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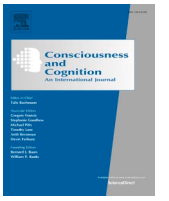

Optimised Multi-Channel Transcranial Direct Current Stimulation (MtDCS) Reveals Differential Involvement of the Right-Ventrolateral Prefrontal Cortex (rVLPFC) and Insular Complex in those Predisposed to Aberrant Experiences

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ABSTRACT

Research has shown a prominent role for cortical hyperexcitability underlying aberrant perceptions, hallucinations, and distortions in human conscious experience – even in neurotypical groups. The rVLPFC has been identified as an important structure in mediating cognitive affective states / feeling conscious states. The current study examined the involvement of the rVLPFC in mediating cognitive affective states in those predisposed to aberrant experiences in the neurotypical population. Participants completed two trait-based measures: (i) the Cortical Hyperexcitability Index_II (CHi_II, a proxy measure of cortical hyperexcitability) and (ii) two factors from the Cambridge Depersonalisation Scale (CDS). An optimised 7-channel MtDCS montage for stimulation conditions (Anodal, Cathodal and Sham) was created targeting the rVLPFC in a single-blind study. At the end of each stimulation session, participants completed a body-threat task (BTAB) while skin conductance responses (SCRs) and psychological responses were recorded. Participants with signs of increasing cortical hyperexcitability showed significant suppression of SCRs in the Cathodal stimulation relative to the Anodal and sSham conditions. Those high on the trait-based measures of depersonalisation-like experiences failed to show reliable effects. Collectively, the findings suggest that baseline brain states can mediate the effects of neurostimulation which would be missed via sample level averaging and without appropriate measures for stratifying individual differences.

Abbreviations: AHE, Aura-like Hallucinatory Experiences; AIC, Anterior Insular Cortex; BF, Bayes Factor; BTAB, Body-Threat Assessment Battery; CDS, Cambridge Depersonalisation Scale; CHI_II, Cortical Hyperexcitability Index II; DLE, Depersonalisation-like Experiences; DPD, Depersonalisation Disorder; DVP, Distorted Visual Perception; E/I, Excitatory/Inhibitory Balance; FDR, False Discovery Rate; HVSD, Heightened Visual Sensitivity and Discomfort; MtDCS, Multi-channel Transcranial Direct Current Stimulation; NS-SCR, Non-specific Skin Conductance Response; rTMS, Repetitive Transcranial Magnetic Stimulation; rVLPFC, Right Ventrolateral Prefrontal Cortex; SCR, Skin Conductance Response; tDCS, Transcranial Direct Current Stimulation.

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1. Introduction

Cortical hyperexcitability is defined as a heightened activation of neural activity in particular systems (Haigh et al., 2012). Aberrant levels of neural excitation have been associated with the co-existence of both elementary and complex hallucinations in visual and other sensory systems (de Boismont, 1853; Siegel, 1977; McGuire et al., 1993; Panayiotopoulos, 1994, 1999; Manford & Andermann, 1998; Bien et al., 2000; Bressloff et al., 2001, 2002; Braun et al., 2003; Sass & Parnas, 2003; Taylor et al., 2003; Allen et al., 2008; Elliott et al., 2009a, 2009b; Braithwaite, Broglia, et al., 2013; Braithwaite, Marchant, et al., 2015; Braithwaite, Mevorach, et al., 2015). Consequently, elevated levels of cortical hyperexcitability are seen as having a pivotal role underlying aberrations of human conscious experience.

In general, such anomalous experiences occur in concert with underlying neurological disorders and clinical conditions such as; (i) migraine with aura, (ii) complex partial seizures (epilepsy) of the temporal lobe, (iii) the Charles-Bonnet syndrome, (iv) psychoses, (v) schizophrenia, (vi) visual stress, and (vii) drug-intoxication (for overviews see; Leão, 1951; Siegel, 1977; Salanova et al., 1992; Ffytche et al., 1998; Ffytche & Howard, 1999; Panayiotopoulos, 1999; Palmer et al., 2000; Hadjikhani et al., 2001; Lauritzen, 2001; Burke, 2002; Braun et al., 2003; Merabet et al., 2003; Allen et al., 2008; Braithwaite, Marchant, et al., 2015; Baumeister et al., 2017; Fong et al., 2020). In addition, neuroimaging studies have shown that the phenomenological content of migraine aura varies with the rate and range of cortical hyperexcitability in sensory cortex – evidencing a link between the presence of hyperexcitable neural states and the contents of visual hallucinations (Hadjikhani et al., 2001).

What is particularly striking is that elevated levels of cortical hyperexcitability have also been revealed in neurotypical groups in the complete absence of a tractable underlying pathology (Ohayon, 2000; Johns & Van Os, 2001; Barkus, et al., 2007; Braithwaite et al., 2011; Diederen et al., 2012; Braithwaite, Broglia, et al., 2013; Preti et al., 2014; Braithwaite, Marchant, et al., 2015; Braithwaite, Mevorach, et al., 2015; Kråkvik et al., 2015; McGrath et al., 2015; Van Os & Reninghaus, 2016; Baumeister et al., 2017). The emerging view is one of a continuum of cortical hyperexcitability / predisposition to aberrant perceptions along which individuals can be placed (Tien, 1991; Van Os et al., 2009). Crucially, the presence of such experiences in neurotypical groups provides insight not only into the characteristics of aberrant experience that require explanation, but also more fundamental aspects of human consciousness.

1.1. Depersonalisation-like experiences

The typical daily experience of self-consciousness consists of; being the agent of one's thoughts, feelings, and actions, stable embodiment and having a salient sense of 'presence' (of being in the here and now) which is the culmination of a legion of multisensory processes (Blanke & Metzinger, 2009; Blanke, 2012; Braithwaite & David, 2016; Dewe et al., 2016). However, the processes facilitating multisensory integration can breakdown leading to striking disorders of consciousness and dissociative states (Brugger, 2002; Critchley et al., 2004; Sanchez-Vives & Slater, 2005; Stein & Stanford, 2008; Blanke & Metzinger, 2009; Craig, 2009; Sierra, 2009; Seth, 2009, 2013; Blanke, 2012; Seth et al., 2012; Clark, 2013; Suzuki et al., 2013; Braithwaite et al., 2014; Kessler & Braithwaite, 2016).

According to the Diagnostic and Statistical Manual 5th Edition / DSM 5, depersonalisation disorder (DPD) is a clinical disorder characterised by dissociative experiences where the patient typically describes a feeling of unreality for the bodily self (depersonalisation), unreality of their surroundings (derealisation) or both (Sierra & David, 2011; American Psychiatric Association, 2013; see also Sierra, 2009 for a review). Patients report feelings of estrangement from themselves; remoteness from their bodies, thoughts, and actions, coupled to a radically altered sense of 'presence' and a dampening of emotional affect (numbness). Collectively, DPD reflects what is, in essence, a profound shift and change in self-consciousness – a sense of 'feeling unreal' (Sierra & Berrios, 1998, 2000; Sierra et al., 2005; Sierra, 2009; Sierra & David, 2011; Medford, 2012; Seth et al., 2012; Seth, 2013; Clark, 2013). DPD can occur comorbidly with other conditions, but also exists in its own right as a specific disorder.

Importantly, unless occurring co-morbidly with other conditions or disorders, DPD is not typically associated with sensory hallucinations or delusions (reality-testing is left intact; Sierra, 2009; Sierra & David, 2011). Instead, the aberrant perceptions are more accurately defined as '*distortions*' in human experience as opposed to perceiving something which has no external reference (e.g., hallucination).

As with the concept of cortical hyperexcitability, "depersonalisation-like experiences" (DLEs) are also reported in the neurotypical/nonclinical population (Sierra, 2009; Dewe et al., 2016, 2018; Sierra & David, 2011; Braithwaite et al., 2020). The prevalence and occurrence of DLE's in the neurotypical population occurs with estimated lifetime rates of between 26 and 74% (Hunter et al., 2004; Michal et al., 2009; Sierra & David; 2011). Accordingly, these experiences reflect many of the thematic components of DPD, albeit in attenuated form (but are no less striking to the observer). Again, aberrant body experiences are a core component of DLEs (Craig, 2009; Sierra & David, 2011; Seth, 2012, 2013; Clark, 2013; Jay et al., 2014, 2016). Conceptually, DLEs themselves can be seen as a continuum, similar to that of cortical hyperexcitability and the concept of Schizotypy (Claridge, 1997), where the frequency and intensity of such experiences can vary on an individual basis. The relationship between DLEs and DPD and whether the presence of increasing DLEs represents a vulnerability to transition to disorder awaits clarification.

Several studies have demonstrated a suppression of autonomic arousal (skin conductance responses / SCRs) to aversive stimuli in DPD patients and similarly in those prone to aberrant DLEs in neurotypical samples (Sierra et al., 2002, 2005; Dewe et al., 2016, 2018; Braithwaite et al., 2020). To account for these observations, researchers have posited a role for a dysfunctional fronto-limbic suppressive network whereby inhibitory networks housed in the right-ventrolateral prefrontal cortex (rVLPFC) are over-active and inappropriately inhibit systems in the anterior insular cortex (AIC), a region responsible for; translating emotion into conscious feeling states, saliency networks, default mode networks, interoceptive awareness, predictive-coding and the mediation of autonomic skin

conductance responses (Sierra & Berrios, 1998; Phillips et al., 2001; Hunter et al., 2003; Phillips & Sierra, 2003; Ochsner & Gross, 2004, 2005; Critchley, 2005; Medford et al., 2006; Eippert et al., 2007; Lemche et al., 2007, 2008; Craig, 2009; Klumpers et al., 2010; Gu et al., 2013; Seth, 2013; Clark, 2013; Jay et al., 2014; Xia et al., 2017; Vinberg et al., 2021).

As a net consequence of these interactions, affective 'feeling states' are divorced from colouring the typical integration between perception and cognition resulting in an attenuated emotional experience, a reduced sense of presence, subjective feelings of 'unreality' and profound alterations in self-consciousness. The above suggestions are also supported by examinations revealing major neuronal projections from the rVLPFC into the AIC and functional imaging, showing that activity in these areas display a functional interdependence – where increased activity in rVLPFC occurred in concert with significantly decreased activation (or absence of activation) in the AIC (see Craig, 2009; Uddin, 2015; Trambaiolli et al., 2022).

Behavioural, brain-imaging and neurostimulation research also support the contention that the rVLPFC has an aberrant over-inhibitory role over the AIC in patients with DPD. Jay et al. (2014) used low-frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) directed at the rVLPFC with DPD patients. The underlying rationale here was to inhibit the brain networks that were thought to be over-inhibiting the AIC, consequently liberating other brain regions receiving major projections from it (the AIC) from such suppressive modulation. Jay et al. (2014) found that the symptoms of DPD were alleviated by low frequency rTMS, as the brain stimulation had an inhibitory effect on inhibitory neural processes. In essence, inhibiting an inhibitory system that is functionally (and anatomically) connected to another neural system, releases these other networks, to function at a more typical level.

Surprisingly, despite aberrant body experiences being identified as a core component of DPD, until recently, body-based aversive imagery or threats have not been used to examine how such stimulation interacts with autonomic responding in such groups. Accordingly, the role of these networks in neurotypical levels of DLEs is unclear. Dewe et al. (2016) (see also, Dewe et al., 2018) were the first to examine DLEs in neurotypical samples where rather than viewing generic images, the observer's own physical body received a threat (via a movie prop syringe). This study provided evidence of suppressed skin conductance responses (SCRs) and autonomic responding to such threats and the magnitude of the suppression was associated with the strength of the DLEs reported. In a parallel development, Braithwaite et al. (2020) introduced a novel Body Threat Assessment Battery (BTAB) that contains dynamic stimuli specifically showing body and non-body (baseline) aversive threats and correspondingly elicit increased autonomic activity (measured by skin conductance responses) to further research body-based processing (and aberrations therein).

1.2. Transcranial direct current brain stimulation

Transcranial direct current stimulation (tDCS) is a safe non-invasive technique of electrical brain stimulation which has been shown to modulate baseline cortical activity in humans (see Nitsche et al., 2008; for a review). Growing evidence suggests that the application of tDCS can modulate cortical excitability, leading to modifications in cognitive and behavioural functions in both neurological/clinical and neurotypical samples (Nitsche & Paulus, 2000; Antal et al., 2003, 2004, 2007, 2011; Nitsche et al., 2008; Vallar & Bolognini, 2011; Jacobson et al., 2012; Braithwaite, Mevorach, et al., 2015).

Although numerous demonstrations of the efficacy of tDCS have been reported, the underlying biophysics of tDCS remains somewhat unclarified. It is generally thought that tDCS exerts its effects by modifying spontaneous neuronal activity via shifting the resting membrane potential in a polarity-dependent manner. By this account, anodal (excitatory) stimulation induces an increase in the background spontaneous firing rate by moving cell membranes more towards a depolarized state thereby making it more likely that they fire. In contrast, cathodal (inhibitory) stimulation reduces cortical excitability by moving cells more towards a hyperpolarized state making them less likely to fire (Lauro et al., 2014).

However, several findings and discussions complicate this simplistic view (Nitsche & Paulus, 2000; Nitsche et al., 2008; Bikson et al., 2016; Parkin et al., 2019; Masina et al., 2021; Lerner et al., 2021) and argue for a more complex account. Individual differences in background baseline neural activity are important for mediating the influence of brain stimulation and hence have implications for examining effects and their subsequent interpretation (Hsu et al., 2016; Romei et al., 2016; Fertonani & Miniussi, 2017; Silvanto et al., 2018; Ovadia-Caro et al., 2019).

These observations highlight that it is becoming increasingly important to measure and take into account potential individual differences in baseline excitability (Benwell et al., 2015; Hsu et al., 2016; Fertonani & Miniussi, 2017; Juan et al., 2017; Dubreuil-Vall et al., 2019) because the differential effects of tDCS may be due to differences in the excitatory/inhibitory (E/I) balance across cortical regions and layers and within their network dynamics (Boroojerdi et al., 2000; Jacobson et al., 2012; Alekseichuk et al., 2016; D'Souza et al., 2016; Romei et al., 2016; De Graaf et al., 2017; Fertonani & Miniussi, 2017; Silvanto et al., 2018; Yang & Sun, 2018). Differences in latent cortical excitability across individuals could thus create heterogeneity in both individual predisposition to aberrant experiences and their responses to tDCS.

However, many previous tDCS studies have focused their analysis at the whole sample level without accounting for background trait or state factors. This may explain, at least in part, failures to replicate findings and why some meta-analyses have failed to find significant tDCS effects (Horvath et al., 2015; Medina & Cason, 2017). Not accounting for baseline excitability may mask or indeed miss subtle, though important, interactions between baseline brain states and stimulation. Current evidence suggests that these network-level interactions play a critical role in mediating the response to low-amplitude brain stimulation (Dmochowski et al., 2011; Miranda et al., 2013; Fox et al, 2014; Ruffini et al., 2014; Kunze et al., 2016; daSilva et al., 2018).

Recent advances and development in technology has resulted in optimised multi-electrode arrays consisting of several anode and cathode configurations, which can be used to simultaneously modulate regions of a distributed functional network model based on electroencephalograph (EEG) systems (Miranda et al., 2013; Ruffini et al., 2014; Fischer et al., 2017; Ruffini et al., 2018). The advantages from this approach are of both methodological and theoretical importance. For example, compared to standard bipolar

methods that utilise large electrodes, a model-driven stimulation design using small electrodes and realistic head models for estimation of current flow, will lead to superior focality and spatial resolution, helping to ensure that the stimulation occurs maximally within the targeted networks and minimally affecting other brain areas (Ruffini et al., 2014, 2018). The increased quantitative properties of multi-channel tDCS (MtDCS) lend themselves to a more precise theory-building process with regards to the targeted brain networks and their ascribed functions.

1.3. Overview:The present study

The present study examined the role of the rVLPFC and its inferred functional relationship with the insula complex in mediating cognitive-affective responses to aversive body-threat stimuli in a neurotypical sample. Participants were measured for: (i) predisposition to aberrant experiences thought to reflect increased degrees of visual cortical hyperexcitability, and (ii) proneness to DLEs. The role of the rVLPFC was assessed via a targeted and optimised MtDCS montage. The montage consisted of multiple anode and cathode electrodes to stimulate this brain region which participates within a distributed functional network. Using electric field modelling techniques, optimal parameters for MtDCS montages were determined (stimulation current and location of all electrodes) to directly identify the optimal targets and parameters for accurate brain stimulation (Miranda et al., 2013; Ruffini et al., 2014, 2018), using a realistic template head model.

