

Modulation of control: Can HD-tDCS targeting the dACC reduce impulsivity?

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ABSTRACT

Background: The dorsal anterior cingulate cortex (dACC) and its neurocircuits are central in impulsivity, and maladaptive dACC activity has been implicated in psychological disorders characterized by high trait impulsivity. High-Definition transcranial Direct Current Stimulation (HD-tDCS) is a non-invasive neuromodulation tool that, with certain electrode configurations, can be optimized for targeting deeper subcortical brain structures, such as the dACC.

Objectives: Using behavioural and electrophysiological measures we investigated whether HD-tDCS targeting the dACC could modulate two key components of impulsivity, inhibitory control and error processing.

Methods: Twenty-three healthy adults with high trait impulsivity participated in two experimental sessions. Participants received active or sham HD-tDCS in counterbalanced order with a wash-out period of at least 3 days, as part of a single-blind, cross-over design. EEG was recorded during the Go-NoGo task before, directly after, and 30 min after HD-tDCS.

Results: HD-tDCS targeting the dACC did not affect inhibitory control performance on the Go-NoGo task, but there was evidence for a delayed change in underlying neurophysiological components of motor inhibition (NoGo P3) and error processing (error related negativity; ERN) after one session of HD-tDCS.

Conclusion: HD-tDCS has potential to modulate underlying neurophysiological components of impulsivity. Future studies should further explore to what degree the dACC was affected and whether multi-session HD-tDCS has the capacity to also induce behavioural changes, particularly in clinical samples characterized by high trait impulsivity.

1. Introduction

Trait impulsivity is a multidimensional construct that predisposes an individual to a range of maladaptive behaviours (Evenden, 1999; Whiteside and Lynam, 2001). More generally defined, it refers to the tendency to act prematurely without adequate forethought about the consequences (Dalley et al., 2011; Evenden, 1999). Trait impulsivity varies across healthy individuals and can be adaptive in some circumstances (Dickman, 1990). For example, impulsive entrepreneurs tend to be less sensitive to negative consequences and are therefore more persistent in completing entrepreneurial actions that are necessary to keep their business running (Wiklund et al., 2018). However,

impulsivity is more generally regarded as a maladaptive personality trait associated with inappropriate or harmful behaviour towards oneself or others, such as recklessness and aggression (Verdejo-García et al., 2008). High trait impulsivity also plays a key role in a broad range of mental illnesses, such as substance use disorders (SUD), attention deficit/hyperactivity disorder (ADHD), and antisocial personality disorder (ASPD; Zisner and Beauchaine, 2016).

Neurocognitive research suggests that impulsivity is highly linked to impaired cognitive control functioning (Dalley et al., 2011). The dorsal anterior cingulate cortex (dACC) is a critical node within broader neurocircuits supporting the robust cognitive functions contributing to impulse control (Botvinick and Cohen, 2014). More specifically, the

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dACC is involved in processes that determine the expected costs and benefits of exercising control over automatic behaviour (Shenhav et al., 2016). Based on this expected value of control, a decision is made on the allocation of cognitive control. Accordingly, the degree of exerted control over automatic behaviour (i.e. inhibitory control) can be regarded as the product of dACC processes. Another cognitive control function that has been directly linked to dACC activity is error processing; the ability to monitor performance in order to detect errors and adaptively learn from them (Hester et al., 2004; Ridderinkhof et al., 2004; Ruchow et al., 2005). Deficits in inhibitory control and error processing can have substantial negative consequences, particularly for individuals who suffer from certain neuropsychological disorders. For example, when strong urges can no longer be inhibited, this can lead to compulsive substance use or antisocial behavior in SUD and ASPD, respectively. Poor error processing, in turn, prevents learning from negative outcomes, thus perpetuating dysfunctional behaviour.

It is therefore not surprising that healthy populations with high trait impulsivity, as well as individuals with externalizing disorders, often show decreased neurophysiological responses related to inhibitory control and error processing (Littel et al., 2012; Ruchow et al., 2005, 2008; Shen et al., 2014). This has been linked to dACC hypoactivation (Goldstein and Volkow, 2011; Olvet and Hajcak, 2008), which makes this region particularly promising as potential target for non-invasive neuromodulation technologies aimed at modifying impulsive behaviour. High-Definition transcranial Direct Current Stimulation (HD-tDCS) is a neuromodulation technique which utilises compact (i.e., $< 5 \text{ cm}^2$) circular gel-based electrodes placed over the scalp to deliver low intensity (typically 0.5 – 2 mA) current into the brain (e.g. Bikson et al., 2019). Past research indicates that HD-tDCS montages have the potential to target brain structures with greater focality than conventional sponge-based tDCS designs (DaSilva et al., 2015). The electric fields produced in the brain during stimulation cause sub-threshold modulation of neuronal membrane potentials (Woods et al., 2016), resulting in changes in excitability. Importantly, certain electrode configurations allow HD-tDCS montages to be optimized for targeting deeper sub-cortical brain structures (Faria et al., 2011; To et al., 2018).

To date, only one study has investigated whether anodal HD-tDCS targeting the dACC could modify cognitive functioning. To et al (2018) used a HD-tDCS montage comprised of one target (anodal) electrode placed anteriorly on the scalp at the midline (position Fz; International 10–20 System) and four return (cathodal) electrodes positioned across the forehead. This configuration was based on computational current flow models indicating that with this HD-tDCS montage the electrical field would peak at the dACC and exit at the forehead. To the best of our knowledge, the study by To et al (2018) is the first and only proof-of-concept study to target the dACC with HD-tDCS and the results indicated that anodal stimulation was associated with improved reaction times and neurophysiological changes in the dACC as measured with source-localized resting-state EEG. However, it is unclear whether the observed behavioural changes were specific to modulation of dACC activity, as brain activity was not recorded during task performance. In addition, faster reaction times after HD-tDCS may partially be attributed to changes in pre-supplementary motor area (pre-SMA) activity, given that electrical currents induced by HD-tDCS targeted at the dACC will also pass through the pre-SMA (To et al., 2018). Finally, it is questionable whether HD-tDCS with 1 mA intensity is sufficient to produce adequate stimulation at the depth of the dACC.

The aim of the current study was to further investigate cognitive changes induced by the HD-tDCS montage used by To et al (2018) with an increased current intensity of 1.5 mA. Specifically, we investigated this montage as a potential neuromodulation technique to change impulsive behaviour, as measured by inhibitory control and error processing on the Go-NoGo task, in individuals with high trait impulsivity. The Go-NoGo task is a gold-standard paradigm to assess error processing and inhibitory control (Luijten et al., 2014). Event related potentials (ERPs) that reflect inhibitory control during the Go-NoGo task are the

NoGo N2 and NoGo P3 (Bokura et al., 2001). It is assumed that the N2 emerges from the dACC and reflects early conflict detection needed to initiate inhibitory control during NoGo trials (Luijten et al., 2014; Nieuwenhuis et al., 2004, 2003; van Veen & Carter, 2002), while the P3 is more a reflection of withholding a prescribed motor response, such as not pressing a button during NoGo trials. In line with this, the NoGo P3 in more anterior brain regions near the motor and premotor cortices (Band and Van Boxtel, 1999; Smith et al., 2008). The error related negativity (ERN) is generated by the dACC after non-inhibited NoGo trials and can be regarded as a neurophysiological measure of error processing (Ridderinkhof et al., 2004; Wang et al., 2005).

