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Failure to Improve Verbal Fluency with Transcranial Direct Current Stimulation

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Abstract—Previous studies in healthy populations have provided equivocal evidence whether the application of anodal transcranial direct current stimulation (tDCS) over the left prefrontal cortex (PFC) can improve performance in verbal fluency tasks. In this double-blind, randomised within-participant study, we investigated whether anodal tDCS over the left PFC improves verbal fluency performance relative to sham tDCS. Forty eight healthy native German speakers performed two verbal fluency tasks after having received 20 min of anodal or sham tDCS over the left PFC. During stimulation, participants performed a picture naming task, which was expected to increase neuronal activity in the targeted region. We found no modulation of verbal fluency performance following anodal tDCS, with virtually identical overall scores across tDCS conditions. Furthermore, initiation time (i.e., time to produce the first correct utterance) was not affected by tDCS. As an unexpected finding, picture naming latencies were significantly longer during anodal compared to sham tDCS. Yet, changes in the naming task were not predictive of performance changes in the fluency task. Overall, the current study found no evidence that verbal fluency performance in healthy speakers could be improved by excitatory stimulation of the left PFC. We argue that previously observed positive effects could be false positives and should be interpreted with caution. The findings from the current study thus cast further doubt on the utility of tDCS in enhancing cognitive performance in the healthy (young) brain.

Key words: language production, left prefrontal cortex, non-invasive brain stimulation, semantic fluency, phonemic fluency.

INTRODUCTION

Verbal fluency is a key cognitive ability which is central to human communication and reflects both verbal and general executive control processing (Shao et al., 2014; Whiteside et al., 2016). To probe this function, speakers are usually asked to produce as many words as possible from a given category (semantic fluency) or starting with a given letter (phonemic fluency) within one minute, where the total number of correct lexical items produced reflects the verbal fluency score. The easy administration and straight-forward evaluation has made verbal fluency tasks a popular tool in measuring linguistic and cognitive function in healthy and clinical populations. On the cortical level, these tasks consistently elicit hemodynamic responses in left prefrontal regions, including precentral as well as middle and inferior frontal gyrus (Costafreda et al., 2006; Meinzer et al., 2009; Birn et al., 2010; Kircher et al., 2011; Wagner et al., 2014). Furthermore, higher grey matter density in the left presupplementary motor area has been associated with higher phonemic fluency performance (Grogan et al., 2009).

Transcranial direct current stimulation (tDCS) has been used to investigate whether actively modulating cortical excitability in specific cortical regions results in a performance increase in healthy volunteers (Flöel, 2012), with the prospect of using it as an adjunct therapy for patients suffering from post-stroke aphasia (Sebastian et al., 2016; Wortman-Jutt and Edwards, 2017). During tDCS, weak electric currents sent through two or more electrodes affixed to the scalp create an electric field in superficial cortical cells. In the motor domain, online anodal tDCS increases cortical excitability in the stimulated area, while cathodal tDCS results in a decrease (Nitsche and Paulus, 2000; Bikson et al., 2016). With respect to the after-effects of tDCS, studies in the primary motor system suggest that tDCS can produce transient changes in neuronal excitability, mediated by synaptic plasticity and outlasting the stimulation protocol by minutes up to hours (Bergmann and Hartwigsen, 2020). These changes are ascribed to long-term potentiation (LTP)-like and long-term depression (LTD)-like facilitation or inhibition of corticospinal excitability, depending on whether the anode or cathode overlays the primary motor

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Abbreviations: LTD, long-term depression; LTP, long-term potentiation; PFC, prefrontal cortex; tDCS, transcranial direct current stimulation.

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cortex (Nitsche and Paulus, 2000). At the neuronal level, such after-effects are expected to be driven by the activation of glutamate N-methyl-D-aspartate receptors that result in a higher postsynaptic calcium concentration (Nitsche and Paulus, 2000, 2011).

For non-motor regions, however, the dissociation of facilitation and inhibition seems to be less straightforward (Klaus and Schutter, 2018a), as anodal tDCS has also been shown to cause performance decreases, while cathodal tDCS can improve performance (Pope and Miall, 2012; Tremblay et al., 2014; Brückner and Kammer, 2017; Klaus and Schutter, 2018c). Combined with the accumulation of null effects observed during or following the application of tDCS (Vannorsdall et al., 2016; Westwood and Romani, 2018) and meta-analytic evidence finding no or very small effect sizes for language tasks in healthy volunteers and clinical populations (Otal et al., 2015; Price et al., 2015; Shah-Basak et al., 2016; Klaus and Schutter, 2018a; Elsner et al., 2019), there is an increasing need to experimentally scrutinize the method's potential to effectively modulate language performance, and, by extension, other cognitive functions.

