

**New Insights into the Role of Cortical Hyperexcitability in the Neurotypical
Population predisposed to Aberrant Experiences.**

by

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Dedication

This is for you dad.

Just wish you could have seen all this.

Dr Dattatraya N Joshi (D.N.)

(1958 – 2019)

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Note of Caution

There are two figures in this thesis that contain imagery pertaining to threat, blood and gore. These figures (2.1 and 3.3 – to a lesser extent) are on pages 62 and 112 respectively, with no surrounding text. If you find this distressing, unpleasant or viewing imagery of this kind puts you in physical danger, you may choose to avoid these pages.

Abstract

Broadly, aberrant experiences are categorised as aberrant perceptual experiences, aberrant body / self-experiences and aberrant beliefs. There is growing evidence that cortical hyperexcitability underlies many aberrant perceptual experiences such as hallucinations, illusions, distortions etc. in the visual domain. Predisposition to these experiences has been associated with a hyperexcitable visual cortex but has not been explored with aberrant body experiences. Given that many conditions and disorders contain both aberrant perceptual and aberrant body experiences, predisposition to cortical hyperexcitability may not be limited to the visual and extra striate cortices and may be involved in mediating atypical cognitive affective states underlying aberrant body experiences. This would then provide evidence for a functional overlap between neural networks involved in certain aberrant perceptual and aberrant body experiences. In part, the main concern with researching aberrant experiences has been the lack of standardised diagnostic tools and methodologies. The present work therefore additionally aimed to explore novel methodological approaches in examining cognitive affective biases underpinning aberrant body experiences.

This thesis is comprised of three empirical studies. Chapter 2 assessed the reliability and utility of methodological improvements made to the newly devised Body-Threat Assessment Battery (BTAB – Braithwaite et al., 2020) as a salient tool in examining aberrant body experiences and associated increases in autonomic activity (as measured by skin conductance responses (SCRs) in addition to introducing a novel FaceReader method as a second objective psychophysiological measure. Chapter 3 investigated whether predisposition to cortical hyperexcitability mediated efficacy of applied brain stimulation (using Multi-channel Transcranial Direct Current – MtDCS) to the right ventrolateral prefrontal cortex (rVLPFC) which has been identified as an important structure in emotion regulation and cognitive affective states as part of multi-sensory integration and aberrant

body experiences. Finally, Chapter 4 explored the role of interoceptive vulnerability in alternative therapeutic strategies (repetitive Transcranial Magnetic Stimulation – rTMS) in maintaining corticomotor efficiency (primary motor cortex – M1) following upper arm immobilisation.

Collectively, this thesis extends and provides new insights, methodologically and theoretically, into cognitive affective biases underlying aberrant experiences.

Chapter 1

Introduction

Aberrant Experiences

Major inconsistencies in normal everyday experiences results in an altered state defined as “aberrant / anomalous experiences”. These aberrant experiences can occur through any of the senses in isolation, such as visual, auditory, olfactory, gustatory and vestibular, or can occur as multi-modal, i.e., expressed through a combination of one or more of these senses (audio-visual, visuo-tactile etc.) (Aleman & Larøi, 2008; Lewandowski et al., 2009; Bell et al., 2010; Ali et al., 2011; Mitchell et al., 2017; Waters & Fernyhough, 2017; Dudley et al., 2019; Fernyhough, 2019; Montagnese et al., 2021; Rogers et al., 2021). This thesis will focus primarily on aberrant experiences in the visual modality.

Overall, aberrant experiences refer to a variety of abnormalities occurring in everyday life. In the current literature, broadly, researchers suggest that aberrant experiences are classified into three main types. Firstly, aberrant perceptual experiences, which are defined as sensory hallucinations / illusions / distortions (Cummings & Miller, 1987; Barodwala & Mulley, 1997; Aleman & Larøi, 2008; Teeple et al., 2009). Secondly, aberrant self-experiences, which are distortions and aberrations of self-consciousness that are thought to follow aberrant perceptual experiences (Postmes et al., 2014; Pienkos et al., 2019; Wright et al., 2020). Thirdly, aberrant beliefs / delusions, that are considered to occur as a consequence of the first two types (Maher, 2006; Jarosinski, 2008; Fletcher & Firth, 2009; Wright et al., 2020). Aberrant beliefs will be considered in Chapter 2, however, in general, are outside of the scope of this thesis and so aberrant perceptual and self-experiences will be discussed in detail below.

Aberrant Perceptual Experiences

In essence, aberrant perceptual experiences have been defined as experiences of veridical (normal) perception that arise without a conforming external stimulus in a waking state (Slade, 1976; Cummings & Miller, 1987; Slade & Bentall, 1988; Bentall, 1990; Barodwala & Mulley, 1997; Allen et al., 2008; Teeple et al., 2009; Waters et al., 2014; Zmigrod et al., 2016; Montagnese et al., 2021). Under this remit, visual hallucinations have been broadly classed as “simple” or “complex” (Teeple et al., 2009; Yacoub & Ferrucci, 2011; Block, 2012; Jan & Castillo, 2012; Waters et al., 2021).

Simple visual hallucinations, typically referred to as basic / elementary / unformed hallucinations, categorise experiences as rudimentary hallucinations which manifest as geometric shapes, spots, shimmering, flashes of light, “bending” of lines and the like (Slade & Bentall, 1988; Panayiotopoulos, 1994; Santhouse et al., 2000; Merabet et al., 2004; Ffytche, 2007; Ali et al., 2011; Block, 2012; Shine et al., 2014; O’Brien et al., 2020). These simple hallucinations are thought to be connected to the primary visual cortex (Kölmel, 1993; Anderson & Rizzo, 1994; Ffytche et al., 2010).

Complex visual hallucinations / formed hallucinations on the other hand have more defined structures such as objects, body parts, faces, events, animals etc. (Slade, 1976; Kölmel, 1993; Manford & Andermann, 1998; Collerton et al., 2005; Yacoub & Ferrucci, 2011; Jan & Castillo, 2012; Collerton, 2016; O’Brien et al., 2020) The occurrence of these complex visual hallucinations is seen with co-activation of associated areas that support perception and attentional networks, which are also known as visual associated pathways and is discussed more in depth below (Kölmel, 1985; Manford & Andermann, 1998, Santhouse et al., 2000; Collerton et al., 2005; Ffytche et al., 2010).

In contrast to hallucinations, visual illusions / distortions have been defined as misrepresentations or misperceptions of existing external stimuli (Coren et al., 1976; Kölmel, 1993; Gregory, 1997; Mocellin et al., 2006; deWit et al., 2015; Coren & Girgus, 2020). These experiences are characterised as perceptual changes in the quality / nature of a real object such as intensity (getting brighter or duller) or changes in the properties (bigger or smaller) (Coren et al., 1976; Mocellin et al., 2006; deWit et al., 2015; Rowland & Lee, 2019; O'Brien et al., 2020).

Collectively, due to the composite nature of aberrant perceptual experiences and the consequent difficulty in accurate definitions (O'Brien et al., 2020; Rogers et al., 2021), the current view in the literature is that the different types of aberrant perceptual experiences can be considered as a continuum / spectrum of perceptual abnormalities that range from veridical perception (normal) to complex hallucinations with misperceptions and distortions lying somewhere in between (Fischer, 1969; Johns & Van OS, 2001; Johns, 2005; Van Os et al., 2009; Rogers et al., 2021).

Aberrant Perceptual Experiences in the Clinical Population

Aberrant perceptual experiences are a common symptomology underlying a host of disorders and conditions in the clinical population. Following are definitions and explanations of a few of these disorders.

Epilepsy

Epilepsy - commonly referred to as “seizure disorder” - is defined as “an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition” (Fisher et al., 2005, p. 471).

Epileptic seizures are transient in nature and occur due to increased / excessive neuronal

activity in the brain (McCormick & Contreras, 2001; Litt & Echauz, 2002; Fisher et al., 2005; Bromfield, 2006; Beghi, 2020). The presentation of a seizure can be due to a variety of factors (including location, current brain state and the like) and can alter various cognitive processes such as perception and affective states (Fisher et al., 2005). These altered states can result in aberrant experiences like depersonalisation, out-of-body experiences, time distortions etc. (Devinsky et al., 1989; Sierra & Berrios, 1998; Elliott et al., 2009; Cavanna, 2014; Medford, 2014). Aberrant perceptual experiences are commonly reported in visual epilepsies with more occurrences of simple visual hallucinations which are typically reported as stars, “balls of light”, halos or streaks (Panayiotopoulos, 1994; Bien et al., 2000; Wilkinson, 2004). Complex visual hallucinations, illusions and distortions are also reported but infrequently (Bien et al., 2000).

Migraines with Aura

Migraines are characterised as severe episodic headaches that occur with a pulsating sensation on either one or both sides of the head (Silberstein et al., 2001). The term “migraine aura” is a type of migraine that refers to the altered visual / sensory or motor phenomena that precedes or accompanies migraine attacks which is reversible (Reuter et al., 2009; Dodick, 2018(a), 2018(b); Chiang et al., 2021). Visual auras are considered the most prevalent form of migraine auras and contain symptoms of unformed hallucinations that can be positive or negative (Panayiotopolous, 1994; De Lange & Cutrer, 2014; Evans, 2014). These visual disturbances manifest as dots (coloured or white), specks, flashes of light, crescents with shimmering edges (scintillations), zig-zag lines or other geometric shapes (De Lange & Cutrer, 2014; Marzoli & Criscuoli, 2017). Complex aberrant experiences like ‘Alice in Wonderland’ syndrome (changes in perception of body, space or time) are also experienced as part of visual auras in migraines however their occurrence is rare (Bayen et al., 2012; Ilik & Ilik, 2014; Liu et al., 2014).

Schizophrenia

Hallucinations are a common diagnosis for schizophrenia and schizophrenic disorders (Mueser et al., 1990; Baegthe et al., 2005; Zmigrod et al., 2016). Although auditory hallucinations are more dominant, visual hallucinations are also present in schizophrenia (roughly 27%) (Bracha et al., 1989; Oertel et al., 2007; Bauer et al., 2011; Waters et al., 2014; Cuchia et al., 2015; Ford et al., 2015; McCarthy-Jones et al., 2017). Both simple (dots, etc.) and complex (faces, events, etc.) visual hallucinations and visual distortions (changes in colour, shape, etc.) are present in those with schizophrenia (Oorshot et al., 2012; Waters et al., 2014; Ford et al., 2015; Keane et al., 2018; Silverstein & Lai, 2021).