The current study is the first to investigate the effects of anodal HD-tDCS targeting the dACC on measures of impulsivity. It extends upon the work of To et al (2018) by utilising a stronger current intensity, assessing the impact of stimulation on behavioural measures of impulsivity and EEG measures of inhibitory control and error processing, tested in a cohort of individuals with high trait impulsivity. As self-reported impulsivity has generally been related to worse performance on the Go-NoGo task (Keilp et al., 2005; Littel et al., 2012), it was hypothesised that anodal HD-tDCS stimulation would result in improved performance on the Go-NoGo task, indicative of an acute reduction in impulsive behaviour. In addition, we hypothesized that anodal HD-tDCS targeting the dACC would increase dACC activity, as shown by larger neurophysiological responses related to inhibitory control (i.e. N2 and P3 amplitudes) and error processing (ERN amplitudes).

2. Results

2.1. Behavioural outcomes

Descriptive data for behavioural performance on the Go-NoGo task can be found in the [supplementary file](#). For all behavioural outcomes on the Go-NoGo task a multilevel model with random intercepts fitted the data (i.e. variance at Level 2 was significant), where $ICC_{Accuracy} = 0.79$, $ICC_{RT_Go} = 0.79$, and $ICC_{RT_post} = 0.60$ (Table 1). Comparing the fitted models on the percentage of correct NoGo trials (accuracy) indicated that the baseline model (M0) was the best fitted model. Consequently, there was no significant change for accuracy across the three time points. In addition, the main effect of Condition was not significant, indicating that accuracy did not differ between the active HD-tDCS and sham HD-tDCS conditions.

For both reaction times on Go trials and reaction times post erroneous trials, the first model with Time as fixed effect (M1) fitted the data best (Table 1). In these models, there was a significant main effect of Time (Baseline to Post 1 and Baseline to Post 2). As shown in Fig. 1A, reaction times on Go trials decreased with an average of 8 ms from Baseline to Post 1 and with an average of 7 ms from Baseline to Post 2. Reaction times post erroneous responses also changed across measurement moments, with an average post reaction time decrease of 24 ms from Baseline to Post 1 and an average decrease of 20 ms from Baseline to Post 2 (Fig. 1B). There was no significant difference between the active HD-tDCS and sham HD-tDCS condition on reaction times.

2.2. Event related potentials

Table 2 shows the descriptive statistics for relevant ERP amplitude values.

The baseline models with random intercepts (M0) fitted the ERP data, where $ICC_{NoGo_N2} = 0.40$, $ICC_{NoGo_P3} = 0.40$, and $ICC_{ERN} = 0.41$ (Table 3). It was therefore confirmed that multilevel analyses could be performed for all ERP outcomes. For the ERP cluster analyses, the baseline model was the best fit for the data indicating that there were no significant main effects for Time and Condition, nor was there a significant cross-level interaction effect for the NoGo N2, NoGo P3 and ERN components.

Multilevel analyses for FCz again revealed that M0 was the best fitted

Table 1

Parameter estimates (se between brackets) and model fit statistics per model for behavioural measures of the Go-NoGo.

Outcome	Fixed part						Random part				Likelihood ratio test ²
	Intercept	Pre-Post1	Pre-Post2	Group	Group * Pre-Post1	Group * Pre-Post2	σ_e^2	σ_{u0}^2	σ_{u1}^2	σ_{u2}^2	
M0	31.06 (3.23)***						61.3	228.9			135.39***
M1	31.07 (3.37)***	-0.44 (1.66)	0.41 (1.68)				62.3	228.5			0.26
M2	31.04 (3.61)***	-0.40 (1.83)	0.42 (1.68)				58.8	268.8	17.6	3.8	2.49
M3	30.75 (3.66)***	-0.40 (1.83)	0.41 (1.68)	0.60 (1.34)			59.4	268.1	17.0	3.6	0.21
M4	31.40 (3.78)***	-1.36 (2.42)	-0.56 (2.35)	-0.72 (2.33)	1.99 (3.27)	1.99 (3.30)	60.4	268.2	16.2	3.4	0.51
RT Go trials:											
M0	318.82 (5.86)***						196.4	756.2			138.43***
M1	323.62 (6.10)***	-8.28 (2.85)**	-6.21 (2.88)*				184.7	757.9			8.91*
M2	323.70 (6.75)***	-8.36 (3.60)*	6.20 (3.47)				148.9	971.9	146.8	121.8	7.81
M3	323.15 (6.83)***	-8.35 (3.61)*	-6.21 (3.47)	1.13 (2.13)			150.1	972.7	146.1	120.9	0.29
M4	320.07 (7.00)***	-3.30 (4.36)	-2.05 (4.29)	7.50 (3.62)*	-10.49 (5.08)*	-8.53 (5.14)	145.6	980.4	150.0	123.4	4.88*
RT post errors:											
M0	305.28 (7.86)***						849.5	1274.5			70.85***
M1	319.18 (8.53)***	-21.92 (5.73)***	-19.69 (5.80)***				745.7	1291.0			16.63***
M2	319.20 (9.98)***	-22.10 (6.46)**	-19.78 (5.81)**				692.9	1935.4	258.9	59.5	7.61
M3	320.51 (10.22)***	-22.12 (6.48)**	-19.74 (5.83)**	-2.73 (4.59)			697.1	1934.3	259.1	60.3	0.36
M4	321.51 (10.71)***	-25.28 (8.46)**	-19.45 (8.11)*	-4.80 (7.97)	6.54 (11.17)	-0.50 (11.29)	707.0	1931.4	258.4	60.7	0.51

M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + random slopes for time. M2: M1 + Level 2 predictor group. M3:M2 + cross-level interaction effect of time and group. RT: Reaction Time. *p < 0.05. **p < 0.01. ***p < 0.001.

