Brain Stimulation 9 (2016) 692–699

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Remote Effects of Non-Invasive Cerebellar Stimulation on Error Processing in Motor Re-Learning

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ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form 21 March 2016
Accepted 10 April 2016
Available online 12 April 2016

Keywords:
Transcranial direct current stimulation
Cerebellum
Force field adaptation
Interference
Anodal
Cathodal

ABSTRACT

Background: While concurrent transcranial direct current stimulation (tDCS) affects motor memory acquisition and long-term retention, it is unclear how behavioral interference modulates long-term tDCS effects. Behavioral interference can be introduced through a secondary task learned in-between motor memory acquisition and later recall of the original task.
Objective/hypothesis: The cerebellum is important for the processing of errors if movements should be adapted to external perturbations (motor memory acquisition). We hypothesized that concurrent cerebellar tDCS during adaptation influences both memory acquisition and re-acquisition if motor errors are enlarged due to behavioral interference.
Methods: In a sham-controlled and double-blinded study, we applied anodal and cathodal tDCS to the ipsilateral cerebellum while subjects adapted reaching movements to an external, clockwise force field perturbation (acquisition task A) with their dominant right arm. Behavioral interference by an oppositely oriented, counter-clockwise perturbation (secondary task B) was introduced in between the acquisition and re-acquisition (24 h later) sessions.
Results: Learning task B disrupted memory retention of A and re-increased motor errors in the re-acquisition session. Anodal but not sham or cathodal tDCS impaired motor memory acquisition and, additionally, increased motor errors during re-acquisition of the original motor memory.
Conclusion(s): Behavioral interference disrupted motor memory retention but tDCS delivered online during memory acquisition induced lasting and robust effects on re-acquisition performance one day later. Our data also suggest different error-processing mechanisms at work during motor memory acquisition and re-acquisition.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique to modulate brain function and behavior [1]. If applied concurrently during motor training, tDCS has the potential to influence learning and memory [2,3]. In particular, tDCS facilitates or inhibits the neurophysiological processes underlying memory acquisition, consolidation and retention [3–5].

Error-based motor learning offers the possibility to investigate mechanisms of motor memory acquisition and interference [6]. One typical task example is arm reaching movements that are perturbed by a robotic device. Over time, participants learn to compensate for these perturbations [7]. In the time after successful adaptation to a given force field A (acquisition), the associated motor memory is susceptible to degradation through adaptation to a new, interfering force field B that perturbs movements in the opposite direction. When the original force field is revisited one day later (re-acquisition, A-B-A paradigm), the errors that occur during re-learning may be comparable to the initial learning session

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Designed research (MT, TS, AV, BP), performed research (MT, TK, LH), contributed unpublished reagents/analytic tools (TS, CS, AF, PR, BP), analyzed data (MT, TS, TK, CS), wrote the paper (MT, TS, CS, BP).
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http://dx.doi.org/10.1016/j.brs.2016.04.007

depending on the time interval between the adaptation to force field A and B [8,9].

The cerebellum is strongly involved in error-based motor learning [10–13]. Patients with acute lesions or degeneration of the cerebellar cortex have difficulties to adapt reaching movements to external (force field) perturbations [14–16]. Particularly impaired is the initial adaptation to large perturbation-induced motor errors which is conceptualized as fast learning in the multiple-state model of motor learning [17–19]. Following this functional implication, we hypothesized a cerebellar involvement not only during initial adaptation to force field A, but also during re-adaptation to A if motor errors are enlarged due to an interfering force field B.

In the present sham-controlled and double-blinded study, we applied tDCS to the cerebellum while healthy participants adapted reaching movements to a force field A. TDCS is widely used to non-invasively alter activity of the cerebellum or other cortical regions [20,21] allowing inference on the causal behavioral role of the stimulated region [3]. After adaptation to force field A, participants were subjected to a secondary reaching task without tDCS, perturbed by an oppositely oriented force field B [9]. The adaptation to force field A was revisited one day later, but this time without simultaneous tDCS.

We hypothesized that tDCS specifically influences the fast error-processing during motor memory acquisition of A. Subsequent interference through learning of B will force subjects to recapitulate initial motor errors that ultimately unfold a remote tDCS-induced memory-deficit during re-acquisition of A.