Lewy Body Dementia

One of the main characteristics of Lewy Body Dementia are the occurrence of recurrent visual hallucinations (Neef & Walling, 2006; McKeith, 2007; Mrak & Griffin, 2007). Visual hallucinations experiences in patients are usually well formed and detailed such as faces, animals and the like (Taylor et al., 2011; Cagnin et al. 2013; Erskine et al., 2019).

Charles-Bonnet Syndrome

Charles-Bonnet syndrome is described as the occurrence of visual hallucinations due to visual loss or severe macular degradation, however without cognitive impairment (Damas-Mora, 1982; Burke, 2002; Ffytche, 2005(a), 2007(b); Jan & Castillo, 2012). Both simple (coloured patterns, grids etc.) and complex (vivid and detailed) hallucinations are experienced by patients (Schultz & Melzack, 1991; Wilkinson, 2004; Jackson & Ferencz, 2009; Yacoub & Ferrucci, 2011; Pang, 2016; Carpenter et al., 2019).

Aberrant Perceptual Experiences in the Neurotypical Population

Although it is thought that aberrant perceptual experiences occur with underlying pathology of a clinical disorder or condition, many studies have shown the prevalence of these experiences in the neurotypical / non-clinical population without cognitive impairment (Tien, 1991; Ohayon, 2000; Johns & Van Os, 2001; Johns, 2005; García-Ptacek et al., 2013; McGrath et al., 2015; Preti et al., 2014; Waters et al., 2014; Pearson et al., 2016; Van Os & Renninghaus, 2016; Rogers et al., 2021). The term neurotypical / non-clinical population is used here to refer to the normal, healthy population that do not have any clinical diagnoses.

The occurrence of these aberrant perceptual experiences in the neurotypical population can occur spontaneously (see citations mentioned above) or be artificially induced. Some examples of artificially induced aberrant perceptual experiences can be as a result of drugs – psychedelic and prescription (Cole & Katz, 1964; Cummings & Miller, 1987; Weller & Wiedemann, 1989; Barodwala & Mulley, 1997; Litjens et al., 2014; Linszen et al., 2018), visually irritative stimuli such as Pattern Glare (Wilkins et al., 1984; Evans & Stevenson, 2008; Merchant, 2021), flicker-induced hallucinations (Allefeld et al., 2011; Becker et al., 2013; Pearson et al., 2016), sensory deprivation of vision (Flynn, 1962; Merabet et al., 2004; Mason & Brady, 2009;) etc. (for a review and other induced aberrant perceptual experiences see - Rogers et al., 2021).

Cortical Hyperexcitability

An important concept to consider in the occurrence of aberrant perceptual experiences is cortical hyperexcitability, defined as heightened excitation of neuronal activity in brain regions that is above expectations (Wilkins et al., 1984; Haigh et al., 2012(a); 2013(b); Bargary et al., 2015). Typically, one example of neuronal communication in the brain is

regulated by amino acid neurotransmitters, glutamate for excitatory and γ -aminobutyric acid (GABA) for inhibitory (Petroff, 2002; Foster & Kemp, 2006; Samardzic et al., 2018). At all times, normal functioning and processing is maintained through an excitation / inhibition balance (E / I) by the neurotransmitters (Foster & Kemp, 2006; Jacob et al., 2008; Carcea & Froemke, 2013; Froemke, 2015; Denève & Machens, 2016; Jardri et al., 2016). When incoming information activates the sensory brain region, an increase in firing rate of excitatory neurons is seen along with excitation of the inhibitory neurons to counteract and maintain stability within the cortex (Palmer et al., 2000; Fong, 2019). Cortical hyperexcitability is seen when there is an unusual E / I balance (e.g., over-excitation) or atrophy (dysfunctional inhibition) in some cases (Carter & Ffytche, 2005).

Uncharacteristic hyperexcitability in sensory neural circuits can manifest into perceptual alterations such as simple or complex hallucinations, distortions etc. (Siegal, 1977; Panayiotopoulos, 1994(a), 1999(b); Bresloff et al., 2001(a), 2002(b); Allen et al., 2008; Braithwaite et al., 2013(a), 2015(b); Fong, 2019; Fong et al., 2019(a), 2020(b)). The literature on cortical hyperexcitability of brain regions has been associated with several clinical disorders that give rise to aberrant perceptual experiences such as epilepsy (Stafstrom, 2006; Badawy et al., 2007(a), 2014(b); Simone et al., 2007; Bauer et al., 2013), migraines with aura (Mulleners et al., 2001; Aurora et al., 2003; Young et al., 2004; Simone et al., 2007; Aurora & Wilkinson, 2007; Palmer et al., 2000; Haigh et al., 2012), schizophrenia (Collerton et al., 2005; Spencer & McCarley, 2005; O'Donnell, 2008; Rogasch et al., 2014), Charles Bonnet Syndrome (Ffytche & Howard, 1999; Burke, 2002; Pang, 2016; Coltheart, 2018; Painter et al., 2018) etc.

In the neurotypical population, many studies have found a relationship between cortical hyperexcitability and aberrant perceptual experiences. For example, behavioural studies using visually irritative stimuli (e.g., Pattern Glare – discussed in depth below) have

induced illusions / simple hallucinations (e.g., bending of lines, shimmering etc.) in the non-clinical population using psychophysiological methods (such as electroencephalogram - EEG / visual evoked potentials - VEP) (Georgeson, 1976; Braithwaite et al., 2013; Braithwaite, Merchant et al., 2015; Braithwaite, Mevorach et al., 2015; Pearson et al., 2016; Fong et al., 2019; Merchant, 2021). Evidence has shown that visual hallucinations are associated with lower alpha power, increased alpha band frequency (as measured by EEG) and decreased phosphene thresholds (using Transcranial Magnetic Stimulation (TMS) over the visual cortex) in migraineurs with aura vs. migraineurs without aura / controls (see Jardri et al., 2016 for a review; also, Young et al., 2004; Aurora & Wilkinson, 2007; daSilva Morgan et al., 2018). In addition, migraineurs with aura have shown larger VEP amplitudes that do not habituate when compared to healthy controls or migraineurs without aura (Aurora & Wilkinson, 2007; Braithwaite, Mevorach et al., 2015). Further evidence from brain imaging and brain stimulation studies have supported this relationship of heightened neural activity underlying aberrant perceptual experiences (Antal et al., 2003(a), 2003(b); Antal & Paulus, 2008; Block, 2012; Braithwaite et al., 2015; daSilva Morgan et al., 2018). Collectively, certain aberrant perceptual experiences are associated with underlying cortical hyperexcitability.

Quantifying Cortical Hyperexcitability

Prior research has demonstrated that, in individuals predisposed to aberrant experiences, the threshold to elicit neural excitation and trigger aberrant perceptual experience is lower, suggesting higher cortical hyperexcitability (Aurora et al., 1999; Young et al., 2004; Aurora & Wilkinson, 2007; Braithwaite et al., 2015). Given the prominence of cortical

hyperexcitability underlying sensory hallucinations, very few methods and tools assessing cognitive biases underpinning cortical hyperexcitability exist.

In behavioural studies, the ‘Pattern Glare Test’ has been commonly used as a measure of predisposition to cortical hyperexcitability (Harle et al., 2006; Evans & Stevenson, 2008; Braithwaite et al., 2013(a); 2015(b); Fong, 2020; Merchant, 2021). Pattern Glare is a phenomenon where spatial features of repetitive contrasting stripes (usually black and white) induce visual distortions / simple unformed hallucinations (Wilkins et al., 1984; Wilkins & Evans, 2001; Evans & Stevenson, 2008; Braithwaite et al., 2013(a); 2015(b); Fong, 2020; Merchant, 2021). In the Pattern Glare Test (Wilkins & Evans 2001; Evans & Stevenson, 2008), three striped gratings with different spatial frequencies (calculated in CPD = cycles per degree of visual angle, see Evans & Stevenson 2008) are presented to participants as Low gratings (0.5 CPD), Medium gratings (3 CPD) and High Gratings (12 CPD) in a randomised order. After viewing each of these gratings, participants would account for the number of aberrant perceptual distortions they experienced (from a list). The number of hallucinatory / sensory aberrations experienced were highest in the 3 CPD gratings and predisposition to cortical hyperexcitability would be identified by each participant’s ratings on the 3 CPD grating or the 12 – 3 CPD grating (Evans & Stevenson, 2008).

The theoretical underpinning of the pattern glare test is that cortical hyperexcitability is due to a disruption/dysfunction in the E / I within the visual cortex (Harle et al., 2006; Evans & Stevenson, 2008; Braithwaite et al., 2013(a); 2015(b); Fong, 2020; Merchant, 2021). If there is a dysfunctional E / I balance within the visual cortex, presentation of 3 CPD gratings would “over-excite” the neuronal network firing rates, which would create an E / I imbalance and give rise to perceptual aberrations or hallucinatory experiences.

Several trait-based measures have been developed over the years in assessing visual stress and visual hallucinations in the neurotypical population. The Launay - Slade Hallucination Scale (Launay & Slade, 1981) was aimed at measuring the predisposition of hallucinatory experiences in the non-clinical population. Similarly, the Meares-Irlen Scale (Irlen, 1983) was developed to measure predisposition to visual distortions. Although in these questionnaires the measurement of predisposition to aberrant perceptual experiences was present, they did not directly measure the specific aberrant perceptual biases underlying cortical hyperexcitability. Other commonly used trait-based measures such as the Cardiff Anomalous Perception Scale (CAPS – Bell et al., 2006) and the Cambridge Depersonalisation Scale (CDS – Sierra & Berrios, 2000) focus mainly on the aberrant experiences themselves and not on the experiences that indicate cortical hyperexcitability (Braithwaite et al., 2015).

