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Contributions of the cerebellum and the motor cortex to acquisition and retention of motor memories

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ABSTRACT

We investigated the contributions of the cerebellum and the motor cortex (M1) to acquisition and retention of human motor memories in a force field reaching task. We found that anodal transcranial direct current stimulation (tDCS) of the cerebellum, a technique that is thought to increase neuronal excitability, increased the ability to learn from error and form an internal model of the field, while cathodal cerebellar stimulation reduced this error-dependent learning. In addition, cathodal cerebellar stimulation disrupted the ability to respond to error within a reaching movement, reducing the gain of the sensory-motor feedback loop. By contrast, anodal M1 stimulation had no significant effects on these variables. During sham stimulation, early in training the acquired motor memory exhibited rapid decay in error-clamp trials. With further training the rate of decay decreased, suggesting that with training the motor memory was transformed from a labile to a more stable state. Surprisingly, neither cerebellar nor M1 stimulation altered these decay patterns. Participants returned 24 hours later and were re-tested in error-clamp trials without stimulation. The cerebellar group that had learned the task with cathodal stimulation exhibited significantly impaired retention, and retention was not improved by M1 anodal stimulation. In summary, non-invasive cerebellar stimulation resulted in polarity-dependent up- or down-regulation of error-dependent motor learning. In addition, cathodal cerebellar stimulation during acquisition impaired the ability to retain the motor memory overnight. Thus, in the force field task we found a critical role for the cerebellum in both formation of motor memory and its retention.

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Introduction

When we interact with a novel object, we learn through trial and error to control that object, producing a motor memory that can be recalled the next time the object is encountered. Force field learning has been used as an experimental paradigm to uncover some of the processes that the brain relies on to accomplish this feat. In a typical experiment, the participant holds the handle of a robotic arm and makes a reaching movement, experiencing novel forces that displace the hand, resulting in error. This error engages short- and long-latency feedback pathways, producing a within-movement motor response to the error. In the subsequent reach the brain predicts some of the novel forces from the onset of the movement, resulting in partial compensation for the robot-induced forces. This trial-to-trial change in the motor commands has a specific pattern: the within-movement error feedback response is shifted earlier in time to produce a predictive response (Thoroughman and Shadmehr, 1999). With training, some of the modifications to the motor commands become a motor memory, as exemplified by the observation that the memory is disengaged when the robot handle is released (Kluzik et al., 2008), and is recalled days (Criscimagna-Hemminger and Shadmehr, 2008; Joiner and Smith, 2008) or months (Shadmehr and Brashers-Krug, 1997) later when the robot handle is grasped.

Formation of this motor memory appears independent of human medial temporal lobe structures (Shadmehr et al., 1998), but dependent on the integrity of the cerebellum (Criscimagna-Hemminger et al., 2010; Donchin et al., 2012; Smith and Shadmehr, 2005), and the motor cortex (Arce et al., 2010b; Li et al., 2001; Orban de Xivry et al., 2011a, 2011b, 2013; Richardson et al., 2006). In particular, a study in humans demonstrated that reversible disruption of the thalamic projections of the cerebellum to the cortex produced within-subject impairments in the ability to learn the force field task (Chen et al., 2006). Therefore, the current evidence points to the cerebellum as one of the structures that plays a critical role in the acquisition of this motor memory.

Here, we used transcranial direct current stimulation (tDCS) to alter function of the cerebellum and quantified the effect of this disruption on

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the ability to learn the force field task. tDCS of the cerebellum is thought to affect the excitability of Purkinje cells (Galea et al., 2009). Anodal cerebellar stimulation, which is thought to elevate the excitability of Purkinje cells, has been shown to increase rates of adaptation in visuomotor (Block and Celnik, 2013; Galea et al., 2010) and gait (Jayaram et al., 2012) tasks, whereas cathodal cerebellar stimulation, which is thought to reduce Purkinje cell excitability, has been shown to decrease rates of gait adaptation (Jayaram et al., 2012). By contrast, anodal stimulation of the motor cortex (M1) had no effect on the rate of visuomotor adaptation, the size of after-effects, or the rate of de-adaptation upon removal of the perturbation (Galea et al., 2011). However, immediately after adaptation and removal of anodal M1 tDCS, those in the stimulation group showed a reduced rate at which the resulting memory decayed in the absence of visual feedback (Galea et al., 2011). These findings led Galea et al. (2011) to propose that whereas the cerebellum may be critical for learning from error, the motor cortex plays a role in retention of the resulting memory. By contrast with the findings of Galea et al. (2011), Hunter et al. (2009) applied anodal stimulation to the motor cortex in a force field task and observed a larger reduction in signed kinematic errors during adaptation than in a sham tDCS condition, suggesting that motor cortical stimulation increased learning from error. Therefore, whereas current evidence suggests that stimulation of the human cerebellum can affect learning from error, it is unclear whether stimulation of the motor cortex affects learning from error and/or retention.

Here, we compared the effects of cerebellar and M1 stimulation on the process of acquisition and retention of motor memories in a force field paradigm. Given previous observations in other motor learning paradigms, we expected that M1 stimulation would not affect the rate of learning from error, whereas anodal cerebellar stimulation would increase this rate and cathodal cerebellar stimulation would decrease the rate of learning. In addition, to specifically test the hypothesis that anodal stimulation of M1 enhances retention of motor memories (Galea et al., 2011), we tested the effects of M1 anodal stimulation on both short-term retention (via blocks of error-clamp trials during the training blocks), and long-term retention (at 24 hours following completion of training).