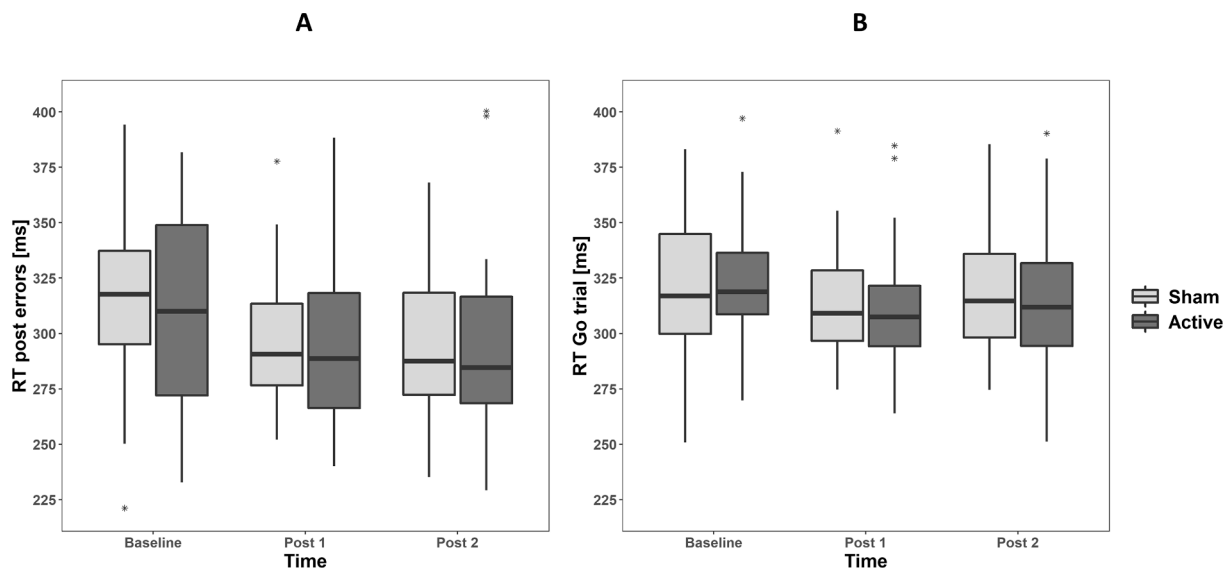


Fig. 1. Box plots representing reaction times (RT) on Go trials (A) and on post erroneous trials (B) for Sham and Active HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 min after HD-tDCS (Post 2). RT significantly decreased from Baseline to Post 1 and from Baseline to Post 2.

model for NoGo N2 and NoGo P3 amplitudes, with no change over measurement moments and no difference between conditions (active HD-tDCS vs. sham HD-tDCS). For the ERN component as measured over electrode site FCz, M1 was the best fitted model. This model indicated that there was a significant main effect of Time (Baseline to Post 2), with reduced ERN amplitudes 30 min after stimulation with both active and

sham HD-tDCS ($b = 2.27, p < 0.001$). There was no significant main effect of Condition or cross-level interaction effect.

M0 was also the best fitted model for NoGo N2 amplitudes measured over Cz, indicating no change over time and no significant difference between conditions. In contrast, M4 was the best fitted model for NoGo P3 and ERN components as measured over Cz. In both models, there was

Table 2
Descriptive data for electrophysiological measures.

	Baseline		Post1		Post2	
	Active tDCS	Sham tDCS	Active tDCS	Sham tDCS	Active tDCS	Sham tDCS
N2	n = 21	n = 21	n = 21	n = 19	n = 20	n = 20
FCz	-6.45 (3.65)	-6.55 (3.23)	-5.97 (4.72)	-6.52 (3.99)	-5.76 (3.41)	-6.74 (2.94)
Cz	-1.65 (2.31)	-1.93 (2.29)	-2.13 (1.93)	-1.91 (2.39)	-2.07 (2.21)	-1.65 (2.38)
P3	n = 20	n = 21	n = 21	n = 19	n = 19	n = 20
FCz	6.41 (5.69)	5.80 (3.96)	5.82 (6.68)	5.06 (5.04)	5.79 (5.25)	4.04 (4.78)
Cz	1.67 (3.89)	1.15 (3.42)	1.12 (4.20)	0.40 (3.66)	0.96 (2.81)	0.34 (3.92)
ERN	n = 18	n = 19	n = 18	n = 15	n = 20	n = 16
FCz	-7.38 (3.07)	-8.58 (5.14)	-7.07 (5.34)	-7.16 (4.63)	-6.36 (4.71)	-6.30 (4.79)
Cz	-1.89 (2.49)	-0.35 (2.56)	-1.46 (1.91)	-0.85 (2.59)	-1.10 (1.97)	-1.04 (2.07)

Note: Mean (SD) for NoGo N2, NoGo P3, and ERN amplitudes (µV) at each relevant electrode side: FCz and Cz.

a significant cross-level interaction effect of Condition with Time (Baseline – Post2), indicating smaller amplitudes after active HD-tDCS at Post 2 for the NoGo P3 ($b = -1.29, p = 0.045$; Fig. 2) and for the ERN ($b = 1.31, p = 0.032$; Fig. 3). In sum, these findings show that HD-tDCS over the dACC modulates both the NoGo P3 and ERN measured over central electrode sites (Cz) 30 min after stimulation.

2.3. HD-tDCS tolerability

A paired samples *t*-test with Condition (Active vs. Sham tDCS) as within-subject factor was performed for the average intensity of adverse effects experienced by each participant. No differences between the conditions were observed regarding adverse effects.

3. Discussion

To the best of our knowledge, this is the first proof-of-concept study to explore whether anodal HD-tDCS targeting the dACC can modulate two key components of impulsivity, namely inhibitory control and error processing, in individuals with high trait impulsivity. We hypothesized that stimulation of the dACC would result in larger ERP amplitudes, and that this would be associated with better performance on the Go-NoGo

task. Surprisingly, we observed reductions in ERP amplitudes indexing motor inhibition (NoGo P3) and error processing (ERN). These occurred 30-minutes after stimulation, consistent with prior reports indicating maximal response to HD-tDCS temporally downstream from the cessation of stimulation (Kuo et al., 2013). These reductions in ERP amplitudes following a single session of stimulation were not accompanied by any observable behavioural modifications. The ERP results might represent improved efficiency of neural resources for inhibitory control and error processing. However, in the absence of any behavioural modifications, it remains unclear if a single session of anodal HD-tDCS targeting the dACC can affect impulsivity.

Past findings on the effects of prefrontal stimulation using conventional (i.e., non-high definition) tDCS montages are consistent with the current results indicating no change in inhibitory control on a behavioural level, as indicated by the absence of accuracy enhancement on the Go-NoGo task, despite subtle brain modifications (Campanella et al., 2017; Cunillera et al., 2016; Lapenta et al., 2014; Sallard et al., 2018; Verveer et al., 2020). The effects of tDCS on proactive inhibitory control, as measured by reaction times on Go trials, have been more mixed. In line with our findings, some studies have observed no change in reaction times on Go trials after tDCS (Campanella et al., 2017; Lapenta et al., 2014), whereas others have reported significant changes in reaction times after tDCS (Cunillera et al., 2016; Verveer et al., 2020). In addition, a recent study reported a larger increase in prefrontal cortex activity as measured by fMRI on Go trials than on NoGo trials after anodal tDCS, while no effects on performance and reaction times were found (Sallard et al., 2018). Inconsistent findings on proactive inhibitory control after tDCS have been attributed to the difficulty of the Go-NoGo task. It was proposed that reaction times do not improve for simple Go-NoGo tasks because of a floor effect (Campanella et al., 2017; Sallard et al., 2018). However, this explanation does not apply to the current data, as we observed faster reaction times at later time points compared to baseline.

Alternatively, ‘online’ HD-tDCS protocols, where stimulation is applied concurrently with task performance, might result in larger effects on Go-NoGo performance than ‘offline’ HD-tDCS, whereby stimulation is applied in the absence of any cognitive engagement. However, it should be noted that online HD-tDCS protocols have also reported neurophysiological changes in the absence of behavioural modulations (Hill et al., 2019). It can also be argued that the variability in wash-out period between participants had an impact on cognitive task performance via task recency interacting with possible practice effects. Yet, we found that the variability in number of days interval between sessions

Table 3
Parameter estimates (se between brackets) and model fit statistics per model for electrophysiological measures of the Go-NoGo task.