One issue with the application of tDCS that complicates generalizability is that there are many experimental degrees of freedom as to how it is applied, and there is no consensus which parameters are most effective. Methodological aspects like stimulation intensity (between 0.75 and 2 mA), duration (between 10 and 30 min), and timing (online vs. offline) as well as electrode size and placement vary substantially between studies, and it is not clear what influence this heterogeneity has on the observed outcome (Bikson et al., 2010; Moliadze et al., 2010; López-Alonso et al., 2015; Saturnino et al., 2015; Cheeran et al., 2017; Mikkonen et al., 2020). Individual variability in the induced electrical field and the subsequent response further complicates things. Furthermore, although tDCS lends itself to a double-blind administration (i.e., neither the participant nor the experimenter know which stimulation condition is administered in a given session) to reduce implicit experimenter bias and participant expectations, to our knowledge only one published study which examined verbal fluency modulation actually made use of this technique (Ghanavati et al., 2019). Combined with typically low sample sizes, frequent between-participant designs, and non-transparent data collection, transcription, and analysis procedures, evidence for the efficacy of tDCS is equivocal and its potential clinical relevance remains questionable. Together, this provides a heterogeneous picture of the efficacy of tDCS in modulating verbal fluency performance as an exemplary cognitive function assessed in previous experimental work. The current study was set up as a conceptual replication study, with the aim to provide more definitive insights into the capability of tDCS to improve cognitive function in healthy participants. To achieve this, we applied a number of changes to previous protocols, which will be outlined in brief here and are described in more detail in the Methods section below.

The majority of previous verbal fluency studies tested performance changes *after* stimulation had ended (i.e., offline). This protocol seems intuitive, as the long term goal should be to establish whether plastic after-effects of tDCS are sufficient to modulate behavior. This means that *during* tDCS application (i.e., online), typically no task is administered (but see Wirth et al., 2011; Vannorsdall et al., 2012, for studies making use of an online task). However, it has been suggested that neuronal networks which are engaged in a concurrent task are preferentially selected by tDCS (Bikson and Rahman, 2013). We thus hypothesized that involving participants in a task which is expected to engage the targeted region during the application of tDCS would augment the neuronal effect, likely via gating mechanisms (Ziemann and Siebner, 2008). Put differently, simple task engagement might pre-activate the network for the modulatory tDCS effect and increase the efficiency of the stimulation protocol. As noted above, there is no simple mapping from cortical excitability to cognitive performance for anodal and cathodal tDCS. Yet, it is well conceivable that a net increase in excitability via anodal tDCS in the network mediating task-relevant computations augments task-related signal and may thus boost the signal-to-noise ratio (Bergmann and Hartwigsen, 2020). Consequently, the combination of a simple task and online stimulation might augment the after-effects of anodal tDCS. Indeed, Pisoni et al. (2018) demonstrated increased cortical excitability in the stimulated area when anodal tDCS over the left PFC was applied during a verbal fluency task. Modulation of cortical excitability was positively correlated with performance enhancement, suggesting that anodal tDCS may have a specific effect on those task-related networks active during stimulation. Consequently, we reasoned that pre-activating the network with a simple naming task should enhance the beneficial after-effect of anodal tDCS on verbal fluency.

In a similar vein, Nozari et al. (2014) showed that administering a low-demand task during cathodal tDCS over the left PFC *improved* performance in a subsequent flanker task, while a high-demand task in combination with cathodal stimulation *impaired* offline performance. In another study, participants performed a lexical decision and a sentence comprehension task during and directly after anodal tDCS over the left PFC (Malyutina et al., 2018). Here, reaction times and accuracy were not affected in either of these tasks, and neither online nor offline. Interestingly, though, for the presumably more difficult sentence comprehension task, participants were descriptively slower during anodal compared to sham tDCS, and this effect doubled after stimulation had ended. In the current study, we chose to engage participants in a picture naming task of unpracticed items for the majority of the stimulation duration, with the assumption that this would cause sufficient recruitment of left prefrontal regions to amplify the subsequent effect on verbal fluency performance.

The electrode montage is a decisive factor in establishing whether the hypothesized cortical region is targeted effectively. The majority of previous studies

used a montage in which the ‘‘active” electrode is placed over the targeted area and the return electrode over the right supraorbital region (cf. Fertonani et al., 2010, 2014; Wirth et al., 2011; Vannorsdall et al., 2012; Klaus and Schutter, 2018c, for alternative placements of the return electrode on the vertex or the right shoulder). Electric field simulations, however, have shown that this montage may not be successful in eliciting the strongest electric fields in the desired area (Klaus and Schutter, 2018b), calling subsequent conclusions about the involvement of a specific cortical area into question. To overcome this caveat, we used a modified montage which placed the anodal electrode slightly posterior to the prefrontal cortex (PFC) (Rampersad et al., 2014) and the return electrode over the participant's forehead. Furthermore, the surface area of the return electrode was four times the size of the active electrode, decreasing its current density and, ultimately, its influence on the cortical tissue. This should allow for a more targeted application of tDCS, with the result that the peak electric fields are located in the left PFC.

Finally, insufficient statistical power is an issue in many psychological and neuroscientific studies (Button et al., 2013; Turner et al., 2018), and tDCS studies pose no exception. Results from previous work are often based on small sample sizes as low as eight participants, which increase the chance of false positives, or between-participant designs which do not allow for a direct comparison of different tDCS conditions within individuals. The current study provides, to the best of our knowledge, the largest within-participant examination of tDCS effects on verbal fluency performance to date. Additionally, to increase transparency of analytical decisions, the current study was preregistered at the Open Science Framework (https://osf.io/4qmxs/), and analyses not planned prior to data collection are marked as exploratory in the Results section.

