Assessing effective connectivity of the cerebellum with cerebral cortex using TMS-EEG

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1. Introduction

Proper cerebellar functioning depends on the effectiveness of efferent connections to the cerebral cortex through the cerebello-dentato-thalamo-cortical pathway, which is indispensable for adequate motor performance. Disorders that affect the cerebellum result in the impairment of this system, leading to deficits and symptoms which include tremor, ataxia, and balance and gait disorder [1]. An accurate assessment of this system’s integrity might therefore represent a biomarker for cerebellar connectivity with cerebral cortex. Thus, if identified, electrophysiological biomarkers could facilitate the conduction of clinical trials that test the efficacy of emerging treatments in cerebellar disorders [2].

With this aim, Ugawa et al. [3] investigated the effects of transcranial magnetic stimulation (TMS) of the cerebellar cortex on contralateral primary motor cortex (M1) excitability. They observed that motor responses to TMS were significantly reduced, when the cerebellum was stimulated 5–10 ms before, a phenomenon termed Cerebellar Brain Inhibition (CBI). This suggested that cerebellar TMS (cbTMS) causes inhibition of M1. This is in accordance with previous observations that the cerebellar output is mostly inhibitory in nature, mediated by Purkinje cells projecting onto the deep cerebellar nuclei [1], thus suggesting that CBI could be a measure of cerebellar functioning [3]. Accordingly, CBI was absent or reduced in patients with degeneration of the cerebellar cortex or lesions in the cerebello-dentato-thalamo-cortical pathway, but was present in patients with lesions in the afferent pathways to the cerebellum [4].

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Cerebellar TMS in combination with electroencephalography (EEG) has the advantage that EEG can record responses of most parts of the cerebral cortex [5], whereas CBI is limited to M1 output measured by electromyography (EMG). Furthermore, motor evoked potentials (MEPs) can vary due to changes in excitability of M1 [6,7]. These advantages of utilizing a TMS-EEG approach were highlighted in a recent study [7].

Several challenges imposed by the TMS-EEG technique have so far largely hindered this endeavor. The electric field (E-Field) induced by TMS has a limited range and can only reach intensities necessary for neuronal depolarization at a few centimeters away from the coil. The comparatively larger distance between the scalp and the cerebellar cortex implies that higher TMS intensities are necessary for effective stimulation in comparison to TMS to the cerebral cortex [8]. A consequence is increased sensory input, as the TMS coil produces a high-pitched sound and stimulates muscles and sensory fibers around the intended target [9]. These inputs elicit multimodal EEG responses to sensory input that can potentially overlap with the cortical EEG response to TMS in certain time-windows, potentially compromising the analysis and interpretation of TMS-EEG results [5,10] starting 60 ms [11] to 70 ms after TMS [12–14]. This has led researchers to suggest the importance of applying control conditions in TMS-EEG experiments in order to clarify the sources of the observed signals [12,13,15].

These caveats have limited previous attempts to investigate TMS-EEG with a cerebellar target. Some of those cbTMS-EEG studies [16,17] probably applied TMS intensities too low for appropriate cbTMS, resulting in an induced E-Field of insufficient depth [8]. Moreover, those studies lacked adequate control for multimodal EEG responses to sensory inputs evoked by auditory and somatosensory inputs, or the incidental co-stimulation of proximal brain regions, in particular the occipital cortex. Indeed, a recent study on cbTMS-EEG has called for caution when interpreting EEG results from cbTMS and stressed the necessity of appropriate control conditions [18]. Therefore, it is rather unclear to what extent the so far published results are due to multimodal EEG responses to sensory input, collateral stimulation of the occipital cortex, or cortical responses caused by effective cerebellar activation by cbTMS. Nevertheless, it is possible that adequate control conditions will allow the identification of true cortical responses to cbTMS. The potential of cbTMS-EEG lies in broadening our understanding of the mechanisms of cerebellar modulation of cerebral cortex activity in both motor and non-motor regions [19], and possibly as a biomarker of cerebellum-thalamo-cortical pathway integrity, make this a worthwhile effort.

To this end, we adapted the design of an optimized sham procedure specifically for cbTMS, which was originally developed for cerebral targets of TMS-EEG [13]. Furthermore, we applied several control conditions in order to confirm the source of the EEG response to cbTMS and address the limitations of previous studies. In this exploratory study, we aimed at identifying EEG responses specific to cbTMS, and hypothesized that cbTMS evokes EEG responses that can be divided into different components depending on their source, with sensory inputs accounting for a significant number of these components, but some attributable specifically to cbTMS.

2. Material and methods

2.1. Subjects

Healthy, right-handed volunteers (according to a laterality index >0.5 in the Edinburgh Handedness Questionnaire [20]) were included in the study. The exclusion criteria were assessed during the initial interview to determine suitability for the study and were as follows: history of psychiatric or neurological disease, current treatment with drugs acting on central nervous system [21], working in night shifts [22] or current pregnancy. Furthermore, a resting motor threshold (RMT) >60% of maximum stimulator output (MSO), as cbTMS intensity was determined as an increment of MSO relative to the RMT in these Experiments, and the maximal cbTMS intensity for any given individual was RMT+40 %MSO. Moreover, volunteers at risk of an addiction were excluded [23], indicated by present or prior history of alcohol or illicit drug abuse or reporting excessive caffeine intake above the upper limit of the caffeine content of a beverage (>120 mg/d) [24].

A total of 53 subjects were screened for participation in the study. Six participants were excluded: 3 participants due to discomfort, 2 because of an RMT >60 %MSO, and 1 because of regular consumption of illicit drugs. One dataset was excluded from the analysis due to noisy EEG data. The total dataset was based on 46 participants, 23 in Experiment #1 (14 females; mean ± 1 standard deviation (SD) age, 24.0 ± 5.2 years) and 23 in Experiment #2 (14 females; mean ± 1SD age, 22.4 ± 2.3 years).