To alleviate these concerns, Braithwaite et al. (2015) developed the Cortical Hyperexcitability Index (CHi) which is a 27-item proxy measure that specifically targeted the aberrant perceptual experiences that reflect underlying cortical hyperexcitability. A further revision and modification of this index was the Cortical Hyperexcitability Index II (CHi_II) that verified and created more distinctive factor structure that was validated and using behavioural (Pattern Glare Test) and neurophysiological (EEG) examinations (Fong et al., 2019 (a), 2020 (b)). This trait-based measure contains three factors, first, the “Heightened Visual Sensitivity and Discomfort” (HVSD) which contains visual stress symptoms that have been previously associated with cortical hyperexcitability (Wilkins, 1995; Huang et al., 2003(a), 2011(b); Braithwaite et al., 2013(a), 2015(b); Fong et al., 2019, Fong, 2020, Merchant 2021). The second factor which measures simple / unformed hallucinatory experiences such as phosphenes, flashes, blurred vision etc. is named the “Aura-like Hallucinatory Experiences” (AHE). And the final factor, “Distorted Visual Perceptions”

(DVP) contains items measuring visual distortions (Fong et al., 2019; see also Braithwaite et al., 2015). Currently, this measure has been the only validated measure quantifying the aberrant perceptual symptoms underlying cortical hyperexcitability and so, this scope of this thesis will aim to provide further evidence into the utility of the CHi_II measure.

Aberrant Self-Experiences

A second class of aberrant experiences that is central to this thesis refers to aberrant experiences of the self. Phenomenologically, self-awareness is characterised on three main aspects; being aware of one's actions, being aware of one's physical location / being distinct from the environment and having agency / being in control of ones' thoughts and actions (Metzinger, 2004; Blanke & Metzinger, 2009; Tsakiris, 2010; Tsakiris et al., 2010; Braithwaite & David, 2016; Dewe, 2018). Typically, self-awareness is achieved through a host of neural processes that are integrated through exteroceptive (external) sources from the senses (e.g., visual, auditory, tactile, vestibular) etc. and interoceptive (internal) information known as 'multi-sensory integration' (Angelaki et al., 2009; Aspell et al., 2011; Faivre et al., 2015; Tsakiris, 2017). This implies that stable self-awareness is malleable to everyday experiences and so, this system is prone to breaking down leading to striking distortions in self-consciousness termed as aberrant self-experiences (Braithwaite et al., 2014; Braithwaite & David, 2016). Aberrant self-experiences are also commonly referred to as aberrant / anomalous body experiences (Dewe, 2018) and will be used interchangeably in this thesis.

Aberrant Self-Experiences in the Clinical Population

Previous research has shown that aberrant self-experiences are a core component of many disorders and conditions. Some examples of these conditions are explained below.

Out-of-Body Experiences / Autoscopy

Out-of-Body Experiences is an hallucination where someone experiences their self from a vantage point outside of their physical self and elevated (O'Blanke & Mohr, 2005; Brugger & Leggenhager, 2014). In this aberrant self-experience, patients feel as though their self is not present within their body.

Depersonalisation

Depersonalisation is a detachment or dissociative disorder where symptomology often contains a feeling of estrangement, detachment, reduced sense of self and emotional numbing (Kihlstron, 2005; Mula, 2009; Dewe, 2018).

Phantom-limb Syndrome

Phantom-limb syndrome is a phenomenon where patients perceive pain or sensation of a body part that does not exist (often following amputation) (Bailey & Morrish, 1941; Chahine & Kanazi, 2007)

Somatophrenia

Paralysed patients sometimes deny ownership of the paralysed limb instead attributing ownership to a third person which is termed as Somatophrenia (O'Blanke, 2012; Brugger & Leggenhager, 2014). Interestingly, this loss of limb ownership in this case is localised to either the hand or foot.

Alice in Wonderland Syndrome

Named after Lewis Carrolls (1865) "Alice Adventures in Wonderland" book, patients experience visual bodily distortions and illusions of themselves (such as smaller limbs, enlarged fingers etc.) (Kitchener, 2004; Liu et al., 2014).

Aberrant Self-Experiences in the Non-Clinical Population

Instances of aberrant self-experiences without underlying psychopathology have been known to occur in the neurotypical population in the form of out-of-body experiences, depersonalisation-like experiences and psychotic-like symptoms (Blackmore, 1982; Johns & van OS, 2001; Verdoux & van OS, 2002; Hunter et al., 2004; Leggenhager et al., 2007(a), 2009(b); Blanke & Metzinger, 2009; Braithwaite et al., 2013; Braithwaite & David; 2016; Dewe et al., 2016 (a), 2018(b); Dewe, 2018).

In research, the Rubber Hand Illusion (Botvinick & Cohen, 1998) is a well-known technique used to induce hallucinations of aberrant self-experiences. In this illusion, a rubber / artificial hand is placed alongside a participants own arm (which is hidden from view). Synchronously, the participants' own hand and the rubber hand are stroked using a brush, which creates a conflict between what the participant is seeing and feeling. When the rubber hand is then stroked asynchronously (participants own hand is not), the conflict is resolved by the participant "accepting" the rubber hand as their own. In this case, a "proprioceptive drift" occurs, where the lack of vision of the own arm creates a situation where the information from the rubber hand is "overwritten" and results in the rubber hand illusion (Botvinick & Cohen, 1998; Kammers et al., 2009). Studies have successfully and extensively induced the Rubber Hand Illusion in the neurotypical population (Ehrsson et al., 2004; Tsakiris & Haggard, 2005; Ehrsson, 2007; Lloyd, 2007; Hägni et al., 2008; Longo et al., 2008; Kammers et al., 2009; Tsakiris, 2010; Aspell et al., 2011).

Based on this phenomenon, other researchers have also successfully induced full-body illusions in the neurotypical population (Mizomoto & Ishikawa, 2005; Altschuler & Ramachandran, 2007; Lenggenhager et al., 2007; for review see Aspell et al., 2011).

Depersonalisation

As mentioned above, aberrant self- / bodily experiences are a common and central symptom in depersonalisation (DPD) which is a dissociative / detachment disorder. As described in Sierra and David (2011), the following are the main symptoms of depersonalisation.

“(i) Complaints of changes in body experience; (ii) automation – like feelings (i.e., loss of feelings of agency; (iii) emotional numbing; (iv) changes in the subjective experience of imagery and autobiographical recollections; and (v) complaints of changes in visual perception of surroundings” (Sierra & David, 2011, p. 100)

Another important characteristic (which is an important consideration in this thesis) of the aberrant body experiences in depersonalisation is the use of phrase “as if” that is often reported by patients along with their experiences, which implies that the patients are aware of the bizarreness of their experiences and that these experiences are not aberrant beliefs / delusions (Hunter et al., 2003(a), 2014(b), 2017(c); Medford et al., 2005; Sierra 2009; Sierra & David, 2011).

Depersonalisation is often accompanied with feelings of disembodiment or loss of body ownership (Medford et al., 2005; Sierra et al., 2005; Sierra, 2009; Sierra & David, 2011). Patients characterise their feelings as subjective changes in body image or body distortions (Sierra & Berrios, 2000; Medford et al., 2005; Sierra, 2009; Sierra & David, 2011). Interestingly, autoscopic phenomena, out-of-body experiences or somatosensory experiences are known to co-occur with depersonalisation, however, depersonalisation symptoms do not include these (Denning & Berrios, 1994; Sierra et al., 2005; Simeon et al., 2008; Anzellotti et al., 2011; Sierra & David, 2011). In addition, it has been noted that patients do not change / manipulate other aspects of the body part in relation to these experiences (such as movement etc.) (Sierra, 2009). Again, qualitatively this suggests that

depersonalisation is a distortion of sorts and that patients are aware of their aberrant body experiences.

In the literature, depersonalisation was reimagined as depersonalisation-derealisation disorder as the bizarre symptoms of loss of self-awareness / disembodiment (depersonalisation) and loss of awareness of their surroundings (derealisation) and were considered to be separate experiences (Sierra et al., 2002; Somer et al. 2013). Derealisation occurs when patients feel divorced from their surroundings or feeling “unreal” (Sierra & Berrios, 2002; Sierra et al., 2002; Sierra, 2009; Sierra & David, 2011; Hunter et al., 2014(a); 2017(b)).

“Emotional numbing” is the critical aspect of depersonalisation this thesis will focus on. Depersonalised patients describe their symptoms as flattened - dulled affect - towards pleasure or fear (Sierra & Berrios, 2000; Sierra, 2009; Sierra & David, 2011; Medford, 2012). Some patients report a complete lack of emotional experiences and so it can be considered that the intensity / quality of dulled affective states in depersonalisation varies (Sierra & Berrios, 2000; Simeon, 2004; Sierra, 2009; Hunter et al., 2013(a), 2017(b)). Interestingly, depersonalised patients also experience reduced empathy (Medford, 2012; Hunter et al., 2013). However, Lawrence et al. (2007) found that although depersonalised patients showed reduced affective empathy compared to healthy controls, there was no difference in cognitive empathy between the groups, providing evidence that depersonalised patients exhibit “intact” empathy. This also is a differentiation between distortion and delusion in depersonalisation.

Depersonalisation symptoms are typically examined using the Cambridge Depersonalization Scale (CDS – Sierra & Berrios, 2000) which measures a range of aberrant experiences that are associated with depersonalisation. This 29-item self-report scale has been clustered into four factors, namely, (i) “Anomalous Body Experience” / ABE (ii) “Emotional

Numbing” / EN (iii) “Anomalous Subjective Recall” / ASR and (iv) “Alienation from Surroundings” / AFS (Sierra et al., 2005). Each item in the factor has a frequency and duration scale due the transient nature of these experiences and a sum of the two (possible maximum of 10 per item) is used for analysis (Sierra et al., 2005). A collective score of > 70 is considered as clinical levels of depersonalisation or predisposition to depersonalisation-like experiences (Sierra et al., 2005; Sierra, 2009; Jay et al., 2014).

In the neurotypical population, the occurrence and prevalence of depersonalisation is well documented. For example, Hunter et al. (2004) estimated that the lifetime rates of occurrence were between 26 -74% (see also Sierra & David, 2011; Michal et al., 2009). Further examples and situations of depersonalisation in the neurotypical population are discussed below.

Typically, depersonalisation occurs as a defence to situations of stress, anxiety, trauma or life-threatening danger (Noller, 1982; Baker et al., 2003; Mohr & Blanke, 2005; Medford et al., 2005; Hunter et al., 2017). In the neurotypical population, depersonalisation-like experiences are almost always triggered by the negative conditions mentioned earlier as well as low mood or fatigue (Sierra et al., 2012; Hunter et al., 2003(a), 2013(b); Tibubos et al., 2018; Salami et al., 2020). As a result of this, researchers (for example, Mohr & Blanke, 2005; Sierra, 2009; Sierra & David, 2011) have posited that the key to understanding the cognitive biases underlying aberrant self-experiences in depersonalisation is dulled emotional experiences and is important for successful multi-sensory integration and stable self-awareness.

