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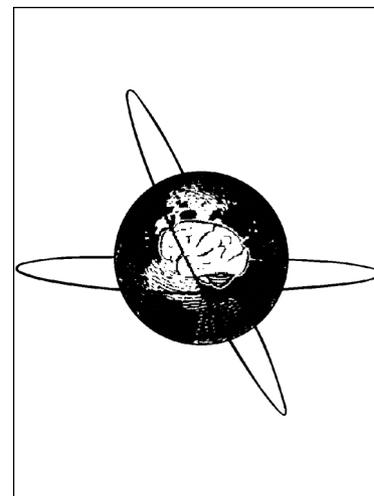
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Cathodal tDCS improves task performance in participants high in Coldheartedness

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Highlights

- First investigation of tDCS effects in relation to psychopathic traits.
- Anodal and cathodal tDCS to right dlPFC modulate response inhibition in the same manner.
- Positive relationship between cathodal tDCS at highest task difficulty level & Coldheartedness trait.

Abbreviations

Dorsolateral prefrontal cortex (dlPFC), parametric Go/No-go task (PGNG), transcranial direct current stimulation (tDCS), percentage accuracy target trials (PCTT), percentage accuracy inhibitory trials (PCIT), Analysis of Variance (ANOVA), excitation/inhibition (E/I), gamma-aminobutyric acid (GABA), False Discovery Rate (FDR).

Abstract

Objective

It is investigated whether personality-related inter-individual differences modulate tDCS effects on response inhibition. Psychopathic personality traits have been associated with a reduced ability to inhibit prepotent responses and as such it is likely that these traits may modulate the effect tDCS has on response inhibition. This study represents the first investigation into the effect of psychopathic traits on tDCS effects in the context of response inhibition, and based on previous research, the psychopathic traits Blame Externalization and Coldheartedness were elected as potential candidates for modulating tDCS effects to right dorsolateral prefrontal cortex.

Methods

Eighteen healthy participants underwent tDCS stimulation (sham, anodal, cathodal) before completing a response inhibition task, the parametric Go/No-go task. This task measures response inhibition under conditions of low and high cognitive load. TDCS stimulation was applied to F4 (international 10-20 system), corresponding to right dorsolateral prefrontal cortex, for 20 minutes with an intensity of 1.5 mA. Analysis of covariance was performed to assess how changes in response inhibition performance across difficulty level and stimulation condition were related to individual differences in psychopathy scores as measured via the Psychopathic Personality Inventory-Revised questionnaire.

Results

A positive relationship was found between greater scores on the Psychopathic Personality Inventory-Revised subscale of Coldheartedness and improvement in Go/No-go task performance after application of cathodal tDCS. This effect specifically related to the high load condition of the Go/No-go task.

Conclusion

The psychopathic personality trait Coldheartedness may represent an imbalance of excitatory and inhibitory inputs to dlPFC. Improvement in functioning on inhibitory tasks after cathodal tDCS may be a result of a shift of excitatory glutamate levels to a more optimum level.

Significance

The current results demonstrate the utility of tDCS as a tool to assess how differences in cortical responsivity are associated with specific personality traits. Additionally, this study represents the first investigation into the influence of psychopathic traits on tDCS effects on dlPFC, and we observed beneficial changes in response inhibition as a result of, especially, cathodal stimulation in participants scoring high on Coldheartedness.

Keywords: parametric Go/No-go task; Psychopathic Personality Inventory-Revised; transcranial direct current stimulation; response inhibition.

1. Introduction

Response inhibition, the inhibition of prepotent responses, is a central characteristic of impulsivity, a personality trait relating to action without forethought and consideration of potential consequences (Eysenck, 1993; Keilp et al., 2005; Reynolds et al., 2006; Sharma et al., 2013; Sharma et al., 2014). Investigating the processes and neural architecture that give rise to optimal inhibitory ability is crucial for improving our current understanding of those expressing 'normal' levels of impulsivity as well as those with elevated or clinically relevant levels of impulsivity (Bari and Robbins, 2013; Bornovalova et al., 2005; Dawe and Loxton, 2004; DeYoung, 2010; Najt et al., 2007; Zermatten et al., 2005). Psychopathy, in its clinical as well as subclinical manifestations, is related to heightened levels of impulsivity (Hare, 2003; Lilienfeld and Andrews, 1996; Lilienfeld and Fowler, 2005) and a means to investigate the effects of heightened levels of impulsivity on response inhibition.

Experimentally, response inhibition is commonly assessed using tasks where accruing sensory input or continued processing of static input may signal a requirement to withhold an automatic response (i.e., Stop Signal and Go/No-go tasks). In the Stop Signal Task (Logan, 1994; Logan et al., 1984; Schachar and Logan, 1990), response inhibition is externally driven by a post-stimulus event signaling the requirement to cancel an ongoing response process, whereas response inhibition in the Go/No-go task is internally driven by an *a priori* rule to refrain from responding to specific targets (Eagle et al., 2008; Rubia et al., 2001).