Experiments were conducted in accordance with the Declaration of Helsinki and within the current TMS safety guidelines of the International Federation of Clinical Neurophysiology [25]. All subjects provided written informed consent prior to participation, and the study was approved by the ethics committee of the medical faculty of the University of Tübingen (364/2020/B02).

Abbreviations

| Abbreviation | Meaning |
|--------------|---------|
| CB-N45       | Negative left-hemispheric deflection peaking 45 ms after the cbTMS pulse |
| CB-P25       | Positive left-hemispheric deflection peaking 25 ms after the cbTMS pulse |
| CBI          | Cerebellar Brain Inhibition |
| cbTMS        | Cerebellar TMS |
| CER-DOWN     | Cerebellar TMS with a downwards induced current in the cerebellar cortex |
| CER-UP       | Cerebellar TMS with an upwards induced current in the cerebellar cortex |
| EEG          | Electroencephalography |
| E-Field      | Electric Field |
| EMG          | Electromyography |
| ES           | Electrical Stimulation |
| FDI          | First Dorsal Interosseus |
| ICA          | Independent Component Analysis |
| ISI          | Interstimulus Interval |
| M1           | Primary motor cortex |
| MEP          | Motor Evoked Potential |
| MS           | Magnetic Stimulation |
| MSO          | Maximum Stimulator Output |
| NRS          | Numeric Rating Scale |
| OCC          | TMS to the occipital cortex with an upwards induced current in the cortex |
| RMT          | Resting motor threshold |
| SD           | Standard Deviation |
| SHAM-MS      | Sham-Magnetic Stimulation |
| TEP          | TMS-evoked potential |
| TFR          | Time-Frequency Representation |
| TMS          | Transcranial Magnetic Stimulation |
2.2. Experimental design

The study involved the measurement of EEG and EMG responses to single-pulse TMS targeting the right cerebellar hemisphere. The study followed a randomized, sham-controlled design. All measurements for an individual participant were conducted on the same day.

Experiment #1 aimed at comparing the EEG response from real cbTMS with an upward current induced in the cerebellum (CER-UP) to a control condition (SHAM-MS). The procedure for the SHAM-MS followed an optimized sham approach [13] with electrical stimulation (ES) of the neck, but in combination with magnetic stimulation (MS) of the right shoulder [11] (Fig. 1). The REAL condition involved cbTMS in addition to all stimuli of the SHAM-MS condition. In principle, this approach aims at delivering approximately equivalent sensory inputs in the CER-UP and SHAM conditions, to achieve comparability between these sensory evoked EEG responses by both conditions.

To demonstrate reproducibility of the results from Experiment #1, a second Experiment was conducted (Experiment #2), with further control conditions but otherwise the same parameters. Namely, an occipital control target (OCC) and cbTMS with a different current direction (CER-DOWN) were introduced (Fig. 1).

After the completion of each experiment, subjects filled out two Numeric Rating Scales (NRS) assessing perceived pain and discomfort on a scale from 0 to 10, with 0 being no pain or discomfort, and 10 being the highest imaginable pain or discomfort [26]. In the first two scales, subjects were asked to indicate the perceived pain or discomfort from the trials they presumed were REAL, and in the second scale for the trials they presumed to be perceived pain or discomfort from the trials they presumed were RMT [20% of maximum stimulator output (MSO)]. RMT was assessed for each participant using the standard relative frequency method [29]. Then, the TMS intensity eliciting MEPs with an average peak-to-peak amplitude of 0.8±0.1 mV was determined [30]. The cbTMS intensity was set as the cbTMS intensity for the rest of the experiment. However, if CBI <85% was not achieved, the highest intensity (RMT+40% MSO) was selected. Continuous EMG was monitored to verify that subjects kept the target muscle relaxed, as voluntary activation of the target muscle has been shown to abolish the CBI [31]. CBI was quantified as the percentage of the mean conditioned over test MEP amplitude. The lowest cbTMS intensity resulting in CBI <85% was set as the cbTMS intensity for the rest of the experiment. However, if CBI <85% was not achieved, the highest intensity (RMT+40% MSO) was selected. This aimed at achieving a homogenous sample and ensuring CBI is comparable across subjects.

Another assessment prior to the TMS-EEG measurements consisted of determining the intensity of the magnetic stimulation to the right shoulder to be applied in the SHAM-MS condition. The SHAM-MS Intensity was determined, by applying ES at a fixed intensity of 25 mA and SHAM-MS to the right shoulder at increasing intensity. The ES intensity was based on the suprathreshold intensity of a recent study [13], but we realized that ES alone was not sufficient to match the strong multisensory input generated by cbTMS. Hence, MS to the right shoulder was added [11] (SHAM-MS, Fig. 1). The N100 amplitudes evoked by ES plus SHAM-MS of increasing intensity were assessed individually to determine at which intensity the N100 potential reached an individual maximum, or “saturation”. The N100 was chosen as a surrogate deflection for EEG sensory evoked responses determined by the intrinsic, non-modality-specific saliency of the stimulus, as somatosensory inputs from TMS pulses are a significant source of sensory evoked responses independent from auditory evoked potentials [32,33] and can overlap with TMS-EEG evoked potentials in time-windows beyond 60–70 ms after TMS [11–14,32]. Five blocks of 60 MS pulses each to the right shoulder were applied, while increasing the stimulation intensity in each block: 50%, 57%, 64%, 70%, and 78%MSO. The resulting EEG signals were processed with visual artefact rejection of channels and trials, and one round of independent component analysis (FastICA) to remove blink artifacts. Finally, the amplitude of the signal in each block was determined trial-by-trial by averaging the signal amplitude within the epoch 75–125 ms after the stimulus to encompass the N100 response and then averaged across the 10 EEG channels that
presented the largest negative deflection. Saturation of the sensory evoked potentials was defined as the block that resulted in an average N100 amplitude within one standard deviation of the previous block’s N100 or less, as these values represent expected values from a distribution, suggesting that further increase of sensory input would no longer result in a significant increase of the N100 amplitude [13]. This SHAM-MS intensity remained fixed for the rest of the experiment.

