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Abstract

Transcranial direct current stimulation (TDCS) is a non-invasive form of brain stimulation applied via a weak electrical current passed between electrodes on the scalp. In recent studies, TDCS has been shown to improve learning when applied to the prefrontal cortex (e.g., Kincses et al. in Neuropsychologia 42:113–117, 2003; Clark et al. Neuroimage in 2010). The present study examined the effects of TDCS delivered at the beginning of training (novice) or after an hour of training (experienced) on participants' ability to detect cues indicative of covert threats. Participants completed two 1-h training sessions. During the first 30 min of each training session, either 0.1 mA or 2.0 mA of anodal TDCS was delivered to the participant. The anode was positioned near F8, and the cathode was placed on the upper left arm. Testing trials immediately followed training. Accuracy in classification of images containing and not-containing threat stimuli during the testing sessions indicated: (1) that mastery of threat detection significantly increased with training, (2) that anodal TDCS at 2 mA significantly enhanced learning, and (3) TDCS was significantly more effective in enhancing test performance when applied in novice learners than in experienced learners. The enhance performance following training with TDCS persisted into the second session when TDCS was delivered early in training.

Keywords: Transcranial direct current stimulation, Learning, Training, Threat detection

Introduction

In a series of animal studies, Bindman et al. (1962) found that the application of direct current to the cerebral cortex modulates cortical excitability, and the change in cortical excitability can persist for more than 3 h after the current is discontinued. In humans, direct current has been safely applied to the brain non-invasively through electrodes placed on the scalp (Wassermann and Grafman 2005). This technique, known as transcranial direct current stimulation (TDCS), has been shown to alter cortical excitability in multiple studies (Liebetanz et al. 2002; Nitsche and Paulus 2009). As in the animal studies of Bindman et al. (1962), TDCS is capable of inducing changes in cortical excitability in humans in both motor and visual cortices that can persist for more than an hour (Nitsche and Paulus 2001; Nitsche et al. 2007; Antal et al. 2004).

These changes in cortical excitability can be positive or negative depending on the electrode configuration. Anodal direct current is applied to the scalp when an electrode, connected to the positive pole of the battery, is connected to the scalp. Cathodal TDCS is applied when an electrode, connected to the negative pole of a battery, is affixed to the scalp. Anodal stimulation appears to increase cortical excitability (Liebetanz et al. 2002), while cathodal stimulation has been shown to diminish the excitability of motor (Nitsche and Paulus 2000; Siebner et al. 2004) or visual cortex (Antal et al. 2004) depending on the placement of the electrode. When both anode and cathode are placed on the scalp, enhanced excitability is expected in the region

underlying the anode and decreased excitability underlying the region of the cathode.

TDCS may affect cortical excitability through multiple mechanisms. Lang et al. (2005) found that anodal TDCS increased rCBF in cortical and subcortical areas. Merzagora et al. (2010) found that anodal stimulation induced significant increases in oxyhemoglobin in the region of the anode. Like changes in cortical excitability, the increase in oxyhemoglobin concentration persisted once TDCS was discontinued. TDCS also reduces GABA but not glutamate activity (Stagg et al. 2009), producing a shift in cortical excitability. Bikson et al. (2004) documented this shift in cortical excitability with electrophysiological recordings that show a reduced threshold for neuronal firing. The combined effects of these subtle increases in rCBF, oxyhemoglobin, and glutamate activity appear to correspond well with reports of clinical efficacy and behavioral changes associated with the administration of TDCS.

Clinically, the effects of TDCS-induced changes in cortical excitability have been explored as a therapeutic intervention in stroke (Boggio et al. 2007), depression (Murphy et al. 2009), pain management (Antal et al. 2008; Fregni et al. 2006), and addiction (Boggio et al. 2008). TDCS has also been examined as a means to enhance performance in normal subjects. Language learning, short-term verbal learning, and working memory for letters are enhanced when the TDCS anode is placed over the left frontal lobe (Floel et al. 2008; Elmer et al. 2009; Fregni et al. 2005).

The current study expands upon previous work documenting the effects of TDCS on learning. Clark et al. (2010) used neuroimaging-guided TDCS to alter cortical excitability in two brain regions involved in threat detection, the right inferior frontal and right parietal cortices. Anodal TDCS was then applied near F8 and P4 in different subjects during training in a threat-detection task. TDCS applied at these locations significantly facilitated learning. The results reported herein examine the effect of TDCS near F8 on learning in the same threat-detection task when applied in naïve subjects compared with subjects with prior experience in this task. We hypothesized that the application of anodal TDCS would facilitate learning differently in novice and experienced learners.

