

## Effects of cerebellar transcranial direct current stimulation on cerebellar-brain inhibition in humans: A systematic evaluation

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### ABSTRACT

**Background:** Cerebellar transcranial direct current stimulation (ctDCS) is increasingly used to modulate cerebellar excitability and plasticity in healthy subjects and various patient populations. ctDCS parameters are poorly standardized, and its physiology remains little understood. Our aim was to compare the physiological effects of three different non-target electrode positions (buccinator muscle, supraorbital region, deltoid muscle).

**Methods:** In the first experiment, physiological after-effects of ctDCS were compared based on cerebellar-brain inhibition (CBI) in a group of 15 healthy right-handed participants. In the second experiment, CBI after-effects of ctDCS were assessed using different transcranial magnetic stimulation (TMS) intensities in 14 participants (CBI recruitment curve). The electric field distribution was calculated for each of the electrode montages based on a single anatomically accurate head model.

**Results:** Anodal and cathodal ctDCS polarities significantly decreased cerebellar-brain inhibition (CBI) with no substantial differences between the montages. Lower cerebellar TMS intensities resulted in decreased CBI following cathodal and increased CBI after anodal ctDCS. Computational modeling revealed minor differences in the electric field distribution between non-target electrode positions based on the effect size.

**Conclusion:** Our results show that the non-target electrode position has no significant impact on modeling results and physiological ctDCS after-effects. The recruitment of the cerebellar-M1 connection, however, varied depending on ctDCS polarity and cerebellar transcranial magnetic stimulation intensity, possibly due to diverse effects on different cell populations in the cerebellar cortex. This may be one of the reasons why ctDCS effects on functional measures are difficult to predict.

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**Abbreviations:** ctDCS, cerebellar transcranial direct current stimulation; M1, primary motor cortex; MEPS, motor evoked potentials; TMS, transcranial magnetic stimulation; CBI, cerebellar-brain inhibition; CS, conditioning stimulus; TS, test stimulus; SUIT, the spatially unbiased infratentorial atlas template; BST, brainstem motor threshold; MSO, maximum stimulator output; FEA, finite element analysis; SI<sub>1mV</sub>, the TMS intensity was adjusted to produce ~1 mV peak-to-peak amplitude MEPS.

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### Introduction

Non-invasive cerebellar stimulation techniques have gained increasing popularity in neuroscience research to study functions of the cerebellum and its connections. Currently, cerebellar tDCS (ctDCS) is by far the most common cerebellar stimulation technique [1–5]. Since cerebellar dysfunction has been associated with a number of different diseases including cerebellar ataxias, essential tremor, Parkinson's disease and dystonias [6–9], ctDCS is increasingly considered as a potential therapeutic tool [10]. Despite its

common use, a systematic evaluation of its stimulation parameters is largely lacking. This may explain why behavioral ctDCS effects are partly inconsistent [11–13]. The aim of the present study was to compare the physiological effects of three different non-target electrode positions: the contralateral supraorbital region [14], the ipsilateral buccinator muscle [15], and the ipsilateral deltoid muscle [16]. In addition, a computational modeling approach was used to compare the distribution of the induced electric field on the level of individual cerebellar lobules between the three electrode montages [17].

The supraorbital region is a common localization of the non-target electrode in tDCS studies [18]. In cerebellar ctDCS, the non-target electrode is often placed over the buccinator muscle or deltoid muscle to avoid additional stimulation of frontal regions with an opposite stimulation polarity. The rationale to use the deltoid muscle is to avoid stimulation of the brainstem [19]. Furthermore, these setups differ in the current flow and the electric field orientation [20]. In the present study, possible differences between non-target electrode positions were assessed based on changes in cerebellar-brain inhibition (CBI). CBI is a physiological parameter of the connectivity strength between the cerebellum and the primary motor cortex (M1; [21–23]). CBI is measured using a double-coil transcranial magnetic stimulation (TMS) paradigm. A subthreshold conditioning stimulus (CS) is applied over the cerebellar cortex which is followed by a suprathreshold test stimulus (TS) over M1. The CS is used to excite the cerebellar cortex resulting in inhibition of the output structure of the cerebellum, i.e. the cerebellar nuclei. Because the output of the cerebellar nuclei is excitatory, facilitation of M1 is reduced. Therefore, the TS over M1 after the CS results in a reduced motor evoked potential (MEP) amplitude compared to the TS-only trials. The difference in MEP amplitude after the TS with vs. without the preceding CS pulse is labeled CBI.

Cathodal ctDCS is expected to decrease, whereas anodal ctDCS is expected to increase excitability of the cerebellar cortex. In their seminal study, Galea et al. [15] found that application of cathodal ctDCS prior to monitoring CBI with motor cortex TMS, in fact, decreased CBI. Anodal ctDCS, on the other hand, lowered the CS threshold for the CBI while maintaining its level (i.e. enabled CBI with lower CS intensities measured by CBI recruitment curve). In contrast, Doeltgen et al. [24] found a decrease of CBI after anodal ctDCS. Respective differences between the results of these two studies were explained by differences in methodology [5].

In the present study, the effect of different non-target electrode localizations was explored by measuring CBI before and for 2 h after 15 min of cathodal, anodal or sham ctDCS administration. ctDCS duration between 15 and 25 min has been used in most previous studies [20]. However, a reversal of tDCS after-effects direction has been previously reported after its prolonged (20 min and longer) administration over the primary motor cortex [25,26]. Thus, we decided to apply ctDCS for 15 min to avoid a possible non-linear impact of longer stimulation durations on cerebellar excitability. We expected to replicate results of Galea et al. [15] with the non-target electrode position over the buccinator muscle or the left supraorbital area due to similarities in the current flow direction. We expected different impacts on CBI comparing these two positions with the extracephalic non-target electrode placement. Both cathodal and anodal ctDCS with the chosen tDCS protocols led to a decrease of CBI. The relatively strong CS intensities in the original protocol could have stimulated not only superficial, but also deeper cerebellar areas. The axonal orientation relative to the stimulating electric field vector determines the change in neuronal excitability [27]. Thus, the heterogeneous orientation of cerebellar neurons in the TMS and ctDCS-affected areas could have resulted in a uniform compound CBI effect regardless of ctDCS polarity. In order to acquire more selective effects from superficial neuronal layers via

weaker TMS, we decided to add a second experiment assessing the CBI recruitment curve: With low CS intensities we aimed to get polarity-specific effects dependent on current flow direction. Furthermore, electric field strength and distribution were simulated based on individual cerebellar lobules to further support electrophysiological findings.