Outcome	Fixed part						Random part				Likelihood ratio test ²
	Intercept	Pre-Post1	Pre-Post2	Group	Group * Pre-Post1	Group * Pre-Post2	σ _e ²	σ _{u0} ²	σ _{u1} ²	σ _{u2} ²	
NoGo N2:											
M0	-4.08 (2.27)						5.4	3.6			79.98***
M1	-4.12 (2.28)	0.01 (0.37)	0.11 (0.37)				5.5	3.6			0.11
M2	-4.12 (2.28)	0.02 (0.37)	0.10 (0.37)				5.4	3.7	0.04	0.10	1.88
M3	-4.25 (2.28)	0.01 (0.37)	0.10 (0.37)	0.24 (0.31)			5.4	3.7	0.04	0.10	0.62
M4	-4.23 (2.29)	0.02 (0.53)	0.05 (0.53)	0.21 (0.52)	-0.02 (0.74)	0.11 (0.74)	5.5	3.7	0.04	0.10	0.03
NoGo P3:											
M0	2.25 (3.22)						10.1	6.6			74.69***
M1	2.57 (3.24)	-0.37 (0.50)	-0.60 (0.50)				10.1	6.5			1.51
M2	2.57 (3.23)	-0.39 (0.50)	-0.60 (0.50)				10.0	6.3	0.2	0.1	1.85
M3	2.31 (3.24)	-0.41 (0.50)	-0.60 (0.50)	0.53 (0.41)			10.0	6.3	0.2	0.1	1.61
M4	2.28 (3.25)	-0.42 (0.72)	0.51 (0.71)	0.58 (0.70)	0.02 (1.00)	-0.18 (0.99)	10.1	6.3	0.2	0.1	0.05
ERN:											
M0	-4.15 (3.06)						8.0	5.5			65.34***
M1	-4.66 (3.07)	0.45 (0.48)	1.08 (0.47)*				7.8	5.7			5.37
M2	-4.66 (3.08)	0.45 (0.48)	1.08 (0.47)*				7.8	5.9	0.0	0.0	0.08
M3	-4.63 (3.08)	0.45 (0.48)	1.09 (0.47)*	-0.06 (0.40)			7.8	5.9	0.0	0.0	0.02
M4	-4.53 (3.09)	0.40 (0.70)	0.80 (0.69)	-0.28 (0.67)	0.12 (0.98)	0.55 (0.95)	7.9	5.9	0.0	0.0	0.38

M0: baseline model with random intercepts and Level 1 predictor time. M1: M0 + random slopes for time. M2: M1 + Level 2 predictor group. M3:M2 + cross-level interaction effect of time and group. Stand.: Standardized coefficients of fixed effects. *p < 0.05. **p < 0.01. ***p < 0.001.

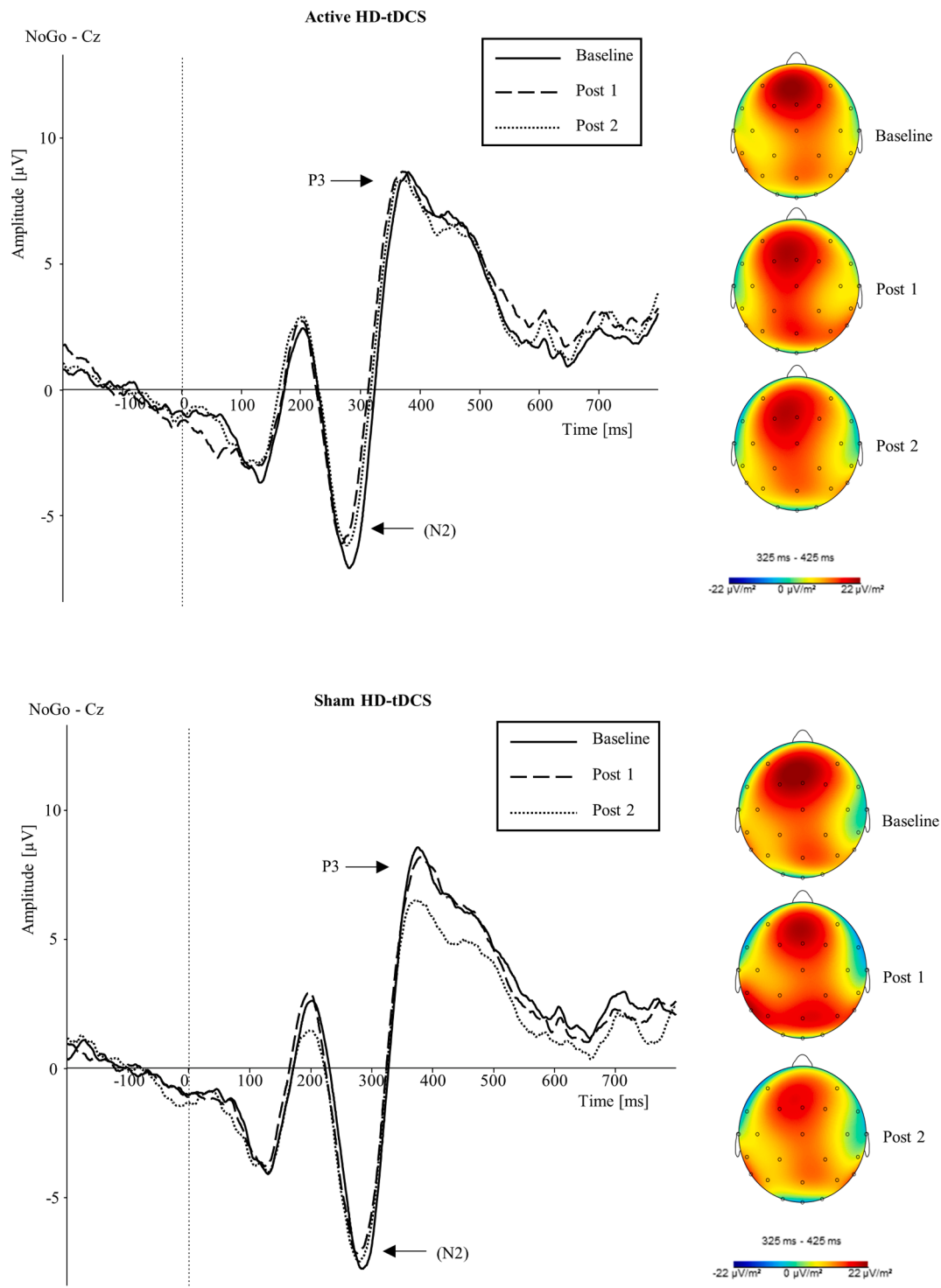


Fig. 2. NoGo P3 activity for Active and Sham HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 min after HD-tDCS (Post 2).

was not associated with behavioural outcomes. Another explanation for the lack of changes in behavioural outcomes might be blinding efficacy and the single-blind design of the current study. Participants were not explicitly asked about blinding and this can be regarded as a limitation.