Methods

Performance in the threat-detection task was measured across two sessions, performed by subjects on the same day separated by 1 h of rest. 2.0 mA TDCS was applied during training in either session 1 (novices) or session 2 (experienced) subjects. Training with TDCS was followed by testing in both conditions.

Participants

Thirty-four healthy participants (mean age 24 ± .92 years, 20 male) gave written informed consent and met the following criteria: English as a first language, no history of head injuries or concussions resulting in loss of consciousness, no history of mental or neurological disorders, no history of dementia or Alzheimer's disease, no history of alcohol or drug abuse, no prescription medication intake affecting the CNS, good or corrected vision, hearing, and motor coordination. All procedures were approved by the Human Research Review Committee at the University of New Mexico.

Threat-detection task

Each participant completed two 1-h sessions of image classification training in the threat-detection task. Stimuli were taken from the DARWARS-AMBUSH! virtual reality training environment (MacMillan et al. 2005) and modified to include cues for possible threats such as explosive devices and enemy warfighters. Explosive devices were concealed by or disguised as dead animals, roadside trash, fruit, flora, rocks, sand, or building structures. Enemies appeared in the form of snipers, suicide bombers, tank drivers, or stone throwers. Participants viewed images for 2 s and were asked to indicate whether a threat was detected in the image or not. Participants responded with a button press using the index or middle finger of their right hand to indicate their response.

The task consisted of a 10-min baseline, 60-min training, and a 10-min post-test. Baseline and post-testing differed only in the specific stimuli presented and each consisted of 100 trials of threat classification without feedback. Training, which occurred between baseline and post-testing, consisted of 4 blocks containing 60 trials each, in which participants received feedback about their response. Feedback was presented in the form of a 5 s audio/visual video clip illustrating the outcome of participant's decision. Correct classification of an image as containing or not containing a threat was accompanied by an audio visual clip congratulating the participant for making progress in the military mission. If the participant correctly identifies an image as having a threat present they might hear "Good going soldier, you saved your platoon." If the participant correctly identifies the image as not having a threat present they might hear ''Good going soldier, the mission is on track.'' Incorrect classification of an image containing a threat was followed by the consequence of the missed threat, such as an explosion or a fellow soldier falling after being injured by a sniper with an audio clip stating ''Soldier, you missed a threat, you are jeopardizing the mission". Incorrect classification of an image not containing a threat was followed by an uneventful audio- visual clip stating ''Soldier don't be a chicken, you are delaying the mission'' or a similarly disapproving message. Each participant completed two sessions, session one consisted of baseline, training, and post-testing, session two consisted of a delayed post-test, training, and post- testing. The two sessions were separated by a 1-h break.

Transcranial direct current stimulation (TDCS)

TDCS was delivered using a 9-volt battery-powered Iomed Phoresor PM850 constant current stimulator and 3.3 cm x 3.3 cm square with rounded corners wet sponge electrode with an approximate surface area of 10.9 cm^2. The anode was positioned near F8, according to the 10 x 20 EEG system. The cathode was placed on the upper left arm. At both sites, the electrodes were secured to the participant's arm and head using a self-adherent wrap. TDCS was delivered at a low-dose (0.1 mA) and/or at our standard-dose (2.0 mA) for 30 min during the first two blocks of training. Participants were randomly assigned to one of three groups: (Control) low-dose TDCS during both the first session and the second session (n = 14, mean age 22 ± 1.03, 9 male), (Experienced) low-dose TDCS during the first session and standard-dose TDCS during the second session (n = 9, mean age 28 ± 2.37, 4 men), or (Novice) standard-dose TDCS during the first session and low-dose TDCS during the second session (n = 11, mean age 23 ± .93, 7 men; Fig. 1). Participants in the experienced group were trained prior to TDCS and were therefore considered experienced during TDCS, participants assigned to the novice group did not receive training prior to TDCS and were considered novices during TDCS. Participants completed three sensation questionnaires throughout the delivery of TDCS ranking sensation on a 0–9-point scale, with each rating standing for the following respectively: no sensation, cold sensation, some tingling, warm sensation, lots of tingling/some itching, very warm, lots of itching, burning (like a sunburn), burning (like scalding water), hurts a lot. The first questionnaire was completed within the first minute, the second after 5 min, and the third after 20 min. Sensation data for the 34 subjects listed earlier is incomplete; however, sensation data from a larger population that completed the same threat- detection task and received 2.0 mA of TDCS at the same location were used for sensation analyses.

Data analysis

The percentage of images correctly identified as containing threats obtained during baseline test, session 1 post-test, and session 2 post-test were quantified. A repeated-measures ANOVA with contrasts was conducted, with performance on baseline test and two post-tests as the within subject variables and the three TDCS condition groups as between subjects variables. In order to evaluate the relationship between self-reported sensation resulting from TDCS and performance, a bivariate correlation was done on a larger population with similar experimental conditions to evaluate correlation between sensations produced by 2 mA TDCS applied near F8 and performance.

