RESEARCH PAPER

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Anodal tDCS applied to the left frontal cortex abrogates scopolamine-induced fear memory deficit *via* the dopaminergic system

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Evidence suggests that transcranial direct current stimulation (tDCS) modulates conditioned fear memories and has effects on cognitive flexibility *via* the dopaminergic system. This study examines whether modulation of scopolamine-induced fear memory deficit by anodal tDCS could be mediated by the dopaminergic system. The male NMRI mice received scopolamine, 30 min before fear conditioning, and showed impaired contextual memory retention. Mice subjected to left frontal anodal stimulation for 20 or 30 min, before fear conditioning, impaired fear memory retrieval. Anodal application for 20 min significantly decreased scopolamine response on fear retention, while the one applied for 30 min did not alter. Moreover, anodal stimulation for 30 min abolished scopolamine-induced fear memory deficit. Dopaminergic antagonists SCH23390 and sulpiride, alone or in combination, prevented the abolishment effect of anodal stimulation on scopolamine-induced fear memory deficit, whereas they did not alter the impairing effect of scopolamine at the dose of 2 mg/kg. Our data suggest that anodal stimulation for 30 min abrogates the impairing effect of scopolamine on fear memory retention. This influence could be prevented by dopaminergic antagonists, indicating the involvement of the dopaminergic system in the effect of anodal stimulation on scopolamine-induced fear memory deficit.

Key words: transcranial direct current stimulation, scopolamine, dopaminergic system, fear conditioning

INTRODUCTION

Cholinergic signaling plays an important modulatory role in fear memories with high adaptive performance against real and potential threats (Tinsley et al., 2004). During contextual fear conditioning, a neutral spatial location will create fear-related behaviors after being associated with an innately fearful stimulus (Maren et al., 2013). Fear-conditioned stimuli increase central acetylcholine release (Acquas et al., 1996), whereas the acetylcholine muscarinic receptor blocker scopolamine impairs the performance of rodents in conditioning tasks (Robinson et al., 2011; Wilson and Fadel, 2017). As fear memory processes alter in some psychopathologies such as posttraumatic

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stress disorder and schizophrenia (Maren et al., 2013) and Alzheimer's disease and other related dementias (Hoefer et al., 2008), it is essential to find ways to improve it.

Recently, studies have shown the potential therapeutic effect of noninvasive transcranial direct current stimulation (tDCS) technique on fear memories (Mungee et al., 2014). Studies have found that this system is effective due to many factors, such as safety, ease of use, painlessness, as well as beneficial effects of the procedure, were found on the motor, sensory, cognitive, and emotional functions in healthy participants as well as in patients with neurological and psychiatric diseases (Brunoni et al., 2011; Nitsche and Paulus, 2011). The tDSC uses a weak direct current between two electrodes, an anode and a cathode, attached to the subject's scalp. Anodal effects on motor cortex neurons is excitatory, whereas cathodal effects is inhibitory. Continuous stimulation for several minutes induces excitability changes that last (Nitsche et al., 2005). Based on animal studies, it is hypothesized that anodal tDCS-mediated effects shift neuronal resting membrane potential toward depolarization and increased spontaneous neuronal firing. In contrast, cathodal-mediated effects shift neuronal resting membrane potential toward hyperpolarization and decreased firing (Bindman et al., 1964). Overall, the studies collected suggest that tDCS can modulate brain plasticity due to synaptic modifications within the stimulated area. Changes in plasticity-related mechanisms are achieved through induction of long-term potentiation (LTP) and upregulation of neuroplasticity-related proteins, such as c-fos, brain-derived neurotrophic factor (BDNF), or N-methyl-D-aspartate receptors (NMDARs) (Cavaleiro et al., 2020). There is evidence for hemispheric lateralization of various cognitive functions and behaviors in the human brain (Toga and Thompson, 2003). For example, the left frontal systems appear to be critical for the cognitive selection caused by the content of working memory and for context-dependent action, the right frontal systems for cognitive selection driven by the external environment and for context-independent behavior (Goldberg et al., 1994). The processing and expression of negative emotions such as fear display a right hemispheric dominance in humans (Canli et al., 1998). In rodents, evidence for cortical lateralization is sparse. Neuroendocrine and autonomic stress responses were shown to be different between left and right medial prefrontal cortex lesions in rats (Sullivan and Gratton, 1999). Infantile handling induced increased locomotion in the open field test after right hemisphere lesions (Denenberg et al., 1978). In the hippocampus, gene expression profiles (Klur et al., 2009), receptor expressions (Kawakami et al., 2003), and long-term potentiation/long-term depression and innervation patterns (Shinohara et al., 2012) displayed specific hemispheric asymmetries. Right and left hemispheric inactivation impaired learning and expression in spatial navigation, respectively (Denenberg et al., 1978). Despite these findings, Wager et al. (2003) found no support for the hypothesis of overall right-lateralization of emotional function, and limited support for valence-specific lateralization of emotional activity in the frontal cortex. Besides, we found that tDCS over the left frontal cortex of mice modulates fear memory dysfunction induced by β_1-adrenoceptor blocker propranolol (Nasehi et al., 2017a) or lithium (Hamdami et al., 2020).