Negative Affective States

Flattened / dulled affective states in depersonalisation are evidenced by attenuated autonomic activity (as indexed by skin conductance responses - SCRs) to aversive stimuli (usually derived from the International Affective Picture System – IAPS; Lang et al., 1997) (Sierra, 2002; Sierra et al., 2005; Lemche et al., 2007). For example, Sierra et al. (2002) found that depersonalised patients exhibited lower SCR amplitudes than healthy controls when observing unpleasant vs. pleasant stimuli (IAPS). Similarly, Giesbrecht et al. (2010) found that depersonalised patients elicited lower SCR (mean rise time to peak) than healthy controls when watching an aversive movie clip (taken from the Hollywood movie – “Silence of the Lambs”). Furthermore, these studies have been supported by evidence in the neurotypical population (Dewe et al., 2016(a), 2018(b)). For example, in a study of using a real-life body threat task, where a pantomimed blood giving procedure was performed on the participants own arm using a fake needle – “Implied Body Threat” Task / IBT (Dewe et al., 2016). It was found that as the intensity of depersonalisation-like experiences (particularly ABE and AFS factors from the CDS) increased, SCRs when viewing the IBT task in neurotypical participants were suppressed. A recent meta-analysis conducted by Horn et al. (2020) examined studies with depersonalised patients and neurotypical individuals reported that those experiencing depersonalisation consistently exhibit lower SCRs to unpleasant or body–threat stimuli. Collectively, these findings show that emotional numbing / flattened affective states in depersonalisation accompanies attenuated autonomic activity.

Principal Theories explaining Attenuated Autonomic Activity

The literature has posited two main theories to account for flattened affective states and attenuated autonomic activity: Prediction Error Theory and Dysfunctional Fronto-Limbic

Suppression. Whilst these two theories propose alternative mechanisms (Bayesian statistical vs. neurobiological), it should be noted that they are seen as complementary (see Chapter 5 for an in-depth discussion), i.e., they should not be considered mutually exclusive.

Prediction Error Theory

This theory utilises Bayesian principles of probabilistic reasoning processes to consolidate interoceptive (internal signals) and exteroceptive (external incoming signals) information in successful multi-sensory integration of cortical functioning (Lee & Mumford, 2003; Friston, 2009; Seth et al., 2012; Clark, 2013; Seth, 2013; Apps & Tsakiris, 2014; Sel, 2014; Gerrans, 2019). Broadly, the mechanism of prediction error occurs from a mismatch between prior information and new incoming information, in this case about the self (Craig, 2002; Seth et al., 2012; Seth, 2013; Apps & Tsakiris, 2014). Prior information / top-down knowledge is gathered and stored by two methods; firstly, the information that is “hard-wired” into neural networks and secondly, the information that is collected over time by new experiences (statistical learning) (Seth et al., 2012; Clark, 2013; Seth, 2013; Apps & Tsakiris, 2014; Sel, 2014). When the existing (top-down) information is encountered with new information (bottom-up) this leads to the prediction error mentioned before. Aitchison and Lengyel (2017) explain that when prediction error is large, this results in neuronal spikes of communication in neural regions. However, if prediction error is small, the brain would work more efficiently as there would be no need for large neuronal spikes that expend more energy. Under this theory, the main goal of the brain is to minimise these prediction errors for successful multi-sensory integration (Craig, 2002; Seth et al., 2012; Seth, 2013; Apps & Tsakiris, 2014).

Given this, the implication is that interoceptive or internal information is important in minimizing this prediction error (Seth et al., 2012; Seth, 2013; Sel, 2014). If the biases

recognising top-down information are flawed, this would result in a mistaken / imprecise prior prediction and lead to a larger prediction error that cannot be reconciled. In the case of stable embodiment / self-experience, the outcome of this large prediction error would be the feelings of unreality, reduced sense of self and thereby a dulled emotional experience overall (Craig, 2002; Seth et al., 2012; Clark, 2013; Seth, 2013; Suzuki et al., 2013). This would imply that the varying degree of feelings of unreality are rooted in the amount of flawed top-down information.

Dysfunctional Fronto-limbic Suppression

The second prominent theoretical view to account for atypical suppression of autonomic activity in depersonalisation comes from a neurobiological perspective proposed by Sierra and Berrios (1998). As mentioned above, experiences of depersonalisation are considered to occur as a defence mechanism in situations that elicit fear, anxiety or threat responses. Based on this, the theory of dysfunctional fronto-limbic suppression relies on two simultaneous neural mechanisms; (i) the inappropriate inhibition of the amygdala and, (ii) hypervigilance / heightened attention (Sierra & Berrios, 1998; Sierra et al., 2005). Typically, anxiety / fear responses are modulated by a threshold (as a coping mechanism) by the frontal regions (specifically right ventrolateral prefrontal cortex – rVLPFC) which inhibits the emotional limbic areas such as the amygdala and anterior insula complex (AIC) to generate affective feeling states (Gu et al., 2013; Seth, 2013; Sel, 2014).

In depersonalisation, this theoretical account posits that a lower threshold of anxiety / fear leads to over inhibition by the rVLPFC that then results in lower affective feeling states. Consequently, the quality of subjective experience is reduced leading to feelings of “unreality” and patients feel unmoored from the body or the environment (aberrant body experiences) (Sierra & Berrios, 1998; Sierra et al., 2005; Sierra, 2009; Sierra & David, 2011,

Dewe, 2018). Processes of heightened attention to aversive / salient stimuli readily trigger this inherent anxiety / fear threshold that prevents the typical integration of perception and cognition and translates into aberrant experiences of self and body. In the case of depersonalisation, lower threshold would be triggered even in non-life-threatening situations which in normal processing seen only with life-threatening / fight-or-flight situations (Sierra & Berrios, 1998; Dewe, 2018).

Right Ventrolateral Pre-Frontal Cortex (rVLPFC) and Emotion Regulation

Conscious control of emotion / emotion regulation has been studied extensively with many cognitive models being theorised. Across these models, fronto-limbic suppression has been suggested as being central to emotion regulation (Ochsner & Gross, 2005; Banks et al., 2007; Sierra & David, 2011). The prefrontal regions have been identified as key for voluntary control of emotional experience based on the type of emotionally evocative event (specifically negative events), attentional control and the intensity of this event (Hare et al., 2005; Banks et al., 2007; Kalisch, 2009; Aldao et al., 2010; Lee et al., 2012; Che et al., 2015; Ferri & Hajcak, 2015; Gratz et al., 2015).

The amygdala has been known to be important in fear processing and other emotional states (Phelps & LeDoux, 2005; Ferri & Hajcak, 2015; Morawetz et al., 2017) as well as attention (Philips et al., 2003). However, activation of the amygdala can be modulated by voluntary control of the individual by using strategies of reappraisal (attentional demands, the individual's objectives, etc.). Several meta-analyses (Phelps, 2006; Buhle et al., 2014; Frank et al., 2014; Di et al., 2017; Berboth & Morawetz, 2021) and studies have demonstrated that amygdala activation is reduced when individuals actively regulate negative affect such as averted gaze, redirected attention and the like (Hariri et al., 2000; Ochsner et al., 2002;

Sabatinelli; 2005(a), 2006(b); Eippert et al., 2007; Lieberman et al., 2007; Foland-Ross et al., 2010). For example, Oschner et al. (2002) found a decreased activation of the amygdala when participants viewed negative images and were asked to reappraise them (voluntarily change the meaning of the image; crying in grief to be reappraised as crying with joy) versus not being asked to reappraise, in which case amygdala activation increased (see also Phelps, 2006 for a review).

In addition to the amygdala, several neural regions have been identified in successful reappraisal strategies; the anterior insula (AI), anterior cingulate cortex (ACC) and the prefrontal cortex (specifically medial and ventral) (Philips et al., 2003; Townsend et al., 2013; Emmert et al., 2016; Paret et al., 2016). Indeed, the co-activation of these regions have been associated with processing and regulating interoceptive physiological changes such as heart rate, arousal, body temperature etc. and exteroceptive (environment) changes (Craig, 2002(a); 2003 (b), 2009(c); Critchley, 2004; Pollatos et al., 2007; Wang et al., 2019; Chen et al., 2021). For example, Wang et al. (2019) found increased activation in the anterior insula cortex (AIC) using brain imaging when participants were asked to focus on their own breathing rhythm, highlighting the importance of this region in interoceptive awareness. These studies provide evidence for the predictive coding theory mentioned above.

The prefrontal cortex specifically rVLPFC has been shown to exert inhibitory control of threat related / fear responses over the amygdala and AIC (Phan et al., 2005; Berkman & Liebermann, 2009). For example, Phan et al. (2005) showed that increased activity in rVLPFC was associated with decreased activation of the amygdala when participants were asked to suppress / reappraise negative affective pictures (from the IAPS) using brain imaging techniques. The role of rVLPFC in down-regulating negative affect has been emphasized in emotion regulation research as well as self-control (Blair et al., 1999; Hariri et al., 2000; Keightley et al., 2003; Lange et al., 2003; Lévesque et al., 2003; Cohen et al., 2013;

Szczepanski & Knight, 2014; Torre & Liebermann, 2018; Chick et al., 2020). Interestingly, Vergallito et al. (2018) found that the rVLPFC would regulate negative affect in preventing “dangerous” situations such as fear / anxiety etc. regardless of their intensity using brain stimulation.

Dysfunctional rVLPFC functioning has been associated with a host of disorders and conditions in the clinical population such as anxiety disorders (generalised) (Hözel et al., 2013), depressive disorders (Kober & Ochsner, 2011; Henderson et al., 2014; Gallucci et al., 2020) etc. Similar observations have been made in the neurotypical / non-clinical population such as social exclusion / rejection / ostracism (Chester & DeWall, 2014; Riva et al., 2014; He et al., 2018(a), 2019 (b)) and aggression and impulsivity (Cohen et al., 2013; Riva et al., 2017; Chen, 2018). In addition, the rVLPFC has been implicated in experiences of Heutoscopy (mirrored illusion) and Autoscopy (Kaladjian et al., 2007; Leitman et al., 2011; Zhang et al., 2019).