Finally, TMS pulses were applied to the right cerebellar hemisphere, inducing a monophasic upward current (CER-UP) [3]. A total of 280 trials were obtained, 140 each corresponding to the REAL and SHAM-MS condition, randomly interleaved. The SHAM-MS consisted of ES to the neck and MS to the right shoulder on the trapezius muscle set to SHAM-MS intensity, without cbTMS (Fig. 1). The REAL condition also consisted of ES to the neck, MS to the right shoulder set to SHAM-MS intensity, and additionally cbTMS, delivered at the same scalp location that was used for assessing CBI, and set to the determined cbTMS intensity. All corresponding stimuli of each condition were delivered.
simultaneously. A jitter was applied to the intertrial interval, to reduce expectancy of the next trial and its sensory inputs [33].

2.5. Experiment #2

The design of Experiment #2 was similar to Experiment #1. Assessments of RMT and cbTMS intensity remained unchanged. However, there was no assessment of SHAM-MS intensity, and the intensity of the SHAM-MS was instead fixed at 85 %MSO. This was decided, as 22/23 subjects reached a maximum of the N100 amplitude at 78 %MSO in Experiment #1. ES was applied in all conditions, as in Experiment #1.

A second control condition was added, namely the Occipital Control Condition (OCC), which involved one block of 280 trials, 140 trials with single-pulse TMS applied to the right occipital cortex, with the coil placed over electrode O2 and the induced current in cortex in upward direction [34], and 140 SHAM-MS trials – as described above (SHAM-MS in Fig. 1). The OCC control experiment was conducted to clarify if possible current spread from cbTMS to occipital cortex could account for EEG responses observed with cbTMS.

Moreover, cbTMS was applied to the right cerebellar hemisphere using an upward induced current at an intensity corresponding to the cbTMS intensity (CER-UP), to replicate findings of Experiment #1. Finally, this was repeated, but with a downward induced current (CER-DOWN). This experiment was performed to demonstrate specificity of cbTMS effects related to current direction, as previous experiments have demonstrated that downward induced current over the lateral cerebellar hemisphere is less effective than upward induced current in eliciting CBI [3].

2.6. Data analysis

Data processing and analysis of EEG and EMG signals were performed utilizing customized scripts on MATLAB 2017b and the FieldTrip open source toolbox [35]. EEG was recorded continuously and then segmented according to trigger markers in the data. These epochs were defined from 0.5 s before to 1 s after the marker and baseline-corrected (−50 ms to −50 ms).

2.7. EEG data preprocessing

For all datasets, data 6 ms before to 20 ms after the marker were removed and interpolated with standard methods. The FieldTrip interpolation method used was “p-chip”. EEG data were then visually inspected in two rounds. In the first round of visual artefact rejection, the FieldTrip method “summary” was used to exclude trials and channels presenting excessive artifacts. In the second round, all trials and respective channels were visually inspected trial-wise (FieldTrip method “trial”) and those containing major artifacts were excluded (Table 1).

A two-step independent component analysis (ICA) was then performed on the resulting data [36]. Before the first round of ICA, the data were demeaned and down-sampled to 1000 Hz. The ICA components were visually inspected and retained or removed, on the basis of their topography, average time course, single-trial time course and power spectrum [37]. In the first round of ICA, only components containing TMS-related artifacts with high amplitude were excluded. Thereafter, a bandpass filter (0.5–100 Hz, zero-phase Butterworth, 3rd order) was applied to the data. The second round of ICA intended to remove components representing eye muscle artifacts, persistent muscle activity and line noise (50 Hz).
Independent component analysis (ICA): means to EEG potentials. These were then subtracted from the single trials. This was performed both trial-by-trial and for the time-locked decomposition on single trials, with frequency-dependent width deviation of the full trial, and baseline correction (C0 response to TMS). This procedure was then followed by z-transformation (TFR). This allowed the removal of the evoked component of the signals were then averaged within the indicated time windows and determined by the algorithm were then visually inspected. The windows were not pre-selected. The positive and negative clusters meaning that the function did not average over time and that time-domain was set to permute freely, parametric cluster-based permutation statistics, which are effective in controlling for false discoveries from multiple testing [39]. The analysis of TEPs involved cluster-based t-tests for identifying the most positive value for cb-N45 clusters across cbTMS conditions were selected and their signal averaged for each subject. Then, the most positive value for the cb-P25 and cb-N45 were determined for each subject within the time-window of the cluster group average. Finally, Gaussian distributions were fitted. A Wilcoxon signed-rank test was applied to the reported pain and discomfort scores to compare the REAL vs. SHAM-MS conditions. Pearson correlation analyses were performed between TEPs and TFRs in the CER-UP conditions in Experiment #1 and #2 vs. the respective CBI and cbTMS intensity values to clarify if these measures of cerebellar-to-cortex connectivity are related.

### 2.8. TMS-EEG evoked potentials (TEPs)

After data preprocessing, EEG epochs representing trials of a given experimental condition (CER-UP#1 and #2, CER-DOWN and OCC) were loaded and subjected to lowpass filtering (45 Hz, zero-phase Butterworth, 3rd order). Then, EEG responses in the REAL and SHAM-MS conditions were calculated by averaging the EEG signal over all subjects and experimental condition for further statistical analysis. Thereafter, SHAM-MS was subtracted from REAL to remove the multimodal EEG responses to sensory input potentially overlapping [13] in time-windows beyond 60 ms [11] to 70 ms [12–14] (see statistical analysis).

### 2.9. TMS-EEG oscillatory response

Time–frequency representations (TFRs) of TMS-related changes in oscillatory power were calculated [35,38] using a Morlet wavelet decomposition on single trials, with frequency-dependent width (wavelet width of 2.6 cycles at 4 Hz, adding 0.2 cycle for each 1 Hz). This was performed both trial-by-trial and for the time-locked average of all trials, which corresponds to the TFRs of the evoked EEG potentials. These were then subtracted from the single trials TFR. This allowed the removal of the evoked component of the time-frequency response, thus obtaining the induced oscillatory response to TMS. This procedure was then followed by z-transforming the TFR of each trial with respect to the mean and standard deviation of the full trial, and baseline correction (−500 ms to −100 ms) [38].