In line with previous brain-stimulation findings, brain-imaging and known neuroanatomical pathways, it was assumed that stimulating the rVLPFC would impact the operation of the insula cortex (a region identified as important in saliency networks, default networks, the generation of conscious feeling/states, interoceptive awareness, predictive-coding, and the mediation of autonomic SCRs (Critchley, 2005; Medford et al., 2006; Lemche et al., 2007, 2008; Jay et al.. 2014; Xia et al., 2017; Vinberg et al., 2021) and this would primarily manifest in autonomic SCR responses to body-threat stimuli.

In addition, consistent with findings on transcranial electrical stimulation (tES) (Horvath et al., 2015; Hsu et al., 2016; Romei et al., 2016; Medina & Cason, 2017; Silvanto et al., 2018), it was expected that the efficacy of MtDCS stimulation would not be all-or-none and that stimulation could be mediated further by individual differences in trait-based signs of cortical hyperexcitability. Furthermore, the study was extended to explore if these brain regions may also be implicated in mediating DLEs in neurotypical samples in line with what has been reported for clinically diagnosed depersonalised patients (Jay et al., 2014, 2016). Collectively, the present study sought to quantify trait-based factors pertaining to aberrant experience (potentially reflecting cortical hyperexcitability) by stratifying participants on a recently devised measure (the Cortical Hyperexcitability Index II - CHi_II - Fong et al, 2019; Braithwaite, Marchant, et al., 2015) and on particular factors pertaining to DLEs (the aberrant body experience and alienation from surroundings factors of the Cambridge Depersonalization Scale: Sierra & Berrios, 2000; Sierra et al., 2005).

Previous work on the CHi_II measure revealed a 3-factor solution; "Heightened Visual Sensitivity and Discomfort" (HVSD), Aura-like Hallucinatory Experiences" (AHE) and "Distorted Visual Perception" (DVP) (Fong et al., 2019). Neurophysiological investigations (electroencephalogram EEG / visual evoked potentials VEP) and behavioural work (Pattern-glare tasks) have validated the underlying assumptions of the measure with migraine patients and neurotypical samples showing different performance patterns as a function of the different factors (Fong et al., 2019, 2020). This work also demonstrated that the factor "AHE" best predicted underlying aberrant degrees of cortical hyperexcitability. Therefore, it was taken a-priori as the primary indicator of aberrant hallucinatory experiences most likely mediated by central cortical processes. This factor was used to examine trait-based estimates of baseline neural states mediating the efficacy of the MtDCS procedure.

The current study is also the first to utilise optimised MtDCS to influence the activity in the rVLPFC and indirectly the insula complex to mediate cognitive-affective processes. For this purpose, a specific 7-channel optimised montage was created to target the rVLPFC.

In summary, this study examined the presence of trait-based predisposition to aberrant experience (reflecting increased cortical hyperexcitability) in mediating cognitive-affective responses as a result of optimised MtDCS directed at the rVLPFC. In addition, the sample was also screened for predisposition to DLEs – as these have been thought to reflect aberrant processing in rVLPFC and insula regions. Psychophysiological (skin conductance responses) and psychological responses (ratings) were quantified where participants viewed a novel computer-based task depicting body-threat scenarios (the BTAB: Braithwaite et al, 2020) under different MtDCS conditions.

2. Method & procedure

2.1. Participants

Thirty-five participants were recruited from Lancaster University, Department of Psychology, UK. Participants' ages were between 18 and 25 years (M = 19 years, SD = 1.48) of which, 22 were Female and 13 were Male. Safety and exclusion criteria prevented participants with debilitating fear of blood/gore/needles, any fitted electrical/medical device, a history of psychiatric/dissociative diagnoses as well as epilepsy/fainting/seizures of unknown origin from taking part. The study was approved by the Lancaster University Ethics Committee (FST19024). All volunteers were compensated for their time with course credits.

A-priori sample size estimation could not be straightforwardly based on a power analysis of previous work because of the novelty of the methods used in the current study and their novel combined use. Nonetheless, a-priori estimations of 30 – 35 participants were based on i) exceeding the sample sizes typically used in previous tDCS research (e.g., 13 to 16 participants, e.g., Antal et al., 2003, 2011; Peña-Gómez et al., 2011), and ii) a consideration that testing half the sample size of our previous brain stimulation research

(Braithwaite, Mevorach, et al., 2015) was appropriate given the fact that MtDCS is a far superior method of brain stimulation (focally and in terms of intensity). In addition, the use of Bayes Facor analyses provided further information regarding the strength of evidence for or against the effect of our independent variables (see Results section).

Out of the 35 participants that took part, two participants could not continue due to initial failed impedance (safety) checks on the MtDCS electrodes. A further 5 participants were excluded from analysis as they did not complete all required sessions and thus failed to produce fully balanced data. An additional participant was also removed from analysis as SCR non-responder based on established guidelines (Dawson et al., 2007; Braithwaite, Watson et al., 2013; Boucsein et al., 2012; Braithwaite et al., 2020). The final sample used for analysis consisted of 27 participants, 10 male and 17 female (*M* Age = 19 years, *SD* = 1.53).

2.2. Measures

2.2.1. Screening measures

Two validated screening questionnaires were used to measure individual predisposition to aberrant experiences associated with cortical hyperexcitability and depersonalisation-like experiences.

Cortical Hyperexcitability Index II (CHi_II). This measure examines a collection of aberrant visual experiences thought to reflect the presence of cortical hyperexcitability (Fong et al., 2019). It has high internal consistency and reliability (Cronbach Alpha 0.90). An exploratory factor analysis revealed a three-factor solution as being the most parsimonious: these were "Heightened Visual Sensitivity and Discomfort" (HVSD), "Aura-like Hallucinatory Experiences" (AHE) and "Distorted Visual Perception" (DVP). All factors had loadings of over 0.40 and there were no cross-loadings of the items. For the present study, we focussed on the "AHE" factor as a measure of cortical hyperexcitability as this arguably represents more centrally mediated hallucinatory experiences and has shown greater predictive power with neurophysiological EEG measures (Fong et al., 2019, 2020). Therefore, the AHE factor was used to stratify participants in terms of their baseline cortical hyperexcitability levels and hence to examine the efficacy of MtDCS brain stimulation.

Cambridge Depersonalisation Scale (CDS) - Anomalous Bodily Experiences and Alienation from Surroundings. The CDS examines susceptibility to aberrant and dissociative experiences related to depersonalisation disorder (Sierra & Berrios 2000; Sierra et al. (2005). Previous work has identified four factors (Sierra et al., 2005) – two of which Anomalous Bodily Experiences: (ABE) and Alienation from Surroundings: (AFS) have been shown to work well in neurotypical populations and these factors represent the more core components of DPD, so only these factors were measured and then pooled into one indicator of "depersonalisation-like-experiences" (DLEs: see Braithwaite, Broglia et al., 2013; Dewe et al., 2016, 2018; Braithwaite et al., 2020 for a similar approach). The combined range of scores of the DLE factor (which contains 13 items in total) is 0–130.

The screening measures (CHi_II and DLE) were standardised by dividing their sum by the number of items on that factor (to control for different number of items on each factor).

2.2.2. Multi-channel transcranial direct current stimulation (MtDCS)

An optimised 7-channel montage was created with a weighted target map specifically designed to target the rVLPFC while leaving the rest of the brain maximally unaffected. This was done initially by highlighting the rVLPFC region via the Stimtargeter tool (Neuroelectrics, Barcelona, ESP) to create a weighted target map for montage optimisation performed by the Stimweaver multi-focal algorithm (Neuroelectrics, Barcelona, ESP) which revealed an optimised solution for the target region (Ruffini et al., 2012, 2014, 2018; Ho et al., 2016). The solutions were modelled on a standard generic reference brain, which was also used to determine the optimised montage.

The design of this focal montage was based on a weighted target map reflecting with a strong weight (W = 10) the desired normal electric field on the rVLPFC cortical surface (E = 0.25 V/m) with the additional requirement of zero electric field on the rest of the brain (W = 10). The final optimization chosen was a montage with the best goodness of fit metric ERNI (error with respect to no intervention) for focusing on the target required to be stimulated [resulting in WCC (Weighted cross correlation of target map and delivered field) = 0.53 and ERNI = −4245 mV^2/m^2 – Fig. 1]. The high definition headcap provides 64 points based on a subset of the 10–10 EEG system (Seeck et al., 2017) for electrode positioning. The electrodes identified for optimal ERNI were AF8, F6, F8, AF4, FC4, FP1, T8 for stimulation (see Fig. 2 and Table 1). The polarity of the electrode combination was determined by the condition (Anodal or Cathodal), i.e., the cathodal condition montage was obtained by reversing the currents in the anodal condition. For safety, during optimization, the total output was constrained to not exceed 2 mA and each stimulation electrode was capped at a maximum current of 1 mA. The stimulator used was Starstim 8 controlled by the NIC2 Software (Neuroelectrics, Barcelona, ESP).

Stimulation occurred for 11 mins in total per session which included a ramp-up (30secs) and ramp-down period (30secs) of electrical current (10mins of full stimulation). In the Sham condition, the stimulator only used the ramp-up and ramp-down protocol to mimic the experience of stimulation. Each participant completed three neuromodulation sessions (Anodal, Cathodal and Sham) in a randomised order and were blind[1] to the nature of the conditions. Sessions were a minimum of one week apart to wash out any potential carry-over stimulation effects across sessions.

[1] Of note, the efficacy of the blinding procedure was not examined in this study.

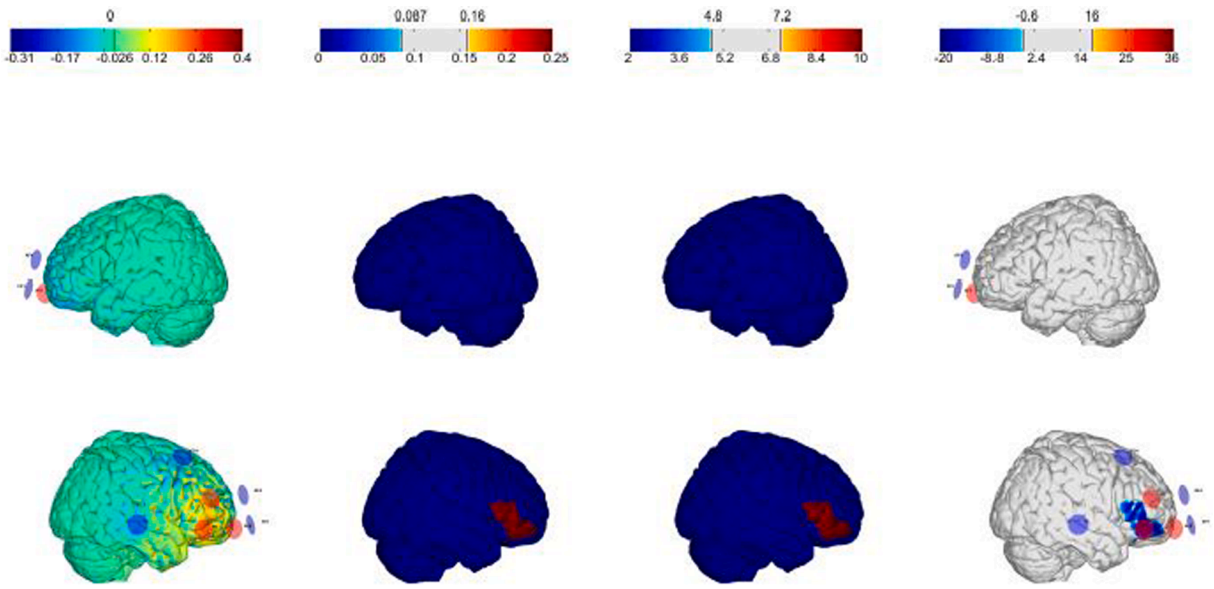

Fig. 1. Optimisation Montage for Anodal Condition: IMax,total = 2 mA, 7 electrode montage, IMax = 0.973 mA, Note: From left to right: Normal component of the E-field En (V/m), target E-field (V/m), target weight and ERNI (mV2/m2) for grey matter.

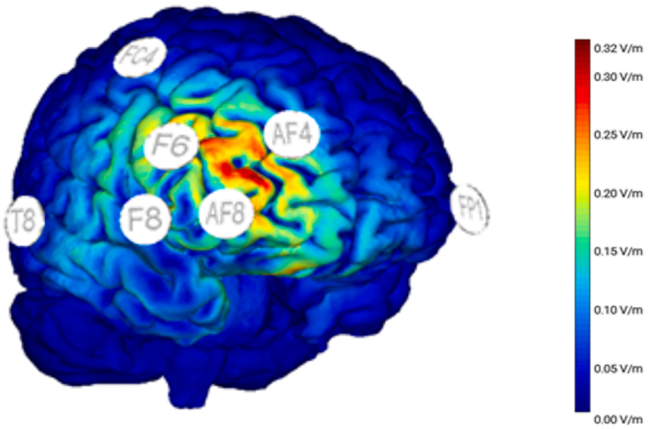

Fig. 2. Representation of the placement of electrodes over the rVLPFC. Note: AF8, F6 and F8 as stimulation channels and AF4, FC4, FP1 and T8 as return channels and magnitude of the electric field.

Table 1
The optimised weighted channels for the Anodal condition from the optimised montage used for the rVLPFC site.

Stimulation Site	Current per electrode (μA)
AF8	755
F6	973
F8	270
AF4	−805
FC4	−563
FP1	−312
T8	−318

Note: Polarities of the applied current per electrode were reversed for the Cathodal condition.

2.2.3. The Body Threat Assessment Battery (BTAB)

The BTAB consists of a selection of high-definition dynamic clips depicting various threats directed to a human body and non-body baselines (Braithwaite et al. 2020). The original task contained 12 body-threat clips (6 from an Egocentric perspective and 6 from Exocentric perspective) and 3 non-body baseline stimuli. In the original study, each clip was shown individually, and normative psychological ratings (arousal, valence, sense of pain, and realism of threat) and psychophysiological responses (Specific threat-related SCRs and non-specific SCRs) were determined (Braithwaite et al., 2020). In addition, at the beginning of the threat clips a 'set-up shot' (an upper body/torso) was included to avoid startle responses and artefacts in the SCRs at the start of stimuli presentation.

The present study used a modified a blocked design (programmed in E-Prime 3.0) where the clips (i.e., a series of threats) were grouped together with the psychological ratings coming at the end of this short series of clips. In each session, participants viewed a total of 10 stimuli separated into three blocks (2 baseline, 4 Ego Threat and 4 Exo Threat). The clips chosen were pseudo-randomised according to the $\bar{X}$ SCR (μS) values (where $\bar{X}$ = mean of difference between SCR onset and its maximum peak and μS = microseimens) described in Braithwaite et al. (2020) so that they were matched in terms of autonomic potency. The 3 blocks of stimuli were randomised within E-Prime 3.0.

Stimuli were presented on a 22 in., 16:9 aspect ratio monitor at 1920 × 1080 resolution, in a darkened room with a viewing distance of ~ 80–90 cm. Additionally, to avoid unfamiliarity to the procedure and stimuli, a practice trial based on a neutral stimulus (body-based setup with a non-threatening stimulus i.e., brush stroking and arm) was shown along with an example on how to complete the rating scale (arousal, valence, pain and realism of threat) questions before stimulation began (see Fig. 3). The total time taken for participants to complete this task was ~ 7 min (5 min to view all video clip blocks and ~ 2 min to answer the psychology self-report ratings).

2.2.4. Psychological self-report ratings

During the BTAB task, participants were asked to report their experiences after each block had finished. These subjective ratings were based on a Likert-type scale across 4 dimensions, namely, emotional valence (−5 to +5), emotional arousal (0 to 9), experience of illusionary/sensory pain (0 to 9) and realism of threat (0 to 9).