In depersonalisation, theoretical accounts view over-inhibition of the rVLPFC results in aberrant self-experiences (Ochsner & Gross, 2004 (a), 2005 (b); Medford et al., 2006; Critchley, 2005; Eippert et al., 2007; Lemche et al., 2007 (a), 2008 (b); Craig, 2009; Klumpers et al., 2010; Clark, 2013; Gu et al., 2013; Seth, 2013; Jay et al., 2014; Xia et al., 2017; Vinberg et al., 2021). For example, Jay et al. (2014) found that low-frequency (facilitating suppression) repetitive Transcranial Magnetic Stimulation (rTMS) over the rVLPFC reduced symptoms of depersonalisation experiences in patients.

Taken together, these studies highlight the importance of these regions and particularly the rVLPFC in maintaining the integrative processes of perception and cognition in stable self-experiences and a dysfunction of the rVLPFC may result in aberrant experiences.

Overview of Methodology

Skin Conductance Responses (SCRs)

In this thesis, psychophysiological measures in the form of SCRs were used in all empirical chapters. In all chapters, the same technologies and devices were used to measure SCRs and so, to avoid repetition, the specificity of those technologies are detailed in each chapter. This section will outline the different measurement techniques of SCRs that would be utilised, and their significance.

The use of SCRs as a measure of emotional arousal / physiological state has been extensive in psychological and psychophysiological research (Venables et al., 1980; Nikula, 1991; Critchley, 2002(a), 2005(b); Dawson et al., 2007; Boucsein, 2012). Electrodermal activity (EDA) is defined as the amount of sweat secreted by the endocrine sweat glands as part of the sympathetic nervous system (Boucsein, 2012). In research, the measurement of skin conductance (a form of EDA) is usually achieved through passing a low-voltage electrical current through two areas of the skin (hypodermis layer) and the activity / flow of current through these two areas is reflective of autonomic activity (Nikula, 1991; Dawson et al., 2007 Boucsein 2012). The electrodes for passing direct current (DC) are usually attached to the distal phalanges of the palm as these are considered to be sensitive to sweat activity and reliable for measuring EDA (Dawson et al., 2007; Boucsein, 2012; Dewe, 2018). Skin conductance data is usually a time-series signal measured in microseimens (μS) with two main components, (i) short, fast-changing fluctuations (phasic) usually as a response to arousal / SCRs and (ii) slow continuous measurement (tonic) of background activity / skin conductance level (SCL).

Phasic SCRs occur as a fast-changing peak and a slow decline to baseline and are considered to reflect responses to a stimulus / event (event-related) 1 – 3 seconds after the

onset of the event (Benedek & Kaernback, 2010). An event-related SCR is calculated as a delta value between peak of the SCR minus the onset of the SCR beyond a given threshold of background activity (Boucsein, 2012; Braithwaite et al., 2013). Typically, the higher the delta value / peak the higher the response. The background threshold from which the onset of the SCR is calculated is generally accepted as 0.01 μ S in current practices due to the development of technology and therefore, more accurate measurements (Boucsein 2012; Dawson et al., 2007; Braithwaite et al., 2013; Dewe, 2018).

Within Phasic SCRs, three main elements are considered in this thesis; strength of SCRs, non-specific SCRs / NS-SCRs (those not event-related) and the frequency of NS-SCRs / F-SCRs. As mentioned above, the event-related SCR is calculated as a delta function occurring 1-3 seconds after the presentation of a stimuli / event. The strength of SCRs can be calculated as magnitude or amplitude (Boucsein, 2012; Braithwaite et al., 2013). In this context, magnitudes of SCRs are those that contain an input value of zero if no SCR was detected during the time frame of stimuli presentation. Amplitudes, in contrast, only contain SCRs which are measurable (non-zero). Prior work examining whether amplitudes or magnitudes are preferred has found that for multiple presentations of stimuli, magnitudes are a better indicator (for in depth discussion see Dawson et al., 2007; Braithwaite et al., 2013(a), 2015(b)) as there may be varying responses for a given period of time. Based on this, the empirical studies in this thesis will consider magnitude data for SCRs and NS-SCRs to reflect strength of autonomic activity.

Individual baseline arousal is typically measured by the second component of skin conductance data, SCL or tonic SCL (Boucsein et al., 2012; Braithwaite et al., 2013). However, as SCL data can vary significantly between individuals and can include phasic SCR information, researchers consider the magnitudes of NS-SCRs as a preferred measurement of background activity (Boucsein, 2012; Boucsein et al., 2012; Braithwaite et

al., 2013(a), 2015(b); Dewe, 2018). In addition, the number of NS-SCRs (frequency) is also considered as a reliable indicator of baseline individual activity (Dawson et al., 2007). Both magnitudes and frequency of NS-SCRs were explored alongside magnitudes of SCRs in this thesis for patterns for between- and within-subject designs.

Indeed, changes in autonomic activity have been associated with the orbitofrontal areas, amygdala, AIC and ACC activation to emotionally evocative stimuli (for example, shocks, facial expressions etc.), attention and decision-making tasks (Damasio, 1994; Büchel et al., 1998; Bechara et al., 2000; Critchley et al., 2000(a), 2001(b); Williams et al., 2001; Critchley, 2002(a), 2005(b); Nagai et al., 2004; Wood et al., 2014). In addition, functional neuroimaging (fMRI) studies have evidenced changes in autonomic activity in these areas induced by fear / threatening stimuli (Büchel et al., 1998; Critchley et al., 2000; Phelps et al., 2001; Williams et al., 2001). Along with the evidence provided for attenuated autonomic activity to aversive stimuli in depersonalised patients and neurotypical population predisposed to such experiences (see above), SCRs are a reliable and established measure of changes in physiological and psychological states.

FaceReader Responses (FRRs)

In Chapter 2, FRR data was utilised as a second objective psychophysiological measure for the first time. Prior research has indicated facial expressions may provide meaningful insight into cognitive-affective states (Fridlund & Cacioppo, 1986; Dimberg 1986; Levenson, 1990; Dimberg et al., 2000; Meng & Huang, 2014; Leppanen et al., 2017; Vartanov et al., 2020; Hofling et al., 2020). Of importance to the current work, facial expressions have the capability to provide valence information that is only assumed in SCRs (negative stimuli = negative arousal and vice versa).

The FaceReader was developed as a non-invasive commercially viable tool (Wolf, 2015; Suhr, 2017) that is widely available and can do online (during the task) as well as offline (post-video) analysis of facial expressions that is an attractive asset in research. There are six basic facial expressions that are identified by the FaceReader (based on Ekman, 1982) namely, happiness, sadness, anger, fear, surprise and disgust (den Uyl & van Kuilenburg, 2005; Loijens & Krips, 2018). The software (Noldus, 2014) achieves this by accurately mapping the face using over 500 key points (virtual grid), eye gaze and recognition of facial structure based on a large database of faces and measuring different facial muscles associated with the six expressions. The movement of these facial muscles is thought to be unconscious and only observable by others (Dimberg et al., 2000; Kret, 2015). A literature review by Blair (2003) noted that spontaneous and controlled emotional expressions are generated by the frontal cortex.

In the present thesis, FRR data was retrieved as a continuous signal data for intensity of each expression as a vector from 0 (expression not present) to +1 (maximum intensity for expression). In addition to the six basic emotions, valence is calculated by the software (per second) as positive expression (sum of intensity) minus negative expression. Note, the vector form of this data set is represented from -1 (maximum negative valence) to +1 (maximum positive valence) for valence. Arousal is also calculated by the software as an intercalation of 20 Action Units (AUs) from the Facial Action Coding System (FACS) (for full description of all AUs and FACS manual - see Ekman et al., 2002; Loijens & Krips, 2018).

Currently, there are no standardisation and normalisation norms identified in the literature and so, the specific analysis procedure used in this thesis is described in Chapter 2.

Multi-Channel Transcranial Direct Current Stimulation (MtDCS)

Transcranial Electric Current Stimulation (tCS / tES) is a non-invasive, sub-threshold neuromodulatory technique (Nitsche & Paulus, 2000; Paulus, 2011). There are currently two types of tCS techniques, (i) transcranial direct current stimulation (tDCS) and (ii) transcranial alternating current stimulation (tACS). tDCS applies a weak continuous direct current to affect action potentials whereas tACS influences frequency bands associated with behaviour using an alternating / oscillating current (see Paulus, 2011; Polanía et al., 2018). The tACS technique is beyond the scope of this thesis and so tDCS and its significance will be discussed in this section.

As mentioned above, stimulation effects via tDCS are achieved by inducing a weak current (1 – 2 mA) that permeates the scalp to induce subthreshold modulation of neuronal membrane potentials (Nitsche & Paulus, 2000; Woods et al., 2016). In the case of tDCS, neuronal activity is changed via de- or hyperpolarisation of stimulated cortical neurons by changing their discharge threshold. This means that already active neurons are manipulated however inactive / dormant neurons are not affected by the induction of current (see Nitsche et al., 2005; Liebetanz et al., 2006; Woods et al., 2016). Broadly, anodal stimulation is excitatory as neuronal discharge threshold is reduced, thereby increasing the probability of discharge, and cathodal stimulation is inhibitory whereby discharge thresholds are increased, reducing the probability of discharge (Nitsche & Paulus, 2000; Nitsche et al., 2003; Ruffini et al., 2014(a), 2018(b)).

Traditionally, in research, a sponge electrode approach has been utilised when applying tDCS (Woods et al., 2016). In this method, two sponges that are dipped in salt water or NaCl solution are applied to the target area and another point on the scalp (as a return current) so that there is an electric flow between the two sponge electrodes (Nitsche &

Paulus, 2000; Woods et al., 2016). This not only activates or suppresses the target cortical area but also adjacent areas thus making focality a contested issue (Miranda et al., 2013; Fox et al., 2014). To address these concerns, Ruffini et al. (2014) developed a multi-channel system which was modelled after EEG electrodes. Therefore, the new multi-channel approach (MtDCS) was utilised, which uses Ag/AgCl gel-based electrodes and software-controlled stimulation intensity which can be placed on multiple points on the scalp to provide for a more targeted method of stimulation (Kuo et al., 2014, Ruffini et al., 2014(a), 2018(b)). Target areas, electrode intensity, electrode position and electrode currents can be personalised by fMRI head scans and computational neuroscience for optimisation (for full procedures see Ruffini et al., 2012(a), 2018(b), Ho et al., 2016).

tDCS neuromodulatory techniques have been useful in potentiating long-term neuronal plasticity (after-effects) in several animal and human (clinical and non-clinical populations) studies, for example depression (Brunoni et al., 2014; Bennabi et al., 2015; Frase et al., 2021), cortical spreading depression in migraines (Liebetanz et al., 2006, Antal et al., 2011; Rocha et al., 2015), working memory enhancement (Hoy et al., 2013), stroke (Fregni et al., 2005; Hummel et al., 2005) etc. For example, Rocha et al. (2015) found that cathodal tDCS over the visual cortex reduced the number of migraine attacks, painkiller intake and duration of each attack in migraineurs when compared to healthy controls (see also, Auvichayapat et al., 2012). In addition, Hummel et al. (2005) showed that hand motor function in stroke patients was significantly improved after tDCS intervention to the motor cortex. Collectively, this demonstrates that tDCS / MtDCS is a promising neuromodulation tool in research.