### 2.10. Statistical analyses

The analyses were performed on the MATLAB platform (R2017b, The Mathworks, USA). We compared the EEG responses from the REAL and SHAM-MS conditions by arithmetic subtraction within each experimental condition: CER-UP#1, CER-UP#2, CER-DOWN and OCC [13]. For the analyses of EEG responses, we used non-parametric cluster-based permutation statistics, which are effective in controlling for false discoveries from multiple testing [39]. The analysis of TEPs involved cluster-based t-tests for identifying the time windows in the REAL vs. SHAM-MS signals that were significantly different. The time-domain was set to permute freely, meaning that the function did not average over time and that time-windows were not pre-selected. The positive and negative clusters determined by the algorithm were then visually inspected. The signals were then averaged within the indicated time windows and compared, yielding the significant EEG channel clusters (threshold: p < 0.05). Analysis of the induced oscillations followed the same procedure but was divided into different frequency bands of interest: theta (0, 4–7 Hz), alpha (8–12 Hz), low beta (13–20 Hz), high beta (21–29 Hz), low gamma (29, 30–40 Hz) and high gamma (29, 60–90 Hz). Subdividing into frequency bands with a known physiological meaning was done because of the exploratory nature of the study, as reducing the degrees of freedom decreases the risk of false positives, while we accepted that this also increased the risk of false negatives. Due to the increased number of tests (n = 6), the threshold of statistical significance was adjusted to p < 0.0083 using the Bonferroni method. A significant cluster was defined as ≥2 neighboring electrodes with p < 0.05. Monte Carlo p-values were calculated via a two-tailed test at the significance level p < 0.025, using 1000 iterations for TEPs and 2000 iterations for induced oscillations [39].

After the analyses detailed in the previous paragraphs had been completed, the amplitude distributions of the cbTMS specific TEPs (cb-P25, cb-N45) identified by the cluster analysis procedure described above were analyzed for the cbTMS conditions (CER-UP#1, CER-UP#2, CER-DOWN) in order to provide normative data. The common significant EEG channels comprising the cb-P25 and cb-N45 clusters across cbTMS conditions were selected and their signal averaged for each subject. Then, the most positive value for the cb-P25 and the most negative value for the cb-N45 were determined for each subject within the time-window of the cluster group average. Finally, Gaussian distributions were fitted. A Wilcoxon signed-rank test was applied to the reported pain and discomfort scores to compare the REAL vs. SHAM-MS conditions. Pearson correlation analyses were performed between TEPs and TFRs in the CER-UP conditions in Experiment #1 and #2 vs. the respective CBI and cbTMS intensity values to clarify if these measures of cerebellar-to-cortex connectivity are related.

### 2.11. Estimation of TMS-induced E-field on the cerebellar cortex

To estimate the intensity of the E-field on the cerebellar cortex induced by the specific setup in this Experiment, a simulation in the SimNIBS® environment was performed [40]. Individual anatomical MRIs were obtained from 8 participants. The T1-weighted MRIs were then segmented and meshed using the built-in headrec tool [41]. In cooperation with the Project Coordinator of SimNIBS®, Prof. Axel Thielscher, an official model of the 50 mm external diameter figure-of-8 branding iron coil utilized in the present experiments to deliver cbTMS was obtained. The specific properties of the coil were assessed in detail with X-rays of the coil and the factory specifications. Two simulations were run for each subject, corresponding to two targets: 1. Left M1; 2. Right cerebellar hemisphere. For the M1 target, the coil model was set on the scalp region atop the left precentral gyrus, with the direction of the E-field perpendicular to the gyrus and setting current intensity corresponding to the individual RMT. For the cerebellar hemisphere, the coil was set on the midpoint between the inion and the right mastoid, corresponding to electrode position P010 (10-10 EEG system) and stimulation intensity set to the individually applied cbTMS intensity.

### 3. Results

#### 3.1. Levels of pain and discomfort

In Experiment #1, there was a significant difference for the reported subjective perceptions from REAL vs. SHAM-MS conditions, with subjects reporting the SHAM-MS to be less painful and more tolerable (both p < 0.05). In contrast, there were no significant differences between REAL vs. SHAM-MS in Experiment #2 for pain (p = 0.50) and tolerability (p = 0.83), when a fixed suprathreshold intensity of SHAM-MS (85%MSO) instead of an individually titrated intensity (50–78%MSO in Experiment #1) was applied. Overall,
subjects reported moderate pain and good tolerability, with considerable interindividual variability (Fig. 2).

3.2. Estimation of TMS-induced E-field on the cerebellar cortex

Simulation of the E-field induced by TMS over M1 yielded an E-field that is centered on the precentral gyrus, with an average peak intensity of 87 V/m. Regarding the cerebellar target, the induced E-field was centered on the right posterior lobe around the horizontal fissure with an average peak intensity of 120 V/m, with the E-field also encompassing some inferior-posterior parts of the occipital cortex (Fig. 3).

3.3. Sensory evoked potentials: saturation procedure

The saturation procedure determined a maximum N100 amplitude elicited by magnetic stimulation over the right shoulder with increasing stimulus intensity plus ES of fixed intensity over the neck (Fig. S1).

3.4. RMT, cbTMS intensity & CBI

RMT (mean ± 1SD) was 42.4 ± 5.8 %MSO in Experiment #1 and 44.1 ± 6.9 %MSO in Experiment #2. cbTMS intensity (mean ± 1SD) was 175.8 ± 20.1% of RMT (74.5 ± 10.7 %MSO) in Experiment #1 and 171.8 ± 22.1% of RMT (75.8 ± 11.1 %MSO) in Experiment #2.

CBI (mean ± 1SD) was 0.85 ± 0.13 for all 46 subjects (Experiment #1: 0.88 ± 0.12; Experiment #2: 0.83 ± 0.14), with 38 subjects being within ±1SD of the mean CBI, indicating a homogenous sample. The presence of CBI is defined as any value < 1.0 [30]. By this definition, a CBI was determined in 21/23 of the subjects in Experiment #1 and 22/23 in Experiment #2.