Despite the overall utility and popularity of the Go/No-go task, populations defined by their expression of elevated impulsivity levels such as those diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD) or bipolar disorder, as well as subclinical psychopaths (American Psychiatric Association, 2013; Lilienfeld and

Andrews, 1996; Lilienfeld and Widows, 2005), fail to exhibit significant behavioural response inhibition deficits as measured in this task, even when neurophysiological differences are apparent (e.g. Altshuler et al., 2005; Carlson and Thai, 2010; Elliott et al., 2004; Kim and Jung, 2014; Smith et al., 2004). It seems likely that the simplicity of this task, in which one stimulus is always associated with a Go response and another always requires withholding of a response (Langenecker et al., 2007a; Plewnia et al., 2013), does not sufficiently tax inhibitory requirements of daily life and may thus obscure individual differences due to generally high accuracy levels.

A modification to the Go/No-go task, the parametric Go/No-go (PGNG) task (Langenecker et al., 2007a), systematically varies the complexity of the No-go signal and has uncovered specific load-dependent deficits in highly impulsive patient groups as well as in healthy participants expressing elevated levels of impulsivity (Langenecker et al., 2010; Ryan et al., 2012; Weidacker et al., 2016). A recent report found that specific aspects of the psychopathic personality, as measured with the Psychopathic Personality Inventory-Revised (PPI-R; Lilienfeld and Andrews, 1996; Lilienfeld and Widows, 2005) were distinctively related to performance in the PGNG task (Weidacker et al., 2016). The PPI-R measures psychopathic traits in non-criminal populations in terms of three dimensions, Fearless Dominance, Impulsive Antisociality, and Coldheartedness. Whereas the first two of these dimensions are subdivided into subscales, the Coldheartedness dimension is considered to index a key component of psychopathy (Berg et al., 2013; Lilienfeld and Andrews, 1996; Lilienfeld and Widows, 2005). Previous research into response inhibition as measured by the PGNG found participants scoring highly on the Blame Externalization subscale of the PPI-R's Impulsive Antisociality dimension demonstrated reduced inhibitory performance on the PGNG task (Weidacker et al.,

2016). The third PPI-R dimension, Coldheartedness, measures the lack of empathy and callousness in feelings and behaviour (Uzieblo et al., 2010), did not show a relationship to the ability to inhibit responses. However, Coldheartedness is of particular interest when investigating the effects of brain stimulation because it is the only aspect of subclinical psychopathy which has been related to increased cortical reactivity to brain stimulation in motor areas (Fecteau et al., 2008). Even though this previous investigation was focused on motor empathy during pain perception, an abnormality in cortical reactivity might not be confined to motoric brain regions and, as such, Coldheartedness may relate to inter-individual differences in response to brain stimulation more widely. Additionally, previous research has shown that participants scoring high in Coldheartedness express reduced activation during face encoding in bilateral dorsolateral prefrontal cortex (dlPFC; Han et al., 2011), and especially right hemisphere dlPFC has been implicated in successful response inhibition (Criaud and Boulinguez, 2013).

Research into neural abnormalities of psychopathic offenders further hints toward a special role for the right dlPFC. Hoppenbrouwers et al. (2014) investigated the level of interhemispheric connectivity after transcranial magnetic stimulation (TMS) of motoric and dlPFC regions and revealed that while interhemispheric signal propagation was no different after stimulation was applied to the left hemisphere, TMS to the right dlPFC and motoric regions resulted into an increase in interhemispheric connectivity (Hoppenbrouwers et al., 2014). Similarly, functional magnetic resonance imaging (fMRI) studies have shown that successful response inhibition in terms of the PGNG activates a predominantly right-lateralized network of frontal and parietal regions, such as middle and inferior frontal gyri when participants perform the second (medium difficult) stage of the PGNG task (Garavan et al.,

1999). Increased difficulty during No-go trials in the standard Go/No-go task (Criaud and Boulinguez, 2013) and response inhibition in the PGNG task both point towards an involvement of right dIPFC (Langenecker et al., 2007b).

Relating performance in response inhibition tasks to functional brain imaging provides important insight into the neural basis of response inhibition, but is limited by the correlational nature of the approach. A better understanding of the role of the right dIPFC in response inhibition can be obtained through studies that investigate performance in relevant tasks as a function of electrical stimulation of this area, modulating activation patterns and thereby altering behavioural outcomes, as can be achieved by means of transcranial direct current stimulation (tDCS). TDCS is a non-invasive method (Nitsche and Paulus, 2000, 2001) that has been found to modulate neural responses in a variety of experimental tasks (Jacobson et al., 2012; Wassermann and Grafman, 2005) by affecting thresholds for neuronal firing within the stimulated regions. In the traditional Go/No-go task, anodal tDCS to either left or right dIPFC did not affect response inhibition (Beeli et al., 2008; Kang et al., 2009), whereas cathodal stimulation to right dIPFC was found to have a detrimental effect (Beeli et al., 2008).