EXPERIMENTAL PROCEDURES

Participants

Using the *pwr* package (Champely, 2017) in R we calculated the required sample size for our relevant contrast (i.e., the effect of tDCS on verbal fluency performance). For a simple *t* test comparison (i.e., anodal vs. sham tDCS), to achieve power of 0.90 at alpha 0.05 with a medium effect size ($d = 0.5$), 44 participants were required. Counterbalancing all experimental factors required a multiple of 8, so we increased our sample size to 48 participants (26 female, mean age: 27.06 years, $SD = 3.72$, range = 19–35). One participant was replaced due to a technical failure in the picture naming task. Participants were recruited from the research participant database of the Max Planck Institute for Human Cognitive and Brain Sciences via phone calls and emails and were paid € 20 for their participation. All were native German speakers, right-handed, and eligible for participating in tDCS studies (i.e., no history of neurological or psychiatric illnesses, no current pregnancy, no drug or alcohol addiction, no skin diseases or allergies, no metallic objects in their heads or any type of stimulator in their body, and no family history of epilepsy). Before the first experimental session, participants were informed about the general procedure of the study and gave written informed consent. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the local ethics committee at the Medical Faculty of the University of Leipzig (115-17-ek).

Design

Real and sham stimulation were randomly assigned across two experimental sessions, with half of the participants receiving active tDCS in the first session and sham tDCS in the second session, and the other half sham tDCS in the first session and active tDCS in the second session. The order of the fluency tasks was counterbalanced across participants and kept constant for both experimental sessions.

Tasks

All participants completed an overt picture naming task during stimulation and a verbal fluency task immediately afterwards. Fig. 1 illustrates two trials per task.

For the verbal fluency tasks (task of interest), two different types (phonemic vs. categorical) with varying difficulty were presented. In both tasks, we used four single items and two alternating items, which were split in two experimental lists (six trials per list), the order of which was counterbalanced across participants and stimulation sessions. For the single items, participants were asked to name as many words as possible starting with a given letter (S, B, K, M) or belonging to a given semantic category (means of transportation, buildings, office supplies, metals), respectively. The alternating categories required participants to alternately produce words starting with two given letters (G/R, H/T), or belonging to two given semantic categories (clothes/flowers, sports/fruit), respectively. Participants received written instructions on the screen and could become accustomed to the procedure by one practice trial per fluency task. For each trial, they had one minute to respond. During the last five seconds, the presented word turned red to indicate that time was almost up. Verbal responses were recorded with a microphone connected to the participant laptop and transcribed offline.

For the picture naming task, 496 pictures from MultiPic (Duñabeitia et al., 2018) were used as visual stimuli. They were presented at the center of the screen, and participants were asked to name them as quickly as possible using a single German noun. The items were split in two lists, with one presented during the first and the other during the second session to avoid repetition. Care was taken that target words did not belong to the semantic categories used in the upcoming categorical fluency task and did not start with one of the letters used in the upcoming phonemic fluency task. Every participant named the items in a different pseudo-randomized order, incorporating the constraints that items belonging to the same semantic category were separated by at least five intervening trials, and that items starting with the same phoneme were separated by at least three intervening

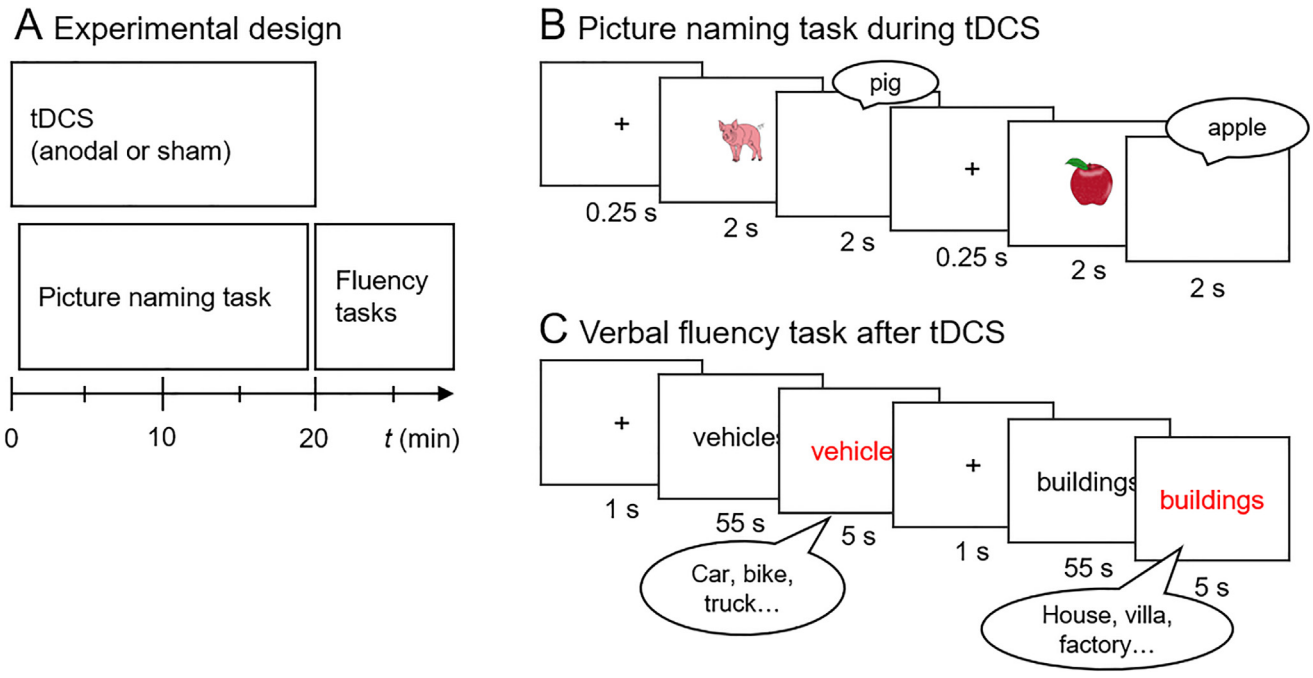

Fig. 1. Illustration of experimental design and two trials per experimental task.

