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No evidence for any effect of multiple sessions of frontal transcranial direct stimulation on mood in healthy older adults

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Abstract

The dorsolateral prefrontal cortex (DLPFC) is part of a network important for emotional regulation and the possibility of modulating activity in this region with transcranial direct current stimulation (TDCS) to change mood has gained great interest, particularly for application in clinical populations. Whilst results in major depressive disorder have been promising, less is known about the effects of TDCS on mood in non-clinical populations. We hypothesized that multiple sessions of anodal TDCS applied over the left DLPFC would enhance mood, primarily as measured by the Profile of Mood States questionnaire, in healthy older adults. In addition, in an exploratory analysis, we examined the potentially moderating role of working memory training. Working memory, just like emotional regulation, taxes the DLPFC, which suggests that engaging in a working memory task whilst receiving TDCS may have a different effect on activity in this region and consequently mood. A total of 123 participants between 65 and 75 years of age were randomly assigned to receive either 20 sessions of TDCS, with or without working memory training, or 20 sessions sham stimulation, with or without working memory training. We found no support for enhancement of mood due to TDCS in healthy older adults, with or without cognitive training.

Keywords: TDCS, mood, DLPFC, healthy, aged

1. Introduction

The dorsolateral prefrontal cortex (DLPFC) has a central role in the regulation of emotions (Buhle, et al., 2014; Kohn, et al., 2014; Ochsner, Silvers, & Buhle, 2012). Findings point to more right-pronounced activity in the DLPFC during negative stimuli processing (Beraha, et al., 2012) and more left-pronounced activity during positive stimuli processing (Herrington, et al., 2010). Studies of depression further confirm the role of the DLPFC in the regulation of emotions and mood (Fitzgerald, Laird, Maller, & Daskalakis, 2008; Hamilton, et al., 2012; Jaworska, Yang, Knott, & Macqueen, 2015; Sacher, et al., 2012). Meta-analyses have found that depressed individuals have decreased activity in the DLPFC at rest, relative to healthy individuals, as well as a lack of activation in the DLPFC when presented with negative stimuli (Fitzgerald, et al., 2008; Hamilton, et al., 2012). Some findings indicate that the hypoactivation concerns the left DLPFC specifically with the right DLPFC actually being hyperactive (Grimm, et al., 2008). The abnormal pattern of activation in the DLPFC in depression has been shown to lead to a failure in attenuating the impact of negative stimuli (Hamilton, et al., 2012).

Given the central role of DLPFC in emotional regulation, it may be possible to modulate mood by changing the pattern of neural activity in this area. This idea gave rise to experimental studies passing electricity through the brain via electrodes already in the 1960's (Costain, Redfearn, & Lippold, 1964). A potential way to do this is to use Transcranial Direct Current Stimulation (TDCS), which is a non-invasive technique with few and mild side effects (Poreisz, Boros, Antal, & Paulus, 2007; Priori, Hallett, & Rothwell, 2009). Two electrodes, one anode and one cathode, are placed on the scalp and a weak electrical current is passed through the brain. Since the electrical current is weak, TDCS does not force neuronal firing but is instead thought to modulate the spontaneous firing of the neurons by affecting the resting membrane potential (Nitsche & Paulus, 2000). Based on findings in the

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motor domain, it has been suggested that anodal stimulation leads to a hyperpolarisation of the underlying region; that is, an increase of the likelihood of neuronal firing, and that cathodal stimulation leads to hypopolarisation (Nitsche & Paulus, 2000).

To date, ten randomised controlled trials (RCTs) have evaluated the effect of TDCS in depression with the two most recent meta-analyses demonstrating effect sizes of around 0.3 on depressive symptoms, supporting its potential as an effective treatment in depression (Brunoni, et al., 2015; Meron, Hedger, Garner, & Baldwin, 2015). All of the ten RCTs placed the anode over the left DLPFC (i.e., aiming to increase the activity in the left DLPFC), whilst the position of the cathode varied between the orbital area and the right DLPFC.