Surprisingly, given the importance of right dIPFC in the traditional Go/No-go task (Criaud and Boulinguez, 2013; Steele et al., 2013), research using tDCS alongside the PGNG task has so far only targeted left dIPFC. Plewnia et al. (2013) examined performance after anodal tDCS, but only observed an effect of tDCS stimulation when taking individual differences in genetic expression into account: Anodal tDCS to left dIPFC reduced Go accuracy at the highest difficulty stage of the PGNG task in participants expressing genes related to elevated dopamine levels in prefrontal cortex. According to Plewnia et al. (2013), excitatory tDCS to left dIPFC

shifted dopaminergic activity resulting in impaired cognitive flexibility at the highest task difficulty. Additionally, participants expressing genes associated with reduced prefrontal dopamine levels were found to be adversely affected by cathodal tDCS during medium difficulty stages of the PGNG task, which may reflect inhibitory tDCS impairing dopamine related signaling from left dlPFC (Nieratschker et al., 2015).

Building on the finding that successful inhibitory performance in the PGNG task has been associated with activity in right dlPFC (Garavan et al., 1999; Langenecker et al., 2007b), prominent effects of individual differences on tDCS stimulation of left dlPFC and PGNG performance, as well as the utility of the PGNG to capture response inhibition deficits depending on psychopathic personality characteristics, the current study investigates whether response inhibition performance as measured by the PGNG can be altered by tDCS to right dlPFC, and especially whether tDCS effects are dependent on psychopathic traits in healthy participants. Based on previous research into the relationship between psychopathic traits and response inhibition performance in this task (Weidacker et al., 2016), it was predicted that Blame Externalization would relate to poor response inhibition performance and that this trait would modulate the effects of tDCS on performance. Second, based on previous research that showed an influence of Coldheartedness on TMS-related effects (Fecteau et al., 2008), Coldheartedness was also considered to modulate tDCS effects on response inhibition, since it is the only psychopathic trait that has, to date, been shown to interact with cortical stimulation (Fecteau et al., 2008).

2. Methods

2.1 Participants

Eighteen right-handed participants (9 males, age: $M = 22.06$, $SE = .98$, ranging from 18 to 32 years) with normal or corrected-to-normal vision participated for partial course credits. The Ethics Committee of Swansea University approved the experiment and informed consent was obtained prior to testing. All participants reported no history of any neurological, psychiatric or psychological conditions in the past. We additionally excluded participants with lifetime history of epilepsy, concussions, hearing problems, current metallic implants, neurostimulators or pregnancy. In addition, excessive responders on No-go trials (mean accuracy $\pm 2*SD$; $N = 2$) were also excluded from the current report. All participants completed three sessions of the experiment, with an interval of two to nine days between subsequent tDCS sessions ($M = 117.42$ hours; $SE = 10.91$) to eliminate tDCS carry-over effects.

2.2 Task Design

The twelve capital letters from “O” to “Z”, shown in white font against a black background (visual angle $\approx .7^\circ \times .9^\circ$) served as stimuli for the PGNG. The experiment was programmed using Matlab R2010b (Mathworks Inc., Ma., USA) and the Psychtoolbox package (Brainard, 1997; Kleiner et al., 2007). The stimuli were presented centrally on an 18” monitor running at a resolution of 1280 x 1024 pixels that was viewed from a distance of approximately 60cm; Keyboard responses were obtained from a standard USB keyboard.

The PGNG task (Langenecker et al., 2007a) involved participants viewing a stream of letters while monitoring for specific targets which changed depending on the stage of the experiment. Letters were presented for 500 ms, interleaved with a jittered inter-stimulus interval (uniformly distributed between 900 ms and 1500 ms in

steps of 50 ms) during which a fixation cross was displayed in the center of the screen. In the first stage of the task, participants were required to press a button with their dominant index finger as soon as they detected any of the target letters “X”, “Y” or “Z” and to ignore all other letters, thereby acquiring a prepotent response to the target letters (this stage did not include any No-go signal). The second stage of the PGNG task introduced an inhibitory component by only requiring button presses to the target letters if the previous target letter differed from the current one (e.g., respond to “X” following “Y”, but not “X” following “X”), ignoring any lure letters that were presented between target letters. In this stage, only the target letters “X” and “Y” were shown in addition to the lure letters. The third stage of the PGNG task measured response inhibition under higher task demands by using the same non-repetition rule as in stage two, while increasing the number of targets to three (i.e., “X”, “Y” and “Z”).

