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The effects of left dorsolateral prefrontal transcranial direct current stimulation on episodic future thinking following acute psychosocial stress

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ABSTRACT

Introduction: Research on stress-related disorders and brain imaging suggests that (acute) stress might impact the capacity to mentally simulate specific episodic future events (EFT) through the effects of cortisol on brain regions supporting this cognitive function, such as the prefrontal cortices. This study aims to examine the mechanisms underlying this link, using transcranial Direct Current Stimulation (tDCS) over the left dorsolateral prefrontal cortex.
Methods: 60 healthy participants were subjected to the Montreal Imaging Stress Task (MIST), followed by either active or sham tDCS. After stimulation, the EFT task was administered. Salivary cortisol was measured throughout the protocol.
Results: Higher cortisol *AUCi* values were linked to less specific episodic future thoughts. Moreover, active tDCS enhanced EFT specificity irrespective of cortisol, especially in high trait ruminators. We did not observe an effect from active tDCS on cortisol *AUCi*, and equally there was no interaction effect between cortisol *AUCi* and stimulation condition predictive for EFT specificity.
Conclusion: Although we did not find evidence for the effects of tDCS on the HPA-system, our data reveal a crucial link between two critical predictors of mental health for the first time, and provide a solution to help rehabilitate EFT deficits.

Trial registration: Netherlands National Trial Register identifier: ntr004..

KEYWORDS
Transcranial direct current stimulation; trait rumination; cortisol; Montreal Imaging Stress Task; episodic future thinking

Introduction

Amongst the most debilitating of mental health impairments is a distorted outlook on the self and the world (Gotlib & Joormann, 2010; Hallford et al., 2019). Crucially underlying this personal narrative is the ability to imagine or simulate experiences that might occur in one's own personal future – termed "episodic future thinking" (Schacter et al., 2008). EFT has been gaining increasing research interest over the past decade. As much as in its adaptive advantages (e.g., Jing et al., 2016), the importance of this cognitive function has been shown in its vulnerability and involvement in psychopathology (Hallford et al., 2018). EFT disturbances – such as overgeneral future thoughts – often mark the onset of stress-related mental health disorders, yet also persist beyond recovery or remission, increasing the risk for recurrence (Mathews & Macleod, 2005; Spinhoven et al., 2006; Newby & Moulds, 2011).

One of the key biophysiological markers of stress is the activation of the hypothalamic–pituitary–adrenal (HPA) axis, cascading to an increase of the stress hormone cortisol in the blood stream. As part of a negative-feedback mechanism to assure homeostasis and stress-recovery, cortisol binds to corticosteroid receptors in brain regions responsible for modulation of the HPA stress-system, including the hippocampus and parts of the medial prefrontal cortex (mPFC) (Herman et al., 1997; Herman et al., 2005). As a result, stress-related cortisol increases can lead to decreased brain activation and potentially undermine cognitive functions that rely on these areas, such as EFT (Dedovic et al., 2009; Pruessner et al., 2008).

Reduced hippocampal activity associates with a lower amount of detail and specificity in imagined future events (Schacter et al., 2012), while mPFC constitutes an important hub in the brain's default mode network (DMN) – a network subserving self-referential processing,

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ruminative tendencies, as well as memory processing and EFT (Delaveau et al., 2014; Raichle, 2015; Schacter et al., 2012). Stress-induced modulation in these regions has been found to result in impairments of cognitive processes relying on the DMN, such as memory retrieval (Het et al., 2005; Hidalgo et al., 2019; Kirschbaum et al., 1996; Tollenaar et al., 2009). For example, Tollenaar and colleagues (2009) found that cortisol increases after acute stress tended to be related to less specific autobiographical memories, while Smeets (2011) similarly found impaired memory retrieval after stress, linked to stress-induced cortisol responses. Of interest, similar results can be hypothesised for the effects of stress on EFT, as it has been suggested that EFT and episodic memory processes draw from overlapping psychological processes, and both rely on a common core network for retrieval and construction of episodic detail (Schacter & Addis, 2007).

In stress-related psychopathology, where long-term cortisol hypersecretion can be linked to malfunctioning of the DMN and reduced volume in the hippocampal area, perhaps due to dendritic loss (Brakowski et al., 2017; Dedovic et al., 2010; Geerlings & Gerritsen, 2017; Ming et al., 2017; Watanabe et al., 1992) it has been found that ruminative processes further mediate this relationship (Raes et al., 2006). Rumination can be defined as a repetitive negative self-referential thinking style about the past, with little or no change and goal-orientation. Such DMN-related maladaptive thought processes might sustain stress and its cognitive repercussions (Zoccola & Dickerson, 2012).

The mental health benefits of stress-recovery thus extend from neurophysiological impact to indirect effects on cognition, tackling two crucial vulnerabilities for stress-related disorders. Importantly, recent advances in the field of neuroscience provide methods to target enhancement in cognition *and* stress-recovery directly and at the same time, by electrically modulating brain activity. Non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS) have been widely used to modulate activity in the healthy as well as in the mentally affected human brain (Dedoncker et al., 2016; Nitsche et al., 2008). tDCS relies on the passing of a weak electrical current through the skull in order to modulate cortical excitability, by lowering the threshold for action potential generation (Stagg et al., 2018). As such, tDCS can be applied to suppress the before mentioned stress-related decreases in brain activation, and further endorse stress-regulation of deeper lying brain areas, while supporting cognitive functions such as EFT.

Several studies demonstrated the effectiveness of tDCS in inhibition of the neuroendocrine stress-response by endorsing prefrontal activation (Antal et al., 2014; Carnevali et al., 2020), and its potential for the treatment of stress-related disorders such as major depressive disorder is being investigated with promising results (Kalu et al., 2012; Razza et al., 2020). Research suggests that this treatment could be more potent for people with a vulnerability for the effects of stress on mood and cognition, as it has been found that effects of neurostimulation on stress-recovery can be modulated by ruminative tendencies (De Witte et al., 2020).