Methods

Participants

We recruited 43 right-handed participants (age 27 ± 3 years; 15 female, 28 male). The study was performed in accordance with the declaration of Helsinki and approved by the local ethics committee of the University of Leipzig. All participants were naïve to the experimental paradigm and underwent a neurological examination before participation. Handedness was verified using Edinburgh Handedness Inventory [22]. Participants were randomly assigned to three groups receiving either anodal, cathodal or sham tDCS. Data from two participants of the cathodal tDCS group were lost because of technical problems with the storage device. The study groups were composed as follows: sham = 15, anodal = 14 and cathodal cerebellar tDCS = 12 participants (age 27 ± 3 years; 13 female, 28 male; Table 1).

Robotic manipulandum ("BioMotionBot")

The task procedure is similar to Focke et al. [23] and Stockinger et al. [24] and explained in detail in the supplemental materials. Briefly, the "BioMotionBot" applied forces [25] while participants reached to one of eight targets around a center position within a horizontal plane. To avoid sequence effects, the target sequence differed for each participant. Movement sets consisted of 16 trials – eight outward and eight inward movements – in which each peripheral target point occurred once. Participants were requested to reach the target within 500 ± 50 ms (movement time). A green circle appeared around the target if movement time was 500 ± 50 ms. Red and orange circles appeared if subjects moved too slow or too fast. Visual feedback was provided throughout the experiment to ensure constant movement time. The "BioMotionBot" generated a clockwise (A) and counterclockwise (B) velocity-dependent force field that applied forces ($k = 20$ Ns/m) perpendicular to the movement direction.

tDCS

The experimenter performing force field training (TK or LH) was blinded and unaware of the type of tDCS application until the end of the experiment. Another experimenter (MT) attached the tDCS electrodes and monitored the stimulation. TDCS was applied on day 1 during adaptation to force field A with a pair of surface-soaked sponge electrodes (5 × 5 cm) using a commercial tDCS device (NeuroConn, Ilmenau, Germany). A constant current of 2 mA (current density 0.08 mA/cm^2) was applied to the right cerebellar hemisphere over a period of 20 min. In the anodal stimulation condition, the anode was placed 2 cm below the inion and 1 cm posterior to the right mastoid process [26] (see Fig. 1A). The cathode was placed over the right musculus buccinator [21] for an almost right-angled orientation of the current in relation to the cerebellar surface. For cathodal stimulation, anode and cathode were placed contrariwise. For sham tDCS, the constant current of 2 mA was applied, according to common practice, for only 30 s before being switched off [27]. TDCS was turned on 30 seconds prior to A1 and covered on average ¾ of the entire learning period (approx. 25–30 minutes).

Experimental design

We used an ABA-paradigm [8] to investigate motor memory interference (Fig. 1B). On day 1, we first familiarized participants under null field conditions (25 sets, 400 trials) ensuring reaching movements in 500 ± 50 ms. After 5 min of rest, a baseline block (96 trials) was conducted under null field conditions and these data were used to exclude between-group differences prior to tDCS. After another 5 min of rest, 25 sets (400 trials) were performed in force field A (A1) with 60-second breaks after each five sets (set breaks). Two and a half hours later, participants were exposed to force field B (B = –A) for 25 sets (400 trials). After 24 h on day 2, participants performed another 25 sets (400 trials) in force field A (A2).

Confounding effects of sleep, physical activity and caffeine on memory consolidation were controlled by interviewing participants on both days (Table 1).

During A1, B and A2, set-breaks of 60 s were inserted after each five sets (80 trials) and participants could release their hand from the handle but remained seated. This allowed us to test tDCS-effects on fast forgetting [17,18]. Each force field session lasted for approximately 30 min. Participants were instructed to sleep at least 6 h between day 1 and 2.

Table 1
Sample characteristics and statistical comparisons using univariate ANOVA.

	Anodal tDCS (n = 14)	Cathodal tDCS (n = 12)	Sham tDCS (n = 15)	Statistics (p-value)
Age (M ± SD)	26.14 (2.51)	27.83 (3.64)	27.27 (2.60)	0.326
Gender (# females)	4	4	5	–
Physical activity (days per week)	2.36 (0.63)	2.58 (0.79)	2.47 (0.83)	0.752
Physical activity (hours per week)	2.57 (1.16)	2.75 (1.06)	2.13 (0.99)	0.307
Body-mass index	23.29 (2.23)	26.50 (7.42)	24.07 (4.03)	0.233
Sleep duration (day 1)	7.29 (0.85)	7.50 (1.19)	7.03 (1.43)	0.598
Sleep duration (day 2)	7.57 (0.65)	7.21 (1.08)	8.03 (0.88)	0.060