3.5. TEPs in the REAL vs. SHAM-MS conditions

Fig. 4 shows the average time courses and time-resolved topographical plots of cbTMS-evoked EEG responses in the REAL (CER-UP) vs. SHAM-MS conditions of Experiments #1 and #2. In addition to the large N100 and P200 midline potentials that are very similar in both conditions, subtraction of SHAM-MS from REAL reveals an early left prefrontal positivity at ~25 ms and a left hemispheric negative potential at ~45 ms specific to the REAL condition in both Experiments. Of note, CER-UP findings were highly replicable across Experiments #1 and #2. Time courses and topographical plots of TEPs of the OCC and CER-DOWN control conditions are shown in Supplementary Fig. S2.

Comparing CER-UP with the SHAM-MS, the cluster-based statistics revealed significant differences in Experiment #1 that were reproduced in Experiment #2. These included significant clusters between 20 and 27 ms (cb-P25) in the left prefrontal cortex, as well as between 35 and 55 ms (cb-N45) in left-hemispheric fronto-parietal cortex, and a positive deflection at the same time in right occipital cortex (Fig. 5, for an enlarged version see Fig. S3). The cb-P25 and cb-N45 was also observed in the CER-DOWN condition of Experiment #2 (Fig. 6B, for an enlarged version see Fig. S4).

The SHAM-MS condition elicited a high-amplitude midline negative deflection 100 ms after the pulse, followed by a positive deflection at 200 ms, centered on frontal-central regions (Fig. 4), corresponding to the N100–P200 complex elicited by multimodal sensory stimuli, which is expected given the considerable multisensory input involved in these conditions [12,13,15]. However, when comparing REAL to SHAM-MS, this resulted in Experiments #1 and #2 in a significant cluster at around 100 ms, as the N100 in the REAL was centered around left parietal electrodes compared to the midline potential in SHAM-MS (Fig. 5). Both Experiments revealed a persistent positive deflection over the right occipital cortex in the REAL condition, which lasted from 180 ms to 320 ms in Experiment #1, and up to 480 ms in Experiment #2. In the same time window, a persistent negative deflection was observed in the region of the left parietal cortex (Fig. 5).

Occipital TMS (OCC) elicited a positive deflection in the targeted right occipital cortex from 20 to 45 ms after the TMS pulse, mirrored by a focal negative deflection in left parietal cortex. In addition, a late positivity occurred from 200 to 480 ms at the site of the stimulated right occipital cortex (Fig. 6A). Note that the early left prefrontal positivity at ~25 ms and the left fronto-parietal negativity at ~45 ms seen in the CER-UP and CER-DOWN conditions were not elicited by occipital TMS.

CER-DOWN resulted in an early positive deflection (20–26 ms) in the left prefrontal cortex, and a negative deflection in left parietal cortex (Fig. 6B), similar to the observed EEG responses in the CER-UP condition of Experiments #1 and #2 (Fig. 5). Furthermore, CER-DOWN also revealed a significant left parietal N100 (Fig. 6B), which was also observed in both CER-UP conditions (Fig. 5). The persistent negative cluster in the late time window of 181–481 ms in the left parietal region was also reproduced (Fig. 6B), but not the persistent positive deflection in the right occipital region observed in CER-UP conditions.

3.6. TFRs in the REAL TMS vs. SHAM-MS conditions

TMS induced oscillations from the REAL (CER-UP) and SHAM-MS conditions revealed significant differences in several time windows and frequency bands, with comparable results in Experiments #1 and #2 (Fig. 7A–B, and Supplementary Fig. S5). REAL cbTMS elicited a broadband increase in oscillatory power at early latencies (~50–200 ms), with increased theta in the frontal regions, increased high beta in left prefrontal regions and increased low and high gamma in frontal and posterior regions. Both experiments also revealed decreased alpha power between 250 and 600 ms in posterior regions (Fig. 7A–B).

TMS of occipital cortex (OCC) resulted in an increase in high gamma power around central posterior regions and an early increase in high beta power centered at the site of stimulation, which was not present in any other condition (Fig. 7C, and Supplementary Fig. S6). CER-DOWN largely reproduced the results from CER-UP (Fig. 7D, and Supplementary Fig. S6). Correlation analyses between CBI or cbTMS intensity with TEP amplitudes, and between CBI or cbTMS intensity with cbTMS induced power changes of the CER-UP conditions yielded no significant linear correlations after Bonferroni correction for multiple comparisons (p < 0.0023).
From the analyses of the amplitude distributions of the cb-P25 and cb-N45 in the conditions involving cbTMS (CER-UP, CER-DOWN), it can be observed that cb-P25 and cb-N45, as well as the SHAM-MS responses were normally distributed (Fig. 8). The expected values of the SHAM-MS responses were always close to 0 mV, while the REAL responses were significantly different from the SHAM-MS responses (Fig. 8). Consequently, it can be observed that for these short-latency responses, the amplitude distributions and expected values of the REAL minus SHAM-MS responses were very similar to the REAL responses. This suggests that for reliable measurement of the early TEPs (cb-P25, cb-N45) the correction by a SHAM condition is not needed. This notion is supported by a recent study applying a comparable SHAM-MS condition involving magnetic stimulation to the shoulder, which found no overlapping of the EEG responses elicited by sensory input with the TEPs before 60 ms [11], as well as other previous studies that did not find overlap of these responses with TEPs before 70 ms [12–14]. Violin plots of the individual cb-P25 and cb-N45 responses derived from the analyses described above can be found in the Supplementary Material (Fig. S7), in which the interindividual variability of the responses can be observed.
4. Discussion

The objective of this study was to unveil EEG responses over cerebral cortex elicited by cbTMS - a challenging endeavor, due to several confounding factors present in the EEG response. As hypothesized, our results show EEG responses from cbTMS that can be attributed to confounding sources. These include EEG responses likely elicited by sensory input, overlapping in time with the TEPs after 60 ms [11] to 70 ms after the TMS pulse [12–14] and EEG responses elicited by collateral stimulation of inferior-posterior
parts of the occipital cortex. Nevertheless, other responses could not be attributed to any tested confounder, and most likely represent specific responses in the cerebral cortex caused by cbTMS.