It has been shown that cognitive processes and symptomatology of diseases involving dopamine are sensitive to the application of tDCS over the dorsolateral prefrontal cortex. It has been suggested that subcortical effects of frontal tDCS reach to the subcortical areas such as dopaminergic areas (Keeser et al., 2011; Pena-Gomez et al., 2012). Also, Tanaka et al. (2013) reported increased extracellular dopamine levels in the rat striatum following tDCS. They proposed that tDCS has a direct and/or indirect effect on the dopaminergic system in the rat basal ganglia. The mesocorticolimbic dopaminergic pathway originating from the ventral tegmental area is particularly sensitive to fear-arousing environmental stimuli, and has been associated with exaggerated responses to fear-related situations (Guarraci et al., 2000; Greba et al., 2001). The conditioned stimuli activate dopaminergic mechanisms in the neural circuits of fear consists of the amygdala, nucleus accumbens and prefrontal cortex (Louilot and Besson, 2000). The involvement of dopamine receptors of the basolateral amygdala in fear memory dysfunction induced by activation of cannabinoid CB1 receptors has been demonstrated (Nasehi et al., 2016).

Considering the modulatory effect of tDCS on fear memories and the link between tDCS stimulation and brain dopaminergic activation, we hypothesized that the dopaminergic system involves in the left frontal anodal stimulation on scopolamine-induced contextual fear memory deficit.

METHODS

Animals

Male NMRI mice (from the animal facility of the Institute for Cognitive Science Studies, Tehran, Iran), weighing 25–30 g, were used for this study. Mice were

housed in groups of eight. Housing was in a 12:12 h light: dark cycle (lights on at 07:00 h) with ad libitum access to food and water. Temperature (22±2°C) was monitored and maintained at a constant level throughout the experiment. All protocols and housing were approved by the Ethical Committee of Tehran University of Medical Sciences and adhered to Animal Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 2010).

Surgery

Mice were anesthetized with ketamine hydrochloride/xylazine (50 mg/kg and 5 mg/kg respectively; i.p.) and placed in a stereotaxic apparatus. A tubular plastic jack (internal diameter: 2.1 mm and contact area: 3.5 mm^2) was surgically fixed onto the skull using dental cement one week before the stimulation protocol. The center of the plastic jack was positioned over the left frontal cortex (+1 mm anteroposterior and 1 mm left to the bregma, according to Paxinos and Franklin (2001) and fixed with dental cement. After surgery, all animals were allowed to recover for one week before undergoing tDCS. During this period, as well as during the electrical stimulations, mice were placed in individual cages.

Stimulation protocol

The jack was filled with saline solution before the stimulation to establish the contact area of the skull. The anodal electrode was screwed into the tubular jack. A larger conventional rubber plate electrode (cathode, 9.5 cm^2) served as the counter electrode and was placed onto the ventral thorax using a jacket. The animals were subjected to only one session of anodal tDCS for 20 or 30 min. An anodal constant current of 0.2 mA was applied transcranially over the frontal cortex using a DC-stimulator (Active Dose II unit made in Activatek company, Taiwan). Sham animals were subjected to the same procedures (surgery, anesthesia and electrode montage), but the current was not delivered. To apply tDCS in awaken mice, animals were restrained in a restrainer during the active or sham tDCS session as described (Nasehi et al., 2017a, 2017b).

