Cerebellar Transcranial Magnetic Stimulation: The Role of Distinct Coils from Different Manufacturers

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Abstract (150/150 Words)

Background: Transcranial magnetic stimulation (TMS) to stimulate the cerebellum is often perceived as uncomfortable. No study has systematically tested which coil design can stimulate the cerebellum with the least discomfort.

Objective: To determine the relationship between perceived discomfort and effectiveness of cerebellar stimulation using different coils: Magstim (70mm, 110mm coated, 110 uncoated), MagVenture and Deymed.

Methods: Utilizing the well-established cerebellar-brain inhibition (CBI) protocol, we assessed how effective the distinct coils were at activating the cerebellum at varying stimulator intensities with respect to participant's maximum tolerated-stimulus intensity (MTI).

Results: Only the Deymed double-cone coil could eliciting CBI at a low intensity (-20% MTI). Magstim (110mm coated/uncoated) and Deymed coils were able to elicit comparable CBI at the MTI, whereas no CBI was found with MagVenture.

Conclusions: Deymed double-cone coil was most effective at a tolerable stimulator intensity. These results can guide coil selection and stimulation parameters when designing cerebellar TMS studies.

Introduction (1512/1500 max)

Transcranial magnetic stimulation (TMS) of the cerebellum has been used to study connectivity between cerebellum and primary motor cortex (M1). Ugawa and colleagues were the first to demonstrate that stimulation over the cerebellum reduced the excitability M1 corticospinal outputs [1]. This phenomenon, termed cerebellar inhibition (CBI), occurs when delivering a TMS 5 to 7ms over the contralateral cerebellar hemisphere prior to a stimulus applied over M1 and has been interpreted a measure of cerebellar excitability [1-3]. Over the years, CBI has provided critical neurophysiological findings, such as a marker for cerebellar involvement in motor learning [4-8] and movement initiation [9, 10], as well as a critical tool utilized for clinical assessments [11-14] demonstrating its application is important and applicable to a wide-range of research questions.

A critical challenge of this technique lies in the fact that the cerebellum is large and far away from the scalp, thus making stimulation difficult to achieve and often requires high stimulation intensities that are of discomfort to participants. Indeed, cerebellar TMS can activate neck muscles, leading to muscle contractions and discomfort [15] that may lead to participant withdrawing from the study [16-18]. While distinct coil types with different discomfort levels have been used to stimulate the cerebellum [19-28], the majority of the studies have used coils from a specific TMS manufacturer, Magstim and there appears no report of CBI being recorded for either MagVenture or Deymed coils. Double-cone coils, which are now available from several TMS coil manufacturers, are capable of achieving greater depth of stimulation, making it an appropriate tool to target the deep lying cerebellum and its motor representations. Thus, we assessed how effective double-cone coils from distinct manufactures (Magstim, MagVenture, and Deymed) are at eliciting cerebellar excitability at varying levels of stimulator-output intensity values.

Methods

We recruited thirteen right-handed healthy volunteers (6 females; 29.69 ± 3.07 years old) whom previously have experienced cerebellar TMS. The study was conducted at University College of London (UCL). All participants provide filled a written consent form approved by the UCL ethics committee and in accordance with the Declaration of Helsinki. None of the participants had history of any neurological symptoms or psychiatric diseases, and no contraindications to TMS were reported [29].

EMG recordings. All participants sat comfortably in a chair with both arms resting on a pillow placed on their lap and were asked to stay 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 2-5000 Hz), sampled (5 kHz per channel;) using a 1401 power analogue to digital converter (Cambridge Electronic Design, Cambridge, UK) and Signal 6.0 software on a computer and stored for off-line analysis.

TMS of M1. 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 with respect to the anteroposterior axis and the motor "hot spot" was identified for the FDI muscle. We established the stimulator intensity required to produce ~1 mV MEP responses.

Cerebellar Stimulation. TMS of the cerebellum was applied with a variety of double-cone coils 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 centred over the right cerebellar cortex, 3 cm lateral to the inion and the current in the coil was directed downwards [1, 23]. For each coil tested, we selected the stimulator intensity based on the maximum tolerated stimulator intensity (MTI) percentage value tolerated by participants. To avoid potential artefacts caused by antidromic stimulation of the pyramidal tract itself [30], 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. We did this for the MTI and values of -20% and -10% MTI. If evidence of pyramidal tract stimulation was found at -10% MTI or -20% MTI, the MTI was adjusted to the lowest value in which MEPs were evoked in order to avoid potential artefacts caused by antidromic stimulation (Fisher et al. 2009). 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]. For each coil, 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 of the coil designs at fixed conditioning stimulus intensities (-0%, -10%, and -

20% MTI). CBI was expressed as the ratio of the conditioned to unconditioned MEP. Pulses that did not result in an MEP (or pulses that resulted in an MEP < 50 μV) were excluded from analysis. This occurred very rarely: we never discarded >2 pulses in a single round and excluded <1% of all measured MEPs overall.