The potential impact of an effective way to modulate mood in clinically depressed individuals is of course undisputed, but such modulation can also be used to deepen our understanding of normal emotional regulation. Our current understanding of neural mechanisms involved in normal emotional regulation remain very limited. In contrast to studies in depression, which commonly administer stimulation over 5-15 sessions, studies in healthy individuals have rarely used more than a single stimulation session (Mondino, Thiffault, & Fecteau, 2015). A recent systematic review (Remue, Baeken, & De Raedt, 2016) concluded that a single session of prefrontally applied TDCS, or the similar method TMS, does not affect mood in healthy individuals. Out of the three published studies that have used multiple TDCS (3-4 stimulations) in healthy individuals, two reported a positive effect on mood (Austin, et al., 2016; Newstead, et al., 2018) while the third not (Motohashi, Yamaguchi, Fujii, & Kitahara, 2013). All three studies placed the anode over the left DLPFC but differed in the placement of the cathode, placing it over the right DLPFC (Austin, et al., 2016), the orbital area (Motohashi, et al., 2013), or the right cerebellum (Newstead, et al., 2018). These studies all had a small number of participants ($n = 12-42$). Thus, the effect of repeated sessions of frontal TDCS on mood in healthy adults remains unclear.

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There are reasons to believe that emotional processing is changing with ageing. Empirical findings indicate that compared to younger adults, older adults attend to negative stimuli to a lesser degree, remember positive stimuli to a higher degree than negative stimuli, and experience less negative affect in general (Charles, Mather, & Carstensen, 2003; Mather & Carstensen, 2003; Reynolds & Gatz, 2001). In terms of brain activity, a frequently reported pattern is that older adults show less activity in the amygdala and other temporo-limbic areas in response to emotional stimuli, but more activity prefrontally, relative to younger adults (Gunning-Dixon, et al., 2003; Roalf, Pruis, Stevens, & Janowsky, 2011). This changed activity pattern has been suggested to explain the often found increased emotional well-being in older adults, possibly through increased emotional control (Nashiro, Sakaki, & Mather, 2012). Despite the indications of important differences in the emotional system between younger and older adults, no study has examined the effect of repeated sessions of TDCS on mood in older healthy adults. We therefore included mood measurements as a part of a large study administering TDCS stimulations and cognitive training, looking at outcomes on cognition (Nilsson, Lebedev, Rydstrom, & Lovden, 2017) and also mood (reported here).

We administered 20 anodal TDCS sessions over left DLPFC in older healthy individuals and hypothesized a positive effect on mood through an increased activity in the left DLPFC. The hypothesis that more DLPFC activity leads to enhanced mood follows from the findings of a hypoactive (left) DLPFC in depression and to some extent also from the association between elevated frontal activity in older adults and well-being (i.e., the possibility that the increased well-being in older adults is caused by enhanced frontal activity).

The primary mood outcome measure, the total mood disturbance score as derived from the Profile of Mood Scale (POMS), was administered prior to any stimulation and subsequently before every fifth stimulation session. The secondary mood outcome measure,

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answer to the question “How are you feeling today?” on a 10-point Likert scale, was administered before every stimulation session, and before and after the intervention period. We predicted larger improvements in mood for the primary and secondary measure over the course of the 4-week intervention period for participants receiving TDCS, relative to participants receiving a sham stimulation.

In a more exploratory aspect of the present investigation, the potentially modulating effect of working memory training on the effect of TDCS on mood was tested. The present study is based on the sample from the REBOOT trial that investigated effects of TDCS on working memory training (Nilsson, et al. (2017). Specifically, participants were not only assigned TDCS or sham stimulation but also simultaneous working memory training or control cognitive training. Whilst TDCS did not improve the cognitive outcomes of working memory training, we took the opportunity to also explore the possibility that working memory training, as a modulator of the effects of TDCS, could affect mood indirectly by its modulation of DLPFC activity (D'Esposito, Postle, & Rypma, 2000). As such, the aim of the present study was to deepen our understanding of the neural correlates of emotional regulation in healthy older individuals. The administration of 20 stimulation sessions in healthy adults is unprecedented and the sample size is by far the largest in the context of TDCS in healthy individuals (Remue, et al., 2016).