The contextual fear conditioning test

Contextual fear conditioning and recall was conducted over two days. Briefly, the chamber for fear conditioning consisted of a transparent acrylic chamber (25 × 25 × 25 cm) and a stainless-steel grid floor equipped with an electric shock generator. The apparatus was placed in a soundproof observation box (55 cm × 53 cm × 67 cm) through which an auditory tone (4 kHz, 35 dB) was delivered to the animal. In the training trial, animals were placed individually into the fear-conditioning chamber and allowed to explore freely for 2 min. They then received an acoustic tone (4 kHz, 30 s, 35 dB) that co-terminated with electric foot shocks (0.5 mA, 2 s). The tone-foot shock pairing was repeated three times with 1-min intervals. 30 s after the final foot shock delivery, the mice were returned to their home cage. 24 h after the training trial, mice were placed in the same chamber to provide contextual stimuli and allowed to move freely for 5 min. The freezing behavior during the 5-min period was recorded as an index of contextual memory. Freezing was defined as the absence of any movement, except for those related to respiration and recorded using a stopwatch. Latency to the freezing was calculated as the delay time until the first freezing behavior. The experiments were carried out by someone blinded to the experimental groups.

Experimental design

The total 136 mice were divided into various groups consisting of eight mice per group and two experiments were conducted:

In experiment 1, mice were randomized into one of nine groups. Group I – saline (10 ml/kg); groups II and III – scopolamine at the doses of 0.02 and 2 mg/kg, respectively; groups IV and V – anodal stimulation for 20 or 30 min, respectively; groups VI and VII – scopolamine (0.02 mg/kg) with anodal stimulation for 20 or 30 min, respectively; groups VIII and IX – scopolamine (2 mg/kg) with anodal stimulation for 20 or 30 min, respectively (Fig. 1).

Experiment 2 was designed using eight groups of animals. The animals were divided into two sets of four groups. In the first set, sham mice received scopolamine (2 mg/kg) plus saline (10 ml/kg), D1-like receptor antagonist SCH23390 (0.005 mg/kg), D2-like receptor antagonist sulpiride (1 mg/kg) or combination of SCH23390 and sulpiride. In the second set, the same groups were subjected to anodal stimulation for 30 min (Fig. 1).

All drugs, except for sulpiride, were dissolved in saline. Sulpiride was dissolved in 5 µl acetic acid and diluted with 0.9% saline and was adjusted to pH 7. In the contextual fear memory test, SCH23390 (0.005 mg/kg) and/or sulpiride (1 mg/kg) was intraperitoneally ad-