4.1. CbTMS-evoked EEG potentials (TEPs)

Most salient were a prefrontal positive deflection contralateral to the cbTMS around 25 ms after the pulse (cb-P25), and a negative deflection that peaked around 45 ms after the pulse (cb-N45) in the parietal and frontal regions contralateral to cbTMS. Moreover, cbTMS caused an increase in oscillatory power in the high-beta frequency band (21–29 Hz) within the first 200 ms after the TMS pulse, located in prefrontal regions contralateral to cbTMS. Importantly, these results were not present in any of the control conditions and are anatomically plausible, reinforcing the notion that these are specific EEG responses caused by cbTMS.

State-of-the-art methods were tested and subsequently improved to ensure effective cbTMS, which poses inherent challenges. Firstly, the E-field induced by TMS capable of depolarizing neuronal populations has a limited depth range and the distance between coil and cerebellar cortex is relatively large [8]. Secondly, there is no direct observable output that informs about effective cbTMS, such as the presence of MEPs when stimulating M1. Here, we assessed CBI as an indirect marker of effective cbTMS for each participant. According to the current view, cbTMS triggers inhibitory efferent signals to the contralateral M1 through activation of cerebellar Purkinje cells, resulting in lower conditioned MEP amplitudes, providing evidence of effective cbTMS [3]. Lesions of cerebellar efferent pathways result in absent or reduced CBI, corroborating the view that CBI tests the integrity of the cerebellodentato-thalamo-motor cortical pathway [42,43].

However, we observed EEG responses specific to cbTMS even in subjects with only small CBI, and no correlation between these responses and CBI was detected. When considering the E-field estimation, it suggests that the main cerebellar region targeted in this study is the lateral cerebellar cortex, around Crura 1 and 2.

Fig. 6. Comparison of TMS-EEG responses from the control conditions and the sham procedure: A. Right occipital TMS (OCC) vs. SHAM-MS; B. cbTMS with downward electric field (CER-DOWN) vs. SHAM-MS. Topographical plots represent results from the cluster-based t-statistics (REAL – SHAM-MS), with the time windows and the p-values of the significant clusters indicated. EEG channels marked as green dots indicate significant clusters. The time course of the averaged signal of the electrodes comprising each significant cluster is displayed in the respective plot to the right (black bar: time of stimulation (0 s) and the period of data exclusion contaminated by the stimulation artefact; gray shaded area: significant time window of the cluster; purple: REAL; green: SHAM-MS; shaded areas correspond to ±1 SEM). For an enlarged version of the Figure, see Fig. S4 in the Supplementary Material. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
Fig. 7. Comparison of TMS-EEG induced oscillations in the REAL minus SHAM-MS conditions. A-D, CER-UP in Experiments #1 and #2, OCC, and CER-DOWN, respectively. The time-frequency plots display the difference in the oscillatory response from the REAL and SHAM-MS conditions (REAL − SHAM-MS), averaged across all channels and all subjects. Black bars indicate the time of stimulation (0 s) and the period of data exclusion contaminated by the stimulation artefact, and the dotted boxes represent the frequencies and time windows where the significant clusters were found. Topographical plots represent the average power difference (REAL − SHAM-MS) within the frequency and time windows where the significant clusters were found. The frequency band, time window and p-value of each significant cluster are indicated next to the respective topographical plot. EEG channels marked as green dots indicate the significant clusters. On the right-hand side of each plot, the respective calibration bar are indicated, with the z-values being a normalization of the power spectral density. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
(Fig. 3), which are linked to frontoparietal regions in the cerebral cortex and the dorsolateral prefrontal cortex [1] and associated with cognitive functions. In contrast, motor functions are localized in anterior regions of the cerebellum [44,45]. This implicates that it is possible to deliver effective TMS to the lateral posterior regions of the cerebellar cortex. It may also explain why specific EEG responses to cbTMS were observed in contralateral prefrontal and parietal regions in this study (Supplementary Fig. S8). Accordingly, recent studies delivering cbTMS theta-burst stimulation to the lateral cerebellum demonstrated direct projections also to non-motor areas [46].

Namely, a negative deflection in the left parietal and frontal regions peaking around 45 ms (cb-N45) after cbTMS was observed and reproduced in both experiments. Fernandez et al. found a similar cluster when stimulating the cerebellum with a double-cone coil but stated that further investigation was necessary to determine if this potential could be specifically attributed to activation of the cerebello-dentato-thalamo-cortical pathway [18]. Our experiments were controlled by SHAM-MS and occipital TMS and allow the conclusion that the cb-N45 is specific to cbTMS. Furthermore, there was evidence of an early (~25 ms) positive prefrontal potential specific to cbTMS (cb-P25) in the CER-UP of Experiment #1, which could be reproduced in the CER-UP and CER-DOWN of Experiment #2. The cb-P25 was not observed in any of the control conditions. We therefore attribute the cb-P25 and the subsequent cb-N45 to an activation specifically of the cerebello-dentato-thalamo-cortical pathway.

This interpretation is anatomically plausible. Most cerebellar efferent projections pass through dentate and thalamic nuclei and the most important of these are motor and sensory loops, parietal loops and prefrontal loops [1]. The cerebellum has been shown to be strongly connected with contralateral prefrontal and associative areas by high-resolution tractography in humans [47,48] and in ex vivo anatomical investigations [49]. Tracer studies utilizing transneural transport of neurotropic viruses in monkeys found the efferent cerebello-dentato-thalamo-cortical pathways to target predominantly the contralateral M1 and the dorsolateral prefrontal cortex [50]. Moreover, connectivity was found between cerebellar and contralateral parietal cortices in human fMRI studies [44,51] and viral tracing studies in nonhuman primates [52]. To what extent the cortical EEG responses evoked by cbTMS reflect excitation or inhibition may be tested by pharmaco-cbTMS-EEG, similar to previous TMS-EEG experiments of M1 that have demonstrated, for instance, that anti-glutamatergic [53] and GABAergic drugs [54] contribute the excitation/inhibition balance in regulating the N45 amplitude.

