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Can Transcranial Direct Current Stimulation Augment Extinction of Conditioned Fear?

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ABSTRACT

Background: Exposure-based therapy parallels extinction learning of conditioned fear. Prior research points to the ventromedial prefrontal cortex as a potential site for the consolidation of extinction learning and subsequent retention of extinction memory.
Objective/hypothesis: The present study aimed to evaluate whether the application of non-invasive transcranial direct current stimulation (tDCS) during extinction learning enhances late extinction and early recall in human participants.
Methods: Forty-four healthy volunteers completed a 2-day Pavlovian fear conditioning, extinction, and recall paradigm while skin conductance activity was continuously measured. Twenty-six participants received 2 mA anodal tDCS over EEG coordinate AF3 during extinction of a first conditioned stimulus. The remaining 18 participants received similar tDCS during extinction of a second conditioned stimulus. Sham stimulation was applied for the balance of extinction trials in both groups. Normalized skin conductance changes were analyzed using linear mixed models to evaluate effects of tDCS over late extinction and early recall trials.
Results: We observed a significant interaction between timing of tDCS during extinction blocks and changes in skin conductance reactivity over late extinction trials. These data indicate that tDCS was associated with accelerated late extinction learning of a second conditioned stimulus after tDCS was combined with extinction learning of a previous conditioned stimulus. No significant effects of tDCS timing were observed on early extinction recall.
Conclusions: Results could be explained by an anxiolytic aftereffect of tDCS and extend previous studies on tDCS-induced modulation of fear and threat related learning processes. These findings support further exploration of the clinical use of tDCS.

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Introduction

Extinction of conditioned fear has been used as a model to explain the therapeutic benefits of exposure-based therapy for anxiety and stress disorders [1,2]. Successful extinction of conditioned fear has been associated with "top-down" modulation by the ventromedial prefrontal cortex (vmPFC) of fear responses originating in the amygdala [3–9]. In addition, other factors besides the amygdala–vmPFC connectivity contribute to extinction success, e.g. time of extinction after fear conditioning [10] and reinforcement rate during conditioning [11]. Nonetheless, facilitating activation of vmPFC during extinction learning may be one mechanism to improve fear extinction as well as the retention of extinction memories.

The idea of increasing neural activity in vmPFC to impact fear expression and extinction has been previously tested in rats. Specifically, invasive electrical stimulation of the rat infralimbic subregion of the rat vmPFC during presentation of conditioned stimulus reduced fear expression, thereby simulating extinction in non-extinguished rats [12]. Similar electrical stimulation during extinction learning reduced conditioned fear expression during extinction and extinction recall [13]. Recent review papers outline the rationale for evaluating non-invasive neuromodulation techniques during extinction-based processes to assess their clinical potential [14–16].

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Transcranial direct current stimulation (tDCS) is one such non-invasive technique that alters cortical excitability via subthreshold modulation of neuronal resting membrane potentials using a weak constant electrical current [17]. Anodal or 'excitatory' stimulation is thought to increase the likelihood of action potentials in underlying cortex, whereas cathodal or 'inhibitory' stimulation may decrease the likelihood of action potentials. There is a rapidly growing body of research showing that prefrontal tDCS in the range of 1–2 mA affects various cognitive functions such as learning, memory and emotional processing [18].

So far, two studies suggest that tDCS can modify fear memories in line with the direction of stimulation. Asthana et al. [19] showed that inhibitory cathodal tDCS over the left dorsolateral prefrontal cortex after fear conditioning resulted in reduced fear expression to the conditioned stimulus during fear extinction 24 hours later. In another study, Mungee et al. [20] observed that excitatory anodal tDCS vs. sham over the right dorsolateral prefrontal cortex after providing a reminder of the conditioned fear stimulus resulted in increased fear expression. These results indicate that prefrontal tDCS could impact fear memory processes.

To our knowledge there are no studies to date that examine the effect of tDCS during extinction learning of conditioned fear in order to improve fear extinction learning and subsequent extinction recall. In this study we evaluated the hypothesis that, compared to sham stimulation, 2 mA anodal tDCS over EEG coordinate AF3 during extinction learning would enhance fear extinction learning as well as extinction recall. In particular, we predicted that active tDCS would result in a greater reduction in skin conductance values, an index of conditioned fear response, compared to sham stimulation across late extinction trials as well as across early recall trials in healthy volunteers. This focus on late extinction and early recall is based on an extensive amount of research in which extinction success has been quantified as a reduction in skin conductance during late extinction trials and early recall trials [7,9,21–23].