Results

Analysis showed a significant main effect of session with 41.8 ± 1.9% threat correct on the baseline test, 67.3 ± 1.6% on the session one post-test and a 71.2 ± 1.9% on the session two post-test ($F(2,62) = 116.79$, P \ .000; Fig. 2). There was not a significant effect of TDCS condition ($F(2,31) = 1.88$, P [.05). However, the interaction

between TDCS condition and test was significant ($F(4,62) = 5.236$, $P = .001$; Fig. 3). Furthermore, tests of within-subjects contrasts indicated a significant interaction when comparing the first post-test to baseline ($F(2,31) = 6.971$, $P = .003$), but not when comparing the second post-test to the first post-test ($F(2,31) = 2.943$, $P > .05$). Correlation coefficients were

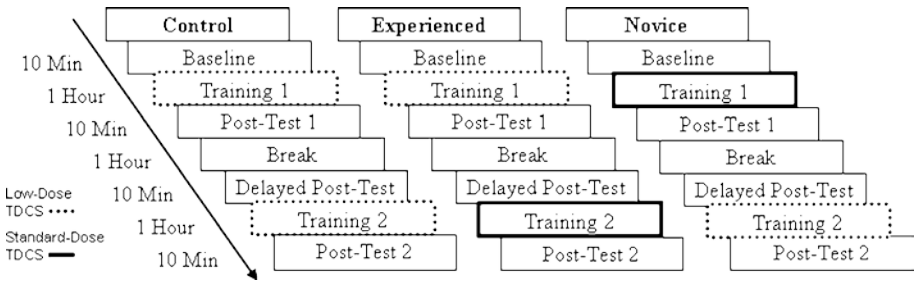

Fig. 1 All three treatment groups completed the same paradigm. Baseline consisted of 100 trials and served as a baseline measure of performance. Training consisted of 4 blocks containing 60 trials each. The first 30 min of training is when TDCS was being administered and the second 30 min without TDCS. Delayed post-test and post-test consisted of 100 trials of threat classification without feedback.

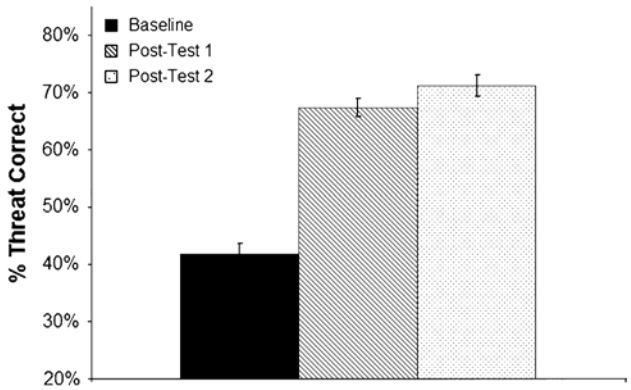

Fig. 2 This figure illustrates the learning effect from the beginning to the end of the task. The X-axis indicates the different testing portions of the task, baseline, post-test 1, and post-test 2. The Y-axis indicates the participants' percentage of accurately identifying threats on these tests. Analysis showed a main effect of session with $41.8 \pm 1.9\%$ threat correct on the baseline test, $67.3 \pm 1.6\%$ on the session one post-test and a $71.2 \pm 1.9\%$ on the session two post-test ($F(2,62) = 116.79$, P\.000)

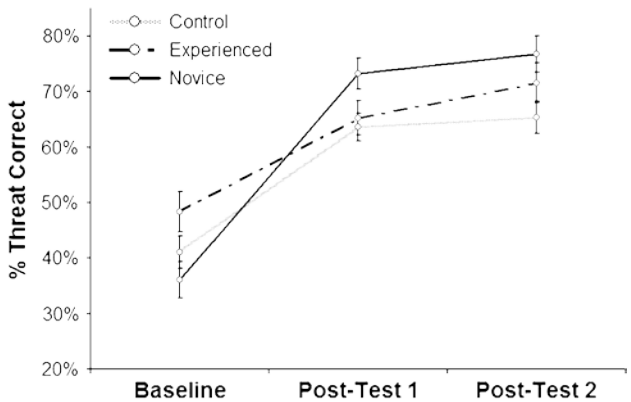

Fig. 3 This figure illustrates the effect TDCS had on learning during the threat detection task. The X-axis indicates the different testing portions of the task, and the Y-axis indicates the participants' percentage of accurately identifying threats during those tests. Furthermore, the lines indicate the interaction between TDCS condition and session based on three different groups, control, experienced, and novice. The interaction between TDCS condition and test was significant ($F(4,62) = 5.236$, $P = .001$)

computed among both post-tests, and 6 self-rated sensation levels. Using the Bonferroni approach to control for Type I error across the 12 correlations, a P value of less than .004 (.05/ 12 = .004) was required for significance. The results of the correlation analysis indicate that 0 out of the 10 correlations were statistically significant at this level.