Statistical analysis was performed with SPSS 20 software (SPSS Inc, Chicago, IL, USA). Repeated measures (RM) analysis of variance (ANOVA) and planned post hoc t-test with Bonferroni correction for multiple comparison were used. Compound symmetry was evaluated with the Mauchly's test and the Greenhouse-Geisser correction was used 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, a RM-ANOVA on the CBI ratio was performed, 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 different coil types and intensities (Figure 1). 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 x INTENSITY interaction ($F_{8,96}$ =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 highest stimulator intensity, 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. For these specific coils, the MTI was found comparable across participants (Table 1). Moreover, at the highest intensity, there was no difference between Deymed and MagStim 110-mm coated and uncoated (all p>0.90), suggesting that larger double-cone coils from these manufactures 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 Deymed double-cone coil was different when compared to MagVenture (p=0.028), indicating that only this manufacturer can reliably activate the cerebellum at a more tolerated stimulator intensity.

Discussion

We report the first evidence of capturing cerebellar–M1 connectivity utilizing a non-Magstim double cone (i.e. Deymed). We found that the Deymed double-cone coil could not only achieve a strong CBI effect, but critically this coil was also capable of eliciting reliable effects at easily

tolerated stimulation intensity (i.e. -20% MTI). These findings are important for the field of non-invasive brain stimulation, as cerebellar function is increasingly investigated with neurostimulation techniques [31, 32] and stimulation itself is commonly reported as uncomfortable. This demonstrates that investigators can have an alternative option when considering research designs aimed at targeting the cerebellum with TMS.

We also demonstrate only larger double cone coils from MagStim, Deymed could elicit reliable CBI at mid- and high- intensities, whereas the MagVenture coil could not produce the CBI effect. As shown before, 70mm double cone coil can also demonstrate CBI [21, 28], however the effect is only shown at the maximally tolerated stimulation intensity. These results suggest that MagStim and Deymed coils could still be utilized for future studies, albeit higher intensities are required with the MagStim coils. The MagVenture double-cone coil does not appear strong enough to excite the cerebellum, however future work will need to investigate if other coils offered by this manufacture is more effective at eliciting the CBI effect. Alternatively, the magnetitic filed of this coil could potentially still reach the cerebellum, however future studies will need to assess this utilizing a different probe of cerebellar excitability other than CBI.

These provide interesting insights for future studies interested in studying cerebellar excitability and connectivity to M1. First, they demonstrate a new coil that can elicit reliable effects at tolerated stimulator intensities. This is critical in the design of future studies of both healthy and patient related studies, as the expectation would translate to fewer study dropouts, as lower intensities that still produce reliable cerebellar stimulation can be less fatiguing for participants. Moreover, they provide evidence that smaller coils are less effective at stimulating the cerebellum. This suggests that studies utilizing figure-of-eight coils or low-intensity values with smaller double cone coils are not effective enough to activate the cerebellum.

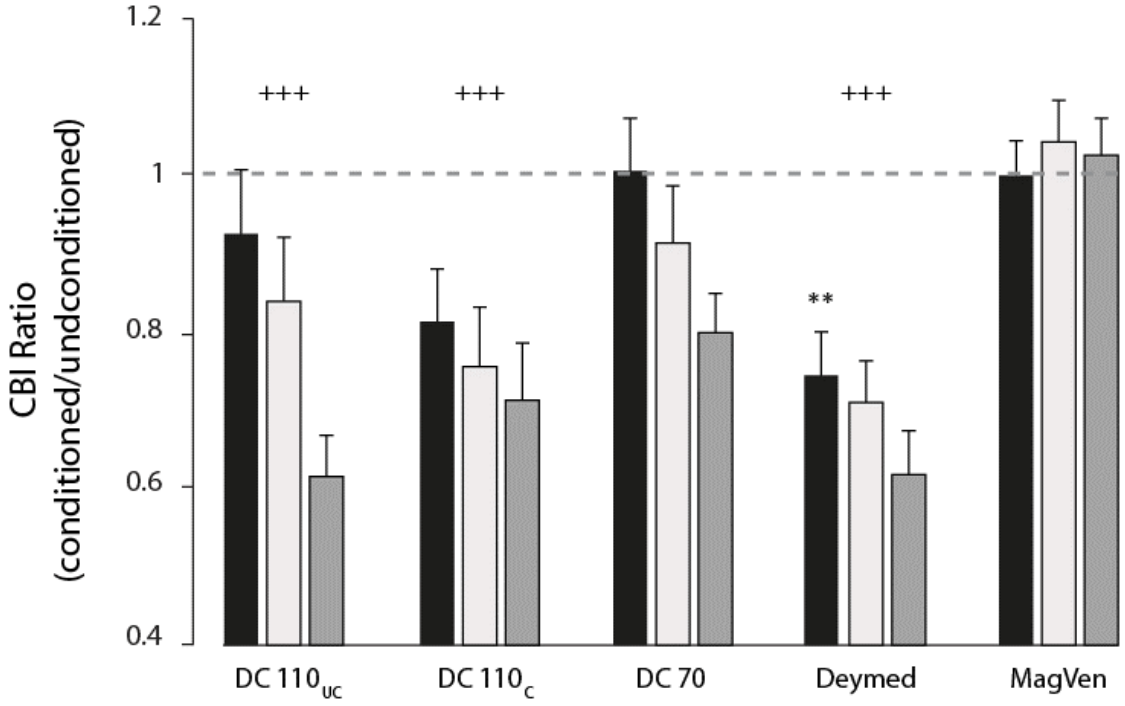

Figure1. Effect of distinct coil stimulation to the cerebellum.

To assess the effect of cerebellar activity, 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 conditiong stimulus intensity ($p < 0.05$). Of note, only the Deymed coil produced an affect at -20% MTI.

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

Table1. The selected MTI value for each coil

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

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