## Materials and methods

### Subjects

Fifteen participants (8 females/7 males) aged  $26.73 \pm 5.19$  years completed *Experiment 1*. Fourteen of these 15 subjects took part in *Experiment 2* (aged  $26.64 \pm 5.37$  years; 7 females/7 males). All subjects were right-handed according to the Edinburgh handedness inventory [28], naïve to both ctDCS and TMS procedures, gave written informed consent and were compensated for their participation. Participants were preselected based on their tolerability of the cerebellar TMS pulse. None of them took any centrally-active medication, had a history of a neurological disease, metallic head implants or present pregnancy. The investigation was approved by the Ethics Committee of the University Hospital Essen.

A head model was constructed from MR images taken from one healthy volunteer (female, 30 years old, not related to the main study group) at the University at Buffalo, New York.

Experiment 1 consisted of eight sessions: two ctDCS polarities (anodal and cathodal) x four conditions (sham, non-target electrode over the right buccinator, left supraorbital, right deltoid). Experiment 2 (CBI recruitment curve) consisted of two sessions: anodal and cathodal ctDCS.

### Cerebellar transcranial direct current stimulation (ctDCS)

tDCS was administered by a battery-driven constant current stimulator (neuroConn GmbH, Ilmenau, Germany) through a pair of rubber electrodes covered with saline-soaked sponges ( $5 \times 5$  cm). The target electrode was centered over the right cerebellar cortex (3 cm lateral to theinion) [15]. The non-target electrode was placed over 1) the right buccinator muscle 2), the left supraorbital area or 3) the right deltoid muscle. Subjects received verum ctDCS (2 mA; anodal or cathodal) for 15 min or sham ctDCS for 30 s over the target area. For sham ctDCS, one of the three positions of the non-target electrode was randomly chosen. The current was ramped up and down for 10 s at the beginning and the end of the stimulation. The minimum interval between two consecutive sessions was one week ( $12.6 \pm 11.4$  days) and the order of sessions was randomized. The subjects were blinded for the type of stimulation (anodal/cathodal/sham). The experimenter was blinded for the polarity of stimulation (anodal/cathodal).

### Transcranial magnetic stimulation (TMS)

*TMS of the primary motor cortex (M1)*. Single-pulse-TMS was delivered over the left M1 with a figure-of-eight magnetic coil (70 mm diameter; Magstim 200 magnetic stimulator, Magstim, UK). The coil was positioned tangentially to the skull with the handle pointing posteriorly and laterally at  $45^\circ$  from the midline. The hotspot was defined as the coil location where the single TMS pulses reliably resulted in the largest motor evoked potentials (MEPs) of the right first dorsal interosseous (FDI) muscle. The TMS intensity was adjusted to produce  $\sim 1$  mV peak-to-peak amplitude MEPs ( $SI_{1mV}$ ). It was kept constant throughout the whole experimental session for the single-pulse MEP recordings.

*TMS of the cerebellum*. Cerebellar TMS was conducted with a double-cone coil (110 mm-diameter, Magstim, UK) placed over the

right cerebellar cortex (3 cm lateral to theinion) with the current in the coil directed downwards. The conditioning stimulus (CS) was set at 5% below the brainstem motor threshold (BST). This was determined by activation of the pyramidal tract by single-pulse TMS with the double-cone coil being placed over theinion. BST was defined as the minimum stimulator output to elicit an EMG response of 50  $\mu$ V in the pre-activated (~10% of the maximum integrated EMG) right FDI muscle in at least 50% of all trials [15,21,29]. If no such EMG response was observed at 80% of the maximum stimulator output (MSO), 75% MSO was used as BST throughout the session. Trials in which the muscle was not relaxed (i.e. visible EMG activity prior the beginning of the MEP) were rejected online, and repeated. If such EMG activity was detected in more than one trial per measurement, the process was stopped, the participant was asked to relax and/or change the hand position, if uncomfortable and the data acquisition was restarted.

**Cerebellar brain inhibition (CBI).** CBI was assessed using a double-pulse TMS protocol. The test stimulus (TS) was applied (at the intensity of  $SI_{1mV}$ ) over the M1 representation of the right FDI muscle via the 70 mm figure-of-eight coil. The CS was applied (at the relative intensity of 5% below the BST) 5 ms prior to TS over the right cerebellar cortex via the double-cone coil [15,21]. The stimuli were organized in blocks of one CS-TS pair and one TS and were applied in a pseudorandomized order. The exact time intervals between the consecutive stimuli were randomized ( $4 \pm 0.4$ s). These blocks were repeated 11 times (22 stimuli in total). The first block and blocks in which the muscle was not relaxed were excluded from the analysis.

**CBI recruitment curve.** To obtain a CBI recruitment curve, five separate CBI recordings (as described in the previous paragraph) were recorded by decreasing the CS intensity by 5% steps (-5%, -10%, -15%, -20%, -25%) relative to the individual BST [15].

**Electromyography.** Surface electromyography (EMG) signals were recorded from the right FDI muscle with a pair of gold surface disc electrodes in a belly-tendon montage. The signals were amplified, band-pass filtered (10 Hz to 1 kHz, sampling rate, 5 kHz) and digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK), controlled by Signal Software (Cambridge Electronic Design, v.2.13), and stored on a laboratory computer for offline analysis.

## Experimental procedures

**Experiment 1: Comparison of the different cerebellar ctDCS non-target electrode montages.** Participants were seated in an armchair with their hands comfortably positioned on a pillow placed over their laps and instructed to stay relaxed during the EMG recordings. In the beginning, the M1 hotspot was identified by TMS and the  $SI_{1mV}$  was determined. Twenty MEPs were recorded at the intensity of  $SI_{1mV}$ . To keep the TMS coil position constant, its exact spot was marked with a waterproof pen. After the MEP recording, BST was determined, and the pre-tDCS CBI was measured. ctDCS was administered afterwards and post-ctDCS TMS measurements (single-pulse MEPs, BST and CBI) were repeated immediately following ctDCS and at 15, 30, 60, 90 and 120 min after ctDCS. For the CBI measurements, the BST and  $SI_{1mV}$  intensities were re-adjusted, if required.