Transcranial Magnetic Stimulation (TMS)

TMS is well-known non-invasive neuromodulatory technique that has been utilised in research since its conceptualisation in the early 1980s (Barker et al., 1985). In the TMS method, stimulation occurs when electrical current is passed through a wire which generates a magnetic pulse, which when placed laterally to the scalp induces current flow in the tissue (Hallett, 2000(a), 2007(b); Maeda et al., 2000; Hummel & Cohen, 2006; Rossini & Rossi, 2007; Barker & Shields, 2016; Iannone et al., 2016; Singh et al., 2019). Whether stimulation is excitatory or inhibitory is determined by the frequency of the voltage that is generated by the magnetic coil. Slow rates of 0.2 – 1 Hz stimulation, also known as low frequency, are inhibitory and higher rates (high frequency stimulation) > 5 Hz are excitatory (Hallett, 2007; Priori et al., 2009; Elder & Taylor, 2014). The coil type, such as round / circular, figure-of-eight, double coil or H-coil determines the focality of the target cortical region (for full explanations of each coil type see Rotenberg et al., 2014).

Within TMS, there are two types of stimulation, namely, monophasic (single pulse stimulation) and biphasic (short repetitive bursts of pulses – rTMS) (Terao & Ugawa, 2002; Barker & Shields, 2016). Monophasic or single pulse stimulation is generally used in measurement of excitability within the cortical region of interest. For example, when applied to the motor cortex, the minimum intensity of low- or high-frequency of voltage required to affect a visible change in muscle activity is determined by single pulse stimulation in a stepwise 5% increase in intensity of stimulator (Rotenberg et al., 2014, Gaffney et al., 2021). In contrast, rTMS is used by researchers to produce a long-lasting effect (after-effects) that can modify the cortical function of any given area that can be used for studying causal effects (Wasserman & Lisanby, 2001; Fitzgerald et al, 2006; Rossini & Rossi, 2007; Wagner et al., 2007; Hoogendam et al., 2010; Rotenberg et al., 2014).

Measurement of cortical excitability is usually achieved in two ways, resting motor threshold (rMT) and motor-evoked potentials (MEP) by electromyography (EMG) (Pascual-Leone et al., 1998; Fitzgerald et al., 2002(a), 2006(b)). As mentioned in the above example, the minimum intensity of high- or low-frequency pulse required to affect a visible change in muscle activity is termed as rMT. Alternatively, MEPs are the average responses at a constant intensity or increases in MEP size as the stimulator intensity is increased creating a response curve (Wasserman, 1998; Fitzgerald et al., 2006). Response curves are usually measured as an area under the curve (a.u.c.) that reflects general cortical excitability (Rotenberg et al., 2014).

TMS has been used in research to study a host of neurological and psychiatric disorders such as depression, schizophrenia, Parkinson's disease, migraines, panic disorders and the like (Pascual-Leone et al., 1998; Tassinari et al., 2003; Couturier, 2005; Clarke et al., 2006; Elahi et al., 2009; Matheson et al., 2010). In neurotypical / healthy populations, TMS has been utilised to examine the causal effects between brain and behaviour in various cortical regions such as, but not limited to, primary motor cortex, visual cortex, frontal areas etc. (Sparing et al., 2002; Gagnon et al., 2011; Bastani & Jaberzadeh, 2012; Bona et al., 2014; Petrichella et al., 2017). For example, Sparing et al. (2002) found that TMS stimulation to the visual cortex increased visual imagery (as measured by phosphene threshold).

The main criticism for TMS in research is lack of a sham procedure which is mainly due to the audible clicking sound as the pulse is being applied (this gets louder at higher intensity) which negates the "blind" condition. In contrast, tDCS techniques can add a sham protocol (see Ruffini et al., 2014) and can be used as a baseline comparison to anodal and cathodal effects. Whilst this shows advantages for tDCS over TMS techniques for research, both neuromodulatory techniques are effective and are consistently utilised in research with promising results.

Bayesian Factor Analysis

In recent years, Bayes Factor (BF) Analysis has gained a growing interest in many research fields including psychological sciences. As p values (Frequentist statistics) have been used with considerable evidence, many interpretational issues have been highlighted and debated amongst researchers (Cohen, 1995; Hubbard & Armstrong, 1997; Nickerson, 2000; Trafimow, 2003; Wagenmakers & Gründwald, 2006; Wagenmakers, 2007). Some examples of concerns with relying on p values for statistical inference were (i) confusion between data given hypothesis and hypothesis given data (ii) significance values of $< 0.001 / 0.05$ are arbitrary, and (iii) true null hypothesis is never 0 in real life and p values do not account for this (iv) p values do not take into consideration that different sample sizes will have differing statistical weight (for full discussion on these issues see; Wagenmakers, 2007; Jarosz & Wiley, 2014).

Bayes Factor analysis has been suggested as an alternative or an addition to p value reporting in science for reproducibility and replicability as well as a more accurate continuous measure of strength of null / alternative hypothesis (Wagenmakers, 2007; Jarosz & Wiley, 2014; Schoot et al., 2014; Etz & Wanderchackhove, 2016(a), 2018(b); Keyzers et al., 2020; Schmalz et al., 2021). The main advantage of using Bayes Factor concurrently with p values is to reconcile borderline effects where Frequentist analysis is considered too conservative and cannot be a quantifiable inference.

The basic difference in approach between Frequentist analysis and BF analysis is the BF values are comparative and that the likelihood of the data is compared from both the null hypothesis and the alternative hypothesis (Kass & Rafferty, 1995; Jeffreys, 1961; Rouder et al., 2009; Jarosz & Wiley, 2014). Put simply, BF is a ratio comparison between the null hypothesis and the alternative hypothesis. The formula as described in Jarosz & Wiley (2014)

in this case would be $BF_{01} = \text{likelihood of the data given } H_0 / \text{likelihood of the data given } H_1$, where BF_{01} gives the likelihood probability of the null hypothesis, H_0 is the null hypothesis and H_1 is the alternative hypothesis. And so, as the number for BF_{01} increases so does the strength of support for the null hypothesis. Alternatively, $BF_{10} = 1 / BF_{01}$ provides support for the alternative hypothesis. If $BF_{10} < 1$ then there is support for the null hypothesis, between 1 – 3 the data is inconclusive / weak (i.e., no interpretation can be made / more data is needed) and if $BF_{10} > 3$ then there is support for the alternative hypothesis and vice versa for BF_{01} values (i.e., if $BF_{01} < 1$ then there is support for the alternative hypothesis).

Many software packages have added the analysis of Bayes Factor in their analysis such as R, SPSS and JASP (Rouder et al., 2009; Wagenmakers, 2007; Love et al., 2019; van Doorn et al., 2021). In addition, Rafferty (1995) and Jeffreys (1961) suggested the following nomenclature for interpreting Bayes Factors, see the Table 1.1 below (Jarosz & Wiley, 2014).

Table 1.1

General nomenclature for Bayes Value interpretation for $BF_{10} > 3$ (as cited in Jarosz & Wiley, 2014)

BF ₁₀ Value Range	Nomenclature	
	Rafferty	Jeffreys
1 – 3	Weak	Anecdotal
3 – 10	Positive	Substantial
10 – 20	Positive	Strong
20 – 30	Strong	Strong
30 – 100	Strong	Very Strong
10 – 150	Strong	Decisive
> 150	Very Strong	Decisive

In this thesis, all empirical chapters will, where appropriate (for example, certain non-parametric tests cannot be represented with a Bayes Factor), p values will be accompanied by BF_{10} values (to show strength for alternative hypothesis). If $BF_{10} < 1$, BF_{01} values will be reported to evidence the strength of the null hypothesis. Taken together, this will provide a broader representation of the data and interpretation in this thesis.

Thesis Motivations and Empirical Chapter Overviews

Given the prevalence of all types of aberrant experiences in the clinical and non-clinical population, the mechanisms underlying the occurrences of such experiences remain under explored (Hunter et al., 2003(a), 2004(b); O'Brien et al., 2020). This may be in part due to the complexity, subjectivity, spontaneity, and variety of the occurrence of these experiences (Weiss & Heckers, 1999; Aynsworth et al., 2017; Rogers et al., 2021). Indeed, research has recognised that aberrant experiences can differ within individuals, as well as collectively, making it problematic to conclusively map the neural and cognitive biases underlying these aberrant experiences (Rogers et al., 2021). Nevertheless, prior research in understanding aberrant experiences from various distinct fields such as clinical, cognitive neuroscience etc. has expanded our knowledge in this field significantly (Jardri et al., 2019).

The majority of the research studying aberrant experiences is based in clinical settings. Whilst this is useful in identifying symptoms, many confounding variables (such as medication effects, other co-occurring conditions, etc.) may hinder our understanding of the cognitive, affective and neural biases underlying aberrant experiences. Considering that aberrant experiences - varying in frequency and quality – can occur in the neurotypical / non-clinical population without any underlying psychopathology, more research in this group will further our insights considerably (Ford et al., 2014; Waters et al., 2014).

One of the main criticisms of research in aberrant experiences is the lack of standardised tools and methodological techniques to produce reproducible and reliable data (Tackett et al., 2019; Moseley et al., 2021; Smailes et al., 2021). It has been suggested that the induction of aberrant experiences in the neurotypical population as a method of research can circumvent some of the complexities mentioned above, however very few studies have specifically employed salient stimuli / tasks (Braithwaite et al., 2020). Flattened and dulled

affective states have been associated with depersonalised patients and those predisposed to depersonalisation-like experiences in the non-clinical population (Philips et al., 2001; Sierra et al., 2002(a), 2006(b); Lemche et al., 2007; Sierra & David, 2011; Dewe et al., 2016(a); 2018(b) also see Horn et al., 2020 for a review). However, aberrant body experiences and atypical cognitive-affective states can occur in many other aberrant visual / perceptual disorders and conditions such as epilepsy, schizophrenia, panic disorders, anxiety disorders etc. (Kober & Ochsner, 2011; Hözel et al., 2013; Henderson et al., 2014; Gallucci et al., 2020). Given the breadth of aberrant experiences in various clinical disorders, developing tools to reliably induce in the non-clinical population would offer researchers a versatility in disentangling the complexity of their underlying neurocognitive biases.