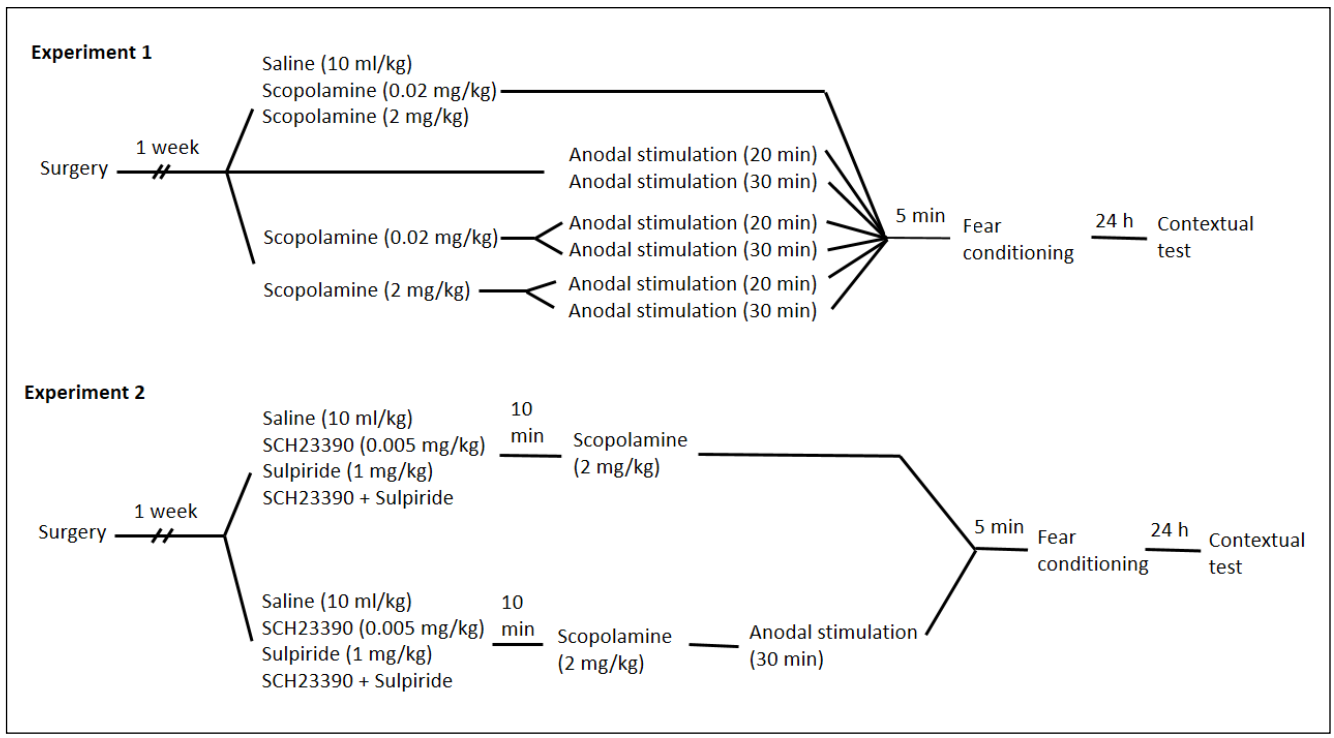

Fig. 1. Study design and schedule of the protocol. Eight mice were used in each group.

ministered 30 min and scopolamine infused 20 min before tDCS stimulation.

Statistical analysis

Various comparisons among experimental groups were interpreted using a two-way ANOVA test followed by Tukey's *post hoc* multiple comparison tests. The freezing time percentage and latency to the freezing of animals in different groups were expressed as a mean and SEM. For all experimental analyses, $P<0.05$ was considered significant. All data were analyzed with the computer program, SPSS software (V 21.0). The graphs were drawn with SigmaPlot (14.0) software.

RESULTS

The effects of scopolamine, anodal stimulation and their combination on contextual fear memory

Two-way ANOVA showed a significant interaction between anodal stimulation during 20 min and scopolamine on the freezing time percentage (scopolamine effect: $F_{(2,42)}=47.96$, $P<0.000$; anodal effect: $F_{(1,42)}=120.50$, $P<0.000$, scopolamine-anodal interaction: $F_{(2,42)}=28.65$, $P<0.000$; Fig. 2A) and latency to the freezing (scopolamine effect: $F_{(2,42)}=99.57$, $P<0.000$; anodal effect: $F_{(1,42)}=14.35$, $P<0.000$, scopolamine-anodal interaction: $F_{(2,42)}=9.76$, $P<0.000$; Fig. 2B). *Post hoc* analysis revealed that scopolamine (2 mg/kg) decreased the freezing time percentage and increased the latency to the freezing. Anodal stimulation for 20 min decreased the freezing time percentage compared to the control group. Anodal stimulation plus scopolamine (0.02 mg/kg) decreased the freezing time percentage and increased the latency to the freezing compared to the scopolamine (0.02 mg/kg)-treated mice.

