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Research report

Cathodal transcranial direct current stimulation (tDCS) applied to the left premotor cortex (PMC) stabilizes a newly learned motor sequence

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HIGHLIGHTS

- Left PMC tDCS during motor sequence learning does not affect reaction times.
- Left PMC tDCS prior to motor sequence learning non-specifically facilitates reaction times.
- Cathodal PMC tDCS prior to motor sequence learning yields reduced interference.
- The PMC might be related to stabilization but not acquisition of a motor sequence.

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ABSTRACT

While the primary motor cortex (M1) is involved in the acquisition the premotor cortex (PMC) has been related to over-night consolidation of a newly learned motor skill. The present study aims at investigating the possible contribution of the left PMC for the stabilization of a motor sequence immediately after acquisition as determined by susceptibility to interference. Thirty six healthy volunteers received anodal, cathodal and sham transcranial direct current stimulation (tDCS) to the left PMC either immediately prior to or during training on a serial reaction time task (SRTT) with the right hand. TDCS was applied for 10 min, respectively. Reaction times were measured prior to training (t1), at the end of training (t2), and after presentation of an interfering random pattern (t3). Beyond interference from learning, the random pattern served as control condition in order to estimate general effects of tDCS on reaction times. TDCS applied during SRTT training did not result in any significant effects neither on acquisition nor on susceptibility to interference. In contrast to this, tDCS prior to SRTT training yielded an unspecific facilitation of reaction times at t2 independent of tDCS polarity. At t3, reduced susceptibility to interference was found following cathodal stimulation. The results suggest the involvement of the PMC in early consolidation and reveal a piece of evidence for the hypothesis that behavioral tDCS effects vary with the activation state of the stimulated area.

1. Introduction

Implicit motor learning plays an important role for the acquisition of new motor skills and is therefore substantial for the successful and effortless interaction with our physical environment. Imaging studies suggest that implicit motor learning requires the interaction of a cortical-subcortical network [1–3]. The primary motor cortex (M1) has been identified as a key structure for the acquisition and early consolidation [4–8] in particular of repetitive movements [9]. After initial acquisition the new motor skill becomes consolidated as indicated by further improvement without additional training (i.e. offline-improvement) [10,11] and/or reduced susceptibility to interference (i.e. stabilization) [12,13]. Within a time period of 6 h after acquisition of a new motor skill an activation shift from prefrontal to posterior parietal and premotor cortices (PPC, PMC) was found using positron emission tomography (PET) [14] suggesting that consolidation may be rather associated with these areas.

The dorsal PMC (dPMC) is involved in the selection of movements guided by visual stimuli [15,16] and is particularly important for choice reaction time tasks requiring subjects to select a response following visual discrimination [17]. Single cell recordings in the monkey's dPMC suggest its relevance for the generation of motor programs from maintained information [18]. These data suggest the involvement of the PMC in motor consolidation to be likely. Support

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for this hypothesis comes from studies showing that modulation of cortical excitability by repetitive transcranial magnetic (rTMS) [19,20] or transcranial direct current stimulation (tDCS) affects consolidation [21,22] without interfering with the acquisition of a motor sequence [6].

TDCS has been proven to successfully modulate cortical excitability and hereby motor learning when applied to M1 [6,23–27]. TDCS effects on motor-evoked potentials (MEP) vary with its polarity suggesting that anodal stimulation enhances cortical excitability via neuronal depolarization while cathodal stimulation yields diminished excitability by hyperpolarization [23,28]. Depending on the intensity and duration of stimulation, effects may persist even after tDCS cessation presumably due to synaptic neuroplasticity [23].

Behavioral tDCS effects on motor sequence consolidation vary with the time point of stimulation: While anodal tDCS applied to the PMC *during* training on a serial reaction time task (SRTT) [29] attenuated stabilization of the learned motor sequence [21], a facilitating effect of tDCS applied *after* training was found when stimulation was carried out during rapid eye movement (REM) sleep but not in awake volunteers [22]. The results led to the hypothesis that tDCS effects may vary with baseline cortical activation as shown for TMS [30] and point to the significance of the PMC for later stages of motor sequence consolidation particularly over-night.