trials. Randomization was implemented using Mix (Van Casteren and Davis, 2006). Verbal responses were recorded with a microphone connected to the participant laptop and offline transcribed and annotated using Praat (Boersma and Weenink, 2018).

tDCS

Stimulation was delivered in a randomized double-blind fashion by a battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) via two electrodes (anode: 5 x 5 cm, current density on skin: 0.08 mA/cm^2; cathode: 10 × 10 cm, current density on skin: 0.02 mA/cm^2). The electrodes were placed in saline-soaked sponges and attached to the head with two elastic bands ensuring maximum contact between the electrodes and the skin. The anode was positioned approximately between FC5 and C5 and the cathode over the centre of the forehead. The electric field was modeled using SimNIBS version 2.0 (Windhoff et al., 2013; Thielscher et al., 2015) on the reconstructed head model provided with the software. The anisotropic finite element model included six compartments and the standard conductivity values (Wagner et al., 2004; Opitz et al., 2015) were used (white matter: σ = 0.126 S/m; grey matter: σ = 0.275 S/m; cerebrospinal fluid: σ = 1.654 S/m; bone: σ = 0.010 S/m; scalp: σ = 0.465 S/m; eye region: σ = 0.250 S/m). The two rubber electrodes (σ = 29.4 S/m) with the cable connectors and electrode gel (σ = 1.000 S/m) were modelled in 3 cm thick sponges. Fig. 2 provides an illustration of the montage and simulated electric field.

After a 30 s ramp-up, stimulation was administered at 2 mA for 20 min, followed by a 30 s ramp-down. Sham tDCS was identical to the active tDCS condition, except that the stimulator stopped delivering tDCS after the ramp-up phase. Experimenter blinding was achieved using a pre-assigned code entered into the DC stimulator at the beginning of each session. Assignment of the respective stimulation conditions was determined by a researcher not involved in data collection, and blinding was only broken once data collection had been completed and recordings had been annotated.

To investigate the efficacy of participant blinding, participants were asked to fill in a questionnaire indicating their perception of the stimulation after each experimental session.

Data analysis

For the verbal fluency performance, a fixed-effect two-way within-participant repeated-measures ANOVA with the dependent variable "performance" (i.e., number of correct words produced per trial) and the independent variables tDCS (real vs. sham) and task (phonemic vs. categorical) was performed. All data points were included in the analysis, and no outlier correction procedure was applied.

For the picture naming task, we used generalised linear mixed effects models and fitted a Gamma distribution with an identity link to account for the non-normal distribution of the naming latency data. The model included the sum-coded fixed effect tDCS condition (real vs. sham) as well as random intercepts for participants and items and random slopes for tDCS condition. Naming latencies deviating from a participant's mean (aggregated by tDCS condition) by more than three standard deviations were treated as outliers and removed from the analyses (289 observations, 1.2%). Furthermore, trials in which an incorrect, a corrected, or no response was given were

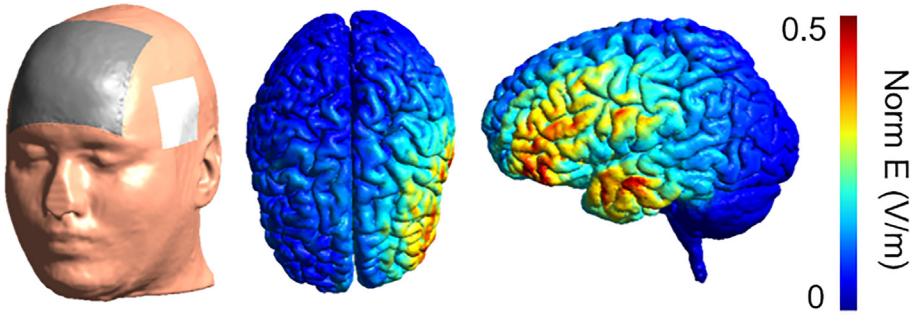

Fig. 2. Electrode montage and corresponding electric field simulation used in the current study. The maximum values correspond to the 99.9th percentile of the electric field, derived from the grey matter volume compartment.

removed from the naming latency analysis (3108 observations, 13.1%).

RESULTS

Raw data associated with the current study are available at https://tinyurl.com/tdcs-fluency.