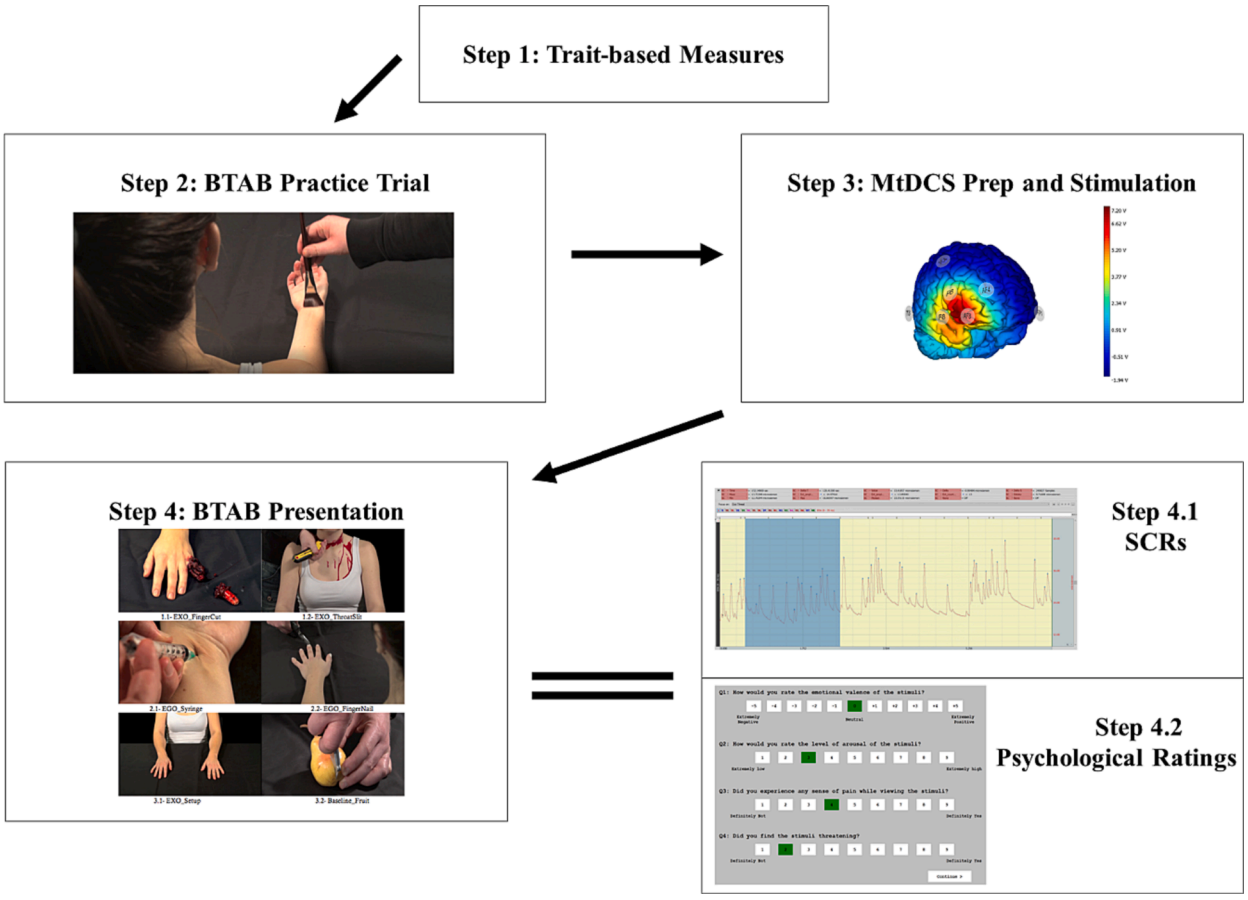

Fig. 3. A schematic illustration of the present procedure completed in Session 1. Note: The screening measures were not repeated in Sessions 2 and 3 as these were trait-based measures and were not dependent on the stimulation.

2.2.5. Skin conductance responses (SCRs)

SCRs were obtained using a BIOPAC MP36R data-acquisition unit (BIOPAC Systems Inc., Goleta, CA). This was connected to a PC running 64-bit Windows 10 Home. All signals were recorded with a 0.05 Hz high-pass filter and sampled at 2000 Hz. Data were collected by applying a small continuous low voltage (0.5 V) current through two disposable pre-gelled EL507 electrodes attached to SS57L sensor leads. The electrodes and leads were attached to the distal phalanges of the index and middle finger on the left hand of the participant. These were attached 10 mins before data was acquired to obtain the clearest/high quality signal.

All SCR responses were gathered and processed in BIOPAC AcqKnowledge v5.0 (BIOPAC Systems Inc., Goleta, CA). An SCR was defined as a magnitude delta function (μS), between the peak value and SCR onset (for more detail, see Braithwaite, Watson et al., 2013; Braithwaite et al., 2020). Where there were no SCRs detected (for a given block), a zero value was recorded. As per Braithwaite et al, (2013), the SCR threshold was set at 0.01 μS. The SCR of interest was defined as the largest/strongest response that occurred during the presentation of a stimulus. All other SCRs during the presentation of the dynamic clips were classed as non-specific SCRs (NS-SCRs) which were analysed for their frequency (F-SCR) and strength as additional measures of autonomic arousal (Nikula, 1991; Boucsein, 2012; Braithwaite et al., 2013b).

All signals were visually inspected for artefacts and when encountered, the signal was down sampled by 200 samples/sec (iteratively) to remove them in that section of the signal. In line with recommended practice, SCR data were normalised by using [SCR (Log + 1)] transformations and standardized by converting to Z-Scores (Dawson et al., 2007; Boucsein et al., 2012; Braithwaite, Watson, et al. 2013; Braithwaite & Watson, 2015; Braithwaite et al., 2020). Previous research (Braithwaite et al., 2020) showed that the two video perspectives (Ego and Exo) were equally efficient at eliciting strong responses and so responses to both viewpoints were combined (average of the largest SCR in each block). Additionally, the Baseline block SCRs, NS-SCRs and F-SCRs were merged into a single Baseline value for analysis.

2.3. Procedure

Each participant began the study by completing the trait-based screening measures (CHi_II and DLE) with order randomised across participants. Following this, participants were shown the practice trial for the BTAB, during which they could ask questions regarding the task. Next, the participants were setup for the MtDCS protocol, which was done in two steps. First, the cranial perimeter / head circumference was measured to find a suitably sized headcap. Second, the headcap was positioned by ensuring the Nasion electrode (FPZ), Central electrode (CZ), Inion electrode (IZ) and the preauricular points (T7 and T8) were correctly aligned on the participant's head (the CZ corresponded to the vertex of the participants' head). Then, the water-soluble electrode gel was injected into each of the 7 stimulation electrodes and subsequently connected to the stimulator (StarStim Necbox 8 – Neuroelectrics, Barcelona, ESP). Safety checks were conducted by confirming the earthing clip (on the earlobe) was secure and the electrodes were guaranteed to be within normal impedance levels (0 – 10 kΩ). In addition, during this stage, the electrodes for the SCRs were attached to the index and middle distal phalanges. Once completed, the stimulator was turned on and stimulation was delivered for 11 mins (including 30 s ramp-up and ramp-down) where safe impedance levels were continuously monitored. During stimulation, participants were asked not to make extraneous movements and to immediately report any adverse effects. Directly after stimulation had ended, the BTAB task began, during which SCRs were recorded (~7 min). This was followed by an exit-questionnaire to ensure that participants did not experience any severely adverse effects[2] during the stimulation. This was repeated for each participant across all sessions (see Fig. 3). Each session took approximately 1.5 h per participant.

3. Results

3.1. Overall statistics

Analyses were conducted using SPSS v27 and JASP v0.14.1. Non-parametric tests (Mann-Whitney U independent samples t-tests, Freidman's χ^2 tests, Kendall's Tau correlations) were conducted for non-normal data. Independent sample t-tests, paired samples t-tests, two-way mixed ANOVAs, within-subject ANOVAs and Pearson's two-tailed *r* correlations were used for the self-report measures to distinguish between the Anodal, Cathodal and Sham data. Where sphericity was violated with an ε of <0.75, a Greenhouse-Geiser correction was used and >0.75, a Huynh-Feldt correction was used. Additionally, all multiple testing was corrected using the False Discovery Rate (FDR) method, FDR correct *p* values are indicated as B&H in the analysis, if the uncorrected *p* value is less than the B&H corrected *p* value, the comparison is considered significant (Benjamini & Hochberg, 1995, see also - Braithwaite et al., 2020).

Comparisons between trait-based predisposition to CHi_II and DLE and responses based on stimulus presentation (psychophysiological and psychological) were achieved through correlational analysis. Follow up analysis was conducted using median splits to identify high and low scorers on each trait-based predisposition screening measure to clarify the pattern of effects for the different stimulation conditions.

Where appropriate, Bayesian statistics (using default Cauchy priors) are reported alongside Frequentist statistics (*p* values). Bayes Factor analysis (BF) not only informs about the alternative hypothesis ($BF_{10} > 1$) but also indicates strength of the null hypothesis ($BF_{10} < 1$). In accordance with Jarosz and Wiley (2014), a BF_{10} between 1–3 would mean the data are inconclusive, 3–10 shows good

[2] See Appendix B. Of note: Adverse symptoms were matched across the three stimulation conditions of MtDCS.

evidence for the alternative, 10–100 as strong and >100 as decisive evidence. For clarity, both BF_{10} (in support of the alternative) and corresponding BF_{01} (support for the null) are provided.

3.2. Psychophysiological responses

Psychophysiological data (magnitudes of SCRs and NS-SCRs) were normalised [Log (SCR + 1)] and standardised using Z-scores.

3.2.1. BTAB maximum SCRs

The baseline stimuli (non-body threat) maximum SCRs and the body-threat stimuli (Threat) maximum SCRs were compared across the three experimental conditions (Anodal, Cathodal and Sham) (Fig. 4). A within-subject ANOVA (with 4 levels, Baseline, Anodal Threat, Cathodal Threat, and Sham Threat) revealed a significant main effect of stimuli type F (3,78) = 5.587, $p < 0.001$, $\eta^2\rho = 0.177$, $BF_{10} = 60.108$, $BF_{01} = 0.017$. Pairwise comparisons using FDR corrections showed that SCRs elicited from viewing the body-threat stimuli were significantly stronger than those elicited from baseline stimuli across all three conditions: Anodal (MD = 0.855, SE = 0.186, $p < 0.001$, B&H = 0.017, $BF_{10} = 270.707$, $BF_{01} = 0.004$), Cathodal (MD = 0.565, SE = 0.191, $p = 0.006$, B&H = 0.033, $BF_{10} = 6.981$, $BF_{01} = 0.143$) and Sham (MD = 0.711, SE = 0.201, $p = 0.002$, B&H = 0.05, $BF_{10} = 23.36$, $BF_{01} = 0.043$).

When analysed at the whole sample level, no reliable differences were observed in the SCRs across the three conditions (Anodal Threat, Cathodal Threat, Sham Threat) by a within-subject ANOVA; F (2,52) = 0.663, $p > 0.05$, $BF_{10} = 0.204$, $BF_{01} = 4.906$. To summarise, in line with previous research, the present sample replicated and showed significantly increased SCR responses to the threat stimuli, relative to baseline stimuli, evidencing that the stimuli were effective at inducing increased autonomic responses. In addition, when viewed across the whole sample, MtDCS did not appear to significantly impact autonomic processes.

3.2.2. BTAB magnitudes of NS-SCRs

Similarly, an analysis of the magnitudes of all non-specific SCRs (NS-SCRs: which were all other SCRs, except the maximum one, that occurred during the viewing of the clip), which provide an index of background autonomic arousal, was conducted using a within-subject ANOVA at 4 levels (Baseline, Anodal Threat, Cathodal Threat and Sham Threat) (Fig. 5). There was a significant main effect of stimuli type F (3,78) = 7.524, $p < 0.001$, $\eta^2\rho = 0.224$, $BF_{10} > 1000$, $BF_{01} < 0.001$. Pairwise comparisons using FDR corrections revealed the baseline block NS-SCR magnitudes were significantly weaker than threat block NS-SCR magnitudes in all three conditions: Anodal (MD = 0.459, SE = 0.112, $p < 0.001$, B&H = 0.017, $BF_{10} = 86.549$, $BF_{01} = 0.012$), Sham (MD = 0.484, SE = 0.118, $p < 0.001$, B&H = 0.033, $BF_{10} = 81.713$, $BF_{01} = 0.012$) and Cathodal (MD = 0.251, SE = 0.114, $p = 0.036$, B&H = 0.05, $BF_{10} = 1.611$, $BF_{01} = 0.621$). However, a within-subject ANOVA comparison between just the threat blocks did not reveal any significant differences in the Frequentist analysis at the whole sample level; F (2,52) = 2.388, $p > 0.05$, $BF_{10} = 1.094$, $BF_{01} = 0.905$.

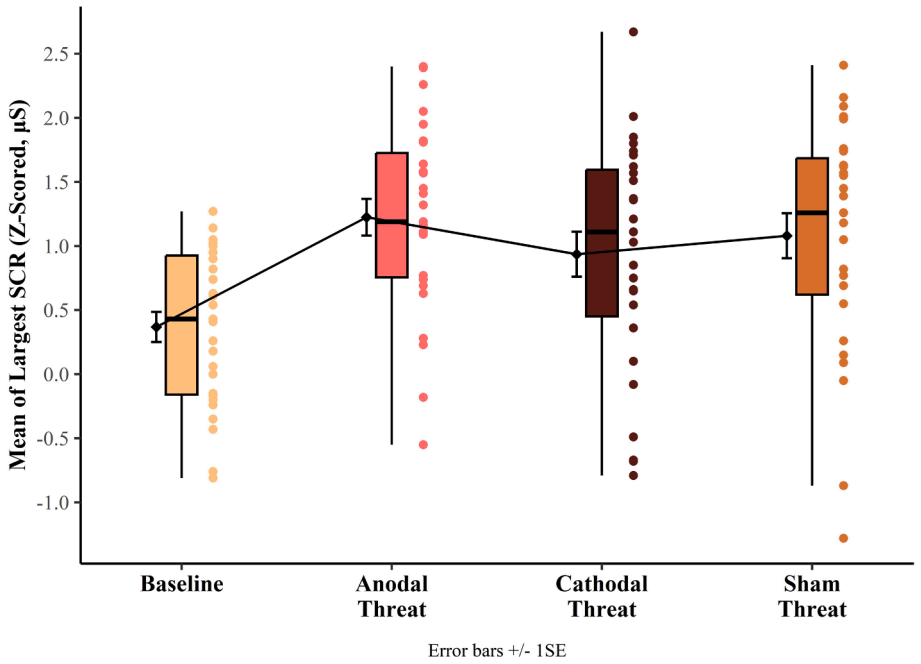

Fig. 4. Comparison of largest SCR (Z- Scored) from each block: Baseline (non-body threat stimuli), Anodal (body-threat stimuli), Cathodal (body-threat stimuli) and Sham (body-threat stimuli).

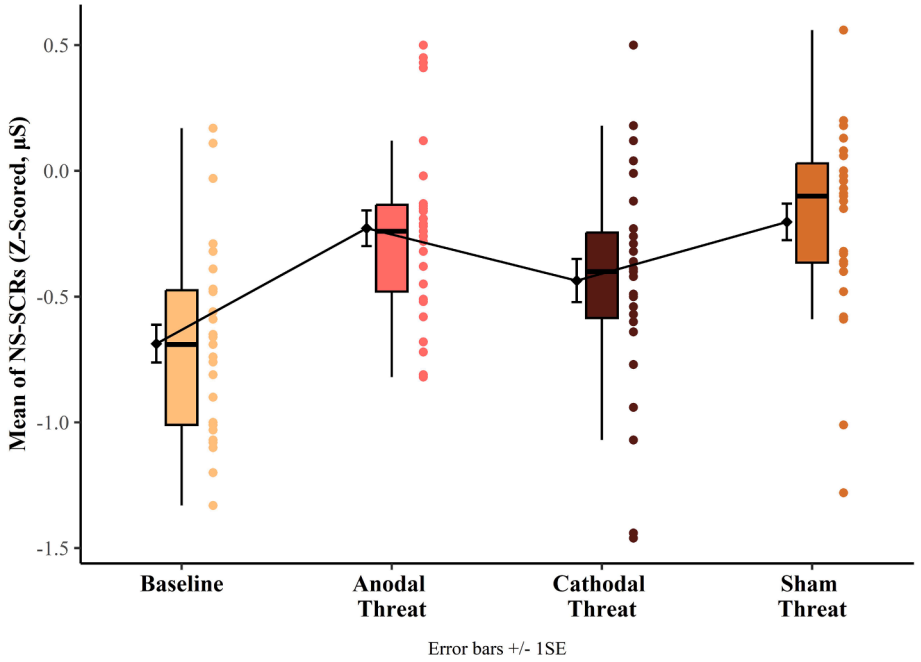

Fig. 5. Comparison of mean NS-SCRs (Z-Scored) from each block: Baseline (non-body stimuli), Anodal (body-threat stimuli), Cathodal (body-threat stimuli) and Sham (body-threat stimuli).