Although accumulating evidence also captures its effects on cognition – including successful memory enhancement (Habich et al., 2017; Javadi, 2012; Manenti et al., 2013) – tDCS modulation of EFT-performance has not yet been subject to study. As the previously outlined evidence on the neuroendocrinology of memory specificity suggests that acute stress could impact EFT through its effects of cortisol on brain regions implicated in the DMN (Barry et al., 2018), and given its importance in stress-related psychopathology, tDCS could both reveal the underlying mechanisms of this important cognitive capacity *and* serve as a possible angle for reduction and rehabilitation of stress-related EFT deficits.

Consequently, the current study aimed to investigate the effects of prefrontal tDCS neurostimulation on EFT performance in the acutely stressed healthy brain. To this end, 60 healthy participants were recruited to take part in a between-subjects sham-controlled study. First, all participants were subjected to the Montreal Imaging Stress Task (MIST) to evoke acute stress (Dedovic et al., 2005). To investigate the effects of tDCS on stress-recovery, either active or sham tDCS was applied after stress, with the anode placed on the left dorsolateral prefrontal cortex (L-DLPFC) and the cathode placed on the contralateral supra-orbital area (orbitofrontal cortex; OFC). Moreover, even though we expect the area under the anode (L-DLPFC) to be modulated by tDCS, the peak of electrical field strength of tDCS has been found to lie in between the anode and the cathode. As the electrical field strength correlates with effective modulation of neurons in the electrical field (Antonenko et al., 2019), this suggests that we would be additionally stimulating the mPFC and thus parts of the DMN (Baeken et al., 2017; De De Witte et al., 2018; See also Figure 2 for a simulation of the electric field distribution with the setup used in this study). Indeed, with this setup we have previously established attenuating effects on DMN-related processes such as rumination (Baeken et al., 2017; Vanderhasselt, Brunoni, et al., 2013). After stimulation, we assessed the effects of stress and tDCS on EFT with an episodic future thinking task (EFT-T; Hallford et al., 2019). Salivary cortisol was measured throughout the protocol. Ruminative processes were assessed by a trait questionnaire before the experiment and several measurements of state (momentary) rumination during the experiment.

Our main hypotheses entail on the one hand the effects of tDCS over the L-DLPFC on stress-recovery, and on the other hand the effects of stress(-recovery) and tDCS on EFT: (1) we expected active tDCS, but not sham to facilitate stress-recovery, indicated by lower cortisol values after stress for the active tDCS condition compared to sham; (2) we hypothesised higher cortisol values to be linked to lower EFT scores, also indicating an indirect effect of tDCS on EFT via stress-recovery (3) we also expected a direct effect of tDCS due to enhancement of activity in EFT-related brain regions, leading to more specificity in EFT for the active tDCS condition compared to sham, irrespective of cortisol levels. Finally, we expected individual differences in trait and state rumination to affect cortisol levels and to modulate tDCS effectiveness.

Methods

Participants

Sixty healthy volunteers between 18 and 30 years old (*M* = *21.98; SD* = *2.35*) participated in the study. The sample consisted of 29 males and 31 females. Participants were recruited through Ghent University student fora as well as social media, and met the following inclusion criteria: (1) no current/history of psychiatric disorders, as evaluated by the screening version of the Mini-International Neuropsychiatric Interview (MINI 5.0.0; Lecrubier et al., 1997; Dutch translation by Overbeek et al., 1999) based on DSM-IV and ICD-10, (2) Beck Depression Inventory (BDI-II-NL; Beck, 1996; Dutch translation by Van der Does, 2002) scores were below 14 points, (3) no implanted metal objects in the body, (4) right-handed, (5) not pregnant, (6) no (family) history of epilepsy, (7) no recent neurosurgical procedures, (8) no pacemaker or implants, (9) no unstable medical condition, (10) no skin conditions on the face, (11) no addiction, current substance abuse or use of psychotropic medication, (12) no heart, lung, or neurological diseases, and (13) no eye diseases. The study was approved by the ethics committee of the Ghent University hospital, all participants gave signed informed consent, and were financially compensated for their participation.

Procedure

In this sham-controlled between-subjects study, participants were pseudo-randomly assigned to either an active-tDCS condition (*N* = *30*) or sham condition (*N* = *30*), considering gender and time of day of participation. Moreover, to limit influence of the circadian rhythm on the activity of the HPA-axis (Goodman et al., 2017), all testing sessions started after 12.30pm and took place at fixed timepoints, either at 12.30pm, 14.30pm and 16.30pm. After the initial online filling out questionnaires (Ruminative Response Scale (RRS; Treynor et al., 2003; Dutch translation by Raes et al., 2003), State-Trait Anxiety Inventory, trait version (STAI-Y-T; Spielberger, 1983)) participants were invited to the lab at Ghent University Hospital (UZGent). To guarantee the quality of cortisol samples, participants were instructed (1) not to sleep less than usual the night before testing, (2) not to undertake heavy physical activities on the day of testing, (3) not to drink alcohol on the day of testing and the night before, (4) not to drink stimulants (e.g., coffee) or smoke 2 hours before testing, (5) not to eat 1.5 hours before testing, (6) not to wear any lipstick and (7) to avoid bleeding by brushing teeth on the day of testing. Participants were asked to arrive at the lab 15 minutes before testing. When testing started, first they gave written consent and were then asked to fill out the questionnaires (BDI II; Beck, 1996 and socio-demographic questions). Approximately 10–15 minutes were provided for giving instructions and completing the questionnaires. Then participants were instructed to relax for a habituation period of 15 minutes. Subsequently, they performed the Montréal Imaging Stress Task (MIST; Dedovic et al., 2005) for 15 minutes, followed by 20 minutes active or sham tDCS stimulation. After stimulation, participants were instructed to perform the EFT task. Cortisol samples were taken (T_1) before the MIST, (T_2) immediately before stimulation, (T_3) immediately after stimulation, (T_4) halfway through the EFT task and (T_5) at the end of the experiment. At timepoints 1, 2, 3 and 5 visual analogue mood scale items (VAS; McCormack et al., 1988) and a state rumination questionnaire (BSRI) were also completed. For a visual representation of the protocol we refer to Figure 1.