Preregistered analyses

Verbal fluency. Fig. 3 illustrates averaged performance of individual participants separated by stimulation condition and task. Following sham tDCS, participants produced 17.02 words (SD = 4.05) in the phonemic task and 13.56 words (SD = 4.64) in the semantic task. Following anodal tDCS, participants produced 17.11 words (SD = 3.99) in the phonemic task and 13.38 words (SD = 4.69) in the semantic task. Overall, more words were produced in the phonemic compared to the semantic task ($F_{1,47}$ = 101.74, p < 0.0001, η^2_G = 0.299). However, there were no differences in the number of words produced per tDCS condition ($F_{1,47}$ = 0.03, p = 0.859, η^2_G < 0.001). There was no significant interaction between tDCS and task ($F_{1,47}$ = 0.38, p = 0.543, η^2_G < 0.001). To account for the non-normal distribution of the dependent variable (W = 0.970, p < 0.001) despite equal variances across stimulation conditions ($F_{95,95}$ = 1.08, p = 0.705), we additionally performed a Wilcoxon signed-rank test to investigate the effect of tDCS collapsed over tasks. Unsurprisingly, this also did not reveal a significant difference between anodal and sham tDCS (z = −0.85, p = 0.445).

Picture naming. Fig. 4 displays the distribution of the naming latencies for all 48 participants by tDCS condition. As expected, naming latencies were not normally distributed. A generalized linear mixed model showed that naming latencies were significantly slower when participants received anodal (M = 972 ms, SD = 272) as opposed to sham tDCS (M = 966 ms, SD = 264; ß = 5.85, SE = 2.20, z = 2.66, p < 0.008).

Exploratory analyses

Verbal fluency. Task difficulty. Because we used two different task difficulty levels (i.e., single-cue and alternating naming), we additionally explored whether this would uncover an effect of tDCS by adding the two-level within-participant factor task difficulty to the ANOVA. However, this merely revealed, again, a main effect of task ($F_{1,47}$ = 80.97, p < 0.0001, η^2_G = 0.179), a main effect of task difficulty ($F_{1,47}$ = 57.00, p < 0.0001, η^2_G = 0.094), and an interaction of task and task difficulty ($F_{1,47}$ = 41.02, p < 0.0001, η^2_G = 0.053). Breaking down the interaction revealed that participants did not differ between the easy and hard condition in the phonemic task (t_{95} = −1.50, p = 0.137), whereas they produced significantly more words in the hard compared to the easy condition in the categorical task (t_{96} = −10.00, p < 0.0001). We will return to this discrepancy in the General Discussion. Crucially, there was no effect of tDCS on fluency performance as a function

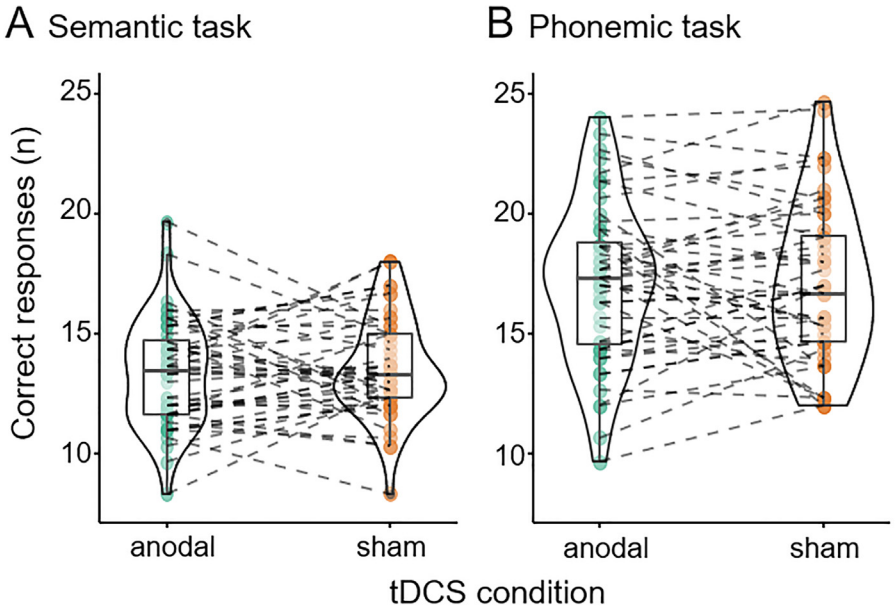

Fig. 3. Mean overall and individual number of words produced in the fluency task, broken down by task and tDCS condition. Please note the different scale of the *y*-axis for the two panels. Plots were created with the *ggstatsplot* package in R (Patil, 2018).

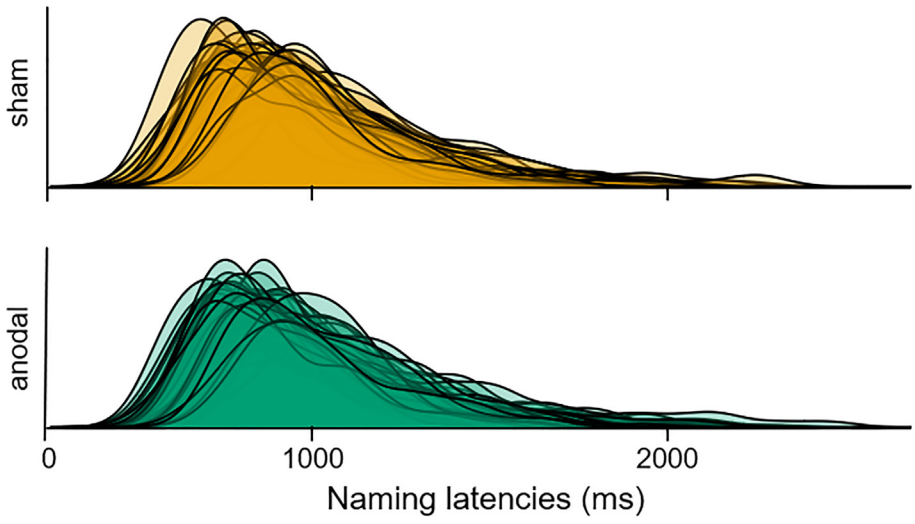

Fig. 4. Distribution of raw naming latencies (in ms) in the picture naming task, executed during administration of tDCS, broken down by tDCS condition and participant.

of task difficulty (for all model terms including tDCS as a factor, Fs < 1).