Collectively, this thesis will examine the neurocognitive biases underlying aberrant experiences in the neurotypical / non-clinical populations. Typically, cognitive affective states / emotional numbing has been studied with aberrant body experiences such as depersonalisation, in which, qualitatively, experiences are considered as distortions and not aberrant perceptual experiences or aberrant beliefs (Hunter et al., 2003(a), 2014(b), 2017(c); Medford et al., 2005; Sierra 2009; Sierra & David, 2011). However, conditions such as out-of-body experiences, Autoscopy and Heutoscopy (as well as the ones mentioned above) contain both aberrant perceptual and aberrant body experiences (Brugger et al., 1997; Brugger, 2002; Blanke et al., 2004; Blanke & Mohr, 2005; Arzy et al., 2006; Blanke & Castillo, 2007; Braithwaite et al., 2011). Given this, this thesis will explore whether aberrant perceptual and aberrant body experiences have distinct or overlapping neural networks.

As mentioned above, the main gap in understanding the neurocognitive biases underlying aberrant experiences has been the lack of standardised methods / diagnostic tools. This thesis will aim to explore novel tools in terms of validating and improving current tools

as well as introducing new novel methodologies. Critically, in addition, this thesis will aim to explore the role of trait- and state-based factors mediating such experiences.

In brain stimulation, as mentioned in the previous section, tDCS and rTMS are two promising non-invasive neuromodulatory techniques that have recently gained a lot of traction in therapeutic and research applications (Iannone et al., 2006; Priori et al., 2009; Singh et al., 2019; Andò et al., 2021). Whilst the mechanics of both types of stimulation techniques differ, the general assumption under both methods is that if effects of stimulation are absent at group level, this implies that stimulation is ineffective or that causal conclusions about the cortical area cannot be reliably drawn, i.e., an all-or-none affair. However, in practice this is not always the case; the efficacy of stimulation is often affected by several inter-individual and methodological variables (Nitsche & Paulus, 2000; Nitsche, 2008; Krause & Cohen Kadosh, 2014; Horvath et al., 2014; Parkin et al., 2019; Masina et al., 2021).

Apart from the stimulation intensity, variance in target area and length of stimulation applied, individual brain states have also been shown to create variability in responses to anodal / excitatory (or high frequency in TMS) stimulation or cathodal / inhibitory (low frequency in TMS) stimulation (Dockery et al., 2009; Peña-Gómez et al., 2011; Berryhill & Jones, 2012; Tseng et al., 2012; Sarkar et al., 2014; Kundu et al., 2014; Benwell et al., 2015; Li et al., 2015; Hsu et al., 2016; Ray et al., 2017). Some research has demonstrated that under the same anodal stimulation condition, in some participants motor cortex excitability was greatly facilitated but weaker in other participants (Siebner et al., 2004; for a review of studies - Ridding & Ziemann, 2010; Fricke et al., 2011; López-Alonso et al., 2014). Prior research has also shown that trait-based individual differences (to reflect predisposition) also affect the efficacy of stimulation (Basten et al., 2011; Krause & Cohen Kadosh, 2014; Horvath et al., 2014). For example, Hamada et al. (2013) showed that even when several factors (such as age, time of day, etc.) affecting individual brain states were controlled for,

participants still showed differences in M1 activity leading to the idea that some intrinsic vulnerabilities (inter-individual variability, e.g., clinical anxiety vs. non-clinical anxiety vs. healthy population) could also affect brain stimulation responses. Therefore, this thesis will explore if predisposition to cortical hyperexcitability (underlying aberrant perceptual experiences) will mediate efficacy of brain stimulation in aberrant body experiences and emotion regulation. This will not only highlight the importance of baseline brain states but will also extend the notion of cortical hyperexcitability as a domain general occurrence and not limited to visual and extra striate cortices.

Empirical Chapter Overviews

- Chapter 2 was mainly methodologically motivated in that new improvements were made in the behavioural paradigm (Body Threat Assessment Battery – BTAB, Braithwaite et al., 2020) in assessing aberrant body experiences. These improvements were undertaken to provide further utility to the BTAB as a salient tool as well as providing an alternative parsimonious experimental approach that could be paired with neuromodulation studies. In addition to established psychophysiological measures (skin conductance responses) and psychological ratings, novel FaceReader technology was utilised a second objective measure in assessing cognitive affective states underlying aberrant body states. Two independent trait-based stratification measures were utilised to evaluate if predisposition to aberrant visual experiences and aberrant beliefs would reveal differences in autonomic responses in viewing aversive body-threat stimuli.
- Chapter 3 explored the role rVLPFC in mediating cognitive affective states in the neurotypical population using a Multi-Channel Transcranial Direct Current Stimulation (MtDCS). This study was based on the findings of Jay et al. (2014) where depersonalised

patients' attenuated skin conductance responses were returned to neurotypical levels by low frequency rTMS. In addition, two trait-based measures (i) a proxy measure of cortical hyperexcitability (Cortical Hyperexcitability Index_II – CHi_II, Fong et al., 2019) and (ii) depersonalisation-like experiences (from two factors of the Cambridge Depersonalisation Scale – CDS, Sierra & Berrios, 2000) were utilised to examine the variability in brain stimulation due to trait predisposition to these experiences. This Chapter is forming the basis of a journal article submission.

- Finally, building from the findings of Chapter 3, Chapter 4 was an exploratory study examining the role of cortical hyperexcitability and interoceptive vulnerability (interoceptive / internal awareness) in alternative therapeutic approaches (rTMS) to maintaining corticomotor efficiency after upper-limb immobilisation. Two trait-based measures of cortical hyperexcitability (CHi_II) and depersonalisation-like experiences (two factors from the CDS) were utilised to stratify the participants. In addition, a state-based measure of interoceptive vulnerability (IV) as measured by SCRs to a pantomimed blood giving procedure (Implied Body Threat – IBT, Dewe et al., 2016) was also employed to assess if interoceptive vulnerability may be an important consideration in alternative therapeutic strategies.

Chapter 2

Body-Threats and the Brain: A Preliminary Examination of Body-Threat Processing with Methodological Improvements and Novel FaceReader Technologies

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Abstract

Aberrant experiences are known to occur in the non-clinical populations without any underlying disorders or conditions. Attenuated autonomic activity (as a measure of skin conductance responses) in viewing aversive stimuli have been shown in the clinical and non-clinical populations with aberrant body experiences. The present study examined the use of new research / diagnostic tools in assessing cognitive affective biases in the non-clinical population predisposed to aberrant experiences. Seventy-nine healthy volunteers were recruited to participate in a within-subject behavioural paradigm. Each participant completed two trait-based measures to assess predisposition to aberrant perceptual experiences (using the MUSEQ measure) and aberrant beliefs (using the positive factor from the CAPE measure). Following this, participants' skin conductance responses, FaceReader responses and psychological ratings were recorded while viewing the novel Body Threat Assessment Battery. Skin conductance responses were successful in showing increased autonomic arousal to viewing body-threat vs. baseline stimuli and this was also reflected by the FaceReader data. However, FaceReader data did not correlate with skin conductance responses or psychological ratings. There was no association between psychophysiological measures and predisposition to aberrant perceptual experiences or aberrant beliefs. Methodological and theoretical implications discussed.

Introduction

Aberrant experiences are known to be a main diagnostic feature of many clinical disorders and conditions such as epilepsy, migraines with aura, schizophrenia, affective disorders, mood disorders, depersonalisation, Charles-Bonnet syndrome etc. (Manford & Andermann, 1998; Ffytche et al., 1998; Ffytche & Howard, 1999; Bien et al., 2000; Burke, 2002; Wilkinson, 2004; Allen et al., 2008; Aleman & Larøi, 2008; Reuter et al., 2009; Sierra, 2009; Bauer et al., 2011; Baumeister et al., 2017). In the non-clinical population, several studies have evidenced the prevalence of aberrant experiences without any underlying disorders or conditions (Tien, 1991; Garcia-Ptacek et al., 2013; Braithwaite et al., 2013; Braithwaite et al., 2015; Pearson et al., 2016; Rogers et al., 2021).

Broadly, aberrant perceptual experiences have been characterised as erroneous percepts without a conforming external stimulus (Haigh et al., 2012; Cardeña et al., 2014). However, due to the lack of a concrete definition that includes all types of aberrant experiences (Hallucination, Distortions, Illusions etc.), the current view is that aberrant experiences can be considered as a continuum from veridical perception to complex hallucinations with illusions and distortions lying somewhere in the middle of this continuum (Van Os et al., 2009; Braithwaite et al., 2015).

Aberrant perceptual experiences are thought to precede aberrant self / body-experiences (Fletcher & Firth, 2009; Wright et al., 2020). Typically, stable self-consciousness is maintained by various multi-sensory processes that combine the environmental stimuli and internal processes (Blanke & Metzinger; 2009; Blanke, 2012). However, it is now known that these processes are prone to breaking down leading to distinct and striking distortions of body image and aberrant body dissociative experiences (Braithwaite & David; 2016). One such example is with depersonalisation disorder which has been associated with aberrant body

experiences / feelings of disembodiment, subjective flattened affect, and reduced sense of self (Sierra, 2009; Sierra & David, 2011). In the literature, it has been theorised that this flattened affect occurs due to a dysfunction (predictive coding errors / over inhibition) in the prefrontal cortex (more specifically the rVLPFC) which is a known inhibitor to the insula and amygdala regions which are important in mediating cognitive affective states (Davidson, 2000; Whalen et al., 2001; Critchley et al., 2004; Eippert et al., 2007; Singer et al., 2009; Seth, 2009(a), 2013(b); Lee et al., 2012; Seth et al., 2012). Studies have shown increased activity in the prefrontal areas is associated with decreased activity in the amygdala (Ochsner et al., 2002; Urry et al., 2006; Banks et al., 2007).