Two-way ANOVA showed a significant interaction between anodal stimulation during 30 min and scopolamine on the freezing time percentage (scopolamine effect: $F_{(2,42)}=14.65$, $P<0.000$; anodal effect: $F_{(1,42)}=0.28$, $P=0.60$, scopolamine-anodal interaction: $F_{(2,42)}=26.99$, $P<0.000$; Fig. 2A) and latency to the freezing (scopolamine effect: $F_{(2,42)}=442.65$, $P<0.000$; anodal effect: $F_{(1,42)}=322.51$, $P<0.000$, scopolamine-anodal interaction: $F_{(2,42)}=428.72$, $P<0.000$; Fig. 2B). *Post hoc* analysis showed that anodal stimulation for 30 min decreased the freezing time percentage compared to the control group. Moreover, anodal stimulation for 30 min plus scopolamine (2 mg/kg) increased the freezing time percent-

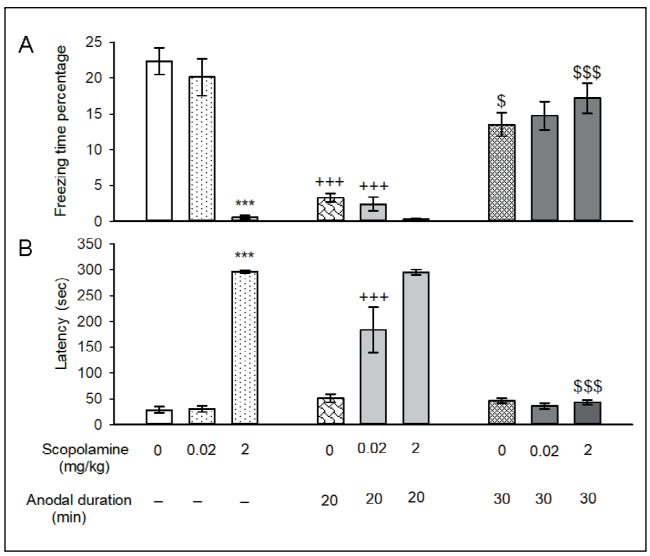

Fig. 2. Effects of scopolamine, anodal stimulation and their combinations on fear memory retention. Data are presented as mean ± SEM. n=8/group. ***P<0.005, **P<0.01 and *P<0.05 compared to the scopolamine (0 mg/kg) group; $^{+++}$P<0.001 and $^{++}$P<0.01 compared to their respective groups in the left panel; $^{\$\$\$}$P<0.001 compared to their respective groups in the left panel.

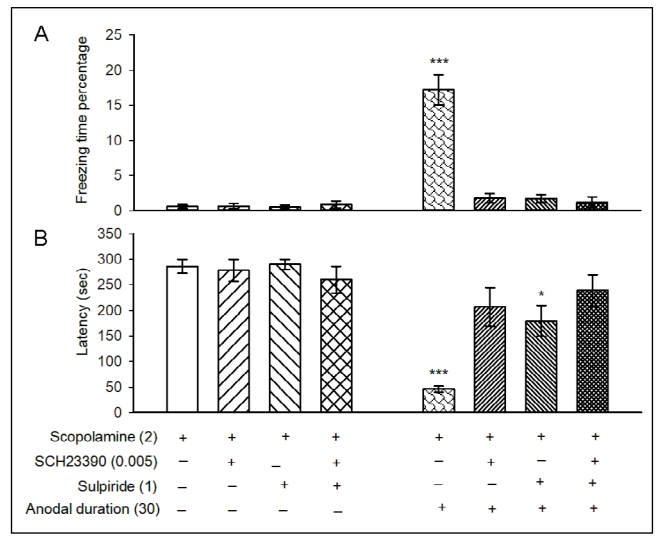

Fig. 3. Effects of SCH23390, sulpiride and their combination with or without anodal stimulation on scopolamine-induced fear memory dysfunction. (A) 30 min anodal stimulation cannot prevent the effect of scopolamine in combination with dopamine receptor antagonists on fear memory retention. (B) tDCS + scopolamine and tDCS + sulpiride + scopolamine groups decreased latency to the freezing compared to their respective groups in the left panel. Data are presented as mean ± SEM. n=8/group. ***P<0.005, **P<0.01 and *P<0.05 compared to their respective groups in the left panel.

age and decreased the latency to the freezing compared to scopolamine (2 mg/kg)-treated group.