3.2.3. BTAB frequency of NS-SCRs

The frequency of NS-SCRs was defined as the total number of NS-SCRs occurring in each block divided by the duration of the block (count per minute or CPM) (Fig. 6). A within-subject ANOVA was conducted with 4 levels (Baseline, Anodal Threat, Cathodal Threat, Sham Threat) which produced a significant effect of stimuli type - F (3,78) = 5.300, $p < 0.01$, $\eta^2\rho = 0.169$, $BF_{10} = 14.861$, $BF_{01} = 0.068$. Pairwise comparisons with FDR corrections showed that the frequency of NS-SCRs occurring in the baseline block was significantly lower than the threat blocks in Anodal condition (MD = 0.833, SE = 0.178, $p < 0.001$, B&H = 0.017, $BF_{10} = 338.401$,

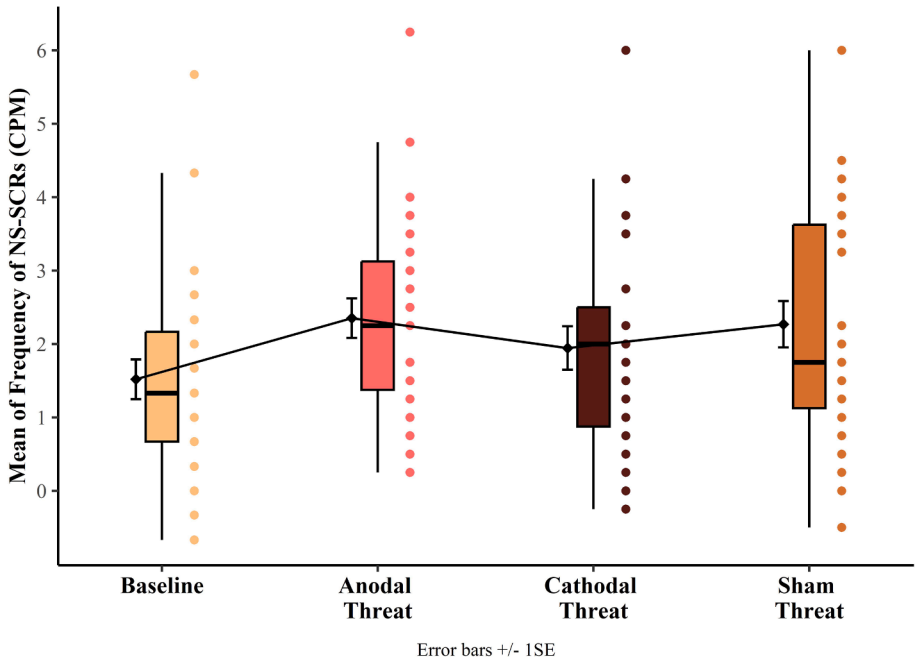

Fig. 6. Comparison of mean frequency NS-SCRs from each block: Baseline (non-body stimuli), Anodal (body-threat stimuli), Cathodal (body-threat stimuli) and Sham (body-threat stimuli).

$BF_{01} = 0.003$) and Sham (MD = 0.750, SE = 0.276, $p = 0.012$, B&H = 0.033, $BF_{10} = 4.083$, $BF_{01} = 0.245$) but not in the Cathodal condition (MD = 0.426, SE = 0.228, $p = 0.074$, B&H = 0.05, $BF_{10} = 0.919$, $BF_{01} = 1.088$). The frequency of SCRs occurring in threat blocks in each condition was also compared, however there were no significant differences were noted at the overall sample level; F (2, 52) = 1.700, $p > 0.05$, $BF_{10} = 0.389$, $BF_{01} = 2.567$.

Taken together, these findings show evidence for the efficacy of BTAB in distinguishing between non-body stimuli and body-threat stimuli.

3.3. The CHi_II and optimised MtDCS brain stimulation

3.3.1. Threat SCRs

Pearson's two-tailed *r* correlations were conducted between the AHE factor from the CHi_II and Threat SCRs from the BTAB task in all three stimulation conditions (Anodal, Cathodal and Sham) (Table 2). A significant negative correlation was observed between AHE and Cathodal condition Threat SCRs suggesting that those scoring higher on this measure showed lower autonomic responses to the aversive body stimuli when subject to the Cathodal stimulation to the rVLPFC (Fig. 7). No significant findings were observed with in the Anodal and Sham conditions. The Bayes values here can be used to infer that the correlation coefficient for the cathodal condition is indeed reliably/significantly distinct from the other two conditions.

To further explore that the different brain-stimulation conditions were indeed inducing significant differences, the AHE measure was used as the independent variable to create a high predisposition group (high AHE, $n = 13$, $M = 1.48$, $SD = 1.04$) and low predisposition group (low AHE, $n = 13$, $M = 0.12$, $SD = 0.16$) by a median-split approach to identify the pattern of effects on brain stimulation (Fig. 8).

A two-way mixed ANOVA was conducted to compare the influence of two variables of group (Between-subjects: high AHE vs. low AHE) and condition (Within-subjects: Anodal, Cathodal and Sham) on Threat SCRs. The main effect of both condition [F (2,48) = 0.646, $p > 0.05$, $BF_{10} = 0.188$, $BF_{01} = 5.328$] and group [F (1,24) = 0.086, $p > 0.05$, $BF_{10} = 0.287$, $BF_{01} = 3.486$] were non-significant,

Table 2
Pearson's coefficients (FDR Corrected) and Bayes values between AHE and Threat SCRs (Z-Scored) under all three stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	*r*	*p* value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
AHE vs. Cathodal	− 0.654*	0.000	0.017	155.880	0.006	Decisive AH
AHE vs. Anodal	0.225	0.260	0.033	0.437	2.288	Inconclusive Null
AHE vs. Sham	0.035	0.861	0.050	0.242	4.124	Good Null

* Significant correlations after using FDR corrections, the correlation pairs are ranked in ascending order.
** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

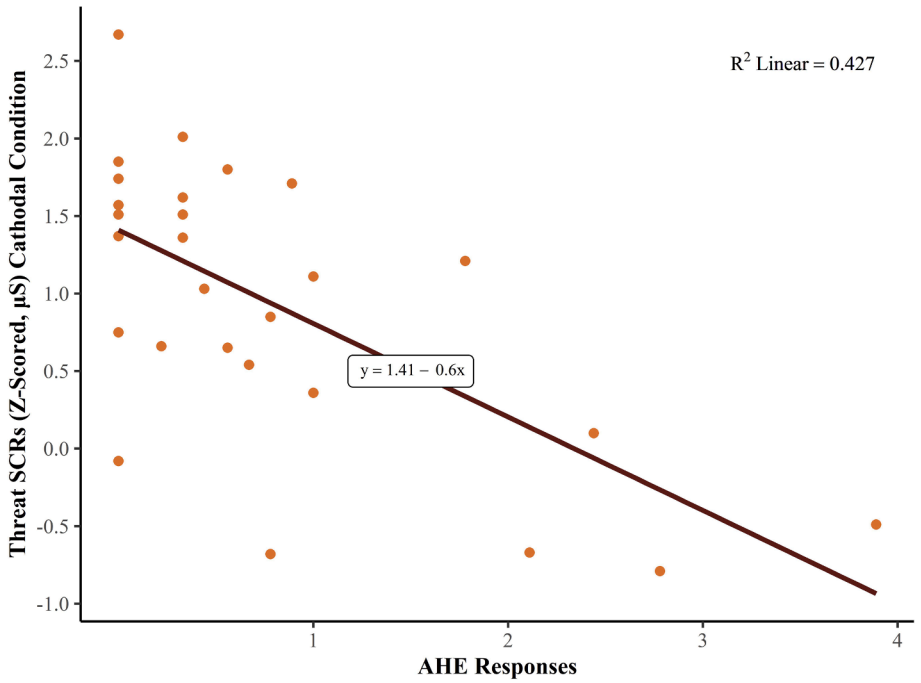

Fig. 7. Scatterplot showing correlation with Threat SCRs (Z-Scored) and AHE factor responses.

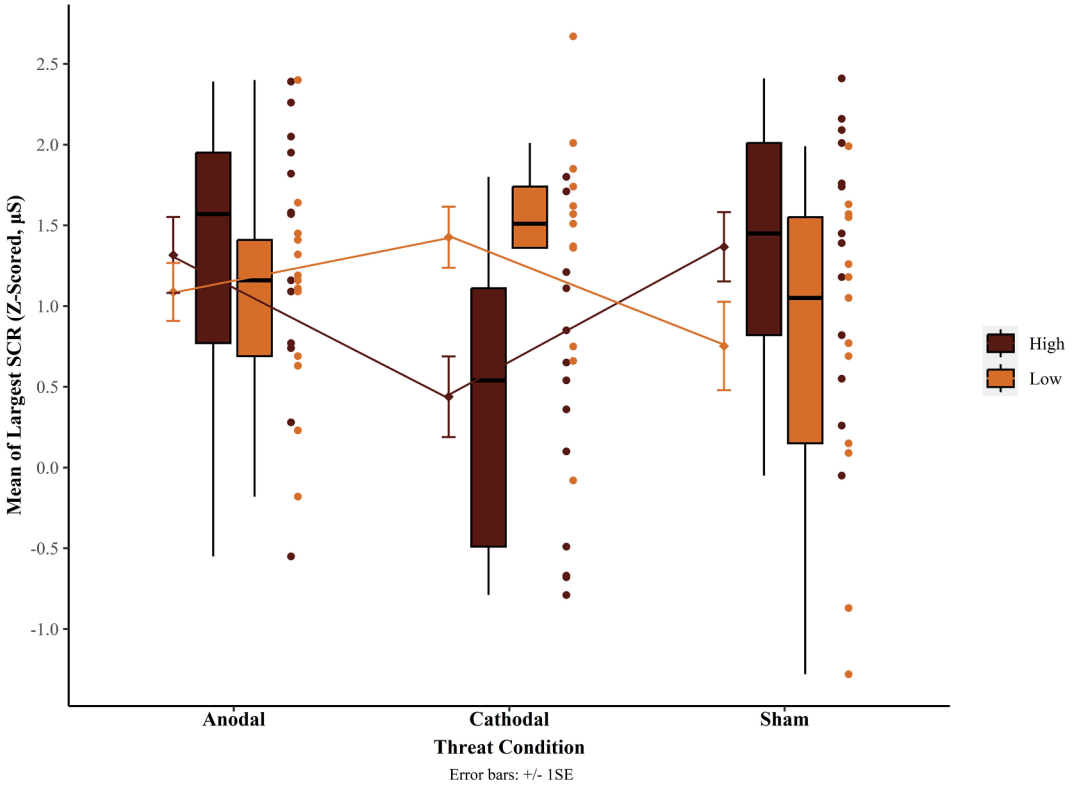

Fig. 8. Threat SCR's (Z-Scored) under all brain stimulation conditions (Anodal, Cathodal and Sham) for the high AHE group and low AHE group.

however, the interaction between group and condition on SCR's was significant, F (2,48) = 6.209, $p = 0.004$, $\eta^2\rho = 0.206$, $BF_{10} = 40.310$, $BF_{01} = 0.025$. To investigate the interaction effect, within-subject ANOVAs were conducted on the high AHE and low AHE groups separately. The high AHE group revealed a significant effect of condition, F (2,24) = 4.719, $p = 0.019$, $\eta^2\rho = 0.282$, $BF_{10} = 7.461$, $BF_{01} = 0.134$. Pairwise comparisons using FDR corrections in the high AHE group showed that under Cathodal stimulation SCRs were significantly weaker relative to the Sham threat condition (MD = 0.929, SE = 0.257, $p = 0.004$, B&H = 0.017, $BF_{10} = 13.592$, $BF_{01} = 0.074$) and Anodal threat condition (MD = 0.878, SE = 0.362, $p = 0.032$, B&H = 0.033, $BF_{10} = 2.269$, $BF_{01} = 0.441$). However, no significant difference was observed between the Anodal threat condition and Sham threat condition (MD = 0. 051, SE = 0.387, $p > 0.05$, B&H = 0.05, $BF_{10} = 0.280$, $BF_{01} = 2.269$. The low AHE group did not show any significant effect in the Frequentist analysis and so no further pairwise comparisons were conducted [F (2, 24) = 2.067, $p > 0.05$, $BF_{10} = 1.048$, $BF_{01} = 0.929$].

Furthermore, independent sample t-tests (FDR corrected) comparing the high AHE group and low AHE group showed a significant effect in the Cathodal condition [t (24) = 3.157, $p = 0.004$, B&H = 0.017, $d = 1.238$, $BF_{10} = 9.777$, $BF_{01} = 0.102$] but not in the Sham condition [t (24) = −1.766, $p > 0.05$, B&H = 0.033, $BF_{10} = 1.109$, $BF_{01} = 0.902$] or the Anodal condition [t (24) = −0.772, $p > 0.05$, B&H = 0.050, $BF_{10} = 0.452$, $BF_{01} = 2.212$]. Overall, the findings show that those scoring high on measures of cortical hyperexcitability displayed significantly more suppression of autonomic responses in the cathodal stimulation condition relative to those scoring low on this factor. It is particularly noteworthy there was some suggestion of mirror-reversed effects for the two groups (Fig. 8).

3.3.2. Magnitudes of NS-SCRs

As above, Pearson's two-tailed r correlations were conducted between the AHE factor and the strength of Threat NS-SCRs under all three stimulation conditions (Anodal, Cathodal and Sham). The frequentist analysis revealed there was a suggestion that the magnitudes of NS-SCRs in the Cathodal condition were correlating negatively with scores on the AHE measure (meaning as AHE scores increased, NS-SCR magnitudes decreased) however, the Bayes Factor analysis modifies this interpretation and suggests it is inconclusive (Table 3).

A mixed two-way ANOVA was conducted to compare the influence of two variables of group (Between-subjects: high AHE vs. low AHE) and condition (Within-subjects: Anodal, Cathodal and Sham) on NS-SCRs in the threat blocks (Fig. 9). Again, the main effects of condition [F (2,48) = 2.212, $p > 0.05$, $BF_{10} = 0.769$, $BF_{01} = 1.232$] and group [F (2,48) = 0.659, $p > 0.05$, $BF_{10} = 0.286$, $BF_{01} = 3.446$] were non-significant, however, the interaction effect of group and condition on NS-SCRs was found to be significant, F (2,48) = 3.268, $p = 0.047$, $\eta^2\rho = 0.120$, $BF_{10} = 3.188$, $BF_{01} = 0.307$.