Discussion

As hypothesized, the results of this study indicate that classification of images containing threats improves with training and that anodal TDCS at approximately F8 enhances the effect of training. More specifically, as indicated by the within-subjects contrasts, there was a significant improvement in learning when standard-dose was applied during the first session; however, when standard- dose was applied during the second session, there were no significant improvements in learning. These results are an indication that standard-dose TDCS is more effective in enhancing learning when delivered early in training. Moreover, there is no significant correlation between perceived sensation and performance; therefore, it can be deduced that effects from TDCS are not from sensation alone. Improved performance with training is a standard result across many tasks and is not considered here in depth. However, the finding that learning enhanced by the application of anodal TDCS near F8 and the importance of application early in the training process warrants a more thorough discussion.

As a result of an fMRI study in which participants viewed the images used in this study, areas of the brain that were most significantly responsive included the right inferior frontal regions (Clark et al. 2010). By applying the anode near EEG location F8 and modulating the broader prefrontal cortex region, we can speculate on which cognitive functions were facilitated through stimulation, including problem-solving skills working memory, and attention (Goldman-Rakie et al. 1996). It is also possible that if we are stimulating smaller regions within the PFC such as the orbitofrontal cortex, we could be facilitating emotional processing such as reward and decision making (McClure et al. 2004; Bechara et al. 2000), which is an important factor in our training paradigm. In addition the inferior frontal gyrus, which is thought to be involved in a person's ability to recognize the actions of others (Chong et al. 2008), another important factor in the training paradigm.
The findings in this study were presaged by previous papers documenting an effect of TDCS in learning. The current findings align with previous research indicating that anodal stimulation can improve learning (Kincses et al. 2003), which evaluated the effects that transcranial direct current stimulation of the prefrontal cortex (PFC) had on probabilistic classification learning (PCL). Results indicated that 10 min of anodal TDCS over PFC significantly improved implicit learning. Other studies also indicated an improvement in learning when TDCS was applied; Hecht et al. (2010) found that when TDCS was applied to the left hemisphere and cathodal was applied to the right hemi- sphere, participants responded quicker on a probabilistic guessing task. Furthermore, Tecchio et al. (2010) found that anodal TDCS enhances procedural consolidation in a nine-element serial finger tapping task. Our findings extend upon these previous findings by applying TDCS near F8 and exploring the facilitation of learning threats.

The observation that TDCS produces a larger effect in naïve subjects when compared with those that have prior experience in the task could be related to the persistent effects of TDCS on brain activity. Several studies have shown that the effects of TDCS remain after TDCS is no longer being delivered. Early work by Bindman et al. (1962) documented the effects of TDCS that persisted for more than 3 h after stimulation was discontinued. Similarly, Priori (2003) demonstrated that TDCS at 1 mA for 10 min induces persistent changes in brain excitability after the offset of TDCS for almost 1 h. Ohn et al. (2008) found that 30 min of anodal TDCS at 1 mA significantly improved working-memory performance, when compared with sham stimulation, and that this effect was maintained for 30 min after the offset of TDCS. In the current study, subjects participated in two training sessions separated by approximately 1 h. Based on the results summarized above, the residual effects from TDCS during the first session of training likely persisted into the second training session. In effect, subjects with TDCS early in training could benefit from enhanced cortical excitability during both training sessions. In contrast, subjects with TDCS during the second training session would have enhanced excitability during a smaller proportion of the training. A difference in the number of training trials during which there was TDCS-induced enhanced cortical excitability could account for the difference between TDCS early and TDCS late groups. Future studies will use a longer time between sessions to determine the length of persistent TDCS effects on learning and examine generalization of threat detection to other learning paradigms such as non- emotional target detection.

In addition, participants may utilize different brain networks after they have learned to perform this task compared with beforehand. Thus, the effect of TDCS placements may vary depending on prior experience.

Previous work from this laboratory (Clark et al. 2010) and others (Wright et al. 2010; Lutz et al. 2009) indicate that brain networks change as participants gain expertise. fMRI recorded during the image classification task indicated that the right inferior frontal cortex activation was low in novices, largest at intermediate levels of performance and reduced during expert levels of performance (B. A. Coffman et al., submitted). In future studies, the effects of applying TDCS to different brain locations at different times during training will be examined in order to maximize effectiveness as training progresses.

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