**Experiment 2: CBI recruitment curve.** Experiment 2 consisted of two experimental sessions. Anodal or cathodal ctDCS was administered with the target electrode positioned over the right cerebellar cortex and the non-target electrode over the right buccinator muscle. Single-pulse MEPs, BST and the CBI recruitment curve were measured before, immediately after ctDCS and 60 and 120 min after stimulation.

## Analysis and statistics

EMG measures were analyzed using NuCursor software (Institute of Neurology, University College London, UK). Statistical analysis was carried out with SPSS (version 23.0, IBM Corp.).

At each time point for every subject individual means of 20 MEP peak-to-peak amplitudes and CBI (the quotient of the conditioned MEP amplitudes produced by CS-TS pair vs. the unconditioned MEP amplitudes produced by TS-only TMS trials) was calculated. Trials in which the muscle was not relaxed (i.e. visible EMG activity prior the beginning of the MEP) were rejected from analysis.

Furthermore, CBI values were averaged for the 0–15–30 and 60–90–120 min post-ctDCS to illustrate the overall ctDCS effects. Additionally, in Experiment 2, to evaluate the overall effect of ctDCS on the CBI recruitment curve, in a secondary analysis CBI values were averaged for each CS intensity at all post-ctDCS time points in a single experimental session. The “session” factor in the analysis described below refers to the four experimental conditions conducted for each polarity: three non-target positions and sham.

**Baseline values.** Individual pre-stimulation MEP amplitudes and maximum stimulator output (%MSO) percentage values for BST in each session were analyzed with repeated measures analyses of variance (RM-ANOVA), using MEP or %MSO value as dependent variable and session as within-subject factor, to exclude between-sessions baseline differences.

**Post-stimulation after-effects.** Separate RM-ANOVAs were performed using MEP amplitude or CBI as the dependent variable, polarity, session and time as within-subject factors.

Mauchly's tests were used to assess the sphericity assumption and Greenhouse–Geisser corrections were applied if necessary. In case of significant results of the ANOVA, exploratory *post hoc* comparisons were performed using Student's t-tests (paired samples, two-tailed,  $p < 0.05$ , not corrected for multiple comparisons) between the mean MEP amplitudes or CBI before and after ctDCS within one experimental session and between the respective time points of verum and sham sessions.

**Modeling of ctDCS effects.** The description of data acquisition and creation of the head model as well as computer simulation of the ctDCS-induced electric field is available in the Supplementary Material, Methods section [30]. Additionally, cerebellar TMS-induced electric field strength and distribution were modeled for the average intensities of conditioning stimuli used in Experiments 1 and 2.

## Results

### Neurophysiological experiment results

All subjects tolerated the procedure well. Side effects reported by the participants were slight tingling and itching of the skin under the electrodes. Two blocks of the CBI data and one single-pulse MEP were excluded due lack of relaxation preceding the TMS pulse. Two subjects failed to show an EMG response at 80% MSO, thus 75% MSO was used as BST for these individuals, as in Ref. [15].

### Experiment 1: Comparison of the different cerebellar ctDCS non-target electrode montages

**Motor cortex and brainstem excitability.** The average baseline MEP and BST values did not differ between sessions (Table 1). There was no significant effect of [SESSION] (Table 3). Cerebellar ctDCS had also no effect on the single pulse-MEP amplitudes (Fig. S2 in Supplementary Material). The RM-ANOVA revealed no significant effect of [POLARITY], [SESSION] or [TIME] or their interactions (all  $p$  values  $> 0.05$ ; for details see Table 3).

**Table 1**  
Pre-ctDCS brainstem thresholds (BST), stimulation intensities ( $SI_{1mV}$ ) and average peak-to-peak amplitudes of single-pulse MEPs and CBI for Experiment 1.

ctDCS	Session	TMS parameter			
		BST	$SI_{1mV}$	MEP	CBI
Cathodal	Sham	68.07 ± 4.11	53.13 ± 9.60	0.99 ± 0.12	0.72 ± 0.15
	Right Buccinator	68.27 ± 3.97	53.33 ± 9.51	1.00 ± 0.11	0.69 ± 0.13
	Left Supraorbital	68.07 ± 3.94	53.20 ± 9.89	0.99 ± 0.12	0.68 ± 0.13
	Right Deltoid	68.20 ± 4.39	52.80 ± 9.17	0.97 ± 0.11	0.70 ± 0.15
Anodal	Sham	68.33 ± 3.92	52.27 ± 8.85	0.96 ± 0.07	0.67 ± 0.19
	Right Buccinator	68.27 ± 4.17	52.13 ± 9.04	0.98 ± 0.08	0.70 ± 0.13
	Left Supraorbital	68.13 ± 3.83	52.13 ± 8.91	0.98 ± 0.12	0.71 ± 0.12
	Right Deltoid	68.00 ± 3.89	52.53 ± 9.58	0.97 ± 0.10	0.69 ± 0.12

**Table 2**  
Pre-ctDCS brainstem thresholds (BST), stimulation intensities ( $SI_{1mV}$ ) and average peak-to-peak amplitudes of single-pulse MEPs and CBI for Experiment 2.

ctDCS	TMS parameter							
	BST	$SI_{1mV}$	MEP	CBI (CS Intensity below BST)				
				5%	10%	15%	20%	25%
Cathodal	67.79 ± 3.51	52.00 ± 8.61	1.00 ± 0.12	0.71 ± 0.15	0.71 ± 0.13	0.89 ± 0.15	0.93 ± 0.12	1.04 ± 0.09
Anodal	68.46 ± 3.20	51.79 ± 7.82	0.98 ± 0.09	0.75 ± 0.17	0.79 ± 0.16	0.82 ± 0.16	0.91 ± 0.12	0.96 ± 0.15

**Cerebellar-brain inhibition.** Pre-ctDCS CBI values did not differ between sessions (Table 1). The respective RM-ANOVA revealed no significant effect of [SESSION] (Table 3). Both stimulation polarities resulted in CBI decrease. In both conditions, MEP amplitudes were larger in paired conditioning stimulus-test stimulus (CS-TS) trials compared to sham (see Fig. 1 for MEP examples in an individual subject). The rmANOVA revealed significant effects of [SESSION] [ $F(3,42) = 9.268$ ,  $p < 0.001$ , partial  $\eta^2 = 0.398$ ] and [TIME] [ $F(6,84) = 12.956$ ,  $p < 0.001$ , partial  $\eta^2 = 0.481$ ] (for details see Table 3 and Fig. 2).