As the interaction was significant, further analysis in terms of within-subject ANOVA on the high AHE and low AHE groups was conducted. In the high AHE group, a significant main effect F (2,24) = 4.182, $p = 0.028$, $\eta^2\rho = 0.258$, $BF_{10} = 6.205$, $BF_{01} = 0.155$) was revealed. Pairwise comparisons using FDR corrections in the high AHE group showed that under Cathodal stimulation NS-SCRs were

Table 3
Pearson's coefficients (FDR corrected) and Bayes values between AHE and magnitudes of Threat NS-SCRs (Z-Scored) under all three stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	*r*	*p* value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
AHE vs. Cathodal	− 0.404	0.036	0.017	1.910	0.523	Inconclusive AH
AHE vs. Anodal	− 0.063	0.755	0.033	0.250	3.995	Good Null
AHE vs. Sham	− 0.013	0.949	0.050	0.239	4.177	Good Null

** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

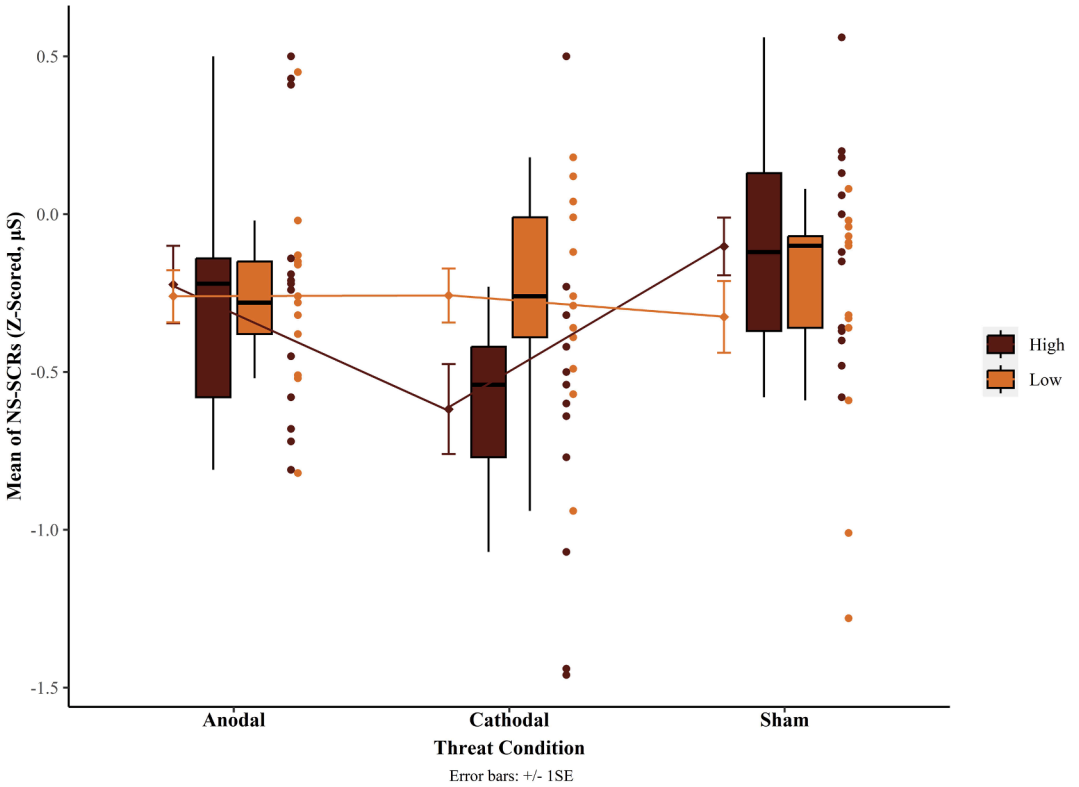

Fig. 9. Magnitudes of Threat NS-SCR's (Z-Scored) under all brain stimulation conditions (Anodal, Cathodal and Sham) for the high AHE group and low AHE group.

significantly weaker relative to the Sham threat block (MD = 0.516, SE = 0.167, $p = 0.009$, B&H = 0.017, $BF_{10} = 6.163$, $BF_{01} = 0.162$) but no significant differences were noted between the Anodal condition and Cathodal condition (MD = 0.395, SE = 0.217, $p > 0.05$, $BF_{10} = 1.005$, $BF_{01} = 0.995$) or the Anodal condition and Sham condition (MD = −0.121, SE = 0.172, $p > 0.05$, $BF_{10} = 0.344$, $BF_{01} = 2.903$). However, as in line with the above findings, the low AHE group did not show a main significant difference and so no further pairwise comparisons were conducted [F (2,24) = 0.153, $p > 0.05$, $BF_{10} = 0.208$, $BF_{01} = 4.815$].

Independent sample t-tests showed no significant effects (FDR corrected) between the high AHE and low AHE groups in the Cathodal condition [t (24) = 2.164, $p = 0.041$, B&H = 0.017, $d = 0.849$, $BF_{10} = 1.881$, $BF_{01} = 0.532$], Sham condition [t (24) = −1.531, $p > 0.05$, B&H = 0.033, $BF_{10} = 0.847$, $BF_{01} = 1.181$] or Anodal condition [t (24) = −0.250, $p > 0.05$, B&H = 0.05, $BF_{10} = 0.371$, $BF_{01} = 2.693$] or.

3.3.3. Frequency of NS-SCRs

Similarly, Pearson's two-tailed r correlations were conducted between the AHE factor and the frequency of Threat NS-SCRs in all three stimulation conditions (Anodal, Cathodal and Sham) though, no significant findings were observed (Table 4).

A mixed two-way ANOVA was conducted to compare the influence of two variables of group (Between-subjects: high AHE vs. low AHE) and condition (Within-subjects: Anodal, Cathodal and Sham) on frequency of NS-SCRs in the threat blocks (Fig. 10). No significant main effect of condition [F (2,48) = 2.495, $p > 0.05$, $BF_{10} = 0.670$, $BF_{01} = 1.492$] or group [F (2,48) = 0.017, $p > 0.05$, $BF_{10} = 0.487$, $BF_{01} = 2.055$] was noted. In this case, the interaction effect between condition and group was also non-significant [F (2,48) = 2.120, $p > 0.05$, $BF_{10} = 0.772$, $BF_{01} = 1.296$] and so, pairwise comparisons were not conducted.

Independent sample t-tests between the two groups in the Frequentist analysis (FDR corrected) did not show any differences in any

Table 4
Pearson's coefficients (FDR corrected) and Bayes values between AHE and frequency of Threat NS-SCRs (CPM) under all three stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	*r*	*p* value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
AHE vs. Cathodal	− 0.427	0.026	0.017	2.482	0.403	Inconclusive AH
AHE vs. Anodal	− 0.364	0.062	0.033	1.251	0.799	Inconclusive AH
AHE vs. Sham	− 0.107	0.597	0.050	0.273	3.666	Good Null

** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

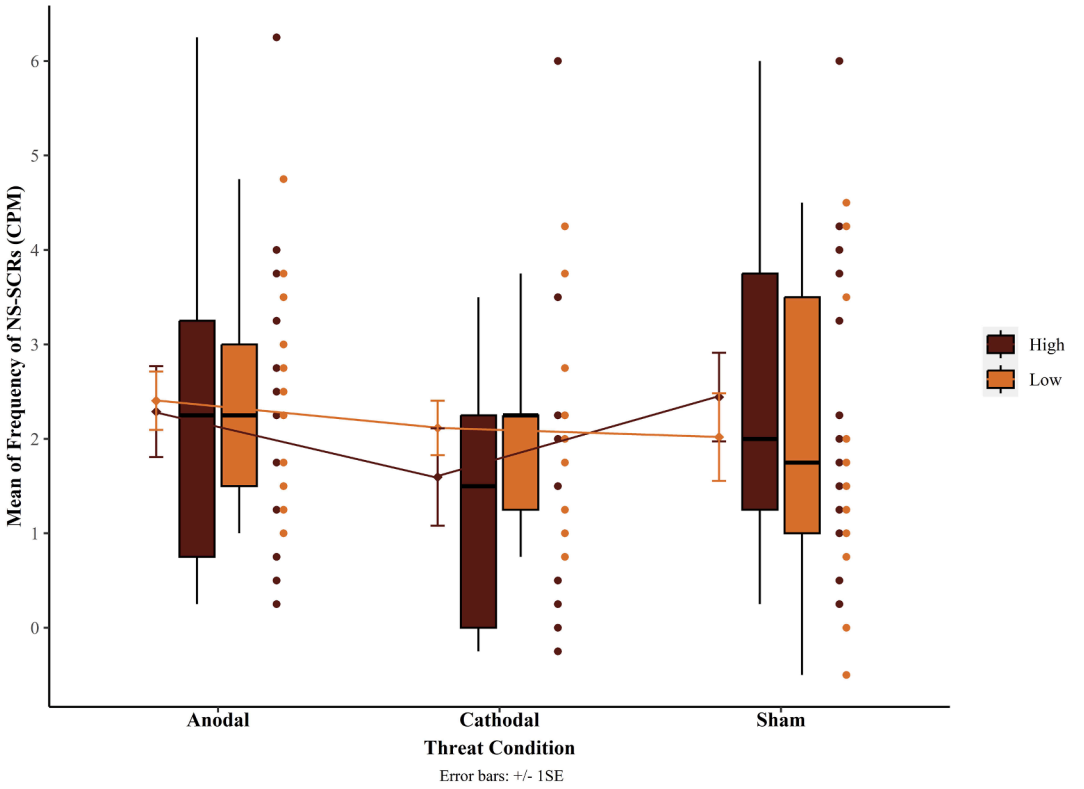

Fig. 10. Frequency of Threat NS-SCRs (CPM) under all brain stimulation conditions (Anodal, Cathodal and Sham) for the high AHE group and low AHE group.

of the conditions: Cathodal [t (24) = 0.880, $p > 0.05$, B&H = 0.017, $BF_{10} = 0.483$, $BF_{01} = 2.071$], Sham [t (24) = −0.641, $p > 0.05$, B&H = 0.033, $BF_{10} = 0.422$, $BF_{01} = 2.367$] or Anodal [t (24) = 0.202, $p > 0.05$, B&H = 0.050, $BF_{10} = 0.368$, $BF_{01} = 2.715$].

3.4. Psychological ratings

3.4.1. BTAB and self-report ratings

The baseline block responses and threat block responses were compared across all four dimensions to examine the efficacy of the BTAB task in eliciting responses to non-body aversive and body-aversive imagery.

Emotional Arousal. A main significant effect of stimuli-type was noted using a Friedman's test between the different blocks χ^2 (3) = 41.224, $p < 0.001$ (Fig. 11a). Post hoc analysis using Wilcoxon's signed rank tests (FDR corrections) showed that the threat stimuli were consistently rated more arousing than the baseline stimuli in all three conditions: Anodal (Z = −4.459, $p < 0.001$, B&H = 0.017), Cathodal (Z = −4.293, $p < 0.001$, B&H = 0.033) and Sham (Z = −4.508, $p < 0.001$, B&H = 0.05). However, no significant differences were noted in the ratings for the threat blocks under different stimulation conditions (p's > 0.05) (Fig. 11a).

Emotional Valence. A Friedman's test revealed an overall difference between the different blocks (Baseline, Anodal Threat, Cathodal Threat and Sham Threat) χ^2 (3) = 42.082, $p < 0.001$ (Fig. 11b). Pairwise comparisons using the Wilcoxon's signed rank tests (FDR corrections) showed that the baseline stimuli were consistently rated more emotionally positive than the threat stimuli in all three conditions: Anodal (Z = −4.344, $p < 0.001$, B&H = 0.017), Cathodal (Z = −4.385, $p < 0.001$ B&H = 0.033) and Sham (Z = −4.494, $p < 0.001$ B&H = 0.05). Similar to above, no significant findings were noted between the threat stimuli in the different

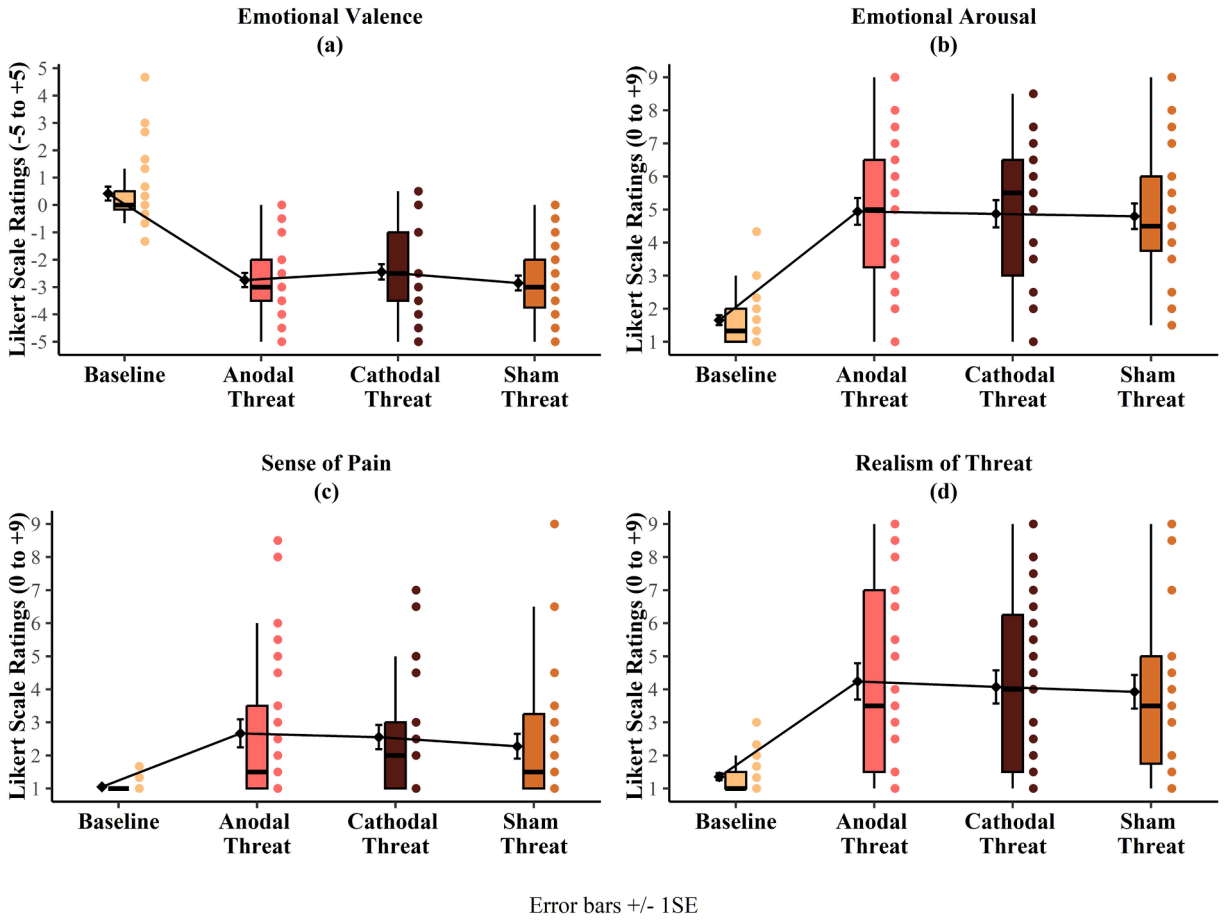

Fig. 11. Differences between Baseline and Threat blocks in each stimulation condition (Anodal, Cathodal and Sham) for the four psychological rating dimensions. Note: In the above figure, the four psychological ratings are illustrated for (a) emotional arousal, (b) emotional valence, (c) sense of illusory pain and (d) realism of threat.

stimulation conditions (p's > 0.05).

Sense of Pain. Friedman's test showed a significant main effect of the different conditions (Baseline, Anodal Threat, Cathodal threat and Sham Threat), χ^2 (3) = 26.966, $p < 0.001$. Pairwise comparisons using Wilcoxon's signed rank tests (FDR corrections) showed that the baseline stimuli were consistently rated less painful than the threat stimuli in all three stimulation conditions: Anodal ($Z = -3.628$, $p < 0.001$, B&H = 0.017), Cathodal ($Z = -3.525$, $p < 0.001$ B&H = 0.033) and Sham ($Z = -3.301$, $p < 0.001$ B&H = 0.05). However, no significant findings are noted for between the threat blocks in the three stimulations conditions (Anodal Cathodal and Sham), all p's > 0.05 (Fig. 11c).

Realism of Threat. Similarly, a Friedman's test revealed a significant main effect between the baseline stimuli and threat stimuli in all three stimulation conditions χ^2 (3) = 34.315, $p < 0.001$ (Fig. 11d). Pairwise comparisons using FDR corrections showed significant differences between the baseline stimuli was rated as less threatening than the threat stimuli in all three conditions: Cathodal ($Z = -4.048$, $p < 0.001$, B&H = 0.017), Sham ($Z = -4.016$, $p < 0.001$, B&H = 0.033), and Anodal ($Z = -4.015$, $p < 0.001$, B&H = 0.05).

However, when only the threat blocks from all conditions (Anodal, Cathodal and Sham) were compared, no reliable differences were noted (all $p > 0.05$). These data showed consistency with the psychophysiological findings in that the baseline stimuli were rated as less aversive/arousing/threatening than the threat stimuli.

3.4.2. CHi-II and self-report ratings

In line with the psychophysiological data, the CHi-II AHE factor was subjected to Pearson two-tailed r correlations and a median-split (to quantify the sample into a high AHE group and low AHE group) analysis. The psychological ratings reported during the BTAB in each session were then compared based on the two groups and the findings are reported below for each dimension (that is, emotional arousal, emotional valence, sense of pain and realism of threat).

Emotional Arousal, Sense of Pain and Realism of Threat. The results from the correlational analysis and two-way ANOVA showed no significant effects (all p's > 0.05, $BF_{10} < 1$, $BF_{01} > 3$) between the two groups in the three stimulation conditions (see Fig. 12 a, c and d).