The lack of behavioural performance enhancement after HD-tDCS does not render neurophysiological modifications irrelevant as a reflection of changes in impulsivity. Few studies to date have investigated the effects of prefrontal tDCS on the NoGo P3 ERP. In line with the current results, prior research has shown decreased NoGo P3 amplitudes after anodal tDCS over the prefrontal cortex, without related changes in

accuracy on inhibitory control trials (Campanella et al., 2017; Cunillera et al., 2016; Verveer et al., 2020). It has been suggested that the P3 reflects the inhibition of motor processes (Band and Van Boxtel, 1999; Smith et al., 2008), and therefore lower P3 amplitudes after (HD-)tDCS may indicate that less neural resources are needed to reach similar motor response inhibition levels as before neurostimulation (Cunillera et al., 2016). Of note, the electrical currents induced by HD-tDCS travel through other brain areas before reaching the dACC. One of these areas is the pre-supplementary motor area (pre-SMA; To et al., 2018); a brain region involved in motor response inhibition during simple Go-NoGo

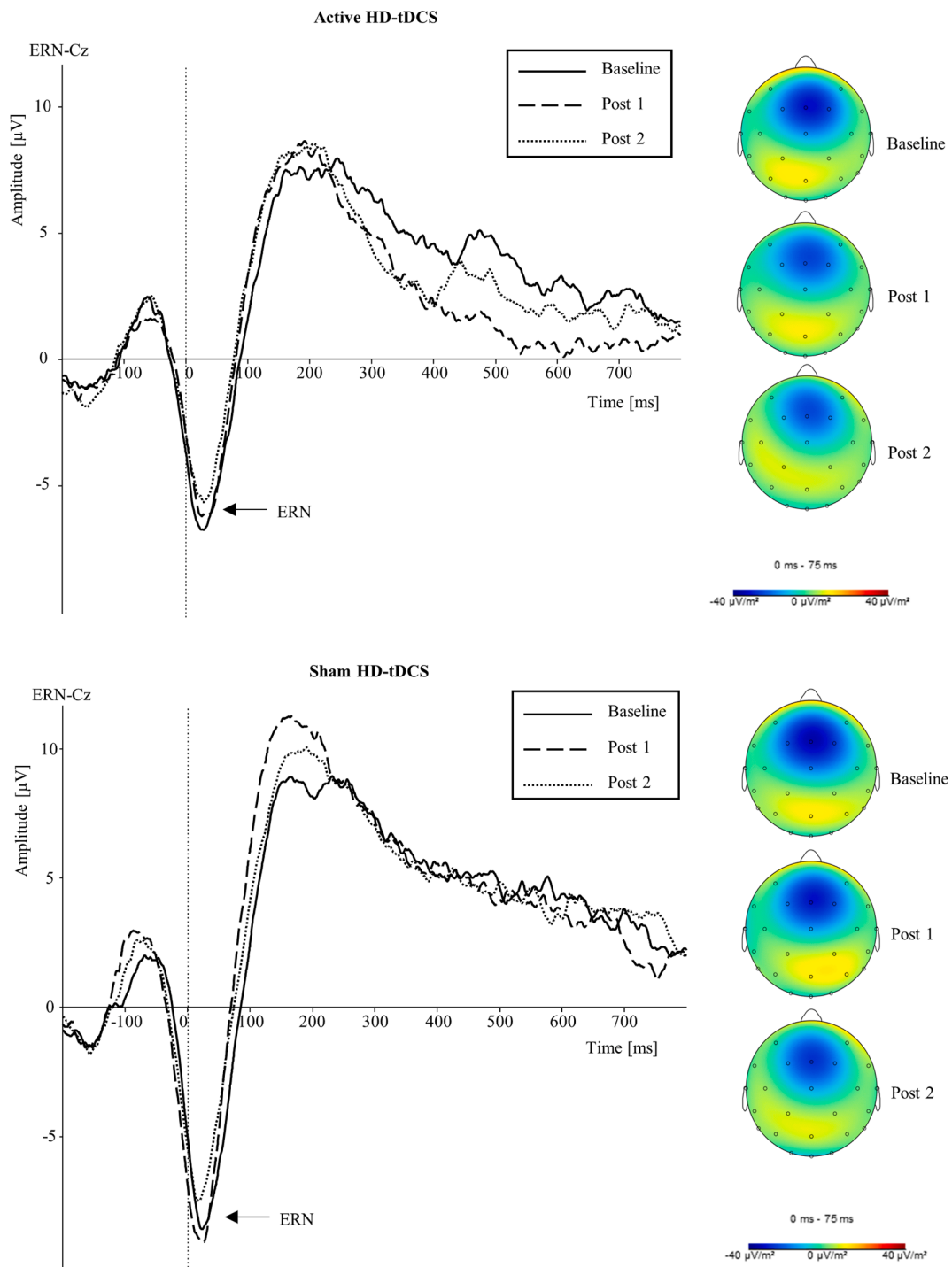


Fig. 3. ERN activity for Active and Sham HD-tDCS at baseline, directly after HD-tDCS (Post 1) and 30 min after HD-tDCS (Post 2).

tasks (Garavan et al., 2006; Mostofsky et al., 2003). We therefore argue that the modulation of neurophysiological correlates of motor response inhibition might be the result of our HD-tDCS montage affecting motor areas. Alternatively, other areas related to inhibitory control, such as the right inferior frontal gyrus (rIFG) and dorsolateral prefrontal cortex (DLPFC), may have been modulated by HD-tDCS, in line with previous results after conventional tDCS over these areas (Campanella et al., 2017; Cunillera et al., 2016; Verveer et al., 2020) and in line with our computational model suggesting stimulation of these brain regions before reaching the dACC (Fig. 5).

Modulation of the ERN component after HD-tDCS may be more

directly linked to modulation of the dACC, as the ERN is generated from the dACC (e.g. Wang et al., 2005). We are unaware of any previous studies reporting tDCS-induced changes in the ERN amplitude, however, modulation of this component has recently been reported following high frequency repetitive transcranial magnetic stimulation (rTMS) over the dACC (Carmi et al., 2018). Due to the lack of behavioural changes in error processing, we again speculate that smaller amplitudes after HD-tDCS indicate improved efficiency regarding the use of neural resources for error processing. It may also be that HD-tDCS caused a shift in brain activity, focalized towards the dACC, resulting in decreased NoGo P3 and ERN amplitudes over central electrode sites.

HD-tDCS targeting the dACC did not result in significant modulations of NoGo N2 amplitudes. As the NoGo N2 is reflective of early conflict detection needed to initiate inhibitory control, the lack of change is in line with the absence of behavioural performance modulations. It was somewhat surprising that we observed no change in the NoGo N2 ERP, as it is generally assumed NoGo N2 amplitudes are generated from the dACC. Yet, it has also been proposed that the inferior frontal cortex (IFC) may contribute to the initiation of N2 amplitudes (Huster et al., 2013). However, when the IFC was targeted with conventional tDCS in previous studies, N2 amplitudes were also not modulated (Campanella et al., 2017; Cunillera et al., 2016).