Averaged CBI for the 0-15-30- and 60-90-120-min measurements after stimulation illustrate the ctDCS effects further (Fig. 3). CBI was decreased in all ctDCS conditions compared to the respective sham condition and to the pre-ctDCS values. In other words, verum tDCS led to less reduction of the MEP amplitude as a result of the CS compared to sham (Figs. 2 and 3). The reduction of CBI was present independent of the non-target electrode position. The respective ANOVA revealed a significant [SESSION] [ $F(3,42) = 6.227$ ,  $p = 0.001$ , partial  $\eta^2 = 0.308$ ], [TIME] [ $F(2,28) = 71.205$ ,  $p < 0.001$ , partial  $\eta^2 = 0.836$ ] and [SESSION] x [TIME] interaction [ $F(6,84) = 3.645$ ,  $p = 0.003$ , partial  $\eta^2 = 0.207$ ] effects. The [SESSION] effect shows the CBI differences between sham and verum conditions. The [TIME] effect reflects the CBI differences between the pre- and post ctDCS values and the [SESSION] x [TIME] interaction reflects the subsequent decrease of CBI after verum stimulation compared to sham condition (Table 3).

#### Experiment 2: CBI recruitment curve

**Motor cortex and brainstem excitability.** The average baseline MEP and BST values did not differ between sessions. The RM-ANOVA revealed no significant effect of [SESSION] (Tables 2 and 3).

**Cerebellar-brain inhibition.** Pre-ctDCS CBI values did not differ between sessions (Tables 2 and 3). Post hoc Student's t-tests also revealed no significant difference between anodal vs cathodal pre-ctDCS CBI values for respective CS intensities (all  $p$  values  $> 0.05$ ).

Conditioning stimulus (CS) intensity reduction led to a gradual decrease of pre-ctDCS cerebellar-brain inhibition (Fig. 4). Similar to Experiment 1, both cathodal and anodal ctDCS resulted in a CBI decrease at a standard CS intensity [5% below BST] (Fig. 4). Cathodal ctDCS resulted in a significant CBI decrease at the CS intensities of -5%, -10% and -20% below BST. The difference was absent in -15% and -25% compared to pre-ctDCS (Figs. 4A and 5A). Anodal

ctDCS resulted in a CBI decrease at CS intensities of -5% and -10% and with no clear difference at -15% and -20% below BST compared to pre-ctDCS effects. At the lowest CS intensity of -25% below BST anodal ctDCS resulted in a reduction of the conditioned MEP amplitude compared to pre-ctDCS values (Figs. 4B and 5B).

At individual time points, cathodal ctDCS resulted in a CBI decrease at a CS intensity of -5% as well as -10% below BST compared to the pre-ctDCS values. The effect was present across all time points (up to 120 min). The decrease of CBI was also present at the 120th minute at the -15% below BST CS intensity, but not at the lower intensities (Fig. 5A). Anodal stimulation resulted in a decrease of CBI at a CS intensity of -5% below BST up to 60 min post-ctDCS (Fig. 5B). A decrease was also present at a CS intensity of -10% below BST immediately after stimulation. Anodal ctDCS also resulted in a significant CBI decrease at lower CS intensities of -15% (immediately after and at 120th minutes post-ctDCS), -20% (immediately post-ctDCS) and -25% (at the 60th minute post-ctDCS) below BST compared to the respective post-cathodal ctDCS values (Fig. 5A and B).

The RM-ANOVA on data not pooled over all time points revealed significant effects of [POLARITY] [ $F(1,13) = 43.573$ ;  $p < 0.001$ ; partial  $\eta^2 = 0.770$ ], [TIME] [ $F(3,39) = 7.615$ ;  $p < 0.001$ ; partial  $\eta^2 = 0.369$ ], [CS INTENSITY] ( $F(4,52) = 3.624$ ;  $p = 0.011$ ; partial  $\eta^2 = 0.218$ ], [POLARITY] x [CS INTENSITY] [ $F(4,52) = 2.606$ ;  $p = 0.046$ ; partial  $\eta^2 = 0.167$ ] and [TIME] x [CS INTENSITY] [ $F(5,703,74,139) = 3.952$ ;  $p = 0.002$ ; partial  $\eta^2 = 0.233$ ] interactions (Table 3). Additionally, the ANOVA on the CBI data pooled over all post-ctDCS time points revealed significant effects of [POLARITY] [ $F(1,13) = 17.010$ ;  $p = 0.001$ , partial  $\eta^2 = 0.567$ ], [TIME] [ $F(1,13) = 21.888$ ;  $p < 0.001$ , partial  $\eta^2 = 0.627$ ], [CS INTENSITY] [ $F(4,52) = 11.802$ ;  $p < 0.001$ , partial  $\eta^2 = 0.476$ ], and significant [POLARITY] x [TIME] [ $F(1,13) = 5.056$ ;  $p = 0.043$ , partial  $\eta^2 = 0.280$ ], [POLARITY] x [CS INTENSITY] [ $F(4,52) = 2.591$ ;  $p = 0.047$ , partial  $\eta^2 = 0.166$ ] and [TIME] x [CS INTENSITY] [ $F(4,52) = 16.680$ ;  $p < 0.001$ , partial  $\eta^2 = 0.562$ ] interactions (Table 3).

The significant effect of [POLARITY] reflects the difference between the anodal and cathodal ctDCS conditions. The [TIME] effect demonstrates the overall differences between the pre- and post ctDCS values. The [CS INTENSITY] effect indicates differences in CBI values obtained with different CS intensities. The [POLARITY] x [TIME] effect reflects CBI differences between the pre- and post-ctDCS values in each polarity condition. The [POLARITY] x [CS