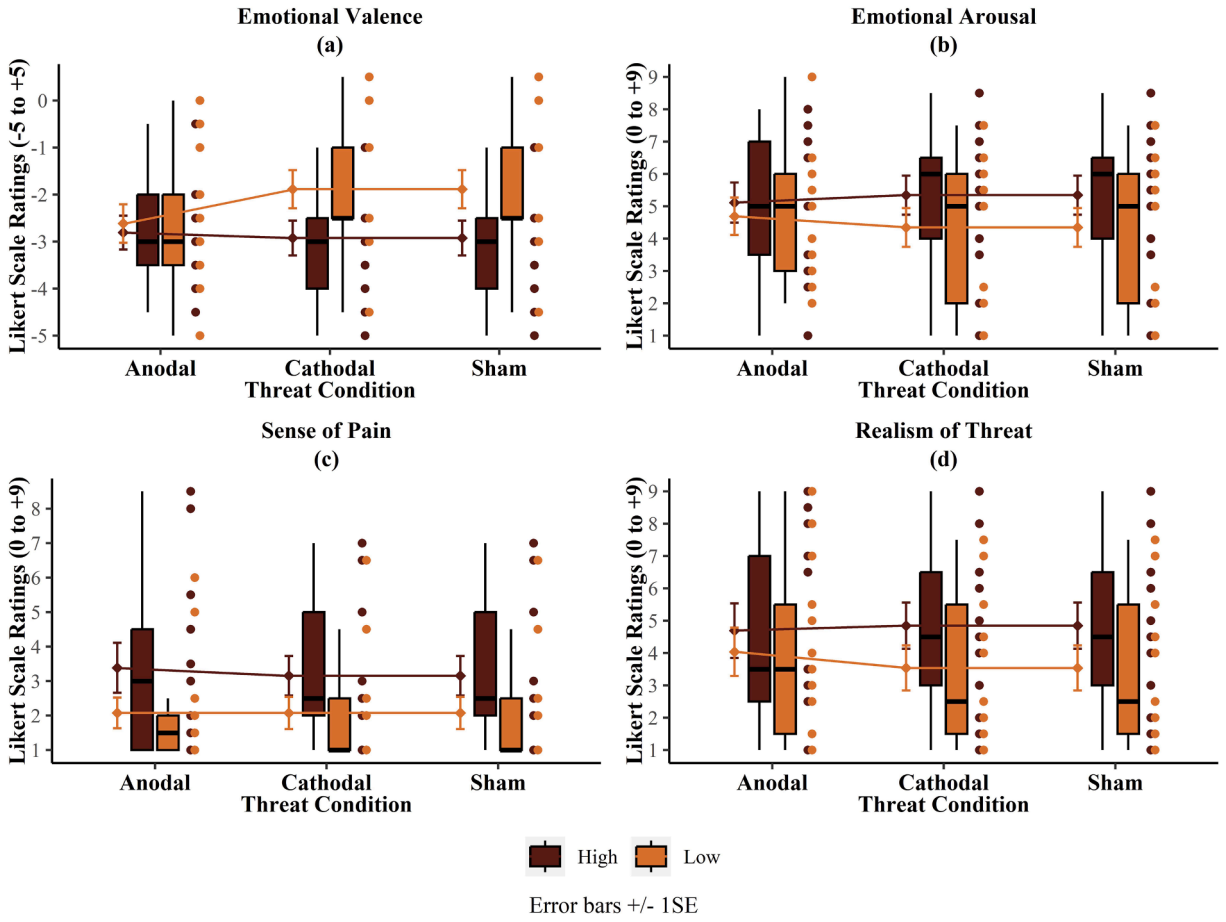

Fig. 12. Differences between high AHE vs. low AHE groups for all stimulation conditions (Anodal, Cathodal, Sham) in the four psychological rating dimensions. Note: In the above figure, the four psychological ratings are illustrated for (a) emotional arousal, (b) emotional valence, (c) sense of illusory pain and (d) realism of threat.

Emotional Valence. As this data followed normality, a Pearson's two-tailed r correlation was conducted to compare responses on the AHE factor and the psychological ratings for valence however, no significant correlations were observed.

An overall 2 (Between-subject: high AHE group and low AHE group) × 3 (Within-subject: Anodal, Cathodal and Sham condition) ANOVA was conducted. Although the main effect of group or condition was not found to be significant $p > 0.05$, $BF_{10} < 1$, $BF_{01} = 1–3$), the interaction effect between group and condition was found to be significant $F(2,48) = 3.296$, $p < 0.05$, $\eta^2\rho = 0.121$, $BF_{10} = 7.988$, $BF_{01} = 0.642$ (Fig. 12b). Further exploration using a within-subject ANOVA revealed no significance in the high AHE group (all p's > 0.05, $BF_{10} < 1$, $BF_{01} > 3$), however, the low AHE group showed a significant difference between the different stimulation conditions $F(2,24) = 8.950$, $p = 0.001$, $\eta^2\rho = 0.427$, $BF_{10} = 23.826$, $BF_{01} = 0.037$. Pairwise comparisons (with FDR corrections) showed that participants reported the valence of the BTAB threat stimuli to be more negative in the Anodal condition than the Cathodal (MD = −0.731, SE = 0.244, $p = 0.011$, B&H = 0.017, $BF_{10} = 5.268$, $BF_{01} = 0.190$) and Sham condition (MD = −0.731, SE = 0.244, $p = 0.011$, B&H = 0.033, $BF_{10} = 5.268$, $BF_{01} = 0.190$). However, one-way ANOVAs between the groups did not reveal any significant results (all p's > 0.05, $BF_{10} = 0–2$, $BF_{01} = 0–3$) and so no further post-hoc tests were conducted.

3.5. *Depersonalisation-like experiences (DLEs)*

The analysis utilising DLE responses largely produced null findings (all p's > 0.05, $BF_{10} < 1$, $BF_{01} > 3$) or in some cases inconclusive with BF_{01} range between 1–3. Table 5 provides a summary overview of the main findings. In the case of "Sense of Pain" ratings in the threat condition, correlational analysis between DLE responses and this component showed a significant positive correlation (see Table 5) in the Anodal condition, suggesting that as the predisposition to DLE increased so did participants sense of illusory pain to viewing the Threat videos in this condition. Further analysis using mixed 2 × 3 ANOVA's and independent t-tests showed that that sense of pain ratings were not affected by stimulation condition (i.e., Anodal, Cathodal and Sham) but instead by predisposition to DLE (High DLE vs. Low DLE). In the interests of clarity, conciseness and transparency, the detailed analyses of these findings are reported in Appendix A.

Table 5
Summary of the main findings from the DLE responses.

Correlation Pair	Coefficient Pearson's r/Kendall's τ	p value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
DLE and Magnitudes of Threat SCRs						
DLE vs. Cathodal	$r = -0.158$	0.432	0.017	0.321	3.118	Good Null
DLE vs. Sham	$r = -0.098$	0.627	0.033	0.268	3.731	Good Null
DLE vs. Anodal	$r = -0.079$	0.694	0.050	0.257	3.896	Good Null
DLE and Magnitudes of NS-SCRs						
DLE vs. Sham	$r = -0.157$	0.434	0.017	0.320	3.126	Good Null
DLE vs. Cathodal	$r = -0.119$	0.555	0.033	0.282	3.547	Good Null
DLE vs. Anodal	$r = -0.039$	0.848	0.050	0.243	4.112	Good Null
DLE and Frequency of NS-SCRs						
DLE vs. Cathodal	$r = -0.391$	0.044	0.017	1.650	0.606	Inconclusive AH
DLE vs. Anodal	$r = -0.108$	0.591	0.033	0.274	3.650	Good Null
DLE vs. Sham	$r = -0.084$	0.677	0.050	0.260	3.851	Good Null
DLE and Sense of Pain Ratings (Threat Condition)						
DLE vs. Anodal	$\tau = 0.366$*	0.012	0.017	7.594	0.132	Good AH
DLE vs. Sham	$\tau = 0.299$	0.043	0.033	2.461	0.406	Inconclusive Null
DLE vs. Cathodal	$\tau = 0.277$	0.059	0.050	1.771	0.565	Inconclusive Null

* Significant correlations after using FDR corrections, the correlation pairs are ranked in ascending order.
** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

4. General discussion

The current study examined the presence of trait-based predisposition to aberrant experience in mediating cognitive-affective responses as a result of optimised MtDCS directed at the rVLPFC / insula complex. Psychophysiological (skin conductance responses) and psychological responses (ratings) were obtained from participants whilst they viewed a novel aversive body-threat task (the BTAB: Braithwaite et al., 2020) under different MtDCS brain stimulation conditions.

The magnitudes of the maximum SCRs were significantly higher for threat stimuli relative to baseline stimuli. This was also the case for the magnitudes of the non-specific SCRs (NS-SCRs) – where the strength of NS-SCRs was reliably increased for threat stimuli relative to non-threat baseline stimuli. In addition, the frequency of NS-SCRs (a measure of tonic autonomic arousal) was significantly increased for threat stimuli relative to baseline stimuli for all but the cathodal condition, which appeared to show some evidence of a suppression in the frequency of NS-SCRs generated (although this was not conclusive).

At the whole sample level, there were no reliable effects of MtDCS brain stimulation on the strength of maximum threat SCRs relative to the sham condition. There were also no reliable effects of MtDCS brain stimulation on the frequency and magnitudes of NS-SCRs. This implies that MtDCS had no effects on the current sample. However, what is striking and noteworthy is that there were clear and significant effects of MtDCS when the sample was examined in relation to scores on a proxy measure of cortical hyperexcitability. This opposes the view that MtDCS had no discernible effects on neural processes, lending support to the notion that using such stratifying measures can speak to the trait-based baseline effects which can interact with and mediate the effects of brain stimulation (Basten et al., 2011; Krause & Cohen Kadosh, 2014; Horvath et al., 2014; Bell et al., 2022).

Cathodal stimulation of the rVLPFC via an optimised 7-channel MtDCS montage produced significantly suppressed SCR magnitudes, relative to the Sham and Anodal condition. As scores on the cortical hyperexcitability measure increased, Threat SCR magnitudes significantly decreased under the Cathodal condition. The Bayes Factor analysis, complementing the correlational analysis and the median-split analysis, support that that this effect was only observed for those scoring high on the CHi_II proxy measure of cortical hyperexcitability. This was not the case for those scoring low on the CHi_II measure – where there were no reliable differences relative to the sham condition. Clearly the inferred degree of trait-based cortical hyperexcitability further mediated the effects of MtDCS and produced a highly selective effect - one that would be missed if averaging only at the whole sample level.

Anodal stimulation produced no reliable effects on SCR responses (maximum Threat SCRs or NS-SCRs) in terms of the strength or the frequency of responses relative to the sham condition. Furthermore, although there appeared to be a difference in the strength of threat SCRs for the sham condition for the high and low AHE groups – this was not reliable and thus both groups displayed similar SCR profiles under no-stimulation (sham) conditions.

Collectively, the psychophysiological findings demonstrated that the MtDCS procedure was successful in influencing autonomic processing and responding but only for those participants showing elevated and increasing signs of cortical hyperexcitability and only for the cathodal condition. The suggestion here is that this is likely due to the stimulatory influence directed at the rVLPFC which in turn impacted on the operation of the anterior insula region – a network with a known functional involvement in saliency networks, the generation of conscious feeling states, interoceptive awareness, predictive-coding, and the mediation of autonomic skin conductance responses (Critchley, 2005; Medford et al., 2006; Lemche et al., 2007, 2008; Jay et al., 2014; Xia et al., 2017; Vinberg et al., 2021).

There is the possibility that the lack of influence from anodal stimulation (for both groups) may reflect something of a 'ceiling effect' in autonomic responding, where no additional response could occur from the application of brain stimulation. This is perhaps

supported by the fact under anodal conditions, Threat SCRs were not reliably stronger than sham, and both were matched for strength of response. This could be due, at least in part, to the potency of the videos to elicit an autonomic response.

Whilst some novel effects in relation to proxy signs of cortical hyperexcitability were observed, this was not the case when the sample was examined in terms of DLEs – one component of which was focused on aberrant body experiences. The DLE measure did not reveal any significant findings for either the magnitudes of maximum SCRs or NS-SCRs. However, it is interesting that the frequency of NS-SCRs did imply signs ($p = 0.044$, $BF_{10} = 1.650$) of a reduction (increased inhibition) in autonomic responding as a function of predisposition to DLEs under cathodal stimulation. Whilst this did not survive FDR corrections, the corresponding Bayes value shows this effect to be inconclusive (and therefore not significant), the trend does go in the opposite direction to that expected from the idea of 'liberating' the AIC through inhibition of the rVLPFC.

Although interpreting null effects should be approached cautiously, the Bayes Factor analysis does allow for some extrapolation here and a tentative explanation can be explored. One reason for the non-significant DLE effects might be due to the questions on the DLE measure being more multifaceted – covering more mid and higher-level multisensory experiences relative to the very specific and focused visual items on the CHi_II measure (which centre on aberrant visual experiences only). In addition, the random-sampling approach led to the high DLE group with a mean score of 3.32 out of a maximum of 13 and so the present sample might not be sufficiently predisposed to aberrant body experiences in order for effects to strongly emerge (Sierra et al., 2005). Irrespective of these possibilities, the general pattern observed is consistent with the findings from the CHi_II and both contrast with the notion of inhibiting an inhibitory region results in increased autonomic responding (at least for neurotypical groups).

On the whole, the psychological ratings followed the pattern seen for the psychophysiological SCR data relating to the BTAB task. Threat stimuli were rated as more arousing, having more realism and being viewed more negatively (valence) relative to non-threat baseline stimuli. However, the results indicated that brain stimulation did not have a reliable impact on the overall psychological ratings. This was also observed even when the sample was split on the basis of the screening measures (AHE and DLE). There was a general trend for the high groups (on both measures) to rate the threat videos as more negatively valanced, emotionally arousing, generating a higher sense of illusory pain, and as more threatening, but the stimulation conditions did not reliably further influence these psychological ratings relative to sham.

A possible reason for this could be that psychological findings do not necessarily always follow SCRs and can at times reflect a dissociation between autonomic processing and reported conscious experience or subjective evaluation (Silvert et al., 2004; Christopoulos et al., 2019). In particular, autonomic/somatic responses to aversive stimuli have been shown to be the initial and immediate perceptual stage (as a survival strategy) following which interpretation, responses and learning are processed (Öhman & Soares, 1993; Silvert et al., 2004; Christopoulos et al., 2019). This implies that the latter stages may be influenced (by various confounding factors, e.g., prior experiences, phobias etc.) and change conscious responses, i.e., degree of threat experienced may be differentially interpreted.

4.1. Theoretical implications

The current study investigated the role of the rVLPFC as an inhibitory network propagating into the AIC which has been implicated in the mediation of a variety of neurobiological processes such as negative cognitive-affective states, autonomic activity, saliency networks and empathy (Craig, 2002, 2003, 2009; Critchley et al., 2004; Critchley, 2005; Ochsner & Gross, 2004, 2005; Lemche et al., 2007; Eippert et al., 2007; Klumpers et al., 2010; Gu et al., 2013; Seth, 2013; Clark, 2013). In addition, the current work examined the role of trait-based predispositions for cortical hyperexcitability and its potential to mediate the efficacy of MtDCS brain stimulation.

Findings from proxy signs of cortical hyperexcitability are particularly interesting. The present findings show, for the first time, that, as aberrant experiences thought to reflect underlying cortical hyperexcitability increase so does the efficacy of MtDCS – but only for the cathodal condition resulting in significantly suppressed autonomic SCRs. In the opposite to a hypothesised result, far from 'releasing' the AIC from aberrant suppression, the protocol adopted here increased suppression and this suppression increased in sympathy with proxy indicators of cortical hyperexcitability.

One possible solution might be that this reflects electrical stimulation primarily interacting with the most active neurons present – and thus effects are manifest here for the high scoring group on proxy measures of hyperexcitability as arguably background neural processes may well be operating at an elevated level of activation (Nitsche & Paulus, 2000; Liebetanz et al., 2002, Nitsche et al., 2005; Li et al., 2015). By this account, it is possible that cathodal stimulation increased activation in networks dedicated to the inhibitory regulation of the AIC, leading to a significant suppression of autonomic responses.

Consequently, rather than inhibiting the action of rVLPFC and increasing the frequency and/or strength of SCRs, cathodal stimulation simply increased the degree of inhibition mediating SCRs. Conceptually this is akin to a kind of functional steering or targeting of specific brain networks (Bikson & Rahman, 2013; Bestmann et al., 2015; Jackson et al., 2016; Kronberg et al., 2017; Vergallito et al., 2022).