The first stage consisted of 270 trials of which 40% required a Go response, i.e. target present trials. The second and third stages consisted of 360 trials each, of which 30% were Go trials and 10% were No-go trials. The presentation of the letter stimuli was pseudo-randomized per stage, subject to the constraint that 1-2 lure letters were shown between target letters and that each target letters was shown equally often within each stage and trial type.

2.3 Transcranial Direct Current Stimulation

TDCS was applied via two saline soaked sponge electrodes (5 X 5 cm) for 20 minutes (including 15s ramp up and down periods) with an intensity of 1.5 mA (HDCstim; Magstim Inc., Dyfed, UK) prior to performing the experimental task. In the cathodal stimulation condition, the cathodal electrode was placed above right dlPFC

(electrode positioning above F4 in the international 10/20 system for electrode placement) with the anodal electrode on the left biceps. For the anodal stimulation condition, electrode positioning was reversed. In the sham condition, electrode positions were counter-balanced such that the positions corresponding to anodal and cathodal stimulation occurred equally often. During sham, the current was turned on for 15s before ramping back down to off to leave the participants with the initial sensation without further stimulation. This method has proven reliable to provide appropriate sham stimulation in previous research (Gandiga et al., 2006). The sequence of the three stimulation conditions was counterbalanced across participants and participants were blind to the type of tDCS stimulation applied. A schematic representation of the study design is shown in Figure 1.

Potential tDCS-related side effects were assessed using pre- and post-tDCS questionnaires enquiring about the presence of headache, neck pain, scalp pain, scalp burn, tingling, skin redness, sleepiness, concentration difficulties and acute mood change.

2.4 Psychopathic Personality Inventory-Revised (PPI-R)

The PPI-R (Lilienfeld and Andrews, 1996; Lilienfeld and Widows, 2005) consists of 154 items, measuring psychopathic tendencies in non-criminal samples via self-report on a 4-point Likert scale (false to true). The scores in the current student sample ($M = 295.5$, $SE = 9.31$) were close to previously reported values on the Dutch validation sample ($M = 284.4$, $SD = 31.76$; Uzieblo et al., 2010). In the current sample, the percentiles of the total score varied between 4 and 100 with a mean of 52.89. Percentile scores exceeding 65 (obtained by 9 participants in our

sample) are considered to be potentially clinically significant deviations from the norm as based on the Dutch validation sample ($N = 1192$; Uzieblo et al., 2010).

Internal consistency, as measure by Cronbach's alpha, for the PPI-R total score ($\alpha = .94$) and its eight subscales (Machiavellian Egocentricity $\alpha = .66$, Social Potency $\alpha = .79$, Coldheartedness $\alpha = .79$, Carefree Nonplanfulness $\alpha = .72$, Fearlessness $\alpha = .83$, Blame Externalization $\alpha = .89$, Impulsive Nonconformity $\alpha = .87$ and Stress Immunity $\alpha = .88$) are acceptable to high in the current sample. Participants completed the PPI-R before the start of the experimental task.

2.5 Statistical Approach

Potential tDCS side-effects (post minus pre stimulation) were investigated with a repeated-measures Analysis of Variance (ANOVA), containing a factor for the type of change induced, and a factor for stimulation condition (sham, anodal, cathodal). Significant interactions were subsequently followed up with paired t-tests.

Separate repeated-measures ANOVAs were performed on the PGNG variables: response times (RT), accuracy on Go trials (i.e., percentage correct target trials [PCTT]), accuracy on No-Go trials, (i.e., percentage correct inhibitory trials [PCIT]) and d' which aggregates the proportion of correct Go trials (hits) with the proportion of (incorrect) responses on No-go trials (false alarms) by subtracting the inverse normal transformation of the false alarm rate from the inverse normal transformation of the hit rate (McNicol, 1972). For each dependent measure, we conducted a Difficulty Stage (3 levels for RT and accuracy on Go trials, 2 levels for accuracy on No-Go trials and for d' scores) x Stimulation Condition (anodal, cathodal, or sham) ANOVA; we found no evidence for violations of the sphericity assumption for any significant effects and therefore no adjustments were made to

the degrees of freedom of the associated statistical tests. Post-hoc paired t-tests were used to follow up significant results and False Discovery Rate (FDR (q); $\alpha = .05$) was used to correct for multiple comparisons.

To assess the effect of psychopathy characteristics, measured by the PPI-R subscales, the scores for these subscales were entered as covariates in separate repeated-measure ANCOVAs using the PGNG variables relating to inhibitory ability (PCIT and d') as dependent measures. Significant interactions between aspects of the psychopathic personality and tDCS stimulation condition were followed by linear regressions using the difference scores between stimulation conditions and corrected by FDR for the number of linear regression.