**Table 3**  
Results of the repeated measures ANOVA.

Parameter	Factor	Df, error Df	F	p	partial $\eta^2$
<b>Experiment 1</b>					
<b>Baseline</b>					
MEP	SESSION	7, 98	0.250	0.971	0.018
BST	SESSION	3.338, 46.733	0.410	0.770	0.028
CBI	SESSION	7, 98	0.295	0.954	0.021
<b>After-effects</b>					
MEP	POLARITY	1, 14	4.054	0.064	0.225
	SESSION	3, 42	0.727	0.542	0.049
	TIME	6, 84	1.235	0.292	0.081
	POLARITY X SESSION	3, 42	0.422	0.738	0.029
	POLARITY X TIME	6, 84	1.422	0.216	0.092
	SESSION X TIME	18, 252	0.960	0.506	0.064
	POLARITY X SESSION X TIME	18, 252	0.435	0.979	0.030
CBI (Non-averaged)	POLARITY	1, 14	1.467	0.246	0.095
	SESSION	3, 42	9.268	<0.001*	0.398
	TIME	6, 84	12.956	<0.001*	0.481
	POLARITY X SESSION	3, 42	0.257	0.856	0.018
	POLARITY X TIME	6, 84	0.584	0.743	0.040
	SESSION X TIME	18, 252	1.190	0.269	0.078
	POLARITY X SESSION X TIME	18, 252	0.646	0.862	0.044
CBI (averaged 0-15-30 and 60-90-120-min values)	POLARITY	1, 14	1.230	0.286	0.081
	SESSION	3, 42	6.227	0.001*	0.308
	TIME	2, 28	71.205	<0.001*	0.836
	POLARITY X SESSION	3, 42	0.133	0.940	0.009
	POLARITY X TIME	2, 28	0.643	0.533	0.044
	SESSION X TIME	6, 84	3.645	0.003*	0.207
	POLARITY X SESSION X TIME	6, 84	1.140	0.346	0.075
<b>Experiment 2</b>					
<b>Baseline</b>					
MEP	SESSION	1, 13	0.353	0.563	0.026
BST	SESSION	1, 13	1.526	0.239	0.105
CBI:					
–5% BST	SESSION	1, 13	0.527	0.481	0.039
–10% BST			2.036	0.177	0.135
–15% BST			1.038	0.327	0.074
–20% BST			0.360	0.559	0.027
–25% BST			2.773	0.120	0.176
<b>After-effects</b>					
CBI-recruitment curve (Non-averaged)	POLARITY	1, 13	43.573	<0.001*	0.770
	TIME	3, 39	7.615	<0.001*	0.369
	CS INTENSITY	4, 52	3.624	0.011*	0.218
	POLARITY X TIME	3, 39	2.059	0.122	0.137
	POLARITY X CS INTENSITY	4, 52	2.606	0.046*	0.167
	TIME X CS INTENSITY	5.703, 74.139	3.952	0.002*	0.233
	POLARITY X TIME X CS INTENSITY	12, 156	0.603	0.837	0.044
CBI-recruitment curve (averaged post-tDCS)	POLARITY	1, 13	17.010	0.001*	0.567
	TIME	1, 13	21.888	<0.001*	0.627
	CS INTENSITY	4, 52	11.802	<0.001*	0.476
	POLARITY X TIME	1, 13	5.056	0.043*	0.280
	POLARITY X CS INTENSITY	4, 52	2.591	0.047*	0.166
	TIME X CS INTENSITY	4, 52	16.680	<0.001*	0.562
	POLARITY X TIME X CS INTENSITY	4, 52	0.517	0.724	0.038

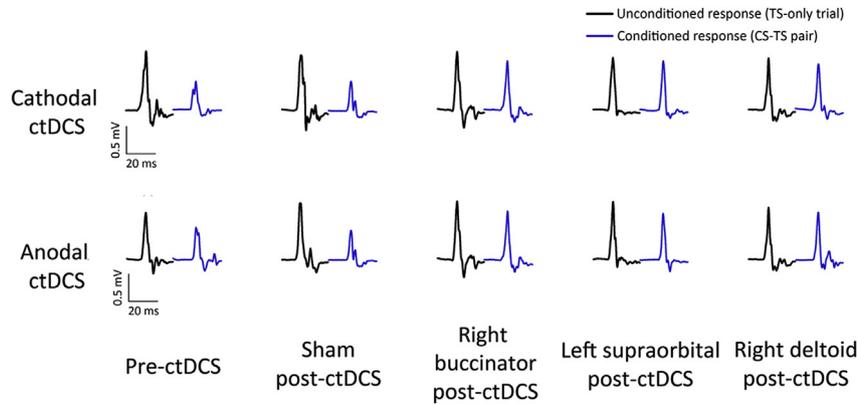
\*Significant results at  $p < 0.05$ .

INTENSITY] interaction reflects that different CS intensities have discernible effects on CBI, dependent on ctDCS polarity. The [TIME] x [CS INTENSITY] interaction shows that CS intensities have no homogeneous effect on CBI during the time course of the experiment (Figs. 4 and 5).

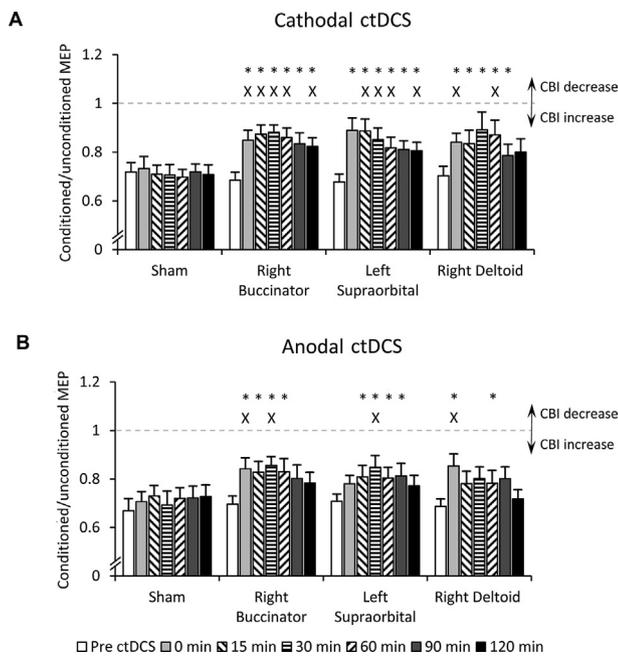
#### Computational modeling results

Computational modeling results are superimposed on the spatially unbiased infratentorial atlas template (SUIT) flatmap of the cerebellum in Fig. 6 [31]. The three montages primarily affected the posterior lobe, more specifically cerebellar lobules Crus II, VIIb,

VIII, and IX of the targeted cerebellar hemisphere. The two-way ANOVA of the modeling data showed significant effects of the factors: [MONTAGE], [LOBULES] and their interactions on the electric field strength in the cerebellum (all  $p$ -values  $< 0.001$ ; Table S2 in Supplementary Material). The partial  $\eta^2$  effect size was 0.006 for [MONTAGE] and 0.1633 for [LOBULES], and 0.007 for their interaction. These effect sizes are small for [MONTAGE] and the [MONTAGE] x [LOBULES] interaction, but large for the [LOBULES] [32]. Post-hoc tests for the effect on Lobules showed that the vermal part of Crus II, as well as the vermal and right hemispherical parts of lobules VIIb, VIIIa, VIIIb were most affected ( $> 0.22$  V/m), as shown in Fig. S3. Nevertheless, the electric field strength was small



**Fig. 1.** Representative raw data of an individual subject. Single trials of motor evoked potentials (MEP) acquired before stimulation, and after ctDCS (sham or verum) are shown. Note that MEP amplitudes increased after ctDCS, irrespective of the current polarity or the non-target electrode position.