Put more simply, the apparent friction with regards to how do proxy signs of increased hyperexcitability (the CHi_II responses) relate to signs of increased inhibition from brain stimulation, can be seen as a three-stage process where; at Stage 1 – there is a latent degree of background trait-based hyperexcitability occurring within the AIC (most likely via projections from hyperexcitable sensory cortices). At Stage 2 – this elicits a stronger inhibitory response from the rVLPFC – resulting in these inhibitory systems working harder to regulate neurophysiological activity in the AIC. Therefore, in Stage 3 – MtDCS is applied to the rVLPFC and it interacts more strongly with the inhibitory processes as those networks are already working harder (e.g., functionally targeted).

Both the rVLPFC and AIC receive projections from multisensory areas, including vision (Crick & Koch, 1995; Miller, 1999; Barcelo et al., 2000; Benchenane et al., 2011). The rVLPFC has been shown to have an increased inhibitory role for negative emotions / feeling states and behavioural responses (Aron et al., 2004; Phan et al., 2005; Banks et al., 2007; Wager et al., 2008; Berkman & Liebermann, 2009; Szczepanski & Knight, 2014; Vergallito et al., 2018; Chick et al., 2020; Gallucci et al., 2020) and the insula complex is also

centrally involved in attentional, somatosensory and autonomic processing (Critchley, 2004; Pollatos et al., 2007; Craig, 2009; Uddin, 2015; Wang et al., 2019; Chen et al., 2021). Consequently, during the processing of potent and aversive body-threatening imagery, activity within the insula would be increased (even more so with the presence of incoming hyperexcitability from visual systems) and associated by an increased involvement of suppressive processes from the rVLPFC. Accordingly, the increased involvement of inhibitory processes from rVLPFC make it more malleable to cathodal brain stimulation and such a mechanism could underlie the observation here of greater autonomic suppression from Cathodal MtDCS over the rVLPFC.

These findings also provide evidence that trait-based indicators of baseline levels of neural activity (via a proxy measure of aberrant experiences which reflect cortical hyperexcitability) can be used to reveal important differences in the efficacy of MtDCS to influence brain processes. This is consistent with a broader literature showing that baseline excitability can have different effects when brain stimulation is applied (Peña-Gómez et al., 2011; Jacobson et al., 2012; Sarkar et al., 2014; Benwell et al., 2015; Romei et al., 2016; De Graaf et al., 2017; Bell et al., 2022).

Based on the current findings, trait-based baselines are important to consider when examining brain stimulation methods. Specifically, stratifying individuals on the basis of trait-based predisposition to cortical hyperexcitability or even the inclusion of a state-based task could provide more thorough insights into the functional interaction between brain-stimulation montages and the background latent activity of neural systems – that may otherwise be missed by general averaging approaches. Along with previous work on exploring EEG profiles (Fong et al., 2019, 2020), the present findings also considerably extend the utility of the CHi_II measure itself in relation to examining the efficacy of MtDCS brain-stimulation.

A prominent theory for the profound phenomenological experiences reported by patients with depersonalisation posits that the rVLPFC over-inhibits the AIC and thus prevents cognitive-affective processes from colouring consciousness (Hunter et al., 2003; Jay et al., 2014, 2016; Critchley, 2005; Craig, 2009; Seth, 2013; Clark, 2013). Jay et al. (2014) provided evidence that by suppressing the rVLPFC (using rTMS), autonomic SCR activity was significantly increased in clinically depersonalised patients. In essence, the experimental protocol was being used to inhibit a brain network that was responsible for aberrant degrees of inhibition and in so doing, liberating the AIC (which receives prominent projections from rVLPFC) from such suppression. As far as trait based DLEs in the current neurotypical sample go, the current findings showed that predisposition to DLEs did not further mediate SCRs in relation to brain stimulation, at least for our neurotypical sample.

It should be acknowledged that the present study differs from that of Jay and colleagues (2014) in several important ways. First, the current study utilised a neurotypical sample that was measured for predisposition to DLEs and not patients with clinically diagnosed levels of these experiences. Second, the sample was also measured for proxy signs of cortical hyperexcitability to examine the efficacy of brain stimulation as a function of differences in background trait-based indicators. Previous research has not addressed this. Third, the current study utilised a form of transcranial electrical stimulation (optimised MtDCS) and not low frequency rTMS. Crucially, cathodal MtDCS applied to the rVLPFC did not 'release' the AIC and produce increased autonomic responding (SCRs) – quite the opposite.

From this, a highly speculative suggestion could be that the present study and that of Jay et al. (2014) might imply an important re-description in the functional relationships of these networks between neurotypical groups and those who have transitioned to disorder. Such possibilities require further investigation.

5. Limitations & Further study

While the use of trait-based measures is a noteworthy advancement in the field, future studies would benefit from an examination of additional state-based measures (i.e., the level of excitability at the time of testing). This is also interesting as some studies have revealed a complex interplay between these factors – suggesting that both are mediated by contributions from interdependent yet also distinct neural systems (see Kühn & Gallinat, 2012; Zmigrod et al., 2016; see also Smith et al., 2013; for evidence from an examination of P50 potentials). Trait- and state-based processes are not one and the same and one does not necessarily always predict the other – though exactly how both interact with brain stimulation protocols remains an area of further study.

Work in this area with aberrant experiences in neurotypicals could also be improved by having a larger range of scores on the DLE measures used here. The absence of effects in this regard may reflect the observation that the present sample was not overly predisposed to DLEs and therefore such effects could not manifest. The present study adopted random sampling and so could not control for this. Future work might want to specifically target and recruit individuals that are highly predisposed to DLEs to examine this matter further and determine how the presence of such experiences may interact with MtDCS (or similar) protocols.

Finally, it should be acknowledged that the a-priori sample size estimations used here were speculative. This was partly due to the fact that a power analysis was deemed inappropriate due to the fact that many of the conditions and methods used in the present study are novel and have not been combined in this way before. While this makes our approach exploratory in this regard, established alternatives do exist and these approaches are based on what the literature has shown previously. In addition, our use of Bayes Factor analyses provides clear evidence of the central effects being either 'decisive' or 'strong' suggesting our sample is more than sufficiently powered to support the main claims. In addition, the computer-modelled optimised multi-channel approach used in the current work results in much more intense stimulation being steered more directly to the specific intended brain regions and thus is more focused and reliable than previous research that has used bipolar approaches with tDCS. Irrespective of these observations, future work which extends the sample to target and include high-scoring DLE participants as well as the sample size per-se could provide be helpful in providing additional insights.

6. Conclusion

The current study provides evidence that the rVLPFC (a region with strong functional and anatomical connections to the AIC) shows

differential involvement in mediating cognitive-affective responses to aversive body-threat stimuli in neurotypical individuals predisposed to aberrant experiences that reflect cortical hyperexcitability. This study has also shown that baseline brain states are important and trait-based stratification of the sample shows differences in the neuromodulatory paradigm that would be otherwise missed. At the whole sample level, no differences in autonomic responses to salient aversive stimuli were observed between Anodal, Cathodal and Sham conditions. However, examination of different stimulation conditions when the sample was divided based on predisposition to aberrant experiences showed suppression of autonomic responses for the high-scoring group only. This raises interesting and exciting prospects for the field, such as, whether benchmark findings may be weakened or modified and if previous studies with null findings are a result of group averaging. The effects from the current study demonstrated that cortical hyperexcitability can be extended beyond the visual and extra striate cortices and plays a role in the inhibitory functioning of the rVLPFC. Whether this is a result of visual projections into the region (already hyperexcitable), or a more domain-general degree of hyperexcitability that exists outside of visual networks but present in the brain region remains to be seen. Taken together, this provides additional evidence to the underlying neural mechanisms mediating stable consciousness and that cortical hyperexcitability may be a critical variable involved in these experiences.

CRediT authorship contribution statement

Shalmali D. Joshi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Giulio Ruffini:** Resources, Writing – review & editing. **Helen E. Nuttall:** Supervision, Writing – review & editing. **Derrick G. Watson:** Formal analysis, Writing – review & editing. **Jason J. Braithwaite:** Conceptualization, Formal analysis, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

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.

Data availability

In line with open science practices, the data from this project is available on the Open Science Framework "https://osf.io/k4wph/".

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Appendix A

Depersonalisation-like experiences and optimised MtDCS brain stimulation

Responses from the ABS and AFS factors of the depersonalisation scale were combined and normalised (responses divided by number of items) to make a composite independent variable labelled "DLE".

Threat SCRs

Pearson's two-tailed *r* correlations were conducted between the responses on the DLE factor and magnitude of Threat SCRs under all three stimulation conditions (Anodal, Cathodal and Sham) but no significant correlations were observed (Table A.1).

Table A.1
Pearson's coefficients (FDR Corrected) and Bayes values between DLE and Threat SCRs (Z-Scored) under all three stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	*r*	*p* value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
DLE vs. Cathodal	− 0.158	0.432	0.017	0.321	3.118	Good Null
DLE vs. Sham	− 0.098	0.627	0.033	0.268	3.731	Good Null
DLE vs. Anodal	− 0.079	0.694	0.050	0.257	3.896	Good Null

** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

The DLE factor was then split using a median to identify a high DLE group ($n = 13$, $M = 3.32$, $SD = 0.82$) and a low DLE group ($n = 13$, $M = 0.85$, $SD = 0.56$) to observe the pattern of effects on brain stimulation (Fig. A.1).

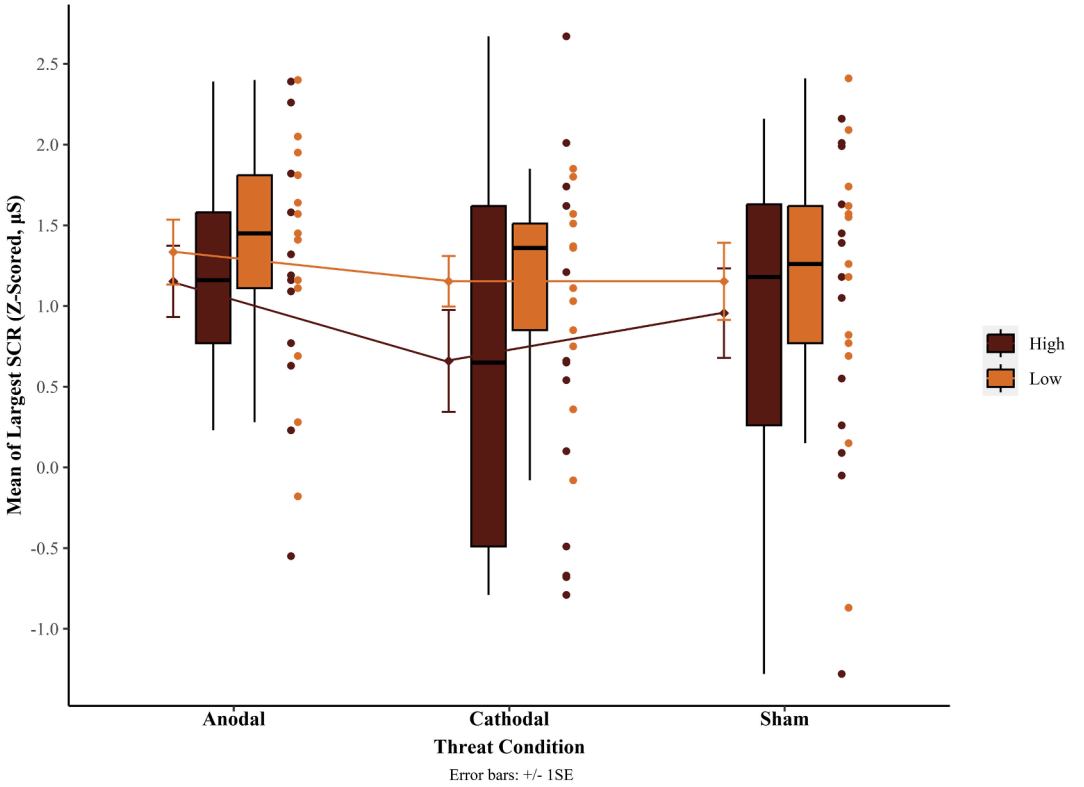

Fig. A.1. Threat SCRs (SCRs) under all three brain stimulation conditions (Anodal, Cathodal and Sham) for the high DLE group and low DLE group.

A two-way mixed ANOVA was conducted to compare the influence of two independent variables of group (Between-subjects: high DLE vs. low DLE) and condition (Within-subjects: Anodal, Cathodal and Sham) on Threat SCRs. No significant main effect of condition [$F(2,48) = 0.833$, $p > 0.05$, $BF_{10} = 0.251$, $BF_{01} = 3.983$] or group [$F(2,48) = 3.492$, $p > 0.05$, $BF_{10} = 0.546$, $BF_{01} = 1.832$] was noted. The interaction effect between condition and group was also non-significant [$F(2,48) = 0.227$, $p > 0.05$, $BF_{10} = 0.228$, $BF_{01} = 4.377$] and so, pairwise comparisons were not conducted.

Independent sample t-tests between the two groups in the Frequentist analysis did not show any differences in any of the conditions: Anodal [$t(24) = -0.611$, $p > 0.05$, $BF_{10} = 0.416$, $BF_{01} = 2.404$], Cathodal [$t(17.591) = -1.401$, $p > 0.05$, $BF_{10} = 0.739$, $BF_{01} = 1.352$] or Sham [$t(24) = -0.532$, $p > 0.05$, $BF_{10} = 0.404$, $BF_{01} = 2.478$].

Magnitudes of NS-SCRs

As above, Pearson's two-tailed r correlations were used to compare the responses on the DLE measure and strength of Threat NS-SCRs under all three stimulation conditions (Anodal, Cathodal and Sham) however, in line with above, no significant findings were noted (Table A.2).

Table A.2
Pearson's coefficients (FDR Corrected) and Bayes values between DLE and magnitudes of Threat NS-SCRs (Z-Scored) under all three stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	*r*	*p* value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
DLE vs. Sham	−0.157	0.434	0.017	0.320	3.126	Good Null
DLE vs. Cathodal	− 0.119	0.555	0.033	0.282	3.547	Good Null
DLE vs. Anodal	−0.039	0.848	0.050	0.243	4.112	Good Null

** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

A 2x3 ANOVA with two variables of group (Between-subjects: high DLE vs. low DLE) and condition (Within-subjects: Anodal, Cathodal and Sham) was conducted on NS-SCRs in the threat blocks (Fig. A.2). However, no significant main effect of condition [$F(2,48) = 2.288$, $p > 0.05$, $BF_{10} = 1.059$, $BF_{01} = 0.943$] or group [$F(2,48) = 3.463$, $p > 0.05$, $BF_{10} = 0.505$, $BF_{01} = 1.980$] was noted. The interaction effect between condition and group was also non-significant [$F(2,48) = 0.386$, $p > 0.05$, $BF_{10} = 0.257$, $BF_{01} = 3.891$] and so, pairwise comparisons were not conducted.

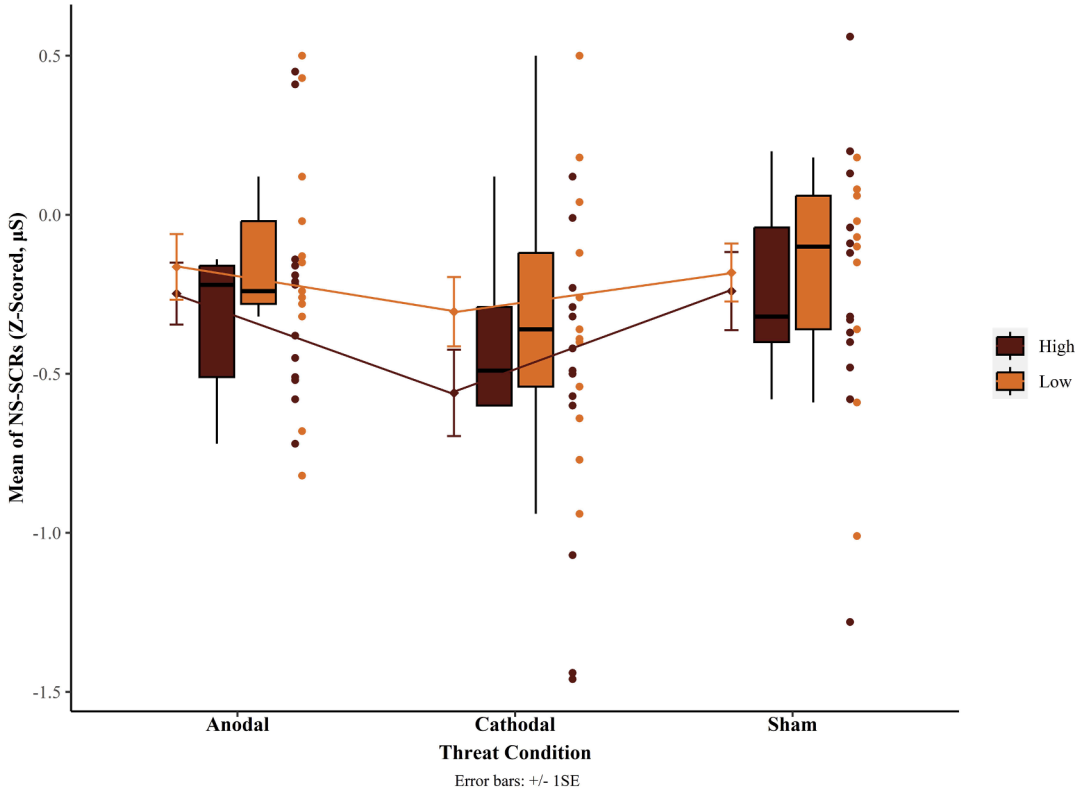

Fig. A.2. Magnitudes of Threat NS-SCRs (Z-Scored) under all three brain stimulation conditions (Anodal, Cathodal and Sham) for the high DLE group and low DLE group.