Session effects. To investigate whether verbal fluency performance differed across sessions, potentially modulated by stimulation condition, we performed an additional ANOVA on total number of words produced including the within-participant factors tDCS and task, as well as the covariate session (first vs. second). However, this only revealed, again, a main effect of task ($F_{1,47}$ = 101.74, p < 0.0001, η^2_G = 0.326), but no main effect of tDCS, or interaction with task (ps > 0.543).

Initiation times. We further investigated whether there would be a systematic effect of tDCS on the speed with which the first item of a trial was produced. However, an ANOVA with the dependent variable onset naming latency and the two within-participant factors task and tDCS only revealed, once more, a main effect of task ($F_{1,47}$ = 37.30, p < 0.0001, η^2_G = 0.115), with initiation times for the phonemic task being significantly shorter than for the categorical task (phonemic: M = 1521 ms, SD = 748; categorical: M = 2168 ms, SD = 1037). Neither the main effect of tDCS nor the interaction with task were significant (ps > 0.463).

Picture naming. Error rates. Aside from the naming latencies, we also investigated whether tDCS had an effect on the frequency of wrong, corrected, or missing responses. On average, participants made 12.8% errors (SD = 5.1) following anodal and 13.3% errors (SD = 5.0) following sham tDCS. We fitted a logistic linear mixed effects model with a binomial outcome to the raw data, adding the fixed effect tDCS, by-participant and by-item intercepts, and a by-participant slope for tDCS. This model revealed no significant effect of tDCS on error rates ($ß$ = −0.04, SE = 0.02, z = −1.60, p = 0.109).

Session effects. To further examine the unexpected interference effect of anodal tDCS on picture naming latencies, we investigated whether this might have been driven by a session effect. We therefore ran another generalised linear mixed effects model in which we added the sum-coded fixed effect session (first vs. second) while keeping the rest of the model identical to that reported above. Overall, participants were slower in the second compared to the first session (session 1: M = 954 ms, SD = 260; session 2: M = 984 ms, SD = 275; main effect of session: $ß$ = −14.52, SE = 2.40, z = −6.07, p < 0.0001). Crucially, however, session and tDCS did not interact ($ß$ = 3.43, SE = 2.57, z = 1.33, p = 0.182), suggesting that the main effect of tDCS we observed was not driven by a disproportionate influence of the order in which participants received tDCS across the two experimental sessions. Furthermore, when only looking at the first session (i.e., treating tDCS as a between-participant factor), the inhibitory effect remained ($ß$ = 6.45, SE = 2.92, z = 2.21, p = 0.027).

Quantile analysis of naming latencies. To explore the possibility that the inhibitory effect of anodal tDCS might have been more pronounced at the upper ends of the distribution (see Fig. 4), we binned all data points in five separate quantiles, leaving between 4043 and 4097 data points per quantile. We ran a generalised linear mixed effects model including the fixed effects tDCS (anodal vs. sham) and quantile (1 through 5, first quantile set as reference level), by-participant and by-item intercepts as well as by-participant slope for tDCS. Pairwise contrasts for each quantile using the *emmeans* package (Lenth, 2019) revealed significant differences between anodal and sham tDCS in the fourth and fifth quantile (Q4: $ß$ = 8.76, SE = 3.07, z = 2.86, p < 0.004; Q5: $ß$ = 16.20, SE = 3.52, z = 4.60, p < 0.0001), but not in the other quantiles (ps > 0.109). Overall, this suggests that anodal tDCS interfered with picture naming in trials which were particularly difficult for participants.

Correlation between online and offline effects. Finally, we investigated whether individual susceptibility to tDCS, or variation in the participant-specific effect (either towards facilitation or interference from anodal tDCS) during the naming task (i.e., the online effect) could predict the potential modulation in verbal fluency performance (i.e., the offline effect). To this end, we correlated the participant-specific beta estimates of the generalized linear mixed model of the naming task with the task change in the verbal fluency task (i.e., words produced after anodal tDCS – words produced after sham tDCS). This analysis did not reveal a significant

relationship between the magnitude of the online and offline tDCS effects ($r = 0.011$, $p = 0.938$).

Tolerability and participant blinding

After each session, participants filled in a questionnaire investigating different sensations (burning, fatigue, itching, metallic taste, pain, pinching, warmth) on a scale of 0 (not at all) to 4 (very strongly) at the end of each session. Furthermore, after the second session they were asked to guess during which session they had received the active stimulation.