Self-report measurements

Online screening and control questionnaires. To ensure comparable active and sham tDCS conditions, several surveys and questionnaires assessing potential confounders (i.e., Depression, Anxiety, smoking, drinking, contraception, body mass index (BMI) and perceived social status (measured using the "social ladder"; Adler et al., 2000)), were carried out prior to the experiment.

Mood. To evaluate mood changes during the experimental protocol, self-reported mood was assessed at 4 times during the experiment: (T_1) before the MIST, (T_2) after the MIST (before stimulation), (T_3) immediately after stimulation, and (T_5) at the end of the experiment. Seven horizontal 10 cm visual analogue scales (VAS; McCormack et al., 1988) were used to detect changes in feelings of "fatigue", "vigor", "anger" "tension", "depression", "cheerfulness' and "stress'. The VAS item scores ranged from 0 to 10.

Trait rumination. In order to assess trait ruminative tendencies, the validated Ruminative Response Scale (RRS-NL-EXT; Treynor et al., 2003; Dutch translation by Raes et al.,

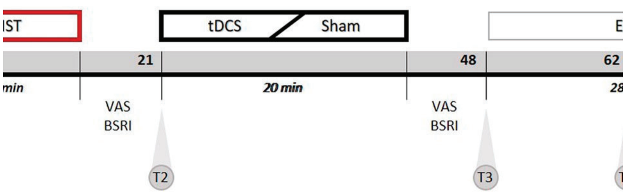

Figure 1. An overview of the study protocol. Note: tDCS = transcranial Direct Current Stimulation; MIST = Montreal Imaging Stress Task; EFT = episodic future thinking; VAS = Visual Analogue Scale; BDI = Beck Depression Inventory; BSRI = Brief State Rumination Inventory.

2003) was filled out by participants. 22 items are used to measure trait rumination.

State rumination. To evaluate state rumination throughout the protocol and the effects of stress and stimulation on rumination, the validated Brief State Rumination Inventory (BSRI) was used (Marchetti et al., 2018). Momentary ruminative thinking is assessed with 8 questions. Answers are given on a VAS scale ranging from 0 (completely disagree) to 100 (completely agree). The scores on each individual question are then summed up to yield one measure of state rumination.

Cortisol assessment

Saliva samples for cortisol assessment were collected using salivettes (Sarstedt, Germany), containing a sterile polyester swab for collecting saliva, yielding a clear and particle-free sample. Cortisol was assessed at 5 times during the experiment: (T_1) before the MIST – in order to get a baseline, (T_2) after the MIST – in order to quantify the effect of the stressor before stimulation, (T_3) immediately after stimulation, in order to measure the peak of cortisol reactivity, (T_4) during the EFT task in between two blocks, in order to measure the effect of stimulation and quantify the stress recovery, and (T_5) at the end of the experiment, equally to quantify recovery. The exact timings of the saliva sampling are shown on Figure 1. Saliva cortisol levels (nmol/L) were determined by Salimetrics enzyme-immunoassay cortisol kit (Salimetrics, State College, PA, USA). Limit of quantification was 0.007 µg/dL and the within-run and between-run variation coefficients were less than 10%. For each subject, all the samples were analysed in duplicate and in the same trial.

Montreal Imaging Stress Task

In order to induce acute stress in our participants and investigate the effects of tDCS on cortisol secretion after stress, we used the MIST (Dedovic et al., 2005). The MIST is a validated tool for inducing psychosocial stress in a functional magnetic imaging environment and evoking physiological responses measurable in cortisol secretion. We used this MRI-compatible protocol as this study is used as precedent of a bigger project which provides the chance to elaborate on our research question in a brain imaging study in the future.

The stress task was conducted before active tDCS or sham stimulation. The procedure consisted of two blocks of 6 minutes each, in which participants were subjected to mental arithmetic tasks. The MIST program displayed a mental arithmetic task, a rotary dial for submission of a response, a text field that provides feedback on the submitted response ("correct," "incorrect," or "timeout"), as well as a performance indicator. On the performance indicator, the participant's score was shown in comparison with a fictional score indicating the average score of participants. The scores were consistently updated depending on the subject's average performance after each trial. Each arithmetic task had a time limit. Both difficulty of the tasks as well as the enforced time limit were automatically adjusted by an adaptive algorithm to be slightly more difficult than what the user was capable of performing, thus leading to a range of 20% to 45% correct answers. Through the fictional average score of all participants, the user however expected a success rate of approximately 85%. Before the task, the investigator explained the task, informing subjects that it is feasible to score in a range of 80% to 90% correct answers, and that scores should not significantly deviate from the average performance of all subjects if the subject's data are to be used in the study. In between blocks, the investigator provides 3 minutes of feedback, showing concern about the bad performance and the usability of the data, and encouraging the subject to do better in a second block.

Transcranial direct current stimulation

tDCS stimulation was delivered by a battery-driven, constant current stimulator (1×1 mini-CT, Soterix Medical Inc.). The EEG 10–20 system was used for the location of the electrodes, based on Beam et al., 2009. tDCS was delivered with a pair of rubber surface electrodes (4.5×4.5 cm $= 20.25$ cm^2) covered with electrode gel – the anode placed on the L-DLPFC (F3), cathode on the over the contralateral supra-orbital area (Fp2). In the active stimulation condition, a direct current of 2 mA was applied for 20 minutes, with 30 s of ramp up/down. For sham tDCS the current was ramped up for 30 s, direclty followed by a 30 s ramp down at the beginning and end of the 20-minute tDCS session (Nitsche et al., 2008). For a simulation of electric field strength distribution on the brain using the tDCS setup described here, we refer to Figure 2.