Increased PMC activation during the initial state of learning [31] suggests its potential involvement in stabilization of the new movement pattern. The present study aims at elucidating whether modulation of left PMC excitability by means of tDCS may interfere with such stabilization of a newly learned motor sequence as indicated by susceptibility to interference. In accordance with previous studies we hypothesized that tDCS does not affect the acquisition but the stabilization of a new motor sequence. Since TMS effects have been shown to depend on the activation level during stimulation suggesting a higher susceptibility of less activated areas [30,32], we expect stronger effects of tDCS applied prior to SRTT training as compared to tDCS applied during training.

2. Material and methods

2.1. Subjects

Thirty six healthy volunteers (18 male) aged between 20 and 30 years (24.0 ± 0.4 years; mean ± standard error of the mean; SEM) were recruited for the study. According to the Edinburgh Handedness Inventory [33] all participants were classified as right-handed with a mean lateralization ratio of 98.9 ± 0.6. Participants with individual or family history of epileptic seizures or other severe neurological, psychiatric or internal diseases were excluded from the study. All volunteers gave their written informed consent prior to their participation. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (study number 3347).

2.2. Paradigm

The study was implemented as a sham-controlled, double-blinded design. Participants were naïve regarding the exact purpose of the study. None of them had received electrical brain stimulation before. Participants and the main investigator were blinded regarding the exact tDCS condition. To this end, a second investigator ran the DC stimulator that was hidden under a paperboard till the end of the experiment.

Participants were assigned to two groups of 18 participants, respectively. One group (10 male) received tDCS immediately prior to training on the SRTT (experiment 1) while in the other group (8 male) tDCS was applied during training (experiment 2). The participants attended three sessions receiving either anodal, cathodal or sham tDCS applied to the left PMC corresponding to Brodmann area 6. Sessions were separated by at least one week in order to minimize carry-over effects. The order of stimulation types was counterbalanced across subjects. To measure tDCS effects on implicit motor sequence learning the SRTT was employed.

2.3. Serial reaction time task (SRTT)

The SRTT represents a standard paradigm for the investigation of motor learning [29]. Four response keys of a custom-made button box anatomically aligned to the right hand corresponded to four horizontally aligned bars presented on a projection screen in front of the participants (distance: 2.55 m; visual angle: 20.21°). The participants were asked to react as fast and as accurately as possible as soon as one of the 4 bars changed its colour from dark blue to light blue with the thumb (1), index finger (2), middle finger (3), or ring finger (4). The correct response triggered the color change of the next bar with a fixed delay of 1 s. The response box was connected to a standard Windows PC. E-Prime (Psychology Software Tools Inc.) was used for timing of the SRTT and recording of reaction times.

The SRTT consisted of a sequential and a randomly varying pattern consisting of eight bars, respectively. Since subjects participated in three subsequent sessions, three versions of the SRTT were adopted to avoid learning effects of the preceding sessions: 4-2-1-3-4-3-1-2 (sequence 1); 3-4-2-1-2-4-3-1 (sequence 2); 3-2-1-4-3-2-4-1 (sequence 3). The participants were kept naive about the sequential order of stimuli. The random condition was applied in order to control for a general facilitation of reaction times – independent of sequence learning and required 8 button presses with respect to randomly presented stimuli. The frequency probability of each single stimulus was kept constant across both conditions.

Each session started with a baseline measurement for the random and sequential condition, respectively. Baseline reaction times were determined by averaging across two sequential and two random trials (i.e. 16 button presses, respectively). After baseline measurement, tDCS was applied for 10 min during rest in experiment 1. Immediately after tDCS, the participants were trained on the SRTT. To this end, the sequence was presented in three blocks interrupted by two breaks of two minutes, respectively. Each block started with two repetitions of the random condition followed by 4 repetitions of the sequence. The breaks were inserted in order to keep the stimulation duration equal in both experiments. In experiment 2, subjects were trained on the SRTT immediately after baseline assessment and tDCS was applied during training. In order to determine possible tDCS effects on motor sequence stabilization the random pattern was presented twice, followed by two repetitions of the sequence. Stabilization was determined immediately after training on the SRTT.

The repetition rate was chosen according to a pilot study in which higher repetition rates (i.e. more than 10) led to an increase of reaction time variability and an overall increase of reaction times.

To control for the possibility of explicit learning participants were asked verbally after each session whether they had recognized anything during the task. Six participants reported to suspect a system or sequence behind the task. One participant was able to reproduce 4, one subject correctly recollected 3 and another one 2 out of 8 items. The experimental procedure is summarized in Fig. 1. Each experimental session took about 30 min including preparation and follow-up-procedures.