**Fig. 2.** Impact of ctDCS on cerebellar-brain inhibition (CBI) up to 120 min post-ctDCS. Shown are group mean ratios of the conditioned MEP amplitude in paired CS-TS trials compared to the unconditioned MEP amplitude in TS-only trials after cathodal (A) and anodal (B) ctDCS. Horizontal axis displays return electrode positions. Error bars indicate S.E.M. \* indicates significant differences between respective pre- and post-stimulation values (Student's t-test, two tailed, paired samples,  $p < 0.05$ ); X indicates significant differences between verum and sham conditions at the individual time points (Student's t-test, two tailed, paired samples,  $p < 0.05$ ).

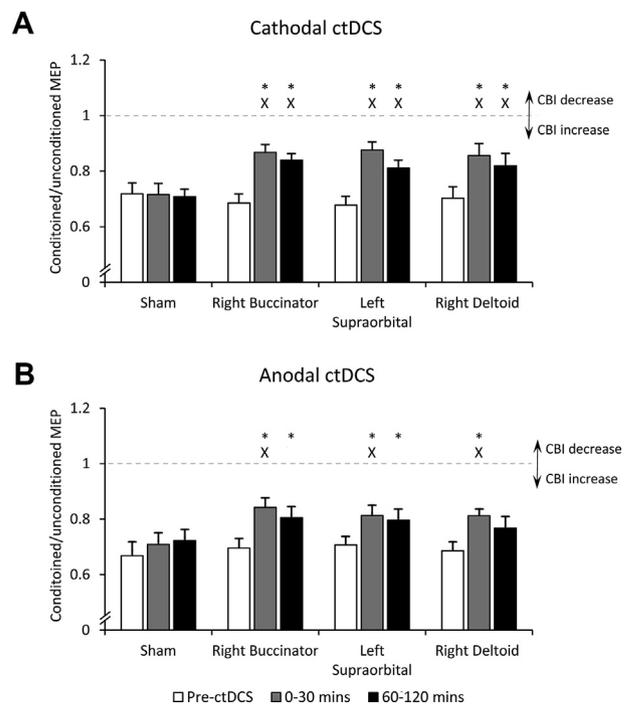
(<0.33 V/m) for all three montages (see Table S3 in Supplementary Material).

Computational modeling of the cerebellar TMS-induced electric field strength revealed that it also affected the posterior lobe of the targeted hemisphere with its primary focus on cerebellar lobules Crus II, Crus I, VIIIa and VIIIb (Fig. S4 in Supplementary Material).

**Discussion**

*Position of the non-target ctDCS electrode*

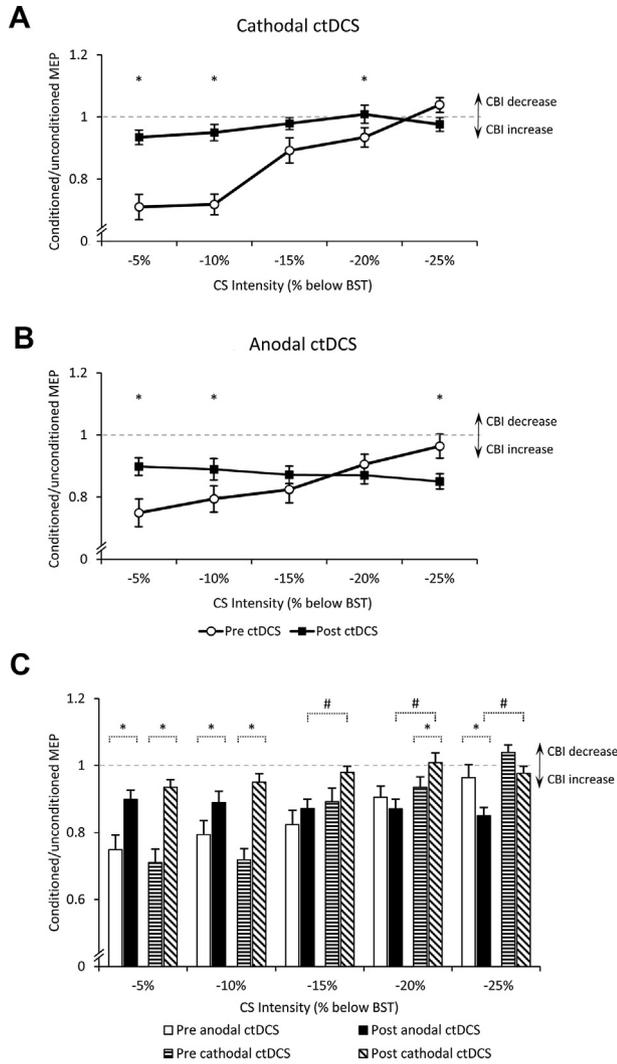
This is the first study which systematically compared possible differences between three commonly used positions of the non-target electrode in ctDCS. Regardless of the non-target electrode



**Fig. 3.** Impact of ctDCS on cerebellar-brain inhibition (CBI) pre-ctDCS, 0–30 min and 60–120 min post-ctDCS. Each post-stimulation column represents the mean of averaged CBI ± S.E.M. values for 0–30 or 60–120-min measurements; \* indicates significant differences between pre- and post-stimulation values (Student's t-test, two tailed, paired samples,  $p < 0.05$ ). X indicates differences between verum and sham conditions at individual time points (Student's t-test, two tailed, paired samples,  $p < 0.05$ ).

position, and stimulation polarity, CBI was significantly decreased for at least 2 h post-ctDCS. This lack of difference in electrophysiological measures is also reflected by the small statistical effect size comparing the cerebellar distribution of the induced electric field between the three non-target electrode positions, as revealed by the results of our simulation procedures.