Episodic future thinking task

The EFT task was conducted after stimulation, to look at the effects of stress and tDCS on specificity of episodic future simulations. The task was run on E-prime 2.0 software (Psychological Software Tools, Pittsburg, PA). It was based on the Autobiographical Memory Test (AMT; Williams & Broadbent, 1986) and adapted for future thinking (instructions based upon the EFT-T used by Hallford and colleagues, e.g., Hallford et al., 2019). It consisted of a 3 (valence: positive, negative, neutral) × 2 (timeframe: near future, distant future) design with specificity of future simulations and response time as outcome measures. During the task, 18 cue words were presented one by one on a screen. The words consisted of positive ($N = 6$), negative ($N = 6$) and neutral ($N = 6$) words taken from validated wordlists (Brysbaert et al., 2014; Marshall et al., 2010; Moors et al., 2013; words can be found in supplementary materials). Words were accompanied by a timeframe instruction either instructing to imagine in the near future (0-5 years later, $N = 9$) or the distant future (5-10

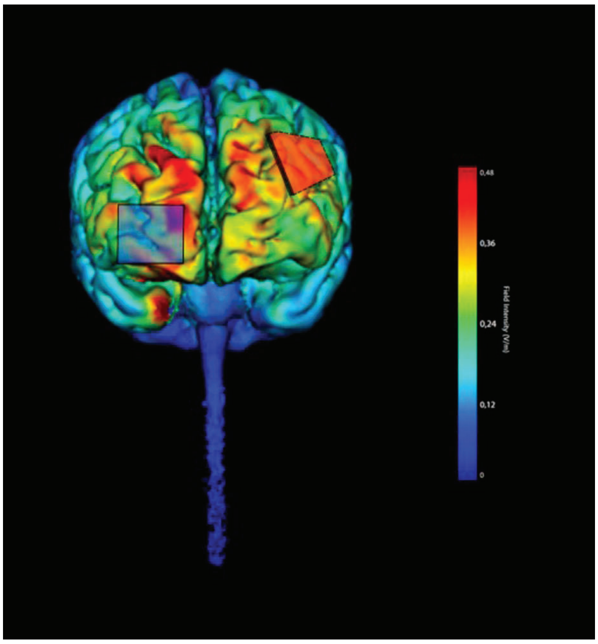

Figure 2. Electric field strength distribution. Electric field strength on the brain surface for simulation of the currently used tDCS montage and parameters in one individual. The tDCS montage is approximated as shown by the blue (cathode on right OFC) and red (anode on left DLPFC) overlay drawings. Electric field strength is represented by the color gradient shown in the bar at the right side of the brain. The more towards the red color, the stronger the electric field; the more towards the blue color shades, the weaker the electric field in the brain. Here, electric field strength is strongest in between the anode and the cathode, covering the mPFC, and underneath both electrodes. Simulation and figure generated using Soterix HD Explore™ software.

years later, N = 9) – to control for the influence of timeframe on specificity (Argembeau & Linden, 2004). Between the three valence categories, words matched on concreteness, word frequency, word length and arousal (for positive and negative words only). Words were pseudo randomly (no 3 consecutive words of the same valence or timeframe) distributed into two blocks with each 9 words that did not differ on these parameters as well as their valence and timeframe, generating a unique wordlist and block order for each participant.

For each cue word participants were asked to imagine an event that could possibly occur in their own personal future and was related to the cue word. Participants were instructed to think of a single event occurring at a certain time and place and that spanned no longer than a day. They were instructed to think about the event through their own eyes and to think of everything they could in as much detail as possible. Each word was presented on the screen for 1 min. During that time, from the moment an idea came to their mind, they had to press a button in order to mark the *construction time* of the thought (e.g., see also Madore et al., 2016 for the differentiation between construction and elaboration time). After pressing the button, they reported their future thought out loud and could elaborate on the thought for the remainder of time, while the answer was being recorded. After each cue word, participants indicated on a scale from 1 to 5 how emotional and how detailed their thoughts were. Each block of 9 words lasted about 12 minutes, instructions were presented for 1 min prior to the experiment, and a cortisol sample was taken for 2.5 minutes in between the two blocks.

Coding. The recordings were later coded as either specific (relating to a specific personal future occurring within 24 h) or non-specific (all other responses; including when no response was given). All responses were coded by an (independent; blind to group designations and study protocol) rater (SDS), together with the first author (LDW; blind to group designations). Inter-rater reliability between these two authors was found to be good (Kappa score of .76).

Statistical analysis

The significance level was set at $p = .05$, two-tailed for all analyses. Analyses were executed using R 3.6.3 (R Core Team, 2013) in conjunction with Rstudio 1.2.1335.

VAS and socio-demographics. To examine whether the stress task provoked a similar psychological stress response during both sessions and whether one session of tDCS did not affect mood, mood changes were analysed using a repeated measures MANOVA, with condition (active vs. sham stimulation) as the between-subjects factor and Time (T_1, T_2, T_3, T_5) as the within-subject factor. The six VAS mood items ("fatigue", "vigor", "anger", "tension", "depression" and "cheerfulness') were used as multiple dependent variables. Independent sample *t*-tests were used to assess whether conditions did not differ on socio-demographic or trait variables that could influence cortisol levels (see Table 1). Where necessary, we applied the Greenhouse-Geisser correction to ensure the assumption of sphericity.