3. Results

3.1 tDCS Side Effects

The repeated measures ANOVA on side effects of tDCS revealed a significant main effect of type of induced change ($F(8,136) = 9.89, p < .001, \eta^2_p = .37$) and a significant interaction between stimulation condition and type of side effect ($F(16, 272) = 1.81, p < .05, \eta^2_p = .10$). Post-hoc paired t-tests indicated that this interaction was due to a small increase in sleepiness from anodal to cathodal tDCS ($t(17) = 2.65, p_{uncorr} = .02$), but this result did not survive corrections for multiple comparisons (FDR corrected cut off threshold = $.002$). The remaining comparisons were not significant ($ts < 1.8$).

3.2 PGNG results independent of psychopathic characteristics

3.2.1 Response times. The response times in the PGNG did not significantly differ across tDCS stimulation conditions ($F_s < 1$ for the main effect and interaction).

However, Difficulty Stage influenced processing speed significantly ($F(2,34) = 25.62$, $p < .001$, $\eta^2_p = .60$). Post-hoc paired t-tests revealed that responses were significantly slower during Difficulty Stage 3 ($M = 540.48$, $SE = 20.32$) compared to both Difficulty Stage 1 ($M = 455.45$, $SE = 15.25$; $t(17) = 8.16$, $p < .001$) and Difficulty Stage 2 ($M = 462.93$, $SE = 15.55$; $t(17) = 5.64$, $p < .001$).

3.2.2 Go Accuracy. The repeated measures ANOVA on PCTT, the percentage accuracy in Go trials, revealed a significant main effect of Difficulty Stage only ($F(2,34) = 8.18$, $p < .005$, $\eta^2_p = .33$). Accuracy on Go trials was significantly higher in Difficulty Stage 1 ($M = 98.72\%$, $SE = .47$) compared to both, Difficulty Stage 3 ($M = 96.28\%$, $SE = .89$; $t(17) = 3.7$, $p = .002$) and Difficulty Stage 2 ($M = 97.52\%$, $SE = .47$; $t(17) = 2.54$, $p = .02$). Difficulty Stages 2 and 3 were, however, not significantly different as indicated by FDR-corrected paired t-tests ($t(17) = 1.89$, $p = .08$). Neither the main effect of Stimulation Condition nor the interaction of Stimulation Condition with Difficulty Stage were statistically significant (all $F_s < 1$).

3.2.3 No-go Accuracy. Taking the proportion of (correctly) withheld responses on No-go trials (PCIT) as an index of response inhibition, a significant main effect of Difficulty Stage ($F(1,17) = 25.57$, $p < .001$, $\eta^2_p = .60$) revealed better inhibition performance in Difficulty Stage 2 ($M = 83.49\%$, $SE = 2.14$) than in Stage 3 ($M = 70.47\%$, $SE = 3.59$; Difficulty Stage 1 did not include No-go trials and did therefore not contribute to this analysis). Neither the main effect of Stimulation Condition nor Stimulation Condition by Stage interactions were statistically significant (all $F_s < 1.5$).

3.2.4 d' scores. The repeated-measures ANOVA on d' scores revealed a significant main effect of Difficulty Stage ($F(1,17) = 26.92, p < .001, \eta^2_p = .61$) with higher d' scores for Stage 2 ($M = 3.18, SE = .14$) than for Stage 3 ($M = 2.56, SE = .16$). None of the effects involving Stimulation Condition were statistically significant (all $F_s < 1$).

3.3 TDCS effects on response inhibition relating to psychopathic characteristics

3.3.1 No-go accuracy. Analyses of the interaction between aspects of psychopathy and response inhibition, as measured by the PCIT, indicated two significant three-way interactions relating to Stimulation Condition and Difficulty Stage interacting with Coldheartedness ($F(2,32) = 3.95, p = .03, \eta^2_p = .2$) and Carefree Nonplanfulness ($F(2,32) = 3.84, p = .03, \eta^2_p = .2$) of the PPI-R. However, after correcting the follow-up linear regressions for multiple comparisons via FDR, none of the linear regressions remained significant. Similarly, the inclusion of the remaining PPI-R subscales as covariates did not reveal any significant interactions with tDCS effects for PCIT.