Materials and methods

Fifty healthy self-reported right-handed volunteers (21 females; mean age ± STD of 24 ± 4.7 years, range 18–38 years) with no known neurological or psychiatric disorders participated in our study. All participants were naive to the purpose of the experiment and gave written informed consent. The study was approved by the Johns Hopkins School of Medicine Institutional Review Board. Participants were screened prior to enrollment in the study to ensure that they did not have conditions that would exclude them from a brain stimulation study (cardiac pacemakers, history of seizure, or aneurysm clips). Participants were also screened to ensure that they were not taking any neurological drugs.

Experiment 1: cerebellar stimulation

We recruited $n = 37$ participants for this experiment. They were divided into three groups: sham ($n = 12$), anodal cerebellar ($n = 15$), and cathodal cerebellar ($n = 10$) stimulation. During analysis of the data we noted that one participant in the cerebellar cathodal group exhibited large errors during field trials and failed to compensate for the forces over the course of the experiment. Although it is possible that this is related to the stimulation (as we will see, cathodal stimulation impaired the ability to learn), to err on the side of caution, the data from this participant were not included in our report.

tDCS (2 mA, 25 min) was delivered by a Phoresor II device (model PM850, IOMED) through two 5 × 5 cm saline-soaked sponge electrodes (Ferrucci et al., 2008; Galea et al., 2009, 2011). The current density was approximately 0.08 mA/cm^2. For the anodal tDCS group, the anode was centered on the right cerebellar cortex, 3 cm lateral to the inion (Galea et al., 2009; Ugawa et al., 1995), with the cathode positioned on the right buccinator muscle (i.e. on the cheek) (Galea et al., 2009, 2011). For the cathodal group the electrode polarity was reversed such that the cathode was placed over the right cerebellar cortex.

The procedures for the sham group were identical to the other groups. Anode and cathode positions were counterbalanced between cerebellum and buccinators. The current was increased over a period of 30 sec and then decreased back to zero. With this procedure, participants are unable to reliably distinguish real from sham stimulation (Gandiga et al., 2006; Kaski et al., 2012).

Both the experimenter and the participant were blind to the type of stimulation, as a third person uninvolved in the experiment controlled the tDCS settings. As illustrated in Fig. 1A, stimulation began with block n2 and concluded with block g2, lasting no more than 25 min. Brain stimulation was applied on Day 1 only. On Day 2, all participants performed block b1. Additionally, block b2 was performed by a subset of participants: $n = 12/12$ anodal cerebellar, $n = 10/12$ sham, and $n = 8/10$ cathodal.

Experiment 2: motor cortex stimulation

To determine whether the effects observed with anodal stimulation of the cerebellum were unique to this structure, or could also be elicited via anodal stimulation of the motor cortex, $n = 14$ additional participants were recruited. They performed the identical experiment during anodal tDCS of left M1 (2 mA, 25 min, 5 × 5 cm electrodes, induced current density of 0.08 mA/cm^2). The anode was positioned on the scalp overlying the "motor hotspot" of the right first dorsal interosseus (FDI) muscle, that is, the optimal position at which a consistent motor evoked potential, as recorded via EMG, could be elicited using minimal intensity transcranial magnetic stimulation (70 mm coil coupled with a Magstim 200). We used FDI (rather than biceps) muscle to localize M1, primarily because it is more easily activated via TMS. The size of the tDCS electrode (25 cm^2) makes it likely that coverage included both muscle representations. The other electrode was positioned on the skin overlying the contralateral supraorbital region.

Behavioral procedures

All volunteers participated in a standard force field task (Shadmehr and Mussa-Ivaldi, 1994). Using the right hand, each participant held the handle of a manipulandum and made center-out movements to a target (1 cm diameter, Fig. 1). The reach was perturbed by a velocity dependent clockwise curl force field that pushed the hand perpendicular to the direction of motion: $f = B\dot{x}$ where f is force on the hand, $B = [0, 13; -13, 0]$ N · s/m, and $\dot{x}$ is hand velocity. In the starting posture, the hand was positioned such that the shoulder and elbow were at 45° and 90° respectively (Fig. 1). Participants were unable to see their hand, which was occluded by an opaque horizontal screen. Instead, visual feedback regarding hand position was provided by a cursor (0.5 cm diameter) that was continuously projected onto the horizontal screen.

On each trial (except generalization trials, see below), one of the two targets appeared on the screen (pseudo-randomized with equal probability). Targets 1 (T1) and 2 (T2) were positioned at 10 cm at 135° and 315° (Fig. 1). The trial was successful if the hand arrived at the target within 400–500 ms after movement onset, with success indicated by an "explosion" of the target (an animation). Feedback regarding movements that were too fast or too slow was indicated via changes in target color. After completion of the trial, the robot brought the hand back to the start position. Participants were instructed to maximize the number of successful trials.

In some trials, an "error-clamp" was applied (Scheidt et al., 2000). In these trials, the force field was turned off. Normally, removal of the field

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