An adequate sham design is critical for meaningful interpretation of results from cbTMS-evoked EEG responses. Here we...
followed our recently described approach of an optimized sham condition [13] that relied on ES, and we added here high-intensity magnetic stimulation of the shoulder to it [11] (SHAM-MS) to elicit a maximum amplitude of the event-related potential N100. This modified SHAM-MS procedure was applied to specifically address the challenges of cbTMS and may not be necessary or feasible when applying TMS to other targets. Indeed, SHAM-MS elicited a sequence of EEG deflections, which included a fronto-central negative deflection after ~100 ms. This response has been described as a multimodal signature of saliency associated to sensory stimuli [55], that overlaps in time with TEPs after 60–70 ms [10–13]. Previous studies have also observed this effect but attributed it, probably erroneously, to be specific to direct cerebellar activation by TMS [16]. However, when subtracting the EEG response of SHAM-MS from REAL cbTMS, a significant left parietal cluster was consistently observed around 100 ms after cbTMS (CER-UP, CER-DOWN). The spatio-temporal representation of the N100 elicited by REAL cbTMS was significantly different from SHAM-MS, as the cluster of channels was located in left parietal instead of midline fronto-central regions, and the early onset of the signal in the TEPs at around 75–80 ms was atypical for a multimodal EEG response to sensory input [5]. This result can be interpreted in multiple ways. Either, it might indicate an insufficiency of the SHAM-MS procedure to fully account for an overlap of responses to multimodal sensory inputs with responses elicited by cbTMS in this time-window [12–14], or, it may represent a specific response to cbTMS.

Further control conditions for incidental stimulation of proximal cortical regions such as the occipital cortex are important, as stressed by a recent study [18]. In our Experiments, cbTMS led to a positive deflection in the occipital cortex at early latencies, followed by a late and long-lasting positivity in this cortical region lasting up to 500 ms after the pulse. It is unlikely that these responses reflect a contamination of the EEG response by posterior muscle artifacts, as these results were reproduced in the OCC condition, where the target of stimulation was not directly over muscle tissue. This demonstrates that collateral stimulation of the occipital cortex is a confounding factor in cbTMS that should be accounted for, which is further suggested by the E-Field estimation (Fig. 3). However, we could demonstrate that stimulation of the right occipital cortex did not produce EEG responses in more anterior brain regions (in contrast to cbTMS), but rather a local response, which was also observed in previous studies with the same occipital target [34].

4.2. CbTMS-induced oscillations

Oscillatory responses in the theta band were observed after sensory stimuli, irrespective of the stimulus modality, and induced theta power increased with stimulation intensity [56]. Likewise, it has been suggested that theta responses in TMS-EEG might be attributed to cortical responses to multisensory input [13]. Previous cbTMS studies, most likely erroneously, attributed this theta response to be a direct effect of cbTMS [17,57]. Our SHAM-MS condition, defined by stronger somatosensory input than in previous studies, did also show this early theta increase (Supplementary Figs. 5–6). A significant early theta response was still present in the CER-UP and CER-DOWN after subtraction of the SHAM-MS (Fig. 7A–B) but was not present in the OCC after SHAM-MS subtraction (Fig. 7C). There is the possibility that somatosensory input was not completely saturated by SHAM-MS, so that the addition of cbTMS increased the somatosensory input to cause the significant theta response when subtracting SHAM-MS from REAL.

Increases in low- and high-gamma power between 50 and 150 ms after stimulation were also present in our measurements. Similar responses within the gamma band have also been observed and even modulated in previous TMS-EEG experiments, present in fronto-central regions and starting at around 50 ms after TMS [58–60]. However, these gamma responses were observed in the OCC and SHAM-MS conditions as well (Supplementary Figs. S5–6). Hence, these gamma responses may represent an unspecific response to cortical activation by multimodal input, which is more pronounced in the REAL condition, given the presence of direct TMS activation in addition to the sensory input. However, caution is advised when interpreting TMS responses in higher frequency bands such as the gamma band, given the risk of contamination by cranial muscle activity that may be evoked by the cbTMS pulse. The late decrease in alpha power ~300 ms after the pulse was previously described as an EEG response specific to TMS of M1, reflecting the activation of cortico-cortical pathways to the primary somatosensory cortex [61]. However, a similar alpha decrease was observed as a response to SHAM-MS (Supplementary Figs. S5–6). Furthermore, this event-related desynchronization was consistent with TMS of M1, when no MEP was elicited, suggesting that the occurrence of this late alpha event-related desynchronization is only present when the stimulation actively involves the corticospinal tract and is associated with proprioceptive sensory feedback [61].

We observed an increase in the high beta frequency band in the OCC at the site of stimulation. However, none of the control conditions induced the specific left-hemispheric prefrontal high beta increase caused by cbTMS (CER-UP, CER-DOWN). Therefore, this likely reflects a direct response to cbTMS projected through the cerebellum-dentato-thalamo-cortical pathway to the contralateral prefrontal region, possibly demonstrating oscillatory coupling of these regions in the beta band. Beta oscillations are associated with sensorimotor function and motor control; both high beta power and cerebellar involvement have been observed during postural maintenance [62–64]. In cerebellar-cerebral cortex networks, beta phase synchronization has been observed in a frontal-temporal-cerebellar network during auditory-to-motor rhythm learning [65]. Within the cerebellum, local field oscillations in the beta range are believed to arise from granule and Golgi cell activity, where this has been functionally associated with cerebellar-cerebral cortex communication during sensorimotor processing, and active movements, further suggesting cerebellar-cerebral cortex communication in this frequency band [66].