The effects of dopamine antagonists with and without anodal stimulation on scopolamine-induced fear memory dysfunction

Two-way ANOVA showed a significant interaction between scopolamine-dopamine antagonist effect and anodal stimulation on freezing time percentage (scopolamine-dopamine antagonist effect: $F_{(3,56)}$=37.74, P<0.000; anodal stimulation effect: $F_{(1,56)}$=58.32, P<0.000; scopolamine-dopamine antagonist/anodal stimulation interaction: $F_{(3,56)}$=38.64, P<0.000; Fig. 3A) and latency to the freezing (scopolamine-dopamine antagonist effect: $F_{(3,56)}$=5.04, P=0.004; anodal stimulation effect: $F_{(1,56)}$=41.63, P<0.000; scopolamine-dopamine antagonist/anodal stimulation interaction: $F_{(3,56)}$=7.43, P<0.000; Fig. 3B). *Post hoc* analysis indicated that 30 min anodal stimulation when applied immediately after scopolamine (2 mg/kg) significantly increased freezing time percentage and decreased latency to the freezing compared to scopolamine-treated group. Moreover, anodal stimulation when applied after sulpiride + scopolamine administration decreased latency to the freezing compared to its respective group in the left panel.

DISCUSSION

Here, we present the evidence that anodal stimulation over the left frontal cortex for 30 min abrogates contextual fear memory deficit induced by scopolamine. Moreover, the anodal application cannot prevent the impairing effect of scopolamine in combination with dopamine antagonists on fear memory retention.

Our data revealed that the intraperitoneal scopolamine administration, before fear conditioning, decreased the freezing time percentage, suggesting a fear memory deficit. Meanwhile, the effective dose of scopolamine increased latency to the freezing. It has been established that muscarinic cholinergic antagonism produces learning and memory deficits similar to the effects produced by hippocampal lesions (Anagnostaras et al., 1995). It appears that the muscarinic antagonists disrupt the hippocampal theta rhythms and induce an acquisition deficit in a variety of the hippocampal-dependent tasks (Vanderwolf et al., 1977; Anagnostaras et al., 1999). Recent studies have indicated that the hippocampus has an important role in Pavlovian fear conditioning. It seems that the acquisition of contextual fear depends on the induction of hippocampal long-term potentiation (LTP) (Maren et al., 1996). Thus, because the hippocampus receives extensive

cholinergic input from the medial septal nucleus (Amaral and Kurz, 1985), one would expect that muscarinic cholinergic antagonist should disrupt contextual fear acquisition, at least to the extent that anticholinergic action can reduce hippocampal function. Although muscarinic antagonists have been shown to produce hyperalgesia (Ghelardini et al., 1998), there is evidence that scopolamine attenuates the electric shock perception (Torquet et al., 2008). Some studies have reported that scopolamine does not modify the pain threshold in the hot plate test (Torquet et al., 2008; Laurino et al., 2017). Based on these findings, the destructive effect of scopolamine on contextual fear memory does not appear to be related to its potential effect on pain.