2. Materials and methods

2.1. Participants

We advertised the study in local newspapers and recruited 142 healthy adults aged 65 to 75 that met full eligibility criteria (primarily: no somatic or psychiatric illness, and no sensory impairment) and gave written informed consent for participation. See the Supplement for full inclusion criteria. One hundred and twenty-three participants completed the study.

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Approval was granted by the regional ethics review board of Stockholm (2014/2188-31/1), and the study was conducted in accordance with the Declaration of Helsinki. A sample size of 120 was targeted to achieve 90% power to study a standardised mean difference of 0.3 on the main outcome of the trial (i.e., working memory), as based on a repeated-measures ANOVA ($\alpha=.05$). See the primary publication for details (Nilsson, et al., 2017).

Table 1. Demographic data for the four experimental groups

Variable	TDCS + WM task (<i>n</i> = 32)	TDCS + control task (<i>n</i> = 30)	Sham TDCS + WM task (<i>n</i> = 33)	Sham TDCS + control task (<i>n</i> = 28)
Age (years)	<i>M</i> = 69.31, <i>SD</i> = 2.73	<i>M</i> = 69.87, <i>SD</i> = 2.91	<i>M</i> = 69.64, <i>SD</i> = 2.97	<i>M</i> = 69.82, <i>SD</i> = 2.62
Sex	16 <i>females</i> , 16 males	17 <i>females</i> , 13 males	22 <i>females</i> , 11 males	16 <i>females</i> , 12 males
Education (years)	<i>M</i> = 15.05, <i>SD</i> = 3.19	<i>M</i> = 14.29, <i>SD</i> = 2.29	<i>M</i> = 14.68, <i>SD</i> = 2.86	<i>M</i> = 15.84, <i>SD</i> = 4.09
Reasoning ability (score)	<i>M</i> = 7.06, <i>SD</i> = 2.72	<i>M</i> = 6.97, <i>SD</i> = 3.02	<i>M</i> = 6.88, <i>SD</i> = 2.36	<i>M</i> = 6.93, <i>SD</i> = 2.26
POMS Tot. Mood Dist.	<i>M</i> = 2.19, <i>SD</i> = 21.26	<i>M</i> = - 0.74, <i>SD</i> = 11.08	<i>M</i> = 1.53, <i>SD</i> = 16.81	<i>M</i> = 2.07, <i>SD</i> = 15.62

2.2. Design and procedure

A mixed factorial design was used with the factors cognitive training (working memory training vs. control training) and stimulation (TDCS vs. sham). Stratified randomisation using age, sex and Ravens Progressive Matrices pre-test scores was used to allocate each participant to one of the four intervention groups. Participants were blinded both in terms of stimulation and training group and experiment leaders were blinded in terms of stimulation. The participants were economically compensated with 50 SEK per assessment occasion during the pre, post and follow-up phase (14 occasions) and 100 SEK per occasion during the intervention phase (20 occasions). Pre - and post testing included comprehensive cognitive testing, brain imaging, and several questionnaires. The intervention period extended over four weeks with 20 occasions of working memory/control training and parallel active/sham TDCS. See Nilsson, et al. (2017) for a detailed description of design and procedure.

2.3. TDCS

A saline-soaked anode (7x5cm) was placed on the scalp, targeting the left DLPFC, corresponding to the F3 in the 10-20 international system for EEG placement. To maximize peak current density underneath the F3 and minimizing the risk of shunting, the anode was shifted slightly laterally, towards F5, and slightly posteriorly (Seibt, Brunoni, Huang, & Bikson, 2015), resulting in that the superior-anterior quarter section and not the centre was positioned over F3. The saline soaked cathode (7x5cm) was placed over the contralateral supraorbital area. The 10/20 BraiNet Placement Cap (Jordan NeuroScience, Inc, California, USA) was used for the electrode placement. Using the DC-STIMULATOR PLUS (neuroConn GmbH, Ilmenau, Germany), a constant direct current of 2mA (current density $57.1 \mu\text{A}/\text{cm}^2$), was delivered for 25 minutes with an additional 8-second ramp-up and a 5-second ramp-down period. For the sham version, the same procedure as in active TDCS was used but the stimulation only lasted for 30 seconds (with an additional 8-second ramp-up and a 5-second ramp-down period). The 30 second stimulation was used to induce the same tingling sensation as experienced when initializing active TDCS (i.e., it was a way to mask whether active or sham TDCS was delivered). The participants' blinding to the type of stimulation they had received was successful with 52% incorrect guesses and 48% correct guesses ($p = .72$ by binomial test). Side effects were evaluated at four occasions during the intervention weeks. At these occasions the participants were administered a 5-point Likert scale (0 = "I did not experience the side effect at all," 5 = "The side effect was so severe that I considered terminating or had to terminate the stimulation") before, during and after the session. Reported side effects were generally very small: the average maximum over the four occasions was 1.265 ($SD = 1.200$). No statistically significant difference was found between