Hypothesis 1 – Cortisol. Type III Analysis of variance (ANOVA) models fitted with the default "stats' package and the "Car" package were used for the analyses investigating the effects of tDCS on stress-recovery and cortisol (Fox & Weisberg, 2019). Before analysis, cortisol values were first log-transformed because they were abnormally distributed, along the lines of e.g., Arch et al., 2014. After log-transformation, all models met the normality assumption. Secondly, we calculated the Area Under the Curve with respect to increase (*AUCi*) as an index of the sensitivity of the HPA-axis to tDCS stimulation, using the formula proposed by Pruessner and colleagues (Pruessner et al., 2003). Since we were mainly interested in the sensitivity of HPA-axis functioning as indicated by the changes in cortisol values over time, our hypotheses were focused on the *AUCi*. For these analyses *AUCi* calculation included all cortisol samples after stress (T_2, T_3, T_4, T_5). With this, we mapped the overall HPA-response during and after tDCS. In order to ensure that effects of tDCS on *AUCi* were not due to differences between groups before stimulation (since we did not include T_1 in the *AUCi* measure), we conducted an independent samples t-test on the difference between baseline cortisol and cortisol after stress. Active tDCS and sham conditions did not differ in reactivity to the MIST (T_2-T_1; $t(47) = -.22$; $p = .83$). We then fitted an ANCOVA with "*AUCi*" as dependent variable, "condition" and "RRS" as predictors and "Cortisol T_1" as covariate, to control for the law of initial values (i.e., a negative correlation between initial value of a given physiological response and the physiological change seen during the paradigm; Block & Bridger, 1958. For information on the variation of cortisol T_1, see Table 2 in the manuscript and Figure 3 in supplementary materials). To decompose interaction effects, (Tukey adjusted) pairwise comparisons were carried out using the "emmeans' package (Lenth et al., 2018).

Hypothesis 2 & 3– EFT. To assess the influence of cortisol and tDCS stimulation on specificity of EFT, we focused on the specificity of the future thoughts as outcome measure. Analyses were performed using generalized linear mixed-effects regression (GLMM) models fitted via the "lme4" package (Bates et al., 2015). Lme4 provides *p*-values based on asymptotic Wald tests. Here, we calculated the *AUCi* using the last three salivary samples (T_3, T_4, T_5) to focus on the effects of cortisol and tDCS on performance *during* the EFT task. Trials in which the recording failed, were removed from the EFT analyses (0,009%). After data preparation, a GLMM model was fitted with "condition" (active tDCS/ sham), "RRS" (trait rumination) and "*AUCi*" as fixed predictors and "subject" as a random intercept. To decompose interaction effects, (Tukey adjusted) pairwise comparisons were carried out using the "emmeans' package (Lenth et al., 2018).

Responders versus non-responders. As not all participants usually show an increase in cortisol levels after the stress task, previous research supports making a distinction between cortisol responders and non-responders. This allows us to investigate whether active tDCS stimulation did have an attenuating effect on the cortisol response specifically in participants reacting more strongly to the stressor with a distinct HPA-axis response. Therefore, we repeated the analyses including a variable distinguishing responders and non-responders. For the classification of cortisol responders, we used the 15,5% baseline-to-peak increase criterion (Miller et al., 2013). Participants were thus classified as responders when cortisol levels increased at least 15,5% after stress (T_2 or T_3 vs. T_1). These results are added to the supplementary materials.

All abovementioned analyses were run 2 times: either (1) including or (2) excluding covariates to control for possible confounders: Age, Sex, BMI, subjective socioeconomic status, time of the beginning of the session, smoking (Yes/No), number of alcoholic units consumed weekly, use of hormonal contraceptives (Yes/No). We included these covariates based on previous research demonstrating their possible influence on the cortisol response to stress (Allen et al., 2014; Gruenewald et al., 2006; Kudielka et al., 2009; Pulopulos et al., 2015; Pulopulos et al., 2018; Quintana et al., 2013; Sjoberg & Saint, 2011; Villada et al., 2017). However, the models including covariates yielded similar significant outcomes and a less optimal model fit, hence only the models without covariates are presented here.

Finally, the effects of stimulation on state rumination were considered for exploratory reasons using a LMM – including the fixed predictors "time" (timepoints: (1) baseline, (2) after stress, (3) after stimulation, (5) at the end of the experiment – see Figure 1), "condition", covariate baseline BSRI and random predictor "subject". BSRI values were square root transformed in order to achieve normal distribution of the data.

Results

VAS and socio-demographics

Conditions (active tDCS/Sham) did not significantly differ on several socio-demographic or trait variables that

Table 1. Means and Standard Deviations of transcranial Direct Current Stimulation (tDCS) and sham conditions on Socio demographic and trait variables. Abbreviations: BMI, Body Mass Index; RRS, Ruminative Response Scale; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory.

	Condition	N	Mean	SD	*P*
Age	tDCS	30	22.07	2.26	.786
	sham	30	21.9	2.47	
BMI	tDCS	30	22.69	3.00	.315
	sham	30	23.49	3.11	
Smoking (%)	tDCS	30	0.07	0.25	.398
	sham	30	0.13	0.35	
Drinking (weekly frequency)	tDCS	30	5.55	6.90	.148
	sham	30	3.43	3.96	
Perceived social status	tDCS	30	4.42	1.15	.541
	sham	30	4.23	1.17	
RRS	tDCS	30	36.30	9.30	.984
	sham	28	36.36	12.25	
BDI	tDCS	30	4.43	3.69	.542
	sham	30	3.87	3.45	
STAI Trait	tDCS	30	74.17	17.51	.641
	sham	30	72.01	16.25	
Hormonal contraceptives (%)	tDCS	16	0.75	0.45	.172
	sham	15	0.93	0.26	

Table 2. Means and Standard Deviations of active transcranial Direct Current Stimulation (tDCS) and sham conditions on cortisol and state measures at different time points across the protocol. No items were reversed. Abbreviations: BSRI, Brief State Rumination Inventory; VAS, Visual Analogue Scale.