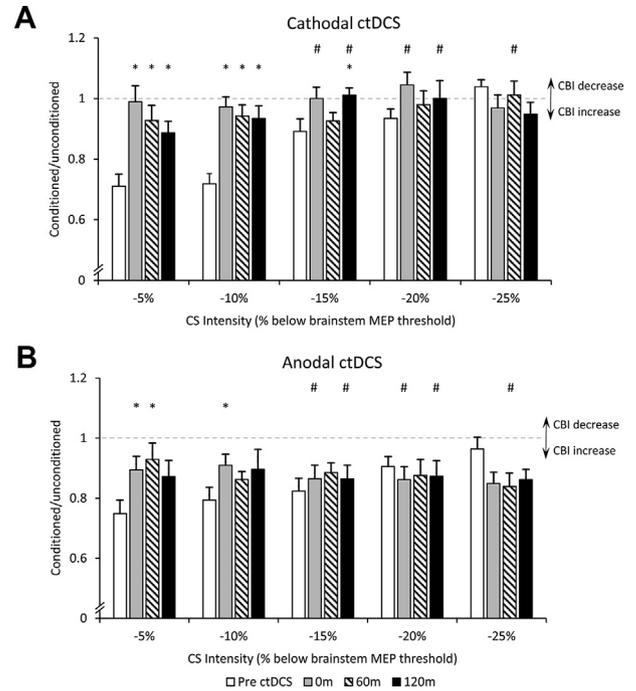
Although previous modeling studies did not compare between non-target electrode positions, findings are in accordance with the present results. For instance, ctDCS modeling studies by Gomez-Tames et al. [33], Rampersad et al. [34] and Parazzini et al. [35] have demonstrated that the highest electric field and current density occurred underneath the stimulation electrode, irrespective of the non-target electrode size and location, with a negligible spread to the occipital cortex or brainstem. As yet, there



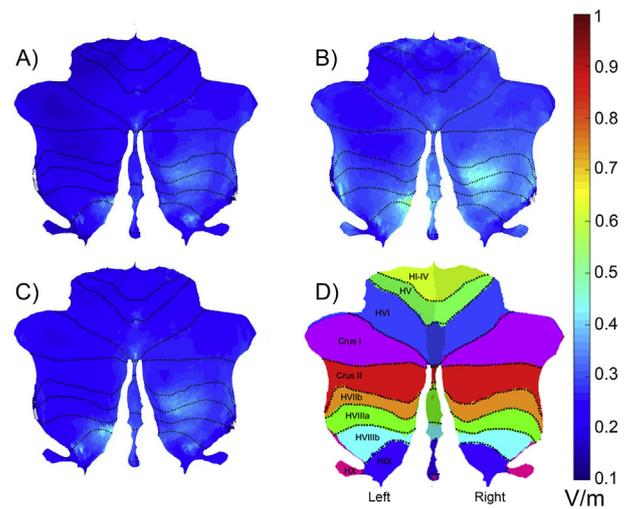
**Fig. 4.** Impact of ctDCS on the CBI recruitment curve. Shown are conditioned CBI amplitude ratios relative to the test pulse following cathodal (A), anodal (B) and (C) both ctDCS polarities. Each post-stimulation point represents the mean of averaged (across all time points) CBIs obtained with the same conditioning stimulus (CS) intensity below the brainstem threshold (BST). \* symbol indicates significant differences between respective pre- and post-ctDCS CBI values (Student's t-test, two tailed, paired samples,  $p < 0.05$ ); # symbol indicates differences between anodal and cathodal ctDCS conditions measured with the same CS intensity (Student's t-test, two tailed, paired samples,  $p < 0.05$ ).

is only one study which compared two non-target electrode positions with a different physiological parameter. Grimaldi and Manto [14] reported that the amplitudes of long-latency stretch reflexes in ataxia patients were significantly reduced after anodal ctDCS of the right cerebellum compared to sham. Changing the non-target electrode position from the contralateral supraorbital area to the ipsilateral deltoid muscle had no impact on the outcome [14]. These results are in line with the results of the present study.

Although these results of physical effects of tDCS are in strong accordance with the physiological results of Experiment 1, future studies should confirm that the position of the non-target electrode is not a critical parameter using other physiological, and behavioral measures. Because modeling data show strongest tDCS effects in the posterior cerebellar lobe, which has been shown to contribute to non-motor function, cognitive parameters would be of particular interest [36].



**Fig. 5.** Impact of ctDCS on the CBI recruitment curve. Shown are mean conditioned CBI amplitude ratios relative to the test pulse following cathodal (A) and anodal (B) ctDCS up to 120 min post-stimulation. Error bars indicate S.E.M. Horizontal axis displays conditioning stimulus (CS) intensity below the brainstem threshold (BST). \* indicates significant differences between respective pre- and post-stimulation values (Student's t-test, two tailed, paired samples,  $p < 0.05$ ); # indicates differences between anodal and cathodal ctDCS conditions measured at individual time points with the same CS intensity (Student's t-test, two tailed, paired samples,  $p < 0.05$ ).



**Fig. 6.** Electric field strength (volt per meter or V/m) superimposed on the surface of the cerebellum for the montages where the non-target electrode is placed over A) the right buccinator muscle, B) the left supraorbital area, C) the right deltoid muscle. The main electrode is placed over the right cerebellum (3 cm right to theinion). D) SUIT flatmap of the cerebellum (<http://www.diedrichsenlab.org/imaging/suit.htm>). Scales are adjusted (shown at top right).

In summary, our results suggest that the non-target electrode position does not play a critical role in ctDCS after-effects. The systematic evaluation of other parameters, such as the current intensity, target electrode placement, repetitive stimulation within one session, multiple stimulation sessions - some of which have

previously been shown to influence the outcome of motor cortex stimulation [25,26] - are yet to be investigated. Therefore, future studies are also needed to compare the effects of different ctDCS intensities. Moreover, cerebellar excitability measures were performed for only 2 h after intervention. The after-effects were still apparent at that time point. Considering the relevance of the duration of ctDCS after-effects in clinical trials, it would be helpful to obtain late (~12–24 h post-ctDCS) CBI measures in the future.