Regarding the current results, there are some limitations. First, it is important to keep in mind that this was a proof-of concept study. Although our computational models indicated that the present HD-tDCS montage could induce electric fields within deeper brain regions corresponding to the dACC, it remains uncertain whether one session of HD-tDCS with 1.5 mA intensity is sufficient to stimulate the dACC to the extent required to successfully modulate behavioural performance. In addition, it should be noted that HD-tDCS currents might have spread to other prefrontal areas. Future studies could utilise functional neuroimaging techniques, such as fMRI, to further investigate to what extent this HD-tDCS montage alters activity within the dACC and other areas. Targeting the posterior cingulate cortex (PCC), rIFG and DLPFC may for example also lead to the modulation of impulsive behaviour. Another limitation is that high-trait impulsivity was measured by means of self-report only. Future studies may consider measuring trait impulsivity by means of behavioural and physiological measures, as these might reflect different aspects of impulsivity (Bernoster et al., 2019). Finally, the current study was a multicentre study with a relatively small sample size. Several geographic and environmental factors might have led to confounding effects, which can be avoided with larger samples. Yet, the cross-over design assists with controlling for the many factors that influence interindividual differences in response to HD-tDCS.

In sum, results of the current study indicate that when delivered to individuals with high self-reported trait impulsivity a single session of HD-tDCS over the dACC can modulate ERPs reflecting motor inhibition and error processing, which form two core constructs of impulsivity. We therefore conclude that HD-tDCS has potential to affect neurophysiological components related to impulsivity. HD-tDCS was not sufficient, however, to modulate behavioural performance on the Go-NoGo task. Multi-session HD-tDCS may have a better capacity to induce behavioural changes in impulsivity and warrant future investigation. This proof-of-concept study could be the first step towards an innovative HD-tDCS intervention in clinical samples characterized by high trait impulsivity (e.g. ADHD, SUD, ASPD).

4. Materials and methods

4.1. Participants

Twenty-three healthy right-handed adults (7 males, 16 females) were recruited from Melbourne, Australia ($n = 14$) and Rotterdam, The Netherlands ($n = 9$) via online advertisements. All participants scored > 47 ($M = 53.0$, $SD = 4.6$) on the Short Version of the Urgency, Pre-meditation, Perseverance, Sensation Seeking and Positive Urgency Impulsive behaviour scale (SUPPS-P; Smith et al., 2009; Cyders, Littlefield et al., 2014), indicative of high trait impulsivity (see SUPPS-P below for cut-off score rational). All participants were non-smokers, aged between 18 and 55 years ($M = 20$, $SD = 2.5$), and educated for an average of 14 ± 2 years. The sample from Melbourne had a mean age of 21.1 years ($SD = 2.8$) and 14 years of education on average ($SD = 2.2$). The sample from Rotterdam had a mean age of 18.9 years ($SD = 1.1$) and 13 years of education on average ($SD = 1.1$). The samples did not significantly differ in number of male and female participants.

Study exclusion criteria were: 1) Have epilepsy or history of seizures; 2) current or lifetime history of DSM-5 defined mental illness as

determined by the Mini Neuropsychiatric Interview 7.1 (Sheehan et al., 1998); 3) self-reported history of traumatic brain injury, neurological illness or diagnosis of ADHD or learning disorder and; 4) current use of psychoactive medications; 5) Currently pregnant or lactating; 6) left-handedness. Eligibility was assessed by a researcher trained for standardised clinical interviewing. The same experimenter who led the study in Melbourne also performed the study in Rotterdam. Written informed consent was obtained from participants before they entered the study and the protocol was approved by the Monash University Human Research Ethics Committee (MUHREC) and the Ethics Review Committee DPECS at Erasmus University. The study was pre-registered with identifier NCT04290533 at ClinicalTrials.gov.

4.2. Experimental design

The study employed a single-blind, cross-over design, with each participant undergoing two experimental sessions (see Fig. 4). For participants from Melbourne, the sessions took place at BrainPark Monash University, and in Rotterdam at the Erasmus Behavioural Lab. In each session, participants received either active or sham HD-tDCS administered in counter-balanced order. Before (Baseline), directly after (Post 1), and 30-minutes after HD-tDCS (Post 2), participants performed the Go-NoGo task whilst EEG was recorded. Post 2 data was collected, as maximal excitation following HD-tDCS can occur temporally downstream from stimulation delivery (Kuo et al., 2013). The first session had a total duration of approximately two hours. The second session took place after a wash-out period of at least 3 days ($M = 7.1$ days, $SD = 3.9$ days), and had a duration of approximately 1.5 h. The variation in number of days between sessions did not correlate with any of the outcome measures. In addition, there were no systematic biases in between session timing (first or second) of the active and sham stimulation conditions for the number of days interval. After both sessions, all participants were reimbursed with a financial compensation of 50 AUD (30 euro).

4.3. Materials and measures

4.3.1. High-Definition transcranial Direct current stimulation

HD-tDCS was delivered by a battery-driven, wireless, multichannel Starstim neurostimulator system (Neuroelectronics, Barcelona, Spain). Direct currents were transmitted through five circular Ag/AgCl PiStim "High-Definition" electrodes that were applied with conductive gel (gel-skin contact area: $\sim 25 \pm 2.5$ mm²) and embedded within an actiCAP (Brain Products, Munich, Germany). The circular shape and smaller size of these electrodes as compared to conventional tDCS electrodes, enables more focal stimulation (DaSilva et al., 2015). The placement of the electrodes was determined by the International 10–20 System, with the anodal electrode placed over the scalp region overlying the dACC (Fz) and four return electrodes montaged over the forehead (Fp1, Fp2, F7, and F8; To et al., 2018). HD-tDCS stimulation duration was 20-minutes, with a 60-second ramp at the beginning and end of the session.

Before commencement of the study, the HD-tDCS montage was modelled with both 1 mA and 1.5 mA intensities to compare the associated electric field strengths used in this study with the one previously used to target the dACC (To et al., 2018). Computational electric field models were conducted using the SimNIBS software (www.simnibs.org; Thielscher et al., 2015) incorporating the extended MNI head model ("MNIhead") included with the software. The model indicated that 1.5 mA would achieve greater impact on brain regions approximating the dACC compared with the 1 mA intensity, which was shown to achieve only minimal current flow across this region (see Fig. 5). After additional piloting, which confirmed the tolerability and potential for blinding of stimulation at 1.5 mA, we deemed this intensity preferable for use in the present protocol.