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the active and the sham group, collapsing the scores over time (all $ps > .136$ by Mann-Whitney U test).

2.4. Measures of Mood

Two measures of mood were the focus of the present study. As our main outcome, we used the sum score scale of POMS 2 for adults called Total Mood Disturbance. We used the latest short form of POMS 2 for adults (POMS 2-A Short) with a short time frame (i.e., participants were asked to rate each item given how they felt “right now”). The Total Mood Disturbance scale is aggregated from adding the scores of the POMS 2 subscales Depression-Rejection, Anger-Hostility, Fatigue-Inertia, Confusion-Bewilderment and Tension Anxiety, and then subtracting the score of the Vigor-Activity subscale. The Total Mood Disturbance scale ranges from -20 to 100, with a higher value indicating a higher mood disturbance. Cronbach’s alpha was calculated to .94 in a normative population aged 50 years and above. The adjusted test-retest reliability coefficient in a normative sample aged 18 and above was .69 for the questionnaire administered one week apart and .54 for the questionnaire administered 30 days apart (Heuchert & McNair, 2012). The participants answered POMS 2 once before the intervention and once at the end of each intervention week (i.e., five measurement occasions in total).

As our secondary outcome of mood, we used the 10-point Likert scale question “How are you feeling today?” (further on referred to as the Daily mood question) where a higher score indicates greater mood. This question was answered with a higher frequency than POMS 2 – at five occasions before the intervention, at each of twenty intervention sessions, and at five occasions after the intervention (i.e., in total at 30 occasions). In addition, the question – “How alert do you feel today?” (Daily Alertness question) was also answered on a

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daily basis but is however not the focus of the present investigation. Both the POMS 2 and the short questions were administered before any cognitive testing or intervention session.

2.5 Working memory and control training

The working memory training focused on updating and switching ability. Updating ability was trained using n-back and running span exercises. Switching ability was trained using task switching and rule switching exercises. The control training consisted of a perceptual matching test. The training programs lasted 40 minutes per session and started five minutes after the onset of TDCS or the sham stimulation to avoid distraction due to the start of the stimulation. See Nilsson, et al. (2017) for a more detailed description of the working memory training as well as the control training.

2.6. Statistical analysis

SPSS 24 (IBM, Armonk, NY) was used for the descriptive statistics while (R Core Team, 2016) was used for all inferential statistics. Multilevel models were specified for the main outcome of POMS total mood and for the secondary outcome of Daily mood with random intercept and slope. The maximum likelihood method and an autoregressive moving average (ARMA 1, 0) covariance structure (Holan, Lund, & Davis, 2010) were used for the estimation. Both models included the main effect of time (occasion 1-5 for POMS total mood, occasion 1-30 for Daily mood), TDCS (active, sham), and cognitive training (working memory training, control training), as well as all possible two way-interactions and the three-way interaction as fixed effects. The package nlme:nlme (Pinheiro, Bates, DebRoy, Sarkar, & Team, 2017) with the optimizer named optim was used. In the spirit of encouraging less dichotomous interpretations of parameter estimates without losing information, cluster bootstrapped confidence intervals were calculated for all estimates and reported instead of p-

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values (samples = 2000, seed = 12345). This was done using private code that can be made available on request. The alpha value was set to .05 for the primary outcome of POMS total mood disturbance (corresponding to a 95% confidence interval) and to .01 for the secondary outcome of the Daily mood question (corresponding to a 99% confidence interval).

