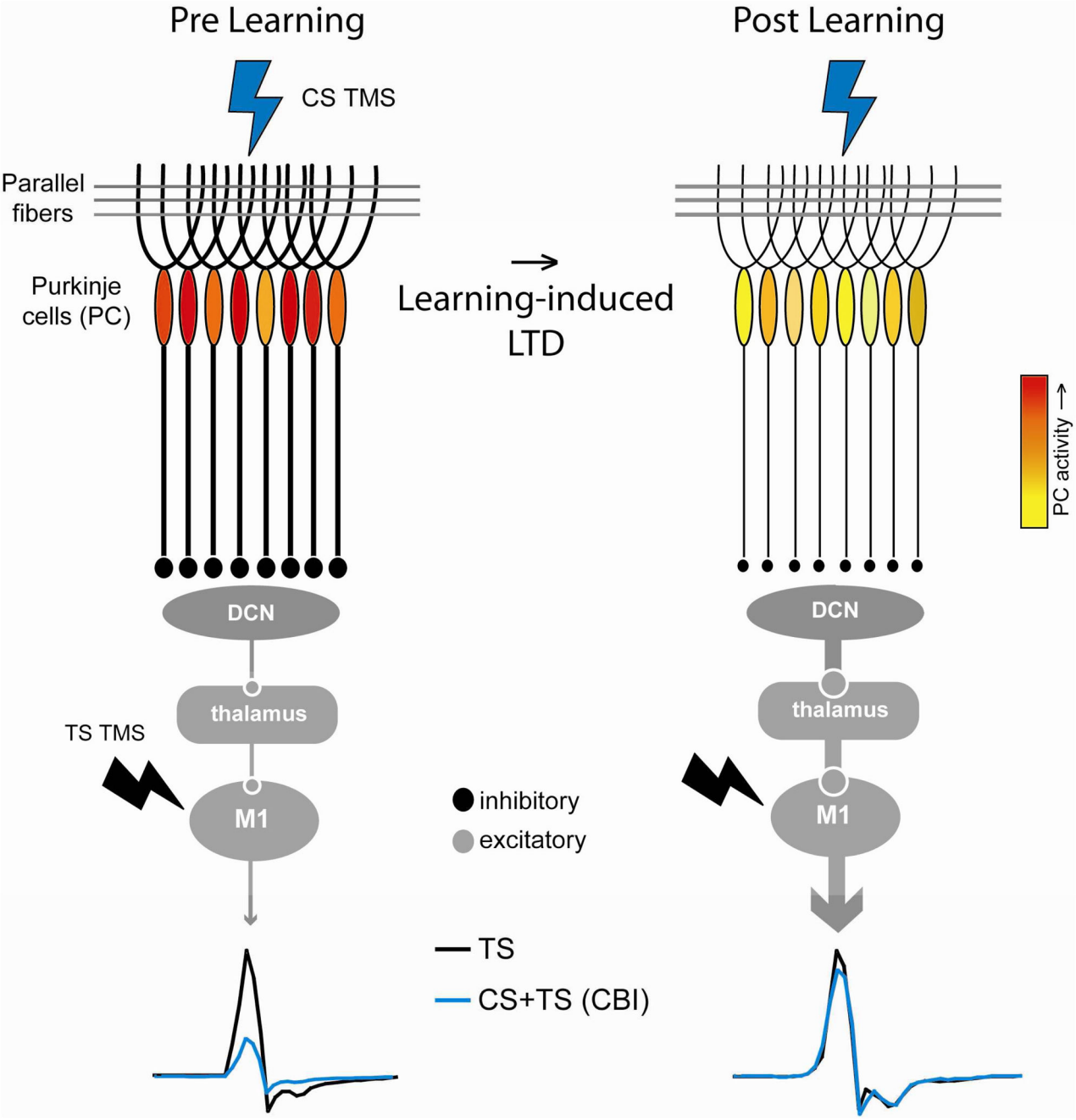

Fig 1.

Schematic representation of the interpretation illustrating how cerebellar-M1 connectivity changes after adaptive motor learning. At baseline (Pre Learning) a conditioning TMS pulse (CS) over the cerebellum (CB) activates Purkinje cells (PC) that in turn inhibit the deep cerebellar nuclei (DCN), which is excitatory via a disynaptic pathway to M1. Thus, combining a CS over the CB with a test stimulus (TS) over M1 results in brief decrease activation of M1. This is evidenced by smaller amplitude motor evoked potentials (MEP) recorded in a hand or leg muscle (blue traces), relative to the MEP elicited by TS without

prior cerebellar stimulation (black traces). If learning results in LTD in the parallel fibre-Purkinje cell complex, as suggested by animal work, then the PC will be less active and therefore less likely to be engaged by a CS to inhibit M1 (Post Learning).