We employed a within-subjects design in which all participants received both active tDCS as well as sham stimulation during the extinction of a conditioned stimulus (CS+). This allowed us to evaluate whether tDCS during the extinction of one CS+, but not CS+ paired with sham, would affect extinction learning and subsequent extinction recall within participants. This design allowed timing of tDCS to occur during extinction of an initial CS+ or a second, subsequent CS+. Although exploratory, this may provide insight into a temporal order effect of tDCS in relation to extinction learning. The selection of excitatory, anodal tDCS and area AF3 as the target location was based on previously discussed literature on the association between increased vmPFC activity and successful extinction learning [3–9,12,13].

Materials and methods

Participants

Fifty-two participants aged 18–50 years were recruited from the Providence metro area by online advertisements and were included in the study. Eight participants were removed from all data analyses: two participants did not tolerate the unconditioned stimulus; one participant did not tolerate skin sensation associated with tDCS; equipment failure during fear conditioning prevented data collection for four participants; one participant screened out after the psychiatric interview. This resulted in a group of 44 participants, 21 females and 23 males for further analyses. All 44 participants denied using psychoactive or other potentially confounding medication, or smoking/use of nicotine replacement options.

Participants were randomly assigned to two study groups: 26 received active tDCS immediately at the onset of the first extinction learning block and sham during the second extinction block. The remaining 18 participants received sham stimulation during the first extinction block and active tDCS during the second extinction block. Table 1 describes the demographic characteristics of the participant sample. Exclusion criteria included current psychiatric disorders or past anxiety or psychotic disorder as assessed by the Mini International Neuropsychiatric Interview (MINI) [24] and contraindications for tDCS. Study procedures were performed in accordance with Declaration of Helsinki and the local IRB (Butler Hospital and Brown University) approved the study. Informed consent was obtained prior to the onset of any study procedures.

Fear conditioning paradigm and procedures

The experimental protocol was adapted from Milad et al. [7,9] and administered over two days. On Day 1, participants underwent three different phases: habituation, conditioning, and extinction. On Day 2, approximately 24 hours after conditioning and extinction, participants were tested on extinction recall.

During both days participants were asked to passively view photographs that would appear on a computer monitor. A set of electrodes was placed over the middle phalanges of the index and middle fingers of the dominant hand and was used to deliver the unpleasant unconditioned stimulus (US), i.e. a non-harmful electrical shock. Before initiation of the habituation phase, the intensity of the electric shock was set individually by each participant, and determined to be 'highly annoying but not painful.' The shock was generated by a Coulbourn Transcutaneous Aversive Finger Stimulator [25]. The mean shock level selected by participants was 2.32 mA out of 4 mA max (SD: 0.97; range: 0.8–4 mA). There was no significant difference of tDCS Timing Group on average shock level, $t(42) = 0.74$, $p = 0.47$. A second set of electrodes was placed on the non-dominant hand to measure skin conductance throughout testing sessions (see details on skin conductance recording and analyses below).

Day 1 – habituation phase

Participants were instructed that the purpose of this phase was to show them all of the possible pictures that they would see in the experiment, and that no shock would be delivered in this phase. Two future conditioned stimuli (CS+: red and blue light) and one unconditioned stimulus (CS–: yellow light) were presented in a

Table 1
Demographics of participants included for analyses.

	All participants (N = 44)	tDCS during 1st extinction block	tDCS during 2nd extinction block
Age (in years)	27.34 (SD 8.18; range 18–50)	27.77 (SD 8.45)	26.72 (SD 7.97)
Sex (F:M ration)	21 F:23 M	10 F:16 M	11 F:7 M
Handedness (# R; L; A)	33; 4; 7	18; 2; 6	15; 2; 1
Ethnicity (#)	31 White/Caucasian; 6 African-American; 4 Hispanic; 2 Asian; 1 biracial.	19 White/Caucasian; 3 African-American; 2 Hispanic; 1 Asian; 1 biracial.	12 White/Caucasian; 3 African-American; 2 Hispanic; 1 Asian; 0 biracial.
Educational level (in years)	14.75 (2.32)	14.42 (SD 2.50)	15.22 (SD 2.02)

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