#### *ctDCS effects on CBI*

We expected CBI to decrease after cathodal ctDCS and to remain unchanged after anodal ctDCS based on the findings by Galea et al. [15]. In contrast, both ctDCS polarities led to a long-lasting decrease in CBI amplitudes at high CS intensities (5% and 10% below BST). In agreement with Galea et al. [15], however, we found that anodal ctDCS lowered the CS threshold for CBI compared to pre-ctDCS values using low CS intensity (25% below BST), i.e. enabled CBI with lower CS intensity measured by CBI recruitment curve. In contrast, CBI amplitudes were decreased at all CS intensities after cathodal ctDCS administration. Similarly to Galea et al. [15], our results show that ctDCS modulated cerebellar excitability without inducing changes in MEP amplitudes and BST. Although Doeltgen et al. [24] did not specifically measure single-pulse MEP amplitudes, in their study anodal ctDCS also induced no change in non-conditioned (TS-only) MEP amplitudes evoked during CBI measurement.

The different effects of ctDCS might be caused by the tool which measures excitability alterations, namely CBI monitored by TMS, especially by the intensity of TMS. The net effect of TMS may be heterogenous based on stimulation intensity because of the affected cerebellar volume [37,38]. Since CS intensity correlates with both penetration depth of the TMS pulse and number of affected cerebellar neurons [37–42], TMS at lower CS intensities may primarily affect the superficial molecular layer. In that case, anodal stimulation may mostly result in parallel fiber activation [43]. An increase in excitability of these structures would lead to Purkinje cell facilitation. As a consequence, inhibition of the excitatory cerebellar nuclei would be increased, and therefore the primary motor cortex would be less facilitated via the dentato-thalamo-cortical pathway. This could explain CBI enhancement after anodal ctDCS using low CS intensities as seen in experiment 2. In contrast, cathodal stimulation would lead to inhibition of these parallel fibers, and therefore induce opposite effects.

In experiment 1, a standard (high) TMS intensity CS was used. Galea et al. [15] argued that this leads to a maximal saturation of output of the cerebellar cortex (that is the Purkinje cells) by the TMS pulse. Therefore, prior anodal tDCS would not result in additional excitation of Purkinje cells and therefore CBI would not increase but remain unchanged. We would like to take this argument a step further to explain the (initially unexpected) anodal ctDCS-induced CBI decrease observed in the present study. In a situation where Purkinje cells are maximally activated via the TMS pulse, the observed anodal tDCS effects may be explained by an increased excitability of inhibitory interneurons in the cerebellar cortex. Facilitation of inhibitory interneurons would result in reduced excitation of the Purkinje cells and decreased CBI. Cathodal ctDCS, on the other hand, is thought to result in direct reduction of Purkinje cell excitability, which would reduce CBI due to the above-mentioned mechanisms [15]. At present, however, the specific impact of ctDCS effects on the different cell populations of the cerebellum is unknown and requires further exploration.

Similar to the present findings, Doeltgen et al. [24] reported CBI reduction after anodal ctDCS. The inconsistency between the results of Galea et al. [15] and Doeltgen et al. [24] were explained by

methodological differences in the CBI protocols, such as CS intensity and coil type [5], which however, cannot easily explain the decrease of CBI following anodal ctDCS in the present study, because our experimental setup was similar to Galea et al. [15]. A possible explanation, however, may be the difference in duration of ctDCS. It was administered for 15 min in the present study, for 20 min in Doeltgen et al. [24] and 25 min in Galea et al. [15]. Since tDCS after-effects are calcium-dependent [44], prolonged exposure to anodal ctDCS, as in the study conducted by Galea et al. [15], could have led to calcium overflow and consequently, a lack or reversal of the net effect of the stimulation due to activation of hyperpolarizing potassium channels [45]. This agrees with the observation by Monte-Silva et al. [26] that doubling the anodal stimulation duration from 13 to 26 min results in a reversal of ctDCS after-effects in the motor cortex. Another reason may be differences in study population. The direction of the excitability shifts largely depends on the neuronal orientation in relation to the electric field vector as well as the extent to which specific neuronal structures are affected [27,46]. Therefore, the net effect of ctDCS may have been different in the present and the Galea et al. [15] study because of differences in complex folding of the cerebellar cortex and orientation of neuronal structures between individual subjects [47].

#### *Limitations*

In the present study, no fixation mechanism of the TMS coils and no neuronavigation for both the TMS and ctDCS targeting were used. Variability of the TMS/tDCS target sites may have affected our results and thus their interpretation. Another limitation is that the TS intensity was set to elicit MEPs with ~1 mV peak-to-peak amplitude in order to keep our experimental design comparable with previous studies by Galea et al. [15]. One possible problem with this method is that  $SI_{1mV}$  could fall closer either to the motor threshold or to the plateau of a saturation level of MEPs for some individuals [48]. Therefore, it may contribute to variability of the results. Finally, the electric field modeling was performed on the MR images of only one subject, unrelated to the main study cohort. Usage of individualized MRI-derived head models from all participants would have been desirable to perform finite element modeling and accurately quantify the actual ctDCS- and TMS-induced electric fields in the cerebellum.

#### **Conclusions**

In sum, the results of the present study demonstrate that ctDCS effects on CBI were independent from the position of the non-target electrode. Thus, the position of the non-target electrode - at least for those tested here - does not seem to be a critical parameter in ctDCS. In future studies, the impact of other parameters, including current intensity, repetition frequency and interval, and target electrode placement, needs to be explored to enhance efficacy, and maybe specificity, of the effects.

We found that cerebellar ctDCS results in long lasting changes of cerebellar-brain inhibition (CBI), a physiological measure of the connectivity between the cerebellar cortex and M1, and suggest that the physiological after-effects of cerebellar ctDCS may depend on the recruitment of different cerebellar cell populations as well as the neuroanatomical complexity of the cerebellar cortex. This might at least partially explain the heterogeneity of ctDCS polarity effects observed in behavioral ctDCS studies [49–61].

#### **Conflicts of interest**

G. Batsikadze, D.-I. Chang, A. Dutta and Z. Rezaee declare no competing financial interests. M. Gerwig received speaker

honoraria and/or travel reimbursement from Novartis, Pfizer and Ipsen Pharma and research support from MSD. S. Herlitze received funding from the German Research Foundation (DFG; SFB 874 Project B10 and SFB 1280 Project A7) and Mercur Research Center Ruhr (Pr-2015-0010). M.A. Nitsche is member of the Scientific Advisory Board of Neuroelectrics, supported by the Mercur Research Center Ruhr, and received funding from the German Research Foundation (DFG; SFB 1280 Project A6). D. Timmann received funding from the German Research Foundation (DFG; SFB 1280 Project A5), Mercur Research Center Ruhr and the German Heredoataxia Foundation (DHAG).

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.04.010>.

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