3.3.2 d' scores. Using d' as the dependent measure replicated the PCIT results for the PPI-R Carefree Nonplanfulness scale ($F(2,32) = 4.29, p = .02, \eta^2_p = .21$), but, again, the post-hoc tests did not survive corrections for multiple comparisons. The Coldheartedness subscale, however, significantly interacted with Stimulation Condition following FDR correction ($F(2,32) = 4.00, p = .03, \eta^2_p = .2$) and also with Difficulty Stage in a three-way, Coldheartedness x Stimulation Condition x Difficulty Stage interaction ($F(2,32) = 5.42, p = .01, \eta^2_p = .25$). In an effort to further

explore the role of psychopathy (as measured by responses to the questions in the Coldheartedness subscale of the PPI-R), we performed linear regressions using the d' difference scores between tDCS stimulation conditions as the dependent measure. Whereas the difference in performance between stimulation conditions was not related to Coldheartedness scores under medium task difficulty (in Stage 2 of the PGNG; R^2 s $< .2$), differences emerged with high task difficulty in Stage 3 of the PGNG task (see Figure 2). An increasing difference between d' scores after cathodal stimulation compared to sham ($R^2 = .58$, $SD_{Resid} = .59$, $b = .11$, $F(1,16) = 21.69$, $p < .001$) was found, that related to increasing scores on Coldheartedness predicting better relative performance following cathodal stimulation on Stage 3 of the PGNG. We observed a similar effect for the difference between d' scores after anodal stimulation and those for the sham condition, although these effects failed to reach traditional levels of statistical significance after correcting for multiple comparisons ($R^2 = .32$, $SD_{Resid} = .64$, $b = .07$, $F(1,16) = 7.47$, $p = .015$; FDR corrected cut off threshold = .011). There was no difference between the d' difference scores for anodal vs. cathodal stimulation related to responses in the Coldheartedness subscale of the PPI-R ($R^2 < .2$).

The inclusion of the remaining PPI-R subscales as covariates in the repeated measures ANCOVAs using d' as dependent measure did not reveal any significant interactions with type of tDCS stimulation.

4. Discussion

Here we present the first investigation into the effect of tDCS stimulation to right DIPFC on response inhibition as a function of inter-individual differences in psychopathic personality traits in a non-clinical sample. Consistent with earlier work

using the PGNG task to study response inhibition (Langenecker et al., 2007a; Votruba and Langenecker, 2013), we found that performance decreased as the PGNG stages progressed, as would be expected given the increasing complexity of the task across the three stages. Importantly, tDCS stimulation to right dIPFC, a cortical region implicated in the control of inhibitory ability, modulated performance as a function of expressed psychopathic traits. While previous findings on the effect of Blame Externalization on response inhibition did not replicate in the current sample, and Blame Externalization did not modulate effects of tDCS on task performance, the expression of Coldheartedness did. Specifically, participants scoring high in Coldheartedness demonstrated improved performance on the response inhibition task following cathodal tDCS to right dIPFC at the highest task difficulty level.

Previous tDCS research using the PGNG task to investigate the role of left dIPFC in response inhibition (Nieratschker et al., 2015; Plewnia et al., 2013) found that neither cathodal nor anodal tDCS affected performance unless inter-individual differences in genetic polymorphism were taken into account. Specifically, variants of the COMT gene, that code for dopamine levels in the prefrontal cortex, interacted with stimulation type; cathodal stimulation reduced accuracy for No-go trials in Difficulty Stage 2 for participants with low dopamine levels (as inferred by their genotype) and anodal stimulation reduced accuracy for Go trials in Difficulty Stage 3 for participants with (inferred) high dopamine levels (Nieratschker et al., 2015; Plewnia et al., 2013). Similarly, our results highlight the importance of inter-individual differences in personality characteristics relating to psychopathy for the investigation of the effects of tDCS on response inhibition. Here we have demonstrated that scores in the Coldheartedness subscale of the PPI-R (Lilienfeld and Andrews, 1996;

Lilienfeld and Widows, 2005) modulated the effects of tDCS on performance. Specifically, performance for participants scoring high on Coldheartedness, reflecting an absence of feelings of guilt and empathy (Berg et al., 2013; Lilienfeld and Andrews, 1996; Lilienfeld and Widows, 2005), was substantially improved by cathodal tDCS when compared to sham stimulation in the current response inhibition task, indicating the interaction between personality traits relating to emotional responses and cognitive functioning, in this case response inhibition.

Previous behavioural research investigating the relationship between Coldheartedness and factors influencing response inhibition in terms of the PGNG found that the psychopathic trait Coldheartedness does not modulate effects of cognitive load in a working memory task (Sadeh and Verona, 2008) or indices of response monitoring (Bresin et al., 2014). It is therefore likely that the improvement seen in the current study is related to improved attentional control or set-shifting due to cathodal tDCS in participants scoring high in Coldheartedness and not to working memory capacity and response monitoring components embedded in the PGNG.

A previous behavioural investigation on the PGNG and PPI-R (Weidacker et al., 2016) as well as research into the Stop Signal Task did not reveal a deficit in response inhibition in individuals scoring high on Coldheartedness per se (Morgan et al., 2011). Similarly in the current study, Coldheartedness interacted with task performance only when taking stimulation condition into account, indicating that it is the response to the tDCS stimulation itself that leads to these participants responding differently, and not that they express a general deficit in response inhibition.