For the sham-condition, the placement of the electrodes was identical to active HD-tDCS condition. To assist with participant blinding, a

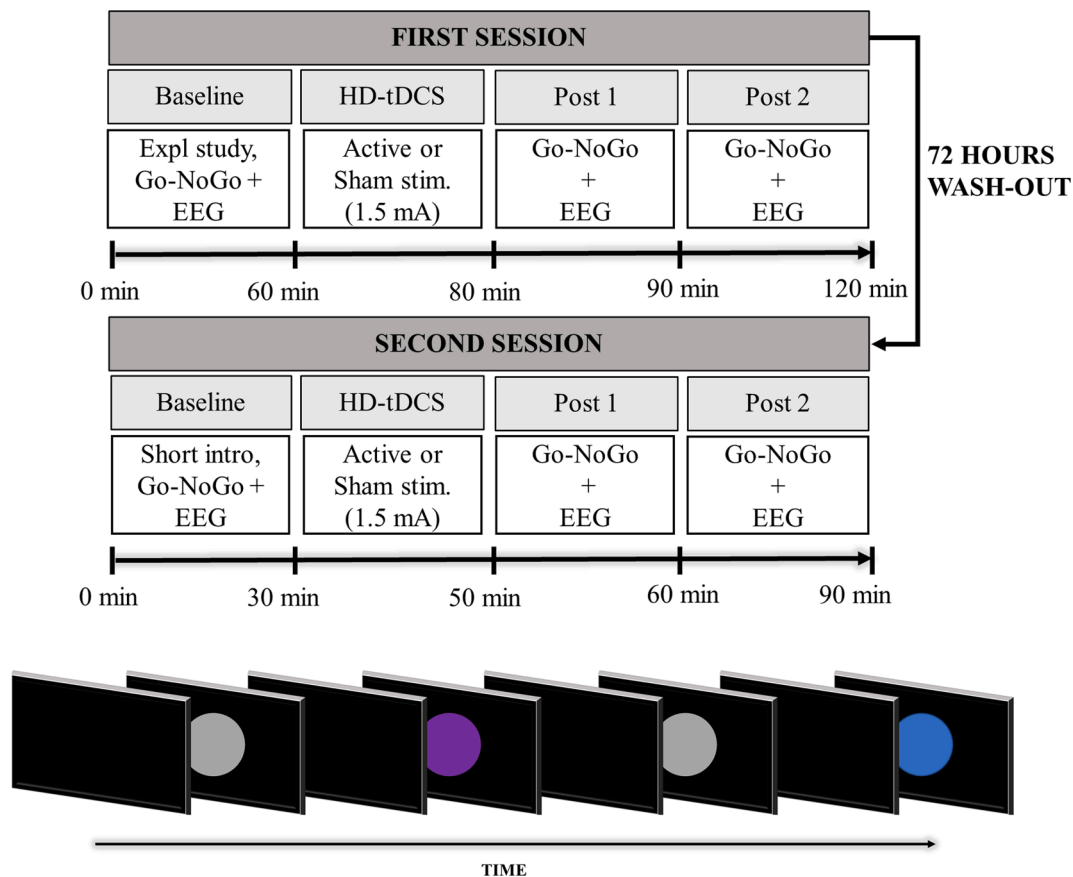


Fig. 4. Study design with example of the Go-NoGo task (grey circles represent Go trials, purple circles reflect IfGo trials, and blue circles are NoGo trials). Individuals with high trait impulsivity received either active or sham HD-tDCS targeted to the dACC (1.5 mA, 20 min stimulation) during the first session. At baseline, directly after (Post 1) and 30 min after HD-tDCS (Post 2) the Go-NoGo task was performed while EEG was recorded. During the second session, participants received the alternate HD-tDCS condition (session order counterbalanced).

60-second active ramp-up phase was applied, identical to the active HD-tDCS condition, however at conclusion of this ramp-up when the current reached 1.5 mA current intensity was gradually ramped down again to 0 mA over the next 60 s (To et al., 2018). The current was then held at 0 mA for the remaining 18-minutes. These sham procedures mimic the transient skin sensation frequently reported at the beginning of active HD-tDCS without producing any conditioning effects on the brain (e.g. Gandiga et al., 2006; Woods et al., 2016).

4.3.2. HD-tDCS tolerability

Immediately following the stimulation period, the intensity of any cutaneous sensations associated with HD-tDCS administration was assessed on a 5-point Likert scale (1 = no sensation, 5 = extreme sensation). The following sensations were rated: itching, burning, or tingling sensations, difficulties with concentrating, acute mood changes, sleepiness, neck pain, and headache.

4.3.3. sUPPS-P

As one of the most accepted theoretical approaches for measuring trait impulsivity (Mallorquí-Bagué et al., 2018), the SUPPS-P (Smith et al., 2009; Cyders et al., 2014) was used to measure trait impulsivity. The SUPPS-P is a widely used validated 20-item scale that measures five dimensions of impulsive behavior: negative urgency, premeditation, perseverance, sensation seeking and positive urgency. Participants are asked to indicate how strongly they agree or disagree on a 4-point Likert scale (1 = agree strongly to 4 = disagree strongly) with statements that relate to impulsive tendencies, such as “When I feel bad, I will often do things I later regret in order to make myself feel better now” and “I tend to lose control when I am in a great mood”. The SUPPS-P demonstrates

strong internal consistency coefficients (0.74–0.88). In addition, the factor structure is comparable to the widely used and well-validated full 64-item version of the UPPS-P (Whiteside et al., 2005; Cyders et al., 2014).

The cut-off score of 47 applied in the current study to indicate high trait impulsivity was determined following analysis of a large database ($n = 485$) of impulsivity, compulsivity and mental health questionnaires completed by a healthy community sample as part of an ongoing unrelated research study at Monash University BrainPark. For this dataset the mean SUPPS-P score was 38.7 ± 8.4 . Thus, the current cut off score represents 1 SD above the mean of a large community sample, indicating the upper end of the community population distribution. We subsequently collected SUPPS-P data from a local community sample in Rotterdam ($n = 387$) and found comparable SUPPS-P scores ($M = 42.3$, $SD = 7.5$).

4.3.4. Go-NoGo task

The Go-NoGo task is one of the most commonly used cognitive tasks to measure inhibitory control processes (Luijten et al., 2014). Three different stimuli are presented in this Go-NoGo task, namely Go stimuli (grey circle), IfGo stimuli (purple circle) and NoGo stimuli (blue circle; see Fig. 4). IfGo stimuli are basically go stimuli with a different colour, added in this version of the Go-NoGo task to control for attentional processes. The rationale is that NoGo stimuli are more attentionally demanding compared to Go stimuli (Gao et al., 2017), and may therefore evoke larger brain responses which are not merely related to response inhibition (Hong et al., 2017).

During the task, participants must press a button as fast as possible for Go stimuli and IfGo stimuli. For NoGo stimuli, participants are