Independent sample t-tests between the two groups in the Frequentist analysis did not show any differences in any of the conditions: Anodal [t (24) = −0.589, $p > 0.05$, $BF_{10} = 0.413$, $BF_{01} = 2.421$], Cathodal [t (24) = − 1.456, $p > 0.05$, $BF_{10} = 0.792$, $BF_{01} = 1.263$] or Sham [t (24) = −0.377, $p > 0.05$, $BF_{10} = 0.383$, $BF_{01} = 2.611$].

Frequency of NS-SCRs

Similarly, Pearson's two-tailed *r* correlations were used to compare the responses on the DLE measure and frequency of Threat NS-SCRs under all three stimulation conditions (Anodal, Cathodal and Sham) but no significant correlations were noted (Table A.3).

Table A.3
Pearson's coefficients (FDR Corrected) and Bayes values between DLE and frequency of Threat NS-SCRs (CPM) under all three stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	*r*	*p* value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
DLE vs. Cathodal	− 0.391	0.044	0.017	1.650	0.606	Inconclusive AH
DLE vs. Anodal	− 0.108	0.591	0.033	0.274	3.650	Good Null
DLE vs. Sham	− 0.084	0.677	0.050	0.260	3.851	Good Null

** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

A mixed 2x3 ANOVA with two variables of group (Between-subjects: high DLE vs. low DLE) and condition (Within-subjects: Anodal, Cathodal and Sham) (Fig. A.3) did not show any significant main effects of condition [F (2,48) = 1.543, $p > 0.05$, $BF_{10} = 0.341$, $BF_{01} = 2.929$] or group [F (2,48) = 1.749, $p > 0.05$, $BF_{10} = 0.831$, $BF_{01} = 1.204$]. The interaction effect was also found to be non-significant [F (2,48) = 1.921, $p > 0.05$, $BF_{10} = 0.659$, $BF_{01} = 1.518$].

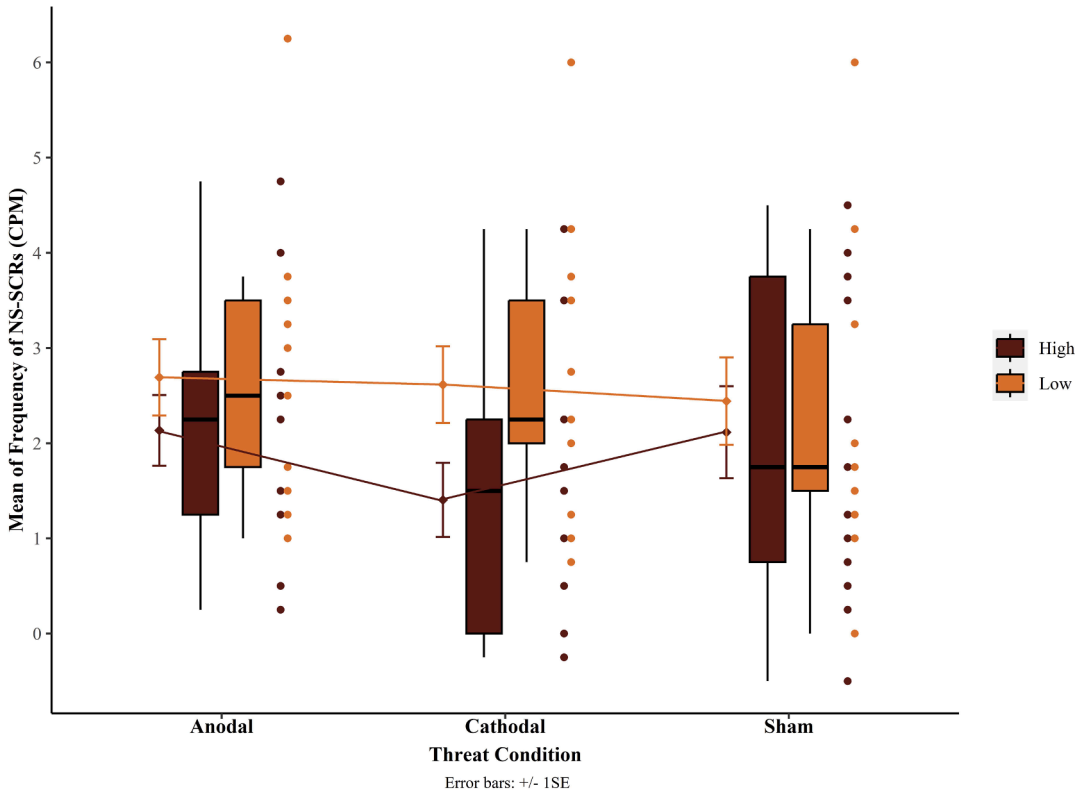

Fig. A.3. Frequency of Threat NS-SCRs (CPM) under all three brain stimulation conditions (Anodal, Cathodal and Sham) for the high DLE group and low DLE group.

The independent sample t-tests between the two groups showed no significant effect (FDR corrected) between the high DLE and low DLE groups in the Cathodal condition [t (24) = 2.161, $p = 0.041$, B&H = 0.017, $d = 0.401$, $BF_{10} = 1.873$, $BF_{01} = 0.532$] but not in the Anodal condition [t (24) = 1.022, $p > 0.05$, B&H = 0.033, $BF_{10} = 0.533$, $BF_{01} = 1.878$] or Sham condition [t (24) = 0.490, $p > 0.05$, B&H = 0.050, $BF_{10} = 0.397$, $BF_{01} = 2.521$]. However, the Bayes analysis suggests that the evidence here is inconclusive.

Depersonalisation-like experiences and self-report ratings

Similar to the above analysis, Pearson's two-tailed *r* correlations (for normal data) and Kendall's Tau (τ) correlations (for non-normal data) followed by two-way ANOVA (for normal data and Friedman's tests for non-normal data) were conducted to compare between the DLE factor and psychological ratings (on all dimensions).

Emotional arousal, emotional valence and realism of threat

This data followed normality however we failed to note any significant effects for the Pearson's two-tailed r correlations or between the groups in all three conditions (all *p*'s > 0.05, $BF_{10} < 1$, $BF_{01} > 3$) (Fig. A.4 a, b and d).

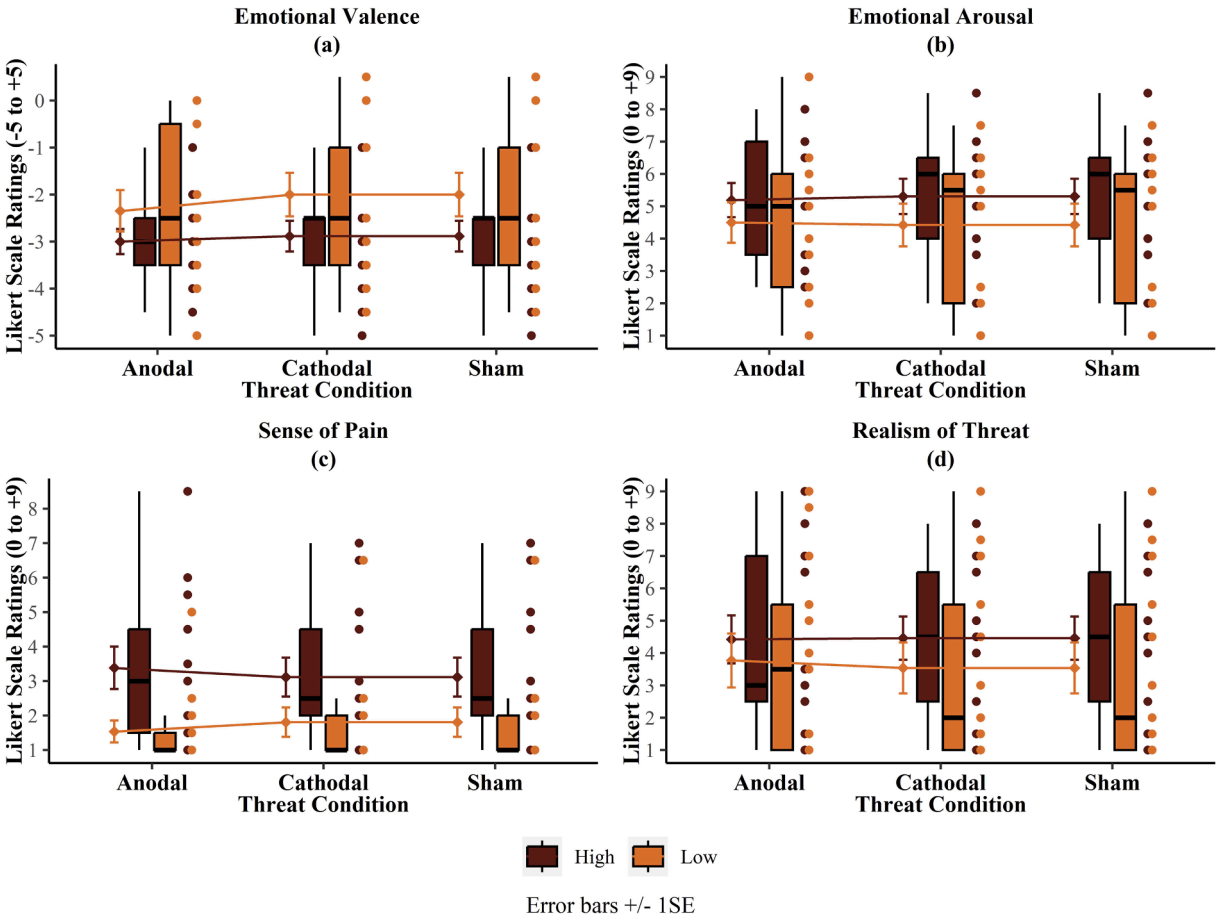

Fig. A.4. Differences between high DLE vs. low DLE groups for all stimulation conditions (Anodal, Cathodal, Sham) in the four psychological rating dimensions. Note: In the above figure, the four psychological ratings are illustrated for (a) emotional arousal, (b) emotional valence, (c) sense of illusory pain and (d) realism of threat.

Sense of pain

As this data did not follow normality, non-parametric analysis was conducted. Kendall's tau correlations between the DLE factor and psychological ratings for sense of pain in all three stimulation conditions (Table A.4). This indicated that higher the scores on the DLE factor in the Anodal stimulation condition higher the sense of pain ratings. No significant correlations were observed in the Cathodal and Sham conditions.

Table A.4
Kendall's τ correlation coefficients (FDR Corrected) and Bayes values between DLE and psychological ratings (sense of pain) for all stimulation conditions (Anodal, Cathodal, Sham).

Correlation Pair	τ	p value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
DLE vs. Anodal	0.366*	0.012	0.017	7.594	0.132	Good AH
DLE vs. Sham	0.299	0.043	0.033	2.461	0.406	Inconclusive Null
DLE vs. Cathodal	0.277	0.059	0.050	1.771	0.565	Inconclusive Null

* Significant correlations after using FDR corrections, the correlation pairs are ranked in ascending order.
** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

No significant differences were noted between the stimulation conditions (Anodal, Cathodal, Sham) in the high DLE and low DLE groups (Fig. A.4 c). However, Mann-Whitney U independent sample t-tests revealed that participants in the high group perceived the stimuli as more painful in every stimulation condition; Anodal ($U = 141$, $p = 0.003$), Cathodal ($U = 123.5$, $p = 0.044$) and Sham ($U = 123.5$, $p = 0.044$).

Appendix B

Severity of adverse symptoms

At the end of each stimulation session, all participants completed a standardised questionnaire measuring adverse symptoms experienced before and after stimulation on a Likert-type scale from 1 (no symptom experienced/absent) to 4 (Severe). Symptoms measured were Headache, Neck pain, Pain under electrodes, Tingling, Itching, Burning, Sleepiness, Concentration or thinking problems, Changes in mood (positive and negative), Nervousness, Scalp pain/irritation, Skin redness and Hearing problems.

Data was standardised by initially converting the Likert-type scale from (0 – 3), then subtracting the symptoms experienced before stimulation from after stimulation (to account for individual differences and pre-existing symptoms) and finally, a mean of adverse symptoms were calculated for each participant for each stimulation condition. The overall severity of adverse effects for the three stimulation conditions of MtDCS were Anodal ($M = 0.21$, $SD = 0.17$), Cathodal ($M = 0.16$, $SD = 0.16$) and Sham ($M = 0.15$, $SD = 0.15$).

As these data did not follow normality, non-parametric analysis was conducted. A Friedman's test showed a significant main effect between the mean of adverse effects experienced in all three stimulation conditions χ^2 (2) = 9.073, $p < 0.05$ (Fig. B.1). However, pairwise comparisons using FDR corrections showed no significant differences between the three stimulation conditions: Anodal vs. Sham (Z = 2.083, $p = 0.037$, B&H = 0.017), Anodal vs. Cathodal (Z = 1.778, $p = 0.075$, B&H = 0.033), and Cathodal vs. Sham (Z = 0.417, $p > 0.05$, B&H = 0.05). Therefore, these potential symptoms of MtDCS were matched across the three stimulation conditions.

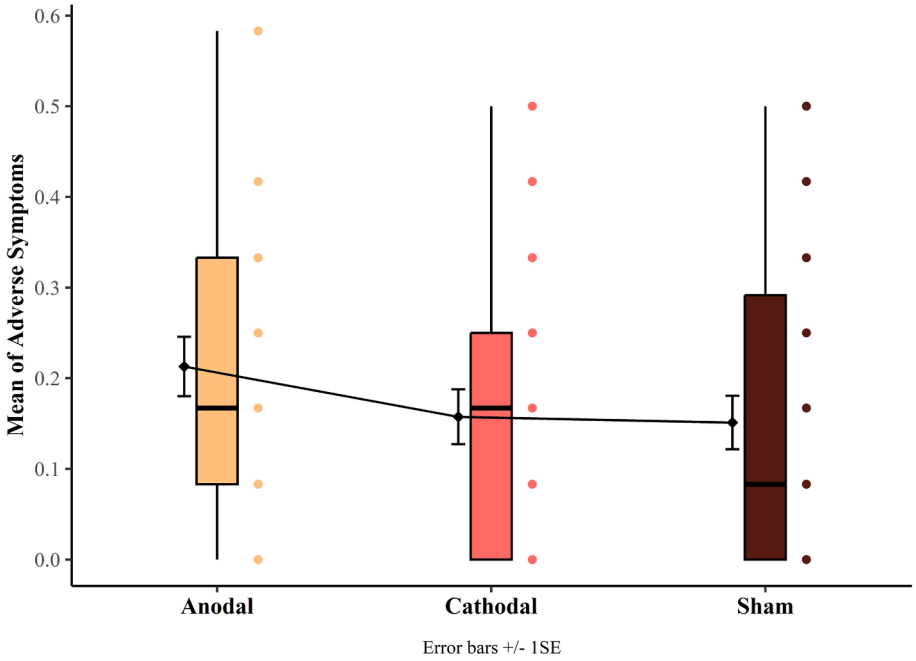

Fig. B.1. Mean of Adverse Symptom experienced in all three stimulation conditions.

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