Higher levels of Coldheartedness have previously been associated with reduced activation in bilateral dIPFC during face encoding (Han et al., 2011) as well

as to TMS-induced modulation of corticospinal excitability during pain perception (Fecteau et al., 2008). Based on these findings, a potential explanation for the current effects of tDCS might be that cortical reactivity is generally higher in individuals scoring high on Coldheartedness, in other words they may be more susceptible to external stimulation.

In line with previous research indicating that the effects of tDCS depend on the initial state of the stimulated neurons (Jacobson et al., 2012; Krause and Kadosh, 2014; Wassermann and Grafman, 2005), Krause et al. (2013) recently suggested that tDCS effects depend on a regional cortical excitation/inhibition (E/I) imbalance, reflecting the ratio of glutamate and gamma-aminobutyric acid (GABA). According to this model, it is the imbalance of these neurotransmitters which leads to reduced performance in cognitive tasks, which can be restored by tDCS, thereby leading to behavioural improvements in task outcomes. Cathodal tDCS in particular has been found to reduce excitatory glutamate levels, which if too high can distort the E/I balance (Foerster et al., 2015; Krause et al., 2013; Stagg et al., 2009). While neurotransmitter assessments in participants expressing psychopathic traits is awaited, previous research has revealed an elevated E/I ratio in patients suffering from ADHD and cathodal tDCS has been found to improve response inhibition in ADHD patients (Soltaninejad et al., 2015) by normalizing the increased E/I ratio of glutamate and GABA found in these participants (Edden et al., 2012). In much the same way as tDCS can affect membrane excitability, TMS can be used to either increase or decrease cortical excitability, depending on the protocol employed. After application of inhibitory, continuous, theta burst stimulation (TBS) to right dlPFC, Cho et al. (2010, 2012) found that impulsive behaviour reduced, as indicated by an increased preference for delayed rewards compared to immediate smaller rewards.

In contrast, increasing cortical excitability by mean of intermittent TBS did not affect impulsive behaviour. The aforementioned research highlights how a reduction in cortical excitability of right dlPFC can be beneficial for impulsivity, similarly to the here observed effect of cathodal tDCS increasing response inhibition performance for those high on Coldheartedness.

That cathodal and anodal tDCS both resulted in enhanced performance in the response inhibition task may be reconciled by a model that assumes that different stimulation conditions are critically affecting different parts of the processing chain. While Cho et al. (2010, 2012) highlighted the beneficial effect of reduced cortical excitability on impulsive behaviours, research on excitatory TMS points towards increased set-shifting and attentional control when applied to the right dlPFC (Vanderhasselt et al., 2006, 2007). Enhanced set-shifting ability due to excitatory TMS would be mirrored by beneficial effects of anodal tDCS in the current investigation, assuming anodal tDCS has an excitatory effect when applied to prefrontal brain regions (see Jacobson et al., 2012 for a discussion). We indeed observed beneficial effects of anodal tDCS on right dlPFC, but of a lesser magnitude than the effects observed for cathodal tDCS.

In line with previous reports on excitability of motor regions (Fecteau et al., 2008), the current results were specifically modulated by the presence of the psychopathic trait Coldheartedness. Most previous investigations on TMS and psychopathy focused on the total psychopathy score and as such were unable to reveal which specific traits of psychopathy relate to the observed effects. However, Hoppenbrouwers et al. (2013) revealed lower baseline cortical inhibition in left dlPFC of psychopathic offenders in addition to abnormalities in right to left interhemispheric connectivity, which was hypothesized to indicate over-inhibition of right dlPFC in

psychopathic offenders (Hoppenbrouwers et al., 2014). Given, in addition to our findings, the observed link between Coldheartedness and reduced levels of dlPFC activation (Han et al., 2011), heightened cortical reactivity (Fecteau et al., 2008) and abnormalities in cortical inhibition (Hoppenbrouwers et al., 2013, 2014), a non-optimal E/I balance in participants expressing elevated levels of Coldheartedness is the most parsimonious account. Furthermore, it is suggested that increases in glutamate levels are partially responsible for enhanced cortical reactivity (Di Lazzaro et al., 2003), as found in high traits of Coldheartedness (Fecteau et al., 2008). Therefore the significant improvement found through tDCS for participants scoring high in Coldheartedness might be the result of a tDCS-mediated reduction in glutamate levels driving the E/I imbalance toward the relative optimum, leading to an improvement in performance on the response inhibition task.

However, no investigation has elucidated the precise nature of the effects of cathodal and anodal tDCS on glutamate and GABA levels in prefrontal regions. While the current results point to increased glutamate levels driving the E/I imbalance, an alternative hypothesis is related to the potential over-inhibition of right dlPFC, due to increased GABAergic inhibitory neurotransmission as hypothesized by Hoppenbrouwers et al. (2014). However, recent tDCS research revealed widespread decreases of a combined marker of glutamine and glutamate after active stimulation conditions, whereas active tDCS did not affect inhibitory GABA levels (Foerster et al., 2015). Thus it is more likely that the current effects are mediated by a tDCS-induced decrease in glutamate than GABA, but this has to be clarified with future research investigating the effects cathodal and anodal tDCS has on neurotransmitters when applied to prefrontal brain regions.

Despite clear and specific findings the study bears some limitations, especially related to the small sample size. While comparable in sample size to other brain stimulation studies (e.g. Cunillera et al., 2014; Ditye et al., 2012) and covering the full range of degrees of psychopathy levels measured with the PPI-R, this might have limited the range of observed effects and provides an explanation why earlier behavioural results based on a larger sample, such as PPI-R Blame Externalization predicting reduced accuracy to No-go trials (Weidacker et al., 2016), could not be replicated in the current report. Similarly, the here reported effect of anodal tDCS on task performance mirrored the effect seen due to cathodal tDCS to right dIPFC, but did not survive correction for multiple comparisons. It has to be mentioned that a similarity in the directionality of effects due to cathodal and anodal tDCS is not uncommon for cognitive behavioural tasks, as Jacobson et al. (2012) pointed out in their meta-analysis. This is especially true when tDCS is applied to cognitive instead of motor function-related brain regions, tDCS effects do not necessarily follow the dichotomy observed in motoric brain regions of excitability due to anodal and inhibition due to cathodal tDCS (Jacobson et al., 2012). Previous fMRI research on the effect of cathodal and anodal tDCS to left dIPFC additionally revealed that both types of stimulations lead to reduced brain activity in frontal brain areas post stimulation (Stagg et al., 2013), possibly explaining earlier reported beneficial effects for both anodal and cathodal tDCS, e.g. verbal comprehension in stroke patients (You et al., 2011). Taken together, the here proposed explanation in terms of a tDCS mediated reduction in glutamate levels is speculative and has to be confirmed by further research even though reviewed results of the detrimental influence of tDCS on glutamate levels (Foerster et al., 2015; Stagg et al., 2009) supports this explanation.

The second limitation is related to the type of brain stimulation employed, while tDCS is a non-invasive method (Nitsche and Paulus, 2000, 2001), the spatial resolution of tDCS is lower than, for example, that of TMS (Fregni et al., 2005). In light of research investigating tDCS current flow through the cortex (Sadleir et al., 2010), given the electrode size and placement, it seems likely that the current montage co-activated adjacent frontal areas such as the inferior frontal gyrus (IFG) as well as deep brain structures that are part of a large-scale network involving the dlPFC (Ridderinkhof et al., 2004; Sadleir, Vannorsdall, Schretlen, & Gordon, 2010). However, previous tDCS research using a response inhibition task was able to reveal divergent effects of stimulating right dlPFC and IFG, thereby hinting towards the separability of tDCS effects relating to these adjacent regions. But, given the current montage, an involvement of the right IFG cannot entirely be ruled out.

A final consideration is that the study was carried out in a single blind manner, without the collection of baseline performance. However, given that the current study represents a within-subject design with complete counterbalancing of the sequence of tDCS sessions across participants, practice effects are expected not to have influenced the here presented results.

Given the complexity and variety of executive functions ascribed to prefrontal cortex, investigating how frontal brain activity relates to individual differences in personality characteristics and the ability to inhibit prepotent responding is particularly challenging. In this light, it is not surprising that the question of how individual differences relate to the neural activity supporting response inhibition has received comparatively little attention. The current study provides the first insight into the interplay between the different aspects of trait psychopathy and stimulation of right dlPFC during a formal assessment of response inhibition. Our findings highlight

the important role of personality characteristics in response inhibition and demonstrate that tDCS can improve performance in the response inhibition task in participants scoring highly on a core aspect of psychopathy: Coldheartedness.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

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Figure 1. Schematic representation of the study design. The sequence of Anodal, Cathodal and Sham stimulation was counterbalanced across participants such that each type of stimulation was applied equally often during each session. Shown are pre- and post-tDCS measures and time in between sessions in hours ($M \pm SE$).

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Figure 2. Scatterplot of the relationship between PPI-R Coldheartedness subscale scores and differences in d' for Stage 3 of the PGNG task. Lines represent the least squares fit to the data with the solid black line corresponding to the fit to the difference scores for cathodal vs. sham stimulation, the solid grey line corresponding to the fit to the difference scores for anodal vs. sham stimulation and the dashed grey line corresponding to the fit to the difference scores for anodal vs. cathodal stimulation.