All participants tolerated the stimulation well and only some of them reported a slight twitch underneath the electrodes, particularly during the ramp-up phase. Results from the sensation questionnaire indicated no significant differences between the stimulation conditions (all ps > 0.139, see Fig. 5). When asked to guess which stimulation they received in each session, 15 out of 48 participants were unsure. However, out of the remaining 33 participants, 27 guessed their respective stimulation order correctly ($X^2 = 13.58$, $p = 0.001$).

DISCUSSION

The goal of the present study was to investigate the modulatory effect of anodal tDCS over the left PFC on verbal fluency performance. In our preregistered analyses, we found no evidence for performance modulation induced by anodal tDCS, as has been reported in previous studies with healthy speakers (Iyer et al., 2005; Cattaneo et al., 2011; Meinzer et al., 2012; Ghanavati et al., 2019) and aphasic patients (Pestalozzi et al., 2018). Instead, the current study joins the ranks of previous work reporting null effects of anodal tDCS on verbal fluency performance (Lee et al., 2013; Vannorsdall et al., 2016; Westwood and Romani, 2018). Exploratory analyses further ruled out potential influences of session and task difficulty. It needs to be noted, however, that this conclusion is based on a single session of applying tDCS over the left PFC and does not speak to the potential to modulate behavior if applied across multiple sessions. Furthermore, because we restricted our sample to healthy young adults we cannot draw any inferences on the effect of tDCS in either older or clinical populations.

Due to the low spatial resolution of regular two-electrode tDCS montages, we likely also induced neuronal excitation in anterior portions of the left temporal lobe (see simulation results in Fig. 2). However, it is unlikely that this obstructed the null results we observed. Previous studies targeting left temporal regions with anodal tDCS also failed to find significant modulations in verbal fluency performance (Penolazzi et al., 2013; Binney et al., 2018), so if anything, anterior temporal lobe excitation provided an additional control that anodal tDCS was not able to modulate performance in our healthy participant sample.

A difference to previous studies is that for the single-category trials in the categorical fluency task, we used relatively difficult categories, whereas for the two-category trials, standard categories were used. We did this on purpose, assuming that for single-category trials, healthy participants might perform at ceiling in the sham condition already. By contrast, we assumed that on two-category trials, the need to switch would incur higher cognitive demands. The fact that we did not observe modulation by tDCS in any of these trials shows that neither retrieval of more difficult lexical items nor switch abilities were affected by the anodal stimulation. It does, however, explain why our sample, on average, performed better in the categorical compared to the phonemic fluency task, which is typically not found in the literature. Furthermore, the fact that performance on two-category trials was higher than on single-category trials in the current study suggests that switching between easy categories is less demanding than retrieving elements from more difficult categories, even in the absence of a switch demand. Arguably, this could have been caused by a ceiling effect in these easy categories, precluding a potential modulation by tDCS. A future study could therefore investigate whether using more difficult categories in two-category trials imposes higher cognitive demand, which might increase susceptibility to tDCS effects.

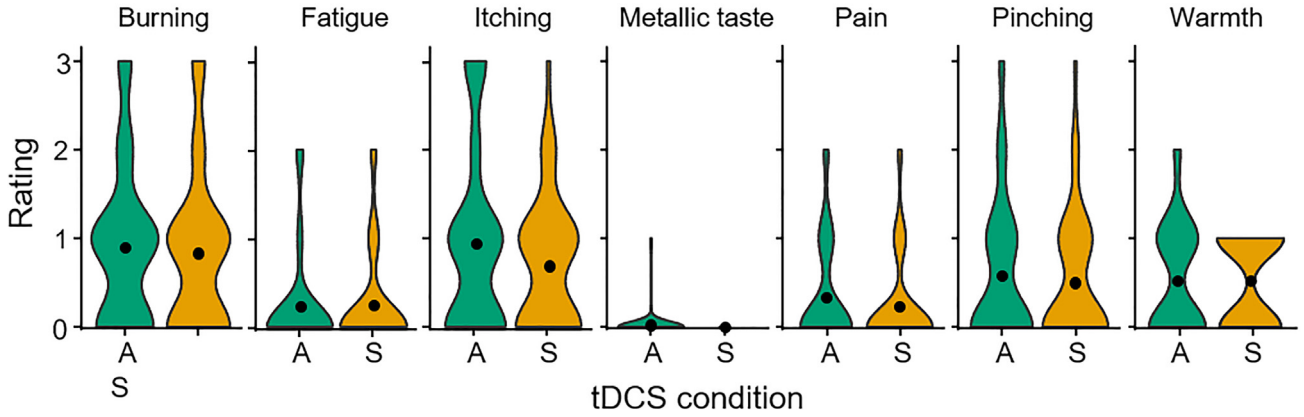

Fig. 5. Mean ratings of sensation questionnaire administered after each experimental session. A = anodal tDCS; S = sham tDCS.

One might argue that we did not observe modulation of verbal fluency performance because the task carried out throughout stimulation was not difficult enough, thus not providing enough baseline involvement of the targeted cortical region. However, given that participants were not familiarized with the pictures prior to the task, we believe that this imposed sufficient demand, as reflected by relatively long naming latencies (means around 1000 ms) and high error rates (13%). Nevertheless, it would be worthwhile to explore whether a task imposing even higher cognitive demands might affect the offline effect differently.