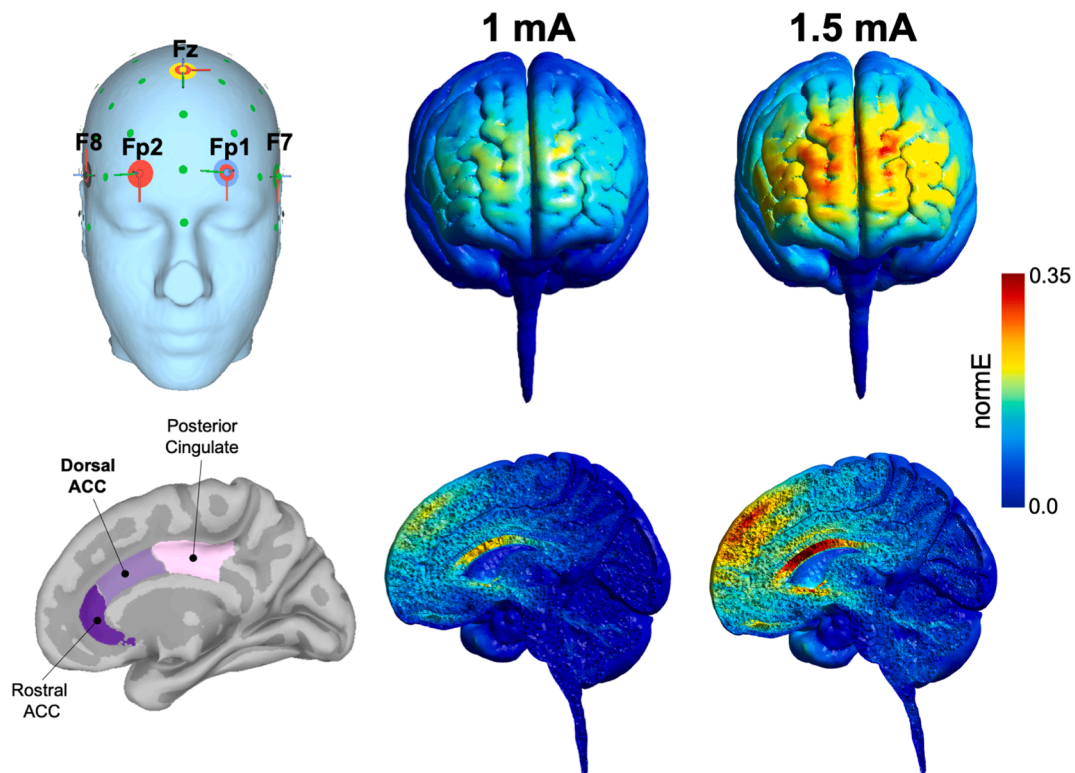


Fig. 5. Computational model of HD-tDCS stimulation with 1 mA and 1.5 mA intensity using the SimNIBS software (www.simnibs.org; Thielscher et al., 2015).

instructed to withhold their response. The task starts with 10 practice trials and comprises a total of 383 trials. Of all trials, 249 (65%) are Go stimuli, 67 (17.5%) are IfGo stimuli and 67 (17.5%) are NoGo stimuli (Dieleman et al., 2020). Stimuli are displayed for 600 ms, followed by a black screen with a duration varying between 900 ms and 1100 ms. The total duration of the task is about ten minutes, including two short breaks.

4.4. EEG recording and processing

EEG activity was recorded using a Brain Products recorder (Brain-Products GmbH, Munich, Germany). Silver chloride (Ag/AgCl) active electrodes were positioned according to the International 10–20 system (F3, F4, FC1, FCz, FC2, FC5, FC6, C3, Cz, C4, CP1, CP2, CP5, CP6, T7, T8, P3, Pz, P4, P7, P8, O1, Oz, O2). Note that brain activity was not recorded over electrode sites Fz, Fp1, Fp2, F7, and F8 since these were used for HD-tDCS electrodes. Two EOG electrodes, above and below the left eye, measured eye movements and two additional external electrodes were placed over the mastoids. All signals were digitized with a sampling rate of 5000 Hz, a 16-bit A/D conversion and a low pass filter of 28 Hz.

Data were processed offline using BrainVision Analyzer 2 (Brain Products GmbH, Munich, Germany). The data were first re-referenced to the mastoids. EEG and EOG data were filtered using a low cutoff of 0.10 Hz and high cutoff of 30 Hz (24 dB/octave slope). Data were segmented into epochs from 200 ms before to 800 ms after response or stimulus presentations. The Gratton and Coles algorithm was used for ocular correction (Gratton et al., 1983). All ERPs were baseline corrected, with the mean 200 ms pre-stimulus period serving as baseline. Artefact rejection was performed with the criterion minimum and maximum baseline-to-peak – 100 to + 100 μ V.

For response inhibition, grand averages were obtained from the correct NoGo trials (segments with incorrect responses were excluded). The N2 was defined as the average negative waveform within the 225–325 ms interval post-stimulus onset and the P3 was determined as

the average value within 325–425 ms after stimulus onset. The time intervals for the N2 and P3 were based on previous literature and verified via visual inspection (e.g. Luijten et al., 2011). For error processing, grand averages were calculated for incorrect button presses. The ERN was quantified as the mean amplitude measure in a time window of 0 to 75 ms after erroneous responses to NoGo trials (Littel et al., 2012). All ERP components in the current study peak over frontocentral sites, therefore the main analyses of ERP data were restricted to electrodes FCz and Cz (Kiefer et al., 1998; Overbeek et al., 2005).

4.5. Data analyses

To include participants with missing data and to fit the nested data structure, multilevel analyses were performed in R using the lme4 package (Bates et al., 2014). Multilevel modelling has been recommended as an approach to investigate change in ERPs across the course of an experiment. That is, multilevel models are one of the most flexible and appropriate methods for repeated-measures designs as they can account for a number of unique sources of variability; are robust to missing observations; and allow for both categorical and continuous predictors at any level of the model (see Volpert-Esmond et al., 2018 for further detail).

Baseline, Post 1, and Post 2 measurements of performance outcomes and ERPs were defined at Level 1, and Participants at Level 2, with Condition (sham HD-tDCS vs. active HD-tDCS) as predictor variable (e.g., Hox, 2010; for a general overview of multilevel analysis procedures). Consistent with previous literature, electrode (FCz and Cz) was added as crossed random factor (Judd et al., 2012; Volpert-Esmond et al., 2018). With this procedure it cannot be tested whether effects of HD-tDCS vary across different electrode sites. Therefore, we conducted additional multilevel analyses for ERPs measured over single electrode sites FCz and Cz.

Separate multilevel analyses were conducted for every outcome variable. Performance on the Go-NoGo task was assessed by the percentage of accurate inhibited NoGo trials, reaction times on Go trials,

and reaction times post errors. For ERP analyses, separate models were fitted to NoGo N2 and P3 amplitudes and to the ERN. EEG data that resulted in too few analyzable ERP segments (≤ 10) as a result of artifact rejection or too few errors (for the ERN) were excluded from analyses. Table 2 shows the number of participants included for each condition.

First, a baseline model was fitted to every outcome variable, including random intercepts across participants (M0). With this model, it was assessed whether multilevel analysis was required. The intraclass correlation ($ICC = \rho = \frac{\sigma_{\mu}^2}{\sigma_{\mu}^2 + \sigma_{\epsilon}^2}$) was consequently calculated using the baseline models' results as an indication of the proportion of total variance explained by the subject variation at Level 2. By significant variance at Level 2, the other models were fitted. The second model included the Level 1 predictors as fixed effects (M1). This model was further extended by adding random slopes for Time (M2). Next, the Level 2 predictor Condition was added to the model (M3). The final model (M4) included cross-level interactions between Level 1 variables and the predictor variable Condition at Level 2. The fit of the models was compared using a significance test on the deviance statistics. The assumptions of normality and linearity were assessed by inspecting the residuals of each best fitted model. Unless otherwise reported, the assumptions were met.

CRedit authorship contribution statement

Ilse Verveer: Conceptualization, Methodology, Validation, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization, Project administration, Funding acquisition. **Aron T. Hill:** Methodology, Software, Data curation, Writing - original draft, Visualization. **Ingmar H.A. Franken:** Conceptualization, Methodology. **Murat Yücel:** . **Josanne N.C. van Dongen:** Software. **Rebecca Segrave:** Conceptualization, Methodology, Validation, Resources, Software, Writing - original draft, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brainres.2021.147282>.

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