		Time (mean (SD))				
State measure	Condition	T1	T2	T3	T4	T5
Cortisol (nmol/l)	tDCS	4.16 (2.77)	3.80 (2.37)	3.60 (2.01)	3.52 (1.92)	2.98 (1.41)
	Sham	4.34 (2.39)	3.88 (2.30)	3.63 (1.86)	3.70 (2.30)	3.30 (2.65)
VAS fatigue	tDCS	3.45 (2.10)	3.33 (2.00)	3.11 (1.88)		2.74 (1.95)
	Sham	2.75 (1.97)	2.69 (2.03)	2.68 (1.82)		2.62 (1.88)
VAS vigor	tDCS	5.53 (1.87)	4.9 (2.24)	5.18 (1.66)		5.46 (1.94)
	Sham	5.36 (2.02)	4.69 (2.26)	4.94 (1.99)		4.88 (2.15)
VAS Anger	tDCS	0.7 (0.68)	2.06 (1.78)	0.97 (1.01)		0.67 (0.83)
	Sham	0.43 (0.74)	1.63 (1.85)	0.75 (1.16)		0.47 (0.61)
VAS Tension	tDCS	1.63 (1.61)	3.85 (2.44)	1.97 (1.53)		1.87 (2.02)
	Sham	1.45 (1.44)	3.37 (2.36)	1.84 (1.65)		1.22 (1.14)
VAS Depression	tDCS	0.69 (0.75)	1.05 (1.07)	0.65 (0.68)		0.59 (0.86)
	Sham	0.6 (1.20)	0.83 (1.22)	0.42 (0.61)		0.39 (0.40)
VAS cheerfulness	tDCS	5.87 (1.87)	4.45 (2.29)	5.10 (2.08)		5.30 (1.82)
	Sham	5.51 (2.28)	4.90 (1.99)	4.91 (2.47)		5.05 (2.61)
VAS Stress	tDCS	1.45 (1.15)	3.74 (2.10)	2.21 (1.94)		1.95 (2.28)
	Sham	2.06 (1.88)	3.52 (2.19)	1.46 (1.45)		1.42 (1.87)
BSRI	tDCS	131.71 (92.00)	205.66 (126.23)	145.367 (103.95)		155.47 (132.89)
	Sham	98.37 (94.71)	152.47 (128.34)	79.99 (84.90)		76.43 (64.67)

could influence the stress response and cortisol levels (see Table 1). For an overview of state variables during the protocol, we refer to Table 2. Participants in the sham condition were not able to tell which condition they were in, as 14 out of 30 guessed they had received active tDCS. In the active group however, there were only 5 of 30 participants who thought they had received sham tDCS. Nevertheless, when adding "perceived condition" as a covariate to the analyses, this did not affect the outcome to the extent that the results changed.

The repeated measures MANOVA revealed a significant effect of "time" ($F(21,25) = 5.60$; $p < .01$). Performing post-hoc univariate ANOVAs on the different VAS items (negative items were not reversed), we found significant effects of time on all items: fatigue ($F(3,110) = 3.67$; $p = .01$), vigor ($F(3,87) = 3.81$; $p = .01$), anger ($F(3,70) = 19.60$; $p < .01$), tension ($F(3,104) = 21,15$; $p < .01$), depression ($F(3,93) = 5.66$; $p < .01$), cheerfulness ($F(3,135) = 6.67$; $p < .01$) and stress ($F(3,117) = 17.80$; $p < .01$). Examining post-hoc pairwise comparisons, all mood items were significantly different on T_2 after the stress test compared to baseline, except for fatigue ($p = 1.00$), and depression ($p = .14$), which were not significantly affected by the stressor. We observed less vigorous and less excited, more angry, tense and stressed (all $p < .01$) feelings after the stress task (see Table 1 for means), indicating a successful psychological stress induction of the MIST. There was no significant main effect of "condition" ($F(7,39) = .44$; $p = .87$) or interaction between "condition" and "time" ($F(21,25) = .83$, $p = .67$), indicating that one session of active or sham tDCS did not affect mood. Conditions did not differ in mood at baseline ($p > .18$).

Main analyses

Hypothesis 1 – Cortisol. When looking at *AUCi* values calculated with all cortisol samples after stress (T_2, T_3, T_4, T_5), investigating the effects of stimulation on a neurobiological level, the first ANCOVA revealed no effect of stimulation condition on "*AUCi*" ($F(78,1) = 0.28$; $p = .60$; $\eta_p^2 = .22$)[1]. RRS had a significant effect on "*AUCi*", with high ruminators having lower *AUCi* scores ($F(1247,1) = 4.44$; $p = .04$; $\eta_p^2 = .82$). Covariate "Cortisol T_1" showed a trend for "*AUCi*"; subjects with high baseline stress tended to also show higher *AUCi* values after stress ($F(1058,1) = 3.78$; $p = .06$; $\eta_p^2 = .79$). The condition x RRS interaction effect was not significant ($F(22,1) = 0.08$; $p = .77$; $\eta_p^2 = .08$).

Hypothesis 2 & 3– EFT. Overall, 62% of future thoughts were coded as "specific". On the self-report scales, participants rated the level of detail comprising their thoughts at about 2.58 on a scale of 1–5. Emotional intensity was rated similarly at 2.54. There were no condition differences on perceived level of detail ($t(57) = .69$; $p = .49$) or emotional intensity ($t(57) = .72$; $p = .48$).

The GLMM accounted for 30% of the observed variance in episodic future thinking during the task ($R^2c = 0.30$). The model revealed no main effect of "condition" on EFT specificity, indicating that EFT is not generally affected by tDCS ($\chi^2_1 = 0.86$; $p = .35$). "*AUCi*" had a significant effect, showing more specific future thoughts for lower *AUCi* scores during the task ($\chi^2_1 = 4.65$; $p = .03$; see Figure 3B). Moreover, a significant interaction was observed between "condition" and "RRS" ($\chi^2_1 = 6.66$; $p = .01$; see Figure 3A). Post hoc tests showed higher EFT scores for subjects with higher trait rumination in the active tDCS condition ($z = 2.47$; $b = .66$; $p = .03$), while in the sham condition no such link was found ($z = -1.00$; $b = -0.19$; $p = .53$). Other main effects or interactions were non-significant ($\chi^2_1 < 0.74$; $p > .39$).