Notably, we combined anodal stimulation of the left PFC with a picture naming task to pre-activate activity in this area and thus enhance the efficacy of tDCS. As an unexpected finding in the preregistered analyses, anodal online tDCS significantly *increased* picture naming latencies relative to sham stimulation. Exploratory analyses showed that this increase seems to have been driven by the most difficult trials and was not affected by stimulation order, and there was no modulation of error rates. Yet, there was no significant after-effect of anodal tDCS on verbal fluency performance. Aside from a true null effect reflecting no modulation of verbal fluency by a single session of anodal tDCS, an alternative explanation for the absence of an offline effect might be related to mechanisms of homeostatic metaplasticity caused by the task-induced pre-activation of the targeted region. Homeostatic metaplasticity has been demonstrated in the motor system, with facilitatory effects of anodal tDCS during stimulation switching towards behavioral inhibition after the end of the stimulation period (Lang et al., 2003; Murakami et al., 2012). Yet, it remains unclear how the execution of a different speech task in combination with anodal tDCS may have affected processing of the task of interest in our study. While it is in principle possible that homeostatic metaplasticity prevented any effects on the second task, we believe that this explanation is unlikely to explain our null findings for the following reasons. First, we used different tasks during and after stimulation. While both tasks should engage the left PFC, their specific cognitive and linguistic demands were different and our task of interest further included a variation in complexity, which precludes a mere null effect based on task repetition. Secondly, a previous study demonstrated that anodal tDCS over left posterior temporal cortex did not significantly affect picture naming during stimulation but significantly facilitated naming latencies immediately after stimulation end (Sparing et al., 2008). While that study was relatively underpowered, there was no evidence for homeostatic metaplasticity induced by repeated task applications. Similarly, Nozari and colleagues (Nozari et al., 2014) reported significant disruption of task performance in a flanker task after cathodal tDCS over the left PFC had been combined with a different task during stimulation, which again does not point towards strong influences of homeostatic metaplasticity in the second task. Finally, if homeostatic metaplasticity reversed the effect observed during stimulation in the task following the intervention, we would still expect a facilitation of verbal fluency, which is not consistent with our findings. Consequently, we think that our results are more likely to reflect a true null effect that is most likely explained by insufficient modulation of task-related activity.

Still, the observed (numerically small) paradoxical inhibition of online tDCS on picture naming latencies observed in our study is difficult to explain. Previous online studies in the speech domain either reported null effects of anodal tDCS in different speech production tasks or behavioral facilitation (Cattaneo et al., 2011; Wirth et al., 2011; Meinzer et al., 2016). Note that some studies also observed paradoxical improvements of cognitive functions during or after cathodal tDCS (Chrysikou et al., 2013; Brückner and Kammer, 2017; Friedrich and Beste, 2018; Klaus and Schutter, 2018c). Yet, to the best of our knowledge, task-induced impairments under anodal stimulation have only been reported in one study that found a stronger semantic interference effect for semantically related pictures after anodal tDCS of the left middle temporal cortex (Pisoni et al., 2012). Since the observed delay in response latencies during anodal tDCS in our study was driven by the most difficult trials, it is conceivable that a potential increase in neural activity induced by anodal tDCS selectively interfered with task processing when task demands increased. Consequently, instead of the expected boost of the signal-to-noise ratio, anodal tDCS may have induced noise in the stimulated area, which interfered with the most difficult trials. This supports the notion of a strong interaction between the current task-induced brain state and the direction of the effect of a given non-invasive brain stimulation protocol, which was previously suggested as an explanation for paradoxical effects of non-invasive brain stimulation (Miniussi et al., 2013; Silvanto and Cattaneo, 2017).

Another finding emerging from the exploratory analyses is that although participants' self-reports of perceived sensations during both experimental sessions did not differ from each other, they guessed the correct stimulation order more often than what would be expected by chance. Thus, the current study adds to previous evidence calling into question the reliability of effective participant blinding in tDCS studies (Greinacher et al., 2019; Turi et al., 2019). Importantly, we only assessed perceived sensations at the very end of each experimental session as opposed to several time points during the administration of tDCS. This may explain the overall non-differences reported between anodal and sham sessions, as some kind of habituation may have taken place when active tDCS was administered. It is, however, possible, that part of the slowing during picture naming may have been caused by the fact that participants were distracted by the ongoing, potentially uncomfortable sensations. However, we find it unlikely that potential differences in sensation alone caused the increase in naming latencies during anodal tDCS compared to sham. In a previous study (Klaus and Schutter, 2018c), we observed task-specific effects of cathodal tDCS over the left prefrontal cortex. Participants performed a language production, comprehension, and flanker task during stimulation. Active tDCS led to *increased* reaction times in the flanker and language

comprehension, but *shorter* naming latencies in the language production task. If only the noxious sensations of the stimulation affected performance, we should have seen a performance decrement across all three tasks. Nevertheless, confounds caused by adverse sensations should be taken into account in future studies. Alternatively, modified sham protocols, as have been validated for high-definition tDCS (Garnett and Den Ouden, 2015; Neri et al., 2020), may provide a more similar comparison of active and sham conditions.

In conclusion, the current study found no evidence that a single session of anodal tDCS to the left PFC improves verbal fluency performance in healthy volunteers. It thus challenges findings from previous studies that did report such a modulation, and suggests that further modifications to the experimental protocol are needed to reliably modulate higher cognitive functions.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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