Within the realm of aberrant experiences, delusional beliefs / aberrant beliefs are thought to arise after aberrant body / self-experiences (Wright et al., 2020). This is most commonly seen in schizophrenia and psychosis but not with depersonalisation. Some theories suggest that aberrant delusional beliefs in psychosis are more localised to the left hemisphere whereas affective states are mediated by the right hemisphere (Gilleen & David, 2004). However, some studies have found activity in the frontal regions relating to attentional cues to be impaired in those predisposed to aberrant delusions which is similar to those in aberrant self-experiences / depersonalisation-like experiences (Corlett et al., 2010; Sass et al., 2013). For example, Corlett et al., 2007 found that patients with psychosis also showed that those with stronger delusion forming symptoms showed aberrant processing in the right prefrontal cortex (rPFC) using fMRI. However, in this study, experimental paradigm was not specific to aversive or threatening stimuli. Given this information, the link between aberrant body experiences and aberrant beliefs is unclear and requires further evaluation.

Taken together, the complexity of the phenomenon of aberrant perceptual experiences, aberrant self-experiences and aberrant delusions, very few standardised diagnostic tools / research methodologies have been developed specifically to understand the

cognitive processes underlying aberrant experiences. One of the main reasons for this is due to the lack of standard research tools / methods within the field. Many studies have utilised non-specific aversive stimuli (mainly from the International Affective Picture System / IAPS; Lang et al., 1997) such as cockroaches, snakes etc. to show elevated autonomic activity to unpleasant stimuli vs. pleasant stimuli (Hamm et al., 1997; Bradley et al., 2001; Perlstein et al., 2002; Moser et al., 2009; Alpers et al., 2011; Aldhafeeri et al., 2012; Bublatzky & Schupp, 2012). Neuroimaging studies have also evidenced elevated autonomic activity / brain activity to unpleasant vs. pleasant studies using either facial expressions (fearful / angry vs. neutral / happy) or animal attacks vs. neutral scenes (Morris et al., 1998; Schupp et al., 2003; Anders et al., 2004; Simmons et al., 2004; Sabatinelli et al., 2007; Moser et al., 2009; Hägele et al., 2016). For example, an event-related brain potential (ERP) study by Moser et al. (2009) utilised images of mutilation (human and animal) as stimuli (drawn from the IAPS) and a neutral set that contained household items and neutral faces. However, the use of these stimuli, whilst elevating autonomic activity do not account for a variety of confounding variables such as past trauma / memories, phobias which inadvertently complicate the attentional load as well as introduce startle reflexes which do not accurately reflect the biases related to body dissociative states (Braithwaite et al., 2020). The processes that are responsible for the breakdown of the multi-sensory integration are considered to be more primal / urgent and triggered when there is a threat to life (Sander et al., 2005; Todd et al., 2012).

Skin conductance responses (SCRs) have been used to assess autonomic responses to salient stimuli in research settings. Unusual SCRs to unpleasant stimuli have been associated with not only depersonalisation but also with anxiety disorders, mood disorders, schizophrenia and the like (Kohler et al., 2000; Aghevli et al., 2003; Takahashi et al., 2004; Shin et al., 2005; Monk et al., 2006; Sierra et al., 2006; Nitschke et al., 2009). Research has

shown that patients with depersonalisation disorders show significant suppression of autonomic responses (measured by skin conductance) to viewing aversive stimuli which implies that these processes occur in stressful situations (Philips et al., 2001; Sierra et al., 2002(a), 2006(b); Lemche et al., 2007; Sierra & David, 2011). This effect has also been shown to occur in the non-clinical population predisposed to depersonalisation-like experiences (Braithwaite et al., 2014; Dewe et al., 2016(a), 2018(b)). Although this is an established measure, it is known that SCRs or the measure of autonomic arousal can be positive or negative. It can be inferred that if SCR measurement is taken when negative stimuli are viewed, that the arousal measured is negative, however, the specificity of negative stimuli must be maintained for this inference.

Facial expressions have been shown to provide meaningful insight into affective states (Fridlund & Cacioppo, 1986; Dimberg 1986; Levenson et al., 1990; Dimberg et al., 2000; Meng & Huang, 2014; Leppanen et al., 2017; Vartanov et al., 2020; Höfling et al., 2020). Facial EMG technique is one of the most commonly used research methods in assessing facial expressions (Cacioppo et al., 1986; Dimberg, 1988; Lang et al., 1993; Wolf et al., 2005; Mauss & Robinson, 2009; Golland et al., 2018; Höfling et al., 2020). However, due to the high-priced equipment needed, invasiveness of procedure and utility of this method is limited to laboratory settings, the FaceReader was developed as a viable and commercially accessible automatic facial coding tool for research (Wolf et al., 2005; Suhr, 2017). The FaceReader is based on the identification of six basic expressions (and a wide database of these expressions) as identified by Ekman, 1982 namely, happiness, sadness, anger, fear, surprise and disgust (den Uyl & van Kuilenburg, 2005; Loijens & Krips, 2018). Based on the six expressions the FaceReader automatically calculates valence (intensity of happy minus sadness, anger, fear and disgust) and arousal (based on the intercalation of 20 Action and Facial Coding System) (as cited in, Loijens & Krips, 2018). The FaceReader has been applied

in many fields including human-computer interaction (Goldberg, 2014), food research (Danner et al., 2014; Leitch et al., 2015; Juodeikiene et al., 2018), marketing research (Lewinski et al., 2014; Breaban & Noussair, 2018; Hadinejad et al., 2019(a), 2021(b)) and others. However, as this technology is still in its infancy, researchers suggest the use of this novel technique to be alongside established methods (such as skin conductance responses) (Höfling et al., 2020). Given that the FaceReader has a variety of applications in various research settings and is easily accessible, the use of this novel technology in consciousness research may reveal further insights into the cognitive biases in impaired autonomic processing in those predisposed to aberrant body experiences.

Overview of the Present Study

The present study examined cognitive affective biases underlying predisposition to aberrant experiences in the neurotypical population. The contribution of this work is (i) methodological – improvements in experimental design and the inclusion of new / novel technologies were explored, and (ii) theoretical in that predisposition to either aberrant perceptual experience or aberrant beliefs were examined in relation to objective psychophysiological responses, FaceReader measures as well as psychological ratings in viewing the Body Threat Assessment Battery (BTAB – Braithwaite et al., 2020).

Participants completed two trait-based screening measures based on (i) predisposition to aberrant visual experiences and (ii) predisposition to aberrant beliefs. Biases in the underlying neurocognition were quantified using two psychophysiological measures, namely skin conductance responses (SCRs) and FaceReader (FRR) responses coupled to psychological ratings all in response to aversive dynamic body-threat stimuli (BTAB – Braithwaite et al., 2020).

Previous research in the field of aberrant body experiences has shown atypical cognitive affective responses when viewing negative stimuli (Philips & Sierra, 2003; Ragsdale et al., 2013). However, most of this work has utilised generic negative stimuli (taken from the IAPS) which do not contain stimuli with the intention to examine aberrant body experiences (see Braithwaite et al., 2020; for a discussion of the further merits of the BTAB).

This is odd in that many neurological and clinical conditions are indeed associated with a variety of aberrant body experiences and body distortions including the out-of-body experience (OBEs), sensed-presence experiences, body-size distortion experiences, and disorders of limb ownership and agency (Brugger et al., 1997; Brugger, 2002; Blanke et al.,

2004; Blanke & Mohr, 2005; Arzy et al., 2006; Blanke & Castillo, 2007; Braithwaite et al., 2011). Such experiences are also common in association with drug use, schizotypy / schizophrenia, psychoses, depersonalisation disorder, migraine and the epilepsies (Blackmore, 1986; Brugger, 2002; Kitchener, 2004; Sierra et al., 2002; Blanke & Arzy, 2005; Arzy et al., 2006; Thakkar et al., 2011; Ferri et al., 2012; Liu et al., 2014; Klaver et al., 2016) as well as being present in neurotypical populations (Hunter et al., 2004; Ehrsson, 2007; Leggenhager et al., 2007; Blanke & Metzinger, 2009; Klaver et al., 2016; Benson et al., 2019). The BTAB was developed to address these methodological concerns by creating specific simulated dynamic body-threat clips and, importantly, non-body threat / baseline stimuli (Braithwaite et al., 2020).

The present study sought to add further evidence for the utility of the BTAB in assessing cognitive biases underlying aberrant body experiences. The original BTAB study presented individual high-definition clips and reported psychophysiological and psychological normative data for each individual clip (Braithwaite et al., 2020). This is particularly useful as these normative data can be used to ensure that any combination of clips used in further research can be matched and equated for their aversive potency across conditions – which is exactly what was done in the present study here.

The rationale here was to produce a situation where a series of short clips were played together as a block (instead of using separate isolated clips). This has the potential to provide a more reliable indicator of autonomic responding and psychological evaluation based on a more stable response to a series of consistent clips (not just one). This in turn also facilitates a more parsimonious experimental approach where resultant analyses do not have to revolve around a clip-by-clip approach (as done by Braithwaite et al, 2020) but can occur at a more conceptual level.

There are additional reasons for examining the utility of this approach from an experimental perspective. In neuromodulation designs of brain stimulation (e.g., transcranial direct-current stimulation) the efficacy of stimulation degrades over time (Liebetanz et al., 2002; Nitsche et al., 2005; Iannone et al., 2016; Priori et al., 2009). This BTAB modification could be of utility in such paradigms, where stimulation would be performed prior to the presentation of each block (e.g., body-threat, baseline). Using this blocked design would allow for reliable measurement of responses within the period of “effective modulation”, i.e., prior to the degradation of neuromodulation. This would therefore provide a tool that would allow researchers to pair neuromodulation with the BTAB for investigating specific cognitive processes underlying aberrant body experiences. By this method, blocks can be customised for any duration (4 / 5 / 6 clips per block) and matched for aversive potency (according to clip analysis in Braithwaite et al., 2020).

Furthermore, some studies have shown spontaneous perspective taking to engage similar neural regions (that are involved in mediating cognitive affective states, i.e., insula and amygdala) (Singer et al., 2004(a), 2009(b); Critchley, 2009; Lamm & Singer, 2010; Critchley & Harrison, 2013). Those individuals that employ spontaneous perspective taking more easily exhibit elevated autonomic activity to viewing others in negative / pain related situations (empathy). The BTAB stimuli have two sets of body-threat videos in two perspectives (egocentric / first-person and exocentric / third person) