Brain Stimulation 13 (2020) 153–156

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Cerebellar transcranial magnetic stimulation: The role of coil type from distinct manufacturers

Danny Spampinato [a, *], Jaime Ibáñez [a, b], Manos Spanoudakis [a], Paul Hammond [a], John C. Rothwell [a]

[a] Department for Clinical and Movement Neurosciences, Institute of Neurology, University College London, United Kingdom
[b] Department of Bioengineering, Imperial College, London, United Kingdom

ARTICLE INFO

Article history:
Received 5 August 2019
Received in revised form
16 September 2019
Accepted 19 September 2019
Available online 12 October 2019

Keywords:
Cerebellum
Transcranial magnetic stimulation
Cerebellar-M1
Connectivity

ABSTRACT

Background: Stimulating the cerebellum with transcranial magnetic stimulation is often perceived as uncomfortable. No study has systematically tested which coil design can effectively trigger a cerebellar response with the least discomfort.
Objective: To determine the relationship between perceived discomfort and effectiveness of cerebellar stimulation using different coils: MagStim (70 mm, 110 mm-coated, 110-uncoated), MagVenture and Deymed.
Methods: Using the cerebellar-brain inhibition (CBI) protocol, we conducted a CBI recruitment curve with respect to each participant's maximum tolerated-stimulus intensity (MTI) to assess how effective each coil was at activating the cerebellum.
Results: Only the Deymed double-cone coil elicited CBI at low intensities (−20% MTI). At the MTI, the MagStim (110 mm coated/uncoated) and Deymed coils produced reliable CBI, whereas no CBI was found with the MagVenture coil.
Conclusion: s: The Deymed double-cone coil was most effective at cerebellar stimulation at tolerable intensities. These results can guide coil selection and stimulation parameters when designing cerebellar TMS studies.

Introduction

Transcranial magnetic stimulation (TMS) has been used to study both cerebellar excitability and connectivity to primary motor cortex (M1). Specifically, cerebellar inhibition (CBI) is an effect observed when a TMS pulse is delivered over the contralateral cerebellar hemisphere 5-to-7ms before applying stimulation over M1 and has been interpreted as a measure of cerebellar excitability [1–3]. CBI has provided critical neurophysiological findings for a wide-range of movement-related research studies aimed to better understand cerebellar involvement in motor learning [4–8] and movement initiation [9,10], as well as provide valuable insights for clinical assessments [11–14].

One critical challenge lies in the fact that the distance from the scalp to the cerebellum is larger than the one to reach M1, thus making stimulation difficult to achieve, requiring higher stimulation intensities that are discomforting to participants. The high intensities used can activate neck muscles [15], potentially leading to participants withdrawal from studies [16–19]. While coils with varying discomfort levels have been used to stimulate the cerebellum [20–29], most studies have used coils from a specific TMS manufacturer (MagStim). Moreover, there are no reports of studies measuring CBI from other manufacturers (MagVenture or Deymed) or the tolerability of each coil. Double-cone coils are currently available from each manufacturer and are considered more appropriate for cerebellar stimulation since they produce greater stimulation depth than figure-of-eight coils. Indeed the reliability of eliciting CBI with figure-of-eight coils currently remains in question [19,22]. Thus, using varying levels of stimulator-output intensities, we compared cerebellar responses elicited from each manufacture's double-cone coil (MagStim, MagVenture, and Deymed).

* Corresponding author. Institute of Neurology, 33 Queen Square, WC1N 3BG, United Kingdom
E-mail address: d.spampinato@ucl.ac.uk (D. Spampinato).

https://doi.org/10.1016/j.brs.2019.09.005

Methods

We recruited thirteen right-handed volunteers (11 Caucasian, 2 Asian-descent; 6 females; 29.69 ± 3.07 years old) who previously experienced cerebellar TMS. The study was conducted at the University College of London (UCL). All participants filled a written consent form approved by the UCL ethics committee and following the Declaration of Helsinki. None of the participants had a history of neurological symptoms or psychiatric diseases, and no contraindications to TMS were reported [30].

EMG recordings. All participants sat comfortably in a chair with both arms resting on a pillow placed on their lap and were required to remain relaxed during the experimental session. Electromyographic (EMG) activity was captured through pairs of disposable electrodes placed over the right first dorsal interosseus (FDI). Unrectified EMG signals were recorded (D360 amplifier, Digitimer Ltd, Welwyn Garden City, UK), amplified (x1000), filtered (bandpass 20–2000 Hz), sampled (5 kHz per channel) using a 1401 power analog-to-digital converter (Cambridge Electronic Design, Cambridge, UK) and Signal 6.0 software on a computer and stored for off-line analysis.

M1 TMS. TMS was delivered using a 70-mm-diameter figure-of-eight coil connected to a MagStim 200 stimulator (MagStim, Whitland, Dyfed, UK). The coil was placed tangentially to the scalp with the handle pointed backward at a 45° angle to the anteroposterior axis. The M1 motor "hot spot" was identified for the FDI muscle. We also established the stimulator intensity required to produce ~1 mV MEP responses.

Cerebellar Stimulation. Cerebellar TMS was applied with a variety of double-cone coils (Fig. 1) from MagStim (70 mm, 110 mm coated, 110 uncoated; MagStim, Whitland, UK), Magventure (model: D-D80; MagVenture, Farum, Denmark) and Deymed (model: 120BFV; Deymed, Hronov, Czech Republic). Each coil was centered over the right cerebellar cortex, 3 cm lateral to the inion. The coil current direction was pointed downwards [1,24]. For each double-cone coil tested, the stimulator output intensity was set to participant's maximum tolerated intensity (MTI). To avoid potential artifacts caused by antidromic stimulation of the pyramidal tract itself [31], we first assessed the brainstem threshold. We then asked participants to pre-activate their right FDI by lifting the index finger and searched if stimulation evoked MEPs in either hand in 3 out of 6 pulses. This was done for all intensities (MTI, −20% MTI, −10% MTI). If MEPs were evoked at −10% MTI or −20% MTI, the MTI was adjusted accordingly to produce no MEPs, thus avoiding potential artifacts caused by antidromic stimulation. This occurred for five participants with the Deymed and MagStim 110 uncoated coils and four individuals with the MagStim 110 coated coil. Importantly, we randomized the order of coil introduction to prevent biasing of the perceived stimulator discomfort.

Cerebellar-M1 connectivity (CBI). To assess CBI, we delivered a TMS conditioning stimulus (CS) over the right cerebellar cortex 5 ms before a test stimulus (TS) pulse over the left M1 [1]. We randomly delivered 15 unconditioned MEPs and 15 conditioned responses of each CS intensity paired with TS over M1 (i.e. 45 total conditioning pulses). This procedure was repeated for each coil at fixed conditioning stimulus intensities (−0%, −10%, and −20% MTI). CBI was expressed as the ratio of conditioned MEPs to unconditioned MEPs. MEPs smaller than 50 μV were excluded from the analysis. This occurred rarely: we never discarded more than 2 MEPs in a single round and we excluded less than 1% of all measured MEPs.

We performed statistical analysis with SPSS 20 software (SPSS Inc, Chicago, IL, USA). We used repeated measures (RM) analysis of variance (ANOVA). When necessary, we used Bonferroni-corrected post hoc t-tests for planned multiple comparisons. We evaluated compound symmetry with the Mauchly's test and used Greenhouse-Geisser corrections when required. Significance was set for p-value ≤0.05. Values are expressed as means ± standard error of the mean (SEM). To investigate the presence of cerebellar activation, we used a RM-ANOVA to compare the CBI ratio values with COIL (MagStim70, MagStim 110 and MagVenture, and Deymed), and INTENSITY (−0%, −10%, −20% of MTI) as within-subject factors.

Results

We found distinct effects of cerebellar excitability across each coil type and stimulator intensities (Fig. 2). RM-ANOVA revealed a significant CBI difference for COIL ($F_{4,96} = 9.251$, $p < 0.001$), INTENSITY ($F_{2,96} = 10.608$, $p < 0.001$) and COIL × INTENSITY

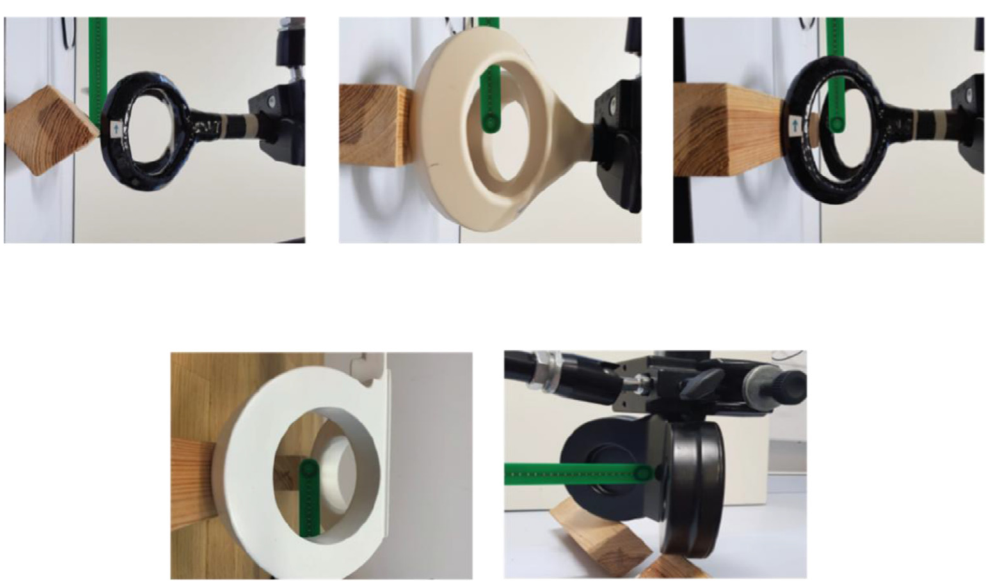

Fig. 1. The distinct double-cone coils used in this study.
Top row (from left to right): Images depicting Magstim coils 70 mm, 110 mm coated and 110 uncoated. *Bottom row*: Images of the Deymed and Magventure coils.

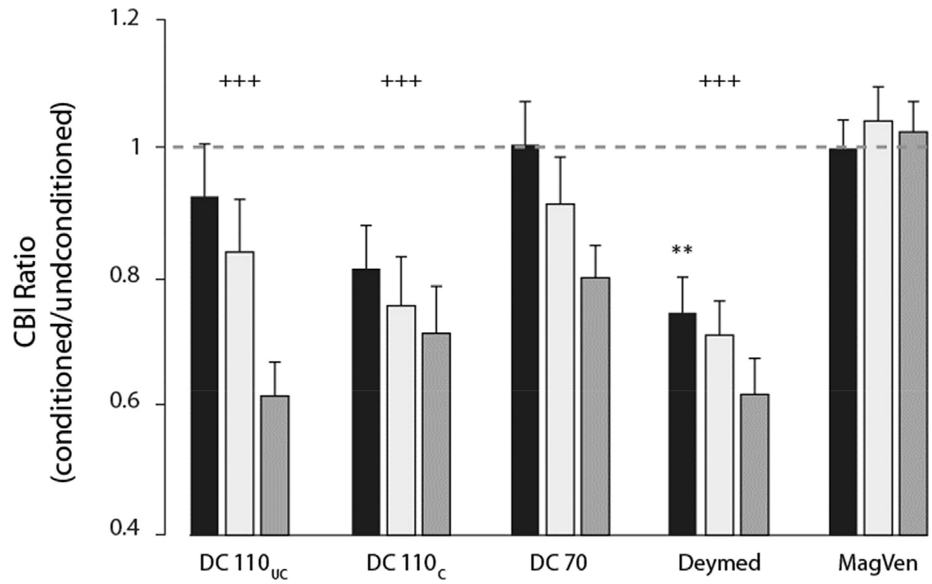

Fig. 2. Effect of distinct coil stimulation to the cerebellum.
To assess cerebellar excitability, we performed a CBI recruitment curve of the conditioning TMS pulse values with respect to the maximum tolerated stimulator-output intensity (MTI). Bar graphs represent mean group data for each block of MEPs collected, with the data normalized by dividing the mean conditioned MEP amplitude by the mean control MEP amplitude (mean ± SE). The different colours represent distinct conditioning TMS intensities: black = −20% MTI; white = −10% MTI; grey = MTI. +++ indicates an overall significant CBI response across all conditioning stimulus parameters (all $p < 0.05$). ** represents a significant value of CBI at the lowest condition stimulus intensity ($p < 0.05$). Of note, only the Deymed coil produced a robust CBI response at −20% MTI.

interaction ($F8,96 = 2.634$, $p = 0.012$). Post-Hoc analysis revealed that the MagVenture overall CBI response was different when compared to Deymed, MagStim 110-mm coated and uncoated (all $p < 0.03$). Specifically, at the MTI, all MagStim and Deymed coils elicited reliable CBI when compared to MagVenture (all $p < 0.05$), suggesting that the MagVenture coil does not activate the cerebellum. The MTI was found comparable across participants for Deymed, MagStim 110-mm coated and uncoated (Table 1). Of note, while the MTI MagStim70 was higher, evidence of CBI was only found at this intensity. Moreover, there was no difference between Deymed and MagStim 110-mm coated and uncoated at the MTI (all $p > 0.90$), suggesting that larger double-cone coils from these manufacturers are all capable of producing a strong CBI effect at high conditioning stimulus intensities.

Importantly, when comparing CBI values at −20% of MTI, only the results obtained with the Deymed coil were significantly different from the ones measured with the MagVenture coil ($p = 0.028$). This indicates that solely the Deymed coil can reliably activate the cerebellum at lower and well-tolerated intensities.

Discussion

We present novel results that a Deymed double-cone coil can assess cerebellar–M1 connectivity. In addition to the Deymed coil producing a robust CBI response at high intensities, this coil type also reliably elicited CBI at lower intensities tolerated by participants. This is important for the field of non-invasive brain stimulation since cerebellar function is increasingly investigated with neurostimulation techniques [32,33] and stimulation itself is commonly reported as uncomfortable. These findings, therefore, present an alternative and more comfortable option for future research designs involving both healthy and neurological patients.

We also demonstrate only larger double-cone coils from MagStim and Deymed could elicit reliable CBI at mid- and high-intensities, whereas the MagVenture coil could not produce the CBI effect. As shown before, 70 mm double-cone coil can also demonstrate CBI [22,29], however, this effect was only for the maximally tolerated stimulation intensity. These results suggest that MagStim and Deymed coils can be utilized for future studies, albeit higher intensities are required with the MagStim coils. The MagVenture system coil does not appear strong enough to excite the cerebellum; however, future work will need to investigate if other coils offered by this manufacturer can elicit a CBI response. We speculate the coil fit on participant's head and coil size may be an important determinant of the efficiency, as all coils displayed similar pulse sizes, and moreover, the overall recorded MTI were found comparable for Deymed and 110 mm Magstim double-cone coils. Although the angle of impact is comparable across coils, subtle differences in coil geometry may also play a role since both Magstim and Magventure coils have slightly curved winding surfaces in comparison to the Deymed coil.

This article provides important insights for future investigations aimed to study cerebellar excitability and cerebellar-M1 connectivity. It provides a novel result that an alternative coil (i.e. Deymed) can elicit reliable cerebellar stimulation at more tolerated stimulator intensities. Applying lower yet effective stimulation is critical for future study designs of both healthy and patient-related studies, as the expectation would translate to fewer participant dropouts. These results also provide evidence that smaller coils are less effective at stimulating the cerebellum, suggesting that caution

Table 1
The selected MTI value for each coil.

Coil Type	MTI
MagStim DC 70 mm	93.08 (2.21)
MagStim DC 110 mm (coated)	77.31 (1.28)
MagStim DC 110 mm (uncoated)	78.08 (1.16)
Deymed 120BFV	79.23 (2.10)
MagVenture D-B80	100 (0)

Values depict the mean maximum tolerated intensity (MTI) conditioning stimulus output for each coil. Standard error values are in parenthesis (mean ± SE).

must be taken when opting for figure-of-eight coils or smaller double-cone coils at low intensities when targeting this brain region.

Declaration of competing interest

The authors declare that there is no conflict of interest for this manuscript. This research is supported by the Medical Research Council (MR/P006671/1).

References

[1] Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol 1995;37(6):703–13.

[2] 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;557(Pt 2):689–700.

[3] Galea JM, Jayaram G, Ajagbe L, Celnik P. Modulation of cerebellar excitability by polarity-specific noninvasive direct current stimulation. J Neurosci: Off J Soc Neurosci 2009;29(28):9115–22.

[4] Spampinato D, Celnik P. Temporal dynamics of cerebellar and motor cortex physiological processes during motor skill learning. Sci Rep 2017;7(40715).

[5] Schlerf JE, Galea JM, Bastian AJ, Celnik PA. Dynamic modulation of cerebellar excitability for abrupt, but not gradual, visuomotor adaptation. J Neurosci: Off J Soc Neurosci 2012;32(34):11610–7.

[6] Schlerf JE, Galea JM, Spampinato D, Celnik PA. Laterality differences in cerebellar-motor cortex connectivity. Cerebr Cortex 2015;25(7):1827–34.

[7] Jayaram G, Galea JM, Bastian AJ, Celnik P. Human locomotor adaptive learning is proportional to depression of cerebellar excitability. Cerebr Cortex 2011;21(8):1901–9. New York, NY: 1991.

[8] Spampinato D, Celnik P. Deconstructing skill learning and its physiological mechanisms. Cortex 2018;104:90–102.

[9] Kassavetis P, Hoffland BS, Saifee TA, Bhatia KP, van de Warrenburg BP, Rothwell JC, et al. Cerebellar brain inhibition is decreased in active and surround muscles at the onset of voluntary movement. Exp Brain Res 2011;209(3):437–42.

[10] Spampinato DA, Block HJ, Celnik PA. Cerebellar-M1 connectivity changes associated with motor learning are somatotopic specific. J Neurosci 2017;37(9):2377–86.

[11] Shirota Y, Hamada M, Hanajima R, Terao Y, Matsumoto H, Ohminami S, et al. Cerebellar dysfunction in progressive supranuclear palsy: a transcranial magnetic stimulation study. Mov Disord 2010;25(14):2413–9.

[12] Daskalakis ZJ, Christensen BK, Fitzgerald PB, Fountain SI, Chen R. Reduced cerebellar inhibition in schizophrenia: a preliminary study. Am J Psychiatry 2005;162(6):1203–5.

[13] Ni Z, Pinto AD, Lang AE, Chen R. Involvement of the cerebellothalamocortical pathway in Parkinson disease. Ann Neurol 2010;68(6):816–24.

[14] Carrillo F, Palomar FJ, Conde V, Diaz-Corrales FJ, Porcacchia P, Fernández-Del-Olmo M. Study of cerebello-thalamocortical pathway by transcranial magnetic stimulation in Parkinson's disease. Brain Stimul 2013;6.

[15] Demirtas-Tatlidede A, Freitas C, Pascual-Leone A, Schmahmann JD. Modulatory effects of theta burst stimulation on cerebellar nonsomatic functions. Cerebellum 2011;10(3):495–503.

[16] 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.

[17] Janssen AM, Munneke MAM, Nonnekes J, van der Kraan T, Nieuwboer A, Toni I, et al. Cerebellar theta burst stimulation does not improve freezing of gait in patients with Parkinson's disease. J Neurol 2017;264(5):963–72.

[18] Jayasekeran V, Rothwell J, Hamdy S. Non-invasive magnetic stimulation of the human cerebellum facilitates cortico-bulbar projections in the swallowing motor system. Neuro Gastroenterol Motil 2011;23(9):1365–2982.

[19] Fernandez L, Major BP, Teo WP, Byrne LK, Enticott PG. The impact of stimulation intensity and coil type on reliability and tolerability of cerebellar brain inhibition (CBI) via dual-coil TMS. Cerebellum 2018;17(5):540–9.

[20] Bologna M, Biasio F, Conte A, Iezzi E, Modugno N, Berardelli A. Effects of cerebellar continuous theta burst stimulation on resting tremor in Parkinson's disease. Park Relat Disord 2015;21.

[21] Bonni S, Ponzo V, Caltagirone C, Koch G. Cerebellar theta burst stimulation in stroke patients with ataxia. Funct Neurol 2014;29(1):41–5.

[22] Hardwick RM, Lesage E, Miall RC. Cerebellar transcranial magnetic stimulation: the role of coil geometry and tissue depth. Brain Stimul 2014;7(5):643–9.

[23] Koch G, Brusa L, Carrillo F, Lo Gerfo E, Torriero S, Oliveri M. Cerebellar magnetic stimulation decreases levodopa-induced dyskinesias in Parkinson disease. Neurology 2009;73.

[24] Pinto AD, Chen R. Suppression of the motor cortex by magnetic stimulation of the cerebellum. Exp Brain Res 2001;140(4):505–10.

[25] Popa T, Russo M, Meunier S. Long-lasting inhibition of cerebellar output. Brain Stimul 2010;3(3):161–9.

[26] Torriero S, Oliveri M, Koch G, Caltagirone C, Petrosini L. Interference of left and right cerebellar rTMS with procedural learning. J Cogn Neurosci 2004;16(9):1605–11.

[27] Torriero S, Oliveri M, Koch G, Lo Gerfo E, Salerno S, Ferlazzo F, et al. Changes in cerebello-motor connectivity during procedural learning by actual execution and observation. J Cogn Neurosci 2011;23(2):338–48.

[28] Uehara S, Mawase F, Celnik P. Learning similar actions by reinforcement or sensory-prediction errors rely on distinct physiological mechanisms. Cerebr Cortex 2017:1–13.

[29] Ginatempo F, Spampinato DA, Manzo N, Rothwell JC, Deriu F. Exploring the connectivity between the cerebellum and facial motor cortex. Brain Stimul 2019 Jul 16;(19):30296–7. https://doi.org/10.1016/j.brs.2019.07.012. pii: S1935-861X.

[30] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMSCG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol : Off J Int Fed Clin Neurophysiol 2009;120(12):2008–39.

[31] Fisher KM, Lai HM, Baker MR, Baker SN. Corticospinal activation confounds cerebellar effects of posterior fossa stimuli. Clin Neurophysiol : Off J Int Fed Clin Neurophysiol 2009;120(12):2109–13.

[32] Grimaldi G, Argyropoulos GP, Bastian A, Cortes M, Davis NJ, Edwards DJ, et al. Cerebellar transcranial direct current stimulation (ctDCS): a novel approach to understanding cerebellar function in health and disease. The Neuroscientist: Rev J Neurobiol Neurol Psychiatry 2016;22(1):83–97.

[33] Tremblay S, Austin D, Hannah R, Rothwell JC. Non-invasive brain stimulation as a tool to study cerebellar-M1 interactions in humans. Cerebellum Ataxias 2016;3(1):19.