State rumination (BSRI)

Finally, we wanted to explore whether the effects of stimulation and rumination on "EFT" might manifest (partially) through a decrease in state rumination. The LMM accounted for 67% of the observed variance in state rumination ($R^2c = 0.67$). The model revealed a significant main effect of "condition" ($\chi^2_1 = 4.24$; $p = .04$), with generally higher BSRI scores for participants who received active tDCS versus sham. A significant effect of time then again reveals the impact of our stressor on state rumination ($\chi^2_3 = 46.94$; $p < .01$). While BSRI scores do not differ from one another in measures during baseline, after stimulation or at the end of the experiment (pairwise comparisons T_1, T_3, T_5; $t < 1.23$; $p > .93$), a significant increase of BSRI after stress was found (pairwise comparisons T_2 vs. T_1, T_3, T_5; $|t| > 6.12$, $p < .01$). In addition, we observed a significant effect of the covariate baseline BSRI ($\chi^2_1 = 136.44$; $p < .01$), where participants with higher baseline BSRI tended to show higher BSRI scores over all timepoints.[1]

Discussion

This study aimed to assess the effects of prefrontal tDCS neurostimulation on EFT performance in healthy subjects following a psychosocial stressor. Our findings show a relationship between the stress system and decreased specificity in EFT, in line with our assumptions. Higher cortisol levels during episodic future thinking led to a drop in performance on the EFT task. Moreover, our data revealed the potential of tDCS to improve EFT performance, irrespective of its effects on cortisol levels during the task. Active, but not sham tDCS enhanced EFT performance in function of trait rumination. Higher rumination scores led to higher EFT scores in the tDCS group, but not in the sham condition.

First, our results suggest that higher cortisol levels during episodic future thinking may impair the capacity to make concrete and specific future projections. While acute stress has previously been shown to debilitate performance on various functions depending upon episodic memory (Hidalgo et al., 2019), our study demonstrates for the first time that cortisol also affects the process of simulating episodic future events. Episodic future simulation might be more vulnerable to stress-related distortions than episodic memory, as it is thought to depend more upon the hippocampus' ability to link different elements of past experiences and reorganise them into a new coherent representation (Addis et al., 2007). Moreover, glucocorticoids primarily act through glucocorticoid receptors mineralocorticoid receptors, located primarily in the hippocampus (De Kloet et al., 1986; Van Eekelen et al., 1988). It would be of interest to compare the differential effects of acute stress on EFT and episodic memory retrieval in future research.

Secondly, the finding that tDCS could enhance specific episodic future thinking – in function of individual differences in rumination – offers a potential solution for stress-related EFT impairments. This observation is in accordance with former research, where increased activation to the mPFC as a result of tDCS was linked to an increase in memory performance in healthy older adults (Huo et al., 2020). Here, with the electrode placement over the DLPFC and OFC, the peak of electrical field strength lies in between the anode and the cathode, in fact targeting the mPFC (Baeken et al., 2017; De Witte et al., 2018; see also Figure 2). The current results indeed support the assumption that our tDCS intervention augmented activity in the mPFC, impacting EFT after being stressed. The fact that participants scoring high on trait rumination tend to benefit more from our intervention equally matches our expectations. As been discussed in previous research unveiling L-DLPFC-tDCS effects modulated by trait rumination (Vanderhasselt et al., 2017), high brooders compensate for intrusive negative thoughts by recruiting more brain activity to brain regions such as the DLPFC that downregulate activation of limbic regions related to the processing of negative information (Vanderhasselt, Baeken, Van Schuerbeek, Vanderhasselt, Baeken, et al., 2013). These differences in brain activity between high and low ruminators can differentially interact with non-invasive brain stimulation. Therefore it is important to take individual differences into account when optimising such treatments.

It could be argued – based on our current results – that the HPA-system is not crucial to consider in order to achieve effects of tDCS on EFT. Indeed, differently from what we hypothesised, we did not initially observe an effect from active tDCS on cortisol AUCi in the entire sample, and in line with this, we found no interaction effect between cortisol AUCi and stimulation condition to be predictive for EFT specificity. In stress-paradigms using cortisol, it is however worthwhile to also consider the cortisol responses to the stressor (MIST). Even though a lack of cortisol response to the stressor by no means indicates a lack of physiological stress in participants, it is possible that participants stressed to the point of an elevated cortisol secretion react differently to our intervention. Hence, we looked into the distinction between participants who responded to the stressor with a significant cortisol elevation, versus those who did not respond as such. Adding the distinction between responders and non-responders, active tDCS did show a faster decrease in cortisol AUCi after stress in the responder group and in function of trait rumination. As provided in the supplementary analyses, it also suggests that the negative effects of cortisol on EFT might be reversed by administering active tDCS stimulation, yet only in participants showing a stress-induced HPA-axis response. Here, performing this analysis on small sample of only 1/3 responders in each group, the results should be interpreted with caution. However, based on the medium to large effect sizes in these analyses – relatively similar to those for the entire sample – we want to argue that these analyses are still worthwhile to consider (see supplementary materials). In sum, this could imply that possible increases in brain activation in the left DLPFC and mPFC blunt the negative impact of cortisol on EFT in this