The between group effects sizes (Cohen's *d*) for the two way-interactions including time were calculated using the mean of the standard deviations from the compared groups post the intervention. In addition, the subscales of POMS and the Daily Alertness question were similarly analysed (see the supplement for details).

Seven of the 123 participants who completed the trial had a baseline score of at least eight on the Depression-Rejection subscale of the POMS questionnaire. The score of eight on the subscale corresponds to 1.5 *SD* above the mean in a healthy population aged 50 (Heuchert & McNair, 2012). In a study of the concurrent predictive validity of the Depression-Rejection scale, the use of the cut off 1.5 *SD* above the mean correctly classified a SCID diagnosis of Major Depression Disorder with an overall predictive value estimated to 80 % (Patterson, et al., 2006). To investigate whether the individuals with higher scores on the Depression-Rejection subscale affected our results in a substantial way, sensitivity analyses using the same statistical models as for the original sample but excluding these seven participants were made.

3. Results

There was no main effect of stimulation (active, sham) or any interaction between time (occasion 1-5; Pre – Week 4/Post in Figure 1) and stimulation (active, sham) for our main outcome POMS total mood disturbance (i.e., all of the confidence intervals included zero). Unstandardized parameter values for the main effect of stimulation; -0.46 (CI -7.61, 5.57) and for the interaction time x stimulation; -0.30 (CI -1.52, 1.07). Between-group Cohen's *d*

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for total mood disturbance at post measure was 0.10 with a 95% confidence interval including zero (-0.48, 0.28). As for our more explorative question of an interaction between time, TDCS, and cognitive training, our analyses showed no support for any modulating effect of cognitive training on the stimulation effect on mood for the POMS Total mood disturbance. Unstandardized parameter values for the interaction Time x Stimulation x Training: -0.07 (CI -1.95, 1.59) See the supplement for details of the model.

There was also no significant main effect of stimulation (active, sham) or any interaction between time (occasion 1-30; Pre-1-5, Session 1-20, Post 1- 5 in Figure 1) and stimulation (active, sham) on the Daily mood question (i.e., all of the confidence intervals included zero. Unstandardized parameter values for the main effect of stimulation; 0.06 (CI (-0.90, 1.10) and for the interaction time x stimulation; -0.01 (CI -0.04, 0.02). Between group Cohen's at post measure was - 0.06 with a 95% confidence interval including zero (-0.45, 0.34). Neither was there support for an interaction of time, TDCS, and cognitive training on mood, as measured with the Daily Mood question. Unstandardized parameter values for the interaction Time x Stimulation x Training: 0.02 (-0.02, 0.06). See the supplement for the details of the model.

The sensitivity analyses, which excluded the seven individuals who scored at least eight on the POMS Depression-Rejection subscale, demonstrated the same outcome. Furthermore, the POMS subscales and Daily Alertness question showed the same pattern of non-significant findings. See the supplement for the details of these analyses as well as descriptive statistics for all time points and outcome measures.

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Fig 1. The effect of TDCS on POMS total mood disturbance. POMS: The Profile of Mood States. Note that the y-axis is broken, total possible range: -25, 100. A higher value indicates more mood disturbance. The error bars correspond to standard deviations. X-axis: time. TDCS: transcranial direct current stimulation.

Fig 2. The effect of TDCS on the Daily mood question. Range 0-10 with a higher value indicating better mood. The error bars correspond to standard deviations. X-axis: time. TDCS: transcranial direct current stimulation

4. Discussion

This study is the first to investigate the effect of multiple prefrontal TDCS on mood in older healthy participants. It greatly exceeds the previous studies in both number of participants (123), number of stimulation sessions (20), and number of mood measurements (5 for main outcome, 30 for secondary outcome). The analyses showed no statistical evidence for enhancement of mood after multiple anodal TDCS over the left DLPFC on the primary mood outcome (POMS total mood disturbance) or on the secondary mood outcome (Daily mood question). There was also no evidence for a modulating effect of working memory training on the TDCS effect on mood for any of the outcome measures.