4.3. Estimation of TMS-induced E-field on the cerebellar cortex

The simulation of the TMS-induced E-field (Fig. 3) showed that the E-field strength in cerebellar cortex exceeds the E-field strength capable of depolarizing corticospinal neurons in M1. This provides strong evidence that cbTMS in this study was sufficient to depolarize neurons in cerebellum. This notion is supported by the CBI results. The design of the coil without casing utilized in the present experiments to deliver cbTMS achieves a closer distance between the E-field on the cerebellar cortex exceeds the E-field on the cerebellar cortex. This may be explained by confounding factors: The variability of the magnitude of CBI may be explained by individual anatomical differences, such as the variations in coil-to-cerebellar cortex distance and position of the peak E-Field on the cerebellar cortex relative to motor cerebellum, as the cbTMS coil was placed based on anatomical landmarks. Nevertheless, the E-field induced by cbTMS in this Experiment was broad, even reaching inferior-posterior
parts of the occipital cortex (Fig. 3), suggesting some, but possibly not full comparability of neuronal populations stimulated across subjects. Furthermore, cerebellar regions associated with motor functions are located in anterior regions [1], thus more challenging to be targeted by TMS, which may also contribute to variable CBI results. Moreover, the E-field estimation indicates that the targeted areas in our study were in the lateral cerebellar cortex, around Crus 1 and 2 (Fig. 3), which are linked to frontoparietal regions in the cerebral cortex and the dorsolateral prefrontal cortex [1], and more related to cognitive functions [44,45]. This might explain why we observed significant cortical response from the stimulation particularly in frontal and parietal regions, even in subjects with small or even absent CBI. Lastly, we observed considerable E-field intensity in the adjacent occipital cortex, which signifies the importance of the occipital target control condition.

4.4. Direction of induced current in cerebellum

Regarding the current direction of cbTMS, there have been discrepancies in the past, and disagreement as to whether the current should flow upwards or downwards in the cerebellar cortex for best assessment of CBI [3,68,69]. Ugawa et al. attributed the significant difference in CBI for different current directions to the cerebellar anatomy, stating that most of the axons of Purkinje cells have a lateromedial and upward orientation towards the dentate nucleus, which would explain why an upward induced current is most effective in eliciting CBI [3]. Fisher et al., however, found that direct activation of the corticospinal tract may contribute to MEP suppression by antidromic corticospinal tract activation [70]. This suggests that different pathways or populations of neurons in the cerebellar cortex could be stimulated depending on the direction of the induced current. We found that both upward and downward induced current in the cerebellar cortex evoked a similar cb-P25 and a high-beta power increase in the contralateral prefrontal cortex. However, the cb-N45 had a slightly different configuration, when stimulating with a downward vs. upward induced current. This further suggests that some of the observed responses are caused by different populations of neurons or axons differentially responsive to distinct directions of current, including antidromic activation of the corticospinal tract.

5. Limitations

In this exploratory study, it was aimed at examining the feasibility of identifying any EEG responses attributable to cbTMS. For this purpose, an established anatomical target was selected to deliver TMS to the lateral cerebellar cortex at intensities likely higher than the minimum intensity necessary to reach the lateral cerebellar cortex, resulting in a broad cerebellar region being stimulated (Fig. 3), demonstrating that targeting based on anatomical landmarks is not specific for differentially targeting specific functional regions of the cerebellum. As a result, the EEG responses observed in this study likely reflect the cortical response to TMS to the lateral posterior cerebellar cortex. This is a relevant issue for future studies, which may utilize neuronavigation to target specific functional regions of the cerebellar cortex with TMS [71], to further investigate EEG responses that are possibly specific to the activation of different cerebellar networks. Also, future investigations may utilize individual hotspot searching for the CBI assessment, which would be especially beneficial when combining it with neuronavigated TMS-EEG [71], as established anatomical targets rely on group-level analysis and may not be optimal for each individual.

Further possible limitations arise from the SHAM-MS design. A possible overlapping in time of the EEG responses elicited by multisensory input with the TEPs was described for time-windows beyond 60–70 ms after the TMS pulse [11–14]. Although the late responses still contain information on the effectiveness of cerebellum-to-cerebral cortex connections, they might not yet allow firm conclusions on the EEG signatures specific to cbTMS, as there is a potential overlap with responses to multisensory input. This problem may even have been accentuated in the present experimental setup, as high-intensity sensory stimulations (ES of the neck, and MS of the shoulder) were added to saturate sensory input. Putative significant interactions, which have not yet been conclusively demonstrated, between TEPs and multimodal EEG responses to sensory input possibly also inherently limit the approach of a simple linear subtraction of the EEG signals of the SHAM-MS and REAL cbTMS conditions. As previous TMS-EEG studies indicated that interference with sensory inputs is relevant only for responses with latencies >70 ms [12–14] or >60 ms [11], the cb-P25 and cb-N45 revealed in the present experiments can be safely attributed to contralateral cerebellar stimulation.

6. Conclusions

The observed early prefrontal cortex (cb-P25) and parietal response (cb-N45) contralateral to cbTMS are specific EEG signatures caused by activation of efferent cerebellar pathways. Furthermore, the increase in induced power in the high beta band in the contralateral prefrontal cortex might reflect oscillatory coupling through these pathways.

Our findings stress the necessity of adequate sham and control conditions when applying cbTMS, as some of the reported findings, in particular late-latency TEPs beyond 60–70 ms after the TMS pulse are possibly overlapping with responses elicited by sensory inputs. When targeting of the cerebellar cortex with TMS is based upon anatomical landmarks, collateral stimulation of the occipital cortex is a confounding factor that should be accounted for.

The specific responses in contralateral prefrontal and parietal cortex may serve as biomarkers for the integrity of the cerebellodentato-thalamo-cortical pathway, but this will need validation by testing clinical populations with a disruption of this pathway.

Credit authorship contribution statement

Lucas Gassmann: Data collection, Data analysis, interpretation, Drafting the article, Final approval of the version to be published: all authors. Pedro Caldana Gordon: Data analysis, interpretation, Critical revision of the article, Final approval of the version to be published: all authors. Ulf Ziemann: Conceptualization, or design of the work, Critical revision of the article, Final approval of the version to be published: all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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