tDCS has been applied to many research issues because this stimulation technique can modulate neural activity in the brain painlessly and non-invasively with weak electrical currents (Matsumoto and Ugawa, 2017). However, there are no formal safety guidelines for the selection of stimulus parameters in tDCS. Nevertheless, several papers have reported that some adverse events persist even after tDCS stimulation. The ongoing events consist of skin lesions similar to burns, which can arise even in healthy subjects, and mania or hypomania in patients with depression (Brunoni et al., 2012; Matsumoto and Ugawa, 2017). Other limitations of the tDCS application are the lack of control conditions over different cortical areas and the lack of systematic monitoring of the duration of the effects (Brunoni et al., 2012). Most studies have examined the effect of tDCS stimulation over the left frontal cortex on a variety of behaviors (Peanlikhit et al., 2017; Pedron et al., 2017; Hamdami et al., 2020), but there is limited support for right-lateralization of emotional function (Wager et al., 2003). On the other hand, experimental evidence suggest that long-term memory processing is strictly dependent on the left hemisphere (Podda et al., 2016). Therefore, we chose to apply tDCS over the left frontal cortex. We observed that the percentage of freezing time significantly decreased by a 20 min or a 30 min anodal tDCS over the left frontal cortex. Overall, it has been observed that cathodal currents produce inhibitory effects, and thus hyperpolarization, whereas anodal currents increase excitability in the form of depolarization (Nitsche and Paulus, 2000; 2001). Even though many studies reported recovery from memory deficits following tDCS stimulation, there are some opposing reports in animal models of disease affecting cognition. There is evidence that tDCS was not able to ameliorate memory symptoms of a triple transgenic (3xTg) mouse model of Alzheimer's disease (Gondard et al., 2019). Some authors have suggested the importance of choosing an optimal current intensity to modulate cortical excitability since LTP alterations were dependent on current intensity (Yoon et al., 2012). However, many factors have been shown to interfere with tDCS outcomes, including the duration and frequency of stimulation (Liebetanz et al., 2006); intensity, and density of the applied current (Liebetanz et al., 2009; Jackson et al., 2017), and electrode size and position in the scalp. On the other hand, the persistence of fear memory depends on the number of cue-shock pairings and the shock intensity. In a recent study, repeated anodal tDCS had no significant effect on the acquisition or retention of fear extinction in mice subjected to fear conditioning with 0.2 mA foot shock, while it significantly lowered freezing during the acquisition of extinction when the intensity of fear conditioning was 1 mA (Van Schuerbeek et al., 2021). Authors found that tDCS reduced generalized fear induced by contextual cues when the intensity of conditioning is high, and extinction training is limited (Van Schuerbeek et al., 2021). Regarding rodent models, data are controversial regarding fear condition. A single session, 20 min anodal tDCS over the right frontal cortex did not alter contextual fear memory retention in mice subjected to fear conditioning with high intensity (Manteghi et al., 2017). Additionally, another study described that while the anodal stimulation did not affect fear retrieval in mice subjected to fear conditioning with 1 mA intensity, post-training cathodal stimulation improved fear memory retrieval (Nasehi et al., 2017b, 2017a). However, left prefrontal anodal and cathodal tDCS impaired the acquisition of both contextual and cued fear memory in mice subjected to fear conditioning with 0.5 mA intensity, which could be explained by activity modulation of deep structures such as the amygdala and hippocampus (Abbasi et al., 2017). These conflicting findings may be due to differences in the intensity and frequency of tDCS stimulation and the shock intensity in fear conditioning. An interesting finding in this study was the destructive effect of 20 min anodal stimulation on fear memory retention was much greater than 30 min. According to researches that focused on the systematic assessment of the effect of tDCS on excitability (Nitsche and Paulus, 2000), a linear dose-effect response is expected. However recent data demonstrated that the relationship between tDCS parameters and the measured effects is not as linear as we thought. For example, a 3 min and a 20 min anodal tDCS decreased immobility duration in the forced swim test, indicating an antidepressant-like behavior, whereas a 10 min did not produce any effect (Peanlikhit et al., 2017). Therefore, an increase in the stimulation duration does not seem to be a successful approach to increase the efficacy of tDCS. For example, the prolongation of anodal tDCS from 13 min to 26 min resulted in reduced motor cortex excitability, most probably caused by intraneuronal calcium overflow (Monte-Silva

et al., 2013). Given the above evidence, it is not surprising that 50% increasing the duration of tDCS stimulation has a different effect than the short stimulation time. However, determining the curve of different tDCS stimulation duration on fear conditioning is suggested to confirm the nonlinear relationship between these two variables.