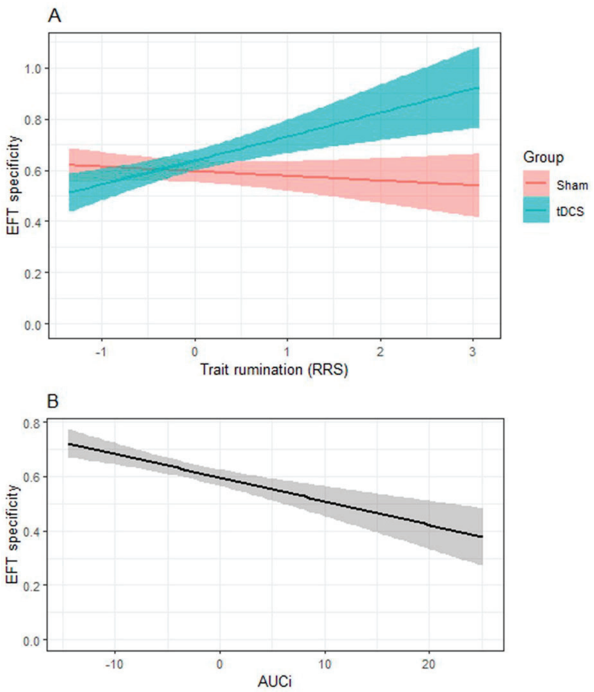

Figure 3. (A) Effects of transcranial Direct Current Stimulation (tDCS) on episodic future thinking (EFT) specificity in function of trait rumination (Ruminative Response Scale, RRS). Trait rumination values are scaled. (B) Effects of cortisol Area Under the Curve with respect to increase (*AUCi*) during the EFT task on EFT specificity. Cortisol values were logtransformed before calculation of *AUCi*.

subsample – at least partly by tDCS facilitating stress-recovery. As such, tDCS might show more effectiveness in individuals who are more sensitive to negative information and experiences.

Finally, and contrary to what we expected, our results indicate that high trait ruminators irrespective of tDCS exhibit lower cortisol AUCi values after stress (T_2, T_3, T_4, T_5) compared to participants with lower trait rumination scores. Although it has been established that high trait rumination can be linked to impaired emotion regulation and sustained stress (Rosenbaum et al., 2018), our results imply a more complex relationship between rumination and the stress system. Likewise, as for the association between rumination and stress, inconsistent results have been reported (for a review, see Zoccola & Dickerson, 2012), with one study equally showing blunted cortisol responses in reaction to a stressor for participants scoring high on depressive rumination (Zoccola et al., 2008). A recent study proposed the cortisol reactivity threshold model as an explanation for the contradictory findings on the relationship between stress reactivity and trait rumination (Vrshek-schallhorn et al., 2018). They argued that the difference between high and low ruminators in cortisol reactivity to a stressor is dependent on the level of severity of the stressor. They compared a non-stressful task to a moderately stressful TSST and a stressful TSST with negative evaluation, and found high ruminators to have a blunted cortisol response in the last (severe stressor) group, while low ruminators showed the highest cortisol reactivity under these conditions. In line with this, the diathesis-stress model assumes the adaptiveness of a cortisol response as a resource-mobilising hormone, and suggests that high internalising risk individuals might show relatively greater HPA activation to minor stressors, leading to greater behavioural activation. In turn, following major stressful life events, insufficient cortisol reactivity would lead to unadaptive behavioural responses. As such, high trait rumination can be seen as an at-risk factor for depression. In sum, the interaction between prefrontal stimulation and rumination seems relevant to the effects of stimulation, but this intricate relationship between rumination and both the stress system and prefrontal stimulation seems not that straightforward and demands further investigation combining stimulation with brain imaging.

Although this study has its strengths – e.g., tDCS to investigate causal involvement of certain brain regions while at the same time testing its therapeutic effectiveness, some limitations should be addressed. First, since this is the first study to assess the effects of stress and cortisol on EFT, the use of tDCS in our paradigm makes it difficult to examine the exact effects of stress on EFT, without involvement of stimulation or stimulation expectancy. Secondly, we only managed to invoke a significant HPA-stress reaction in one third of our sample (a recent review documented a cortisol non-responder rate between 47.5 and 65.0% based on 4 studies; Noack et al., 2019). Nevertheless, medium to large effect sizes even in responders allow us to still reliably consider these data. Moreover, due to the short delay between the stressor and the tDCS stimulation, it is possible that the peak of cortisol secretion was affected by tDCS. Another issue to consider is the timing of the EFT task versus the stressor in our protocol. As the EFT task was performed relatively late (more at the end of the recovery period and after stimulation) the effects of the stressor itself might have waned off; usually lasting approximately 60 minutes (Dedovic et al., 2005). Finally, it should be noted that we did not include a baseline measure of the EFT task, as we were reluctant to add a potentially stressful event before the onset of the stressor (which could contaminate the stress reaction), and decided to focus on the between subjects effects of tDCS versus sham stimulation. We can therefore not entirely exclude the possibility of random differences in EFT proficiency between sham and tDCS groups. However, the latter seems unlikely given the absence of a main effect of condition and the interaction with trait rumination.

Overall, our results demonstrate the adverse effects of stress on specificity in episodic future thoughts on the one hand, and on the other hand the effectiveness of active tDCS over the left DLPFC to restore or boost this cognitive function. Irrespective of its effects on cortisol but modulated by trait rumination, we found active, but not sham tDCS to enhance EFT performance. This integrative study is distinctive from the current literature because it is the first that brings together these two crucial vulnerabilities for depression in direct relation to a potential treatment – that could act on both cognitive and physiological aspects at the same time. Our results propose tDCS as a potential solution to help rehabilitate cortisol-induced EFT deficits through its ameliorating effects on EFT specificity, notwithstanding the lack of effects on the HPA-system in non-depressed healthy volunteers.

Note

1. It should be noted that the stress task provoked only a moder ate to low cortisol response and not all participants showed an increase in cortisol levels after the stress task. In this case it would be of interest to repeat the analyses including a variable distinguishing responders from nonresponders, to investigate whether active tDCS stimulation did have an attenuating effect on the cortisol response when the stress task triggered an HPA axis response to stress. All analyses including this dis tinction can be found in the supplementary materials, but results should be interpreted with caution due to low power and small sample size.

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