Previous evidence of reduced depressive symptoms following anodal TDCS over the DLPFC in major depressive disorder suggested that TDCS can influence emotional regulation (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Brunoni, et al., 2015; Meron, et al., 2015). However, the participants in our study were not depressed, which implies that their ability to regulate emotions was at a well-functioning level already at baseline. It is therefore possible that the lack of mood enhancement in the present and previous studies is due to a restriction of mood enhancing effects of TDCS to populations with abnormal emotional regulation. Additionally, effects on mood may be particularly unlikely in a healthy older population given findings that older adults in general experience less negative affect, possibly due to better emotional regulation relative to young adults (Kryla-Lighthall & Mather, 2009; Nashiro, et al., 2012). A related limitation of the present study is that we did not formally evaluate the presence of depression in the screening phase, which means that the sample may not have been entirely healthy in this regard. However, sensitivity analyses, in which participants with possible depression were excluded, resulted in the same overall outcome.

Electrode placement may also have contributed to the results. Placement of the anode over the left DLPFC and the cathode over the supraorbital area, or alternatively with the

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placement of the cathode over the right DLPFC, has become the standard in studies of mood (Brunoni, Ferrucci, Fregni, Boggio, & Priori, 2012; Remue, et al., 2016). All studies of healthy individuals so far have placed the anode according to this standard but they have differed in the cathodal placement. Newstead, et al. (2018) and Austin, et al. (2016) found positive mood effects with a cathodal placement over the right cerebellum and the right DLPFC, respectively. The cathodal placement can be motivated by findings of possible hyperactivity in the right DLPFC in depression (Grimm, et al., 2008) and the cerebellum has increasingly gained interest as region important for emotion (Newstead, et al., 2018). However, Motohashi, et al. (2013) found no evidence of an effect on mood with a cathodal placement over the orbital area, arguably consistent with the results reported here. Thus, it cannot be excluded that the cathodal placements over the supraorbital region in the present study rendered the stimulation ineffective for mood modulation.

No other previous study has investigated the effect of multiple sessions of TDCS on mood in a healthy older population and important consideration is the neural changes that come with age. Brain activity patterns are known to be different in older relative to younger adults (Gunning-Dixon, et al., 2003; Roalf, et al., 2011), and normal aging has been linked to several neural changes that affect plasticity negatively, particularly in hippocampal and frontal regions (Burke & Barnes, 2006; Lovden et al., 2010). Given the uncertainty concerning the precise neurophysiological mechanism of TDCS, particularly in non-motor areas such as the DLPFC, it is difficult to speculate in how age may affect the physiological response to TDCS (Heise, et al., 2014; Horvath, Carter, & Forte, 2015). Future research will be required to discern how age may limit the potentially mood-enhancing effects of TDCS in the healthy population.

The present study had several strengths, including its randomized, double-blind, sham-controlled design as well as its' sample size. It is therefore reasonable to also consider the

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possibility that a positive effect of anodal TDCS over the left DLPFC on mood is in fact unlikely for healthy, older adults. Such an interpretation would follow the pattern of no detectable effects on mood in healthy individuals following a single TDCS session (Remue, et al., 2016). This interpretation can also be considered in the context of a number of recent reviews and meta-analyses demonstrating no or very small effect of TDCS in the healthy population for outcomes such as cognition (Nilsson, et al., 2017; Westwood & Romani, 2017). Concerns have recently been raised regarding the amount of inter- as well intra-individual differences in response to TDCS as well as often overlooked variables such as thick hair and sweat, that substantially can influence the effects of TDCS. Furthermore, the physiological mechanisms and the overall efficacy of TDCS have also been questioned recently (Horvath, Carter, & Forte, 2014; Horvath, et al., 2015). It will be important for future studies to systematically investigate these non-trivial concerns in an effort to allow the field to advance.

5. Conclusions

The present study represents the first investigation of the effect of multiple sessions of frontal TDCS in healthy older individuals. We found no evidence of a mood-enhancing effect of twenty sessions of anodal TDCS over the left DLPFC. Although TDCS may be beneficial in some contexts, for example for treatment of clinical depressive symptoms, we conclude that the TDCS protocol used here is unlikely to improve mood in non-depressed older individuals.

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