The obtained data revealed that anodal tDCS for 20 min significantly decreased the response of subthreshold dose of scopolamine on fear memory. In comparison, 30 min anodal activation abrogated the impairing effect of the effective dose of scopolamine on contextual fear memory. Furthermore, 20 min anodal stimulation when applied immediately after the subthreshold dose of scopolamine increased latency to the freezing. In comparison, 30 min anodal application decreased latency to the freezing compared to the effective dose of scopolamine. Previous experiments have demonstrated that anodal tDCS increases cerebral blood flow (Merzagora et al., 2010), and enhances neural plasticity in the brain (Fritsch et al., 2010; Jiang et al., 2012). Many clinical studies have reported that anodal tDCS provides therapeutic benefits in patients with various neurological disorders, such as stroke (Hummel et al., 2005), multiple system atrophy (Alexoudi et al., 2018), schizophrenia (Schwippel et al., 2018), Parkinson's (Fregni et al., 2006) and Alzheimer's (Ferrucci et al., 2008) disease. The therapeutic potential of anodal tDCS for cognitive decline in the rat model of streptozotocin-induced diabetic (Wu et al., 2017), traumatic brain injury (Yoon et al., 2016), attention deficit/hyperactivity (Leffa et al., 2015), and Alzheimer's disorder (Yu et al., 2015) has been supported. There is evidence that anodal stimulation enhances synaptic plasticity through an increased BDNF signaling in the motor cortex (Fritsch et al., 2010) and in subcortical brain regions, e.g., the hippocampus (Podda et al., 2016). It is speculated that anodal tDCS applied to the frontal cortex may cause an extensive effect over distant structures, including the basal forebrain and hippocampus throughout a distributed and interconnected cortical-subcortical network. Neurons directly stimulated by the anodal tDCS will, in turn, modulate the activity of adjacent neurons and activate neuronal circuits related to learning and memory function. So the influences of the anodal tDCS are potentiated. Besides, the release of neurotransmitters such as dopamine and acetylcholine are possible candidates following these effects of tDCS (Yu et al., 2015). tDCS potentially modulates the function of all polarizable brain cell types in physiological conditions and also modulates synaptic plasticity abnormalities and minimizes memory and learning deficits in many neuropsychiatric diseases. Considering the neuromodulatory effect and the different durations of tDCS stimulation, a duration-dependent effect of anodal stimulation on scopolamine response in the contextual fear memory is suggested. Besides, a modulatory effect for anodal stimulation on scopolamine response in fear memory is proposed.

We found that 30 min anodal stimulation did not prevent the impairing effect of scopolamine plus D1-like dopamine receptor antagonist SCH23390, D2-like dopamine receptor antagonist sulpiride or their combination on contextual fear memory. It should be noted that dopaminergic agents alone or in combination did not affect the impairing effect of scopolamine. Moreover, anodal stimulation when delivered after sulpiride and scopolamine administrations, decreased latency to freezing compared to mice who received sulpiride and scopolamine without anodal stimulation. These observations showed that the dopaminergic system has a vital role in anodal stimulation on scopolamine-induced amnesia, so that inactivation of dopamine receptors *via* dopamine receptor antagonists abolished the improving effect of the anode on contextual fear memory dysfunction induced by scopolamine. The reciprocal interaction between dopaminergic systems and tDCS has been suggested. It is possible that the precognitive beneficial effects of tDCS to be mediated by modulating of mesocorticolimbic dopamine transmission. Besides, tDCS is linked to a dopamine release within the prefrontal cortex (Fonteneau et al., 2018). The involvement of hippocampal and striatal dopaminergic neurotransmission of spontaneously hypertensive rats in the improvement of short-term memory deficits following anodal stimulation on the frontal cortex has been proposed by Leffa et al. (2015). According to the literature, dopamine antagonists have no effect on motor activity or pain at the dose used (Bittencourt and Takahashi, 1997; Fredriksson and Archer, 2002; Centonze et al., 2003; Ivanova et al., 2021). Given the above findings, it is not surprising to suggest that the dopaminergic system is involved in the positive effect of anodal stimulation on contextual fear memory dysfunction induced by scopolamine. This paradigm of the combining anodal stimulation with dopaminergic drugs could be an option for treating fear memory deficits in humans.

CONCLUSION

In conclusion, the present study provides evidence that anodal stimulation before fear conditioning can protect contextual fear memory dysfunction of scopolamine-treated mice, in a duration-dependent manner. It appears that the dopaminergic system is involved in the beneficial effect of anodal stimulation on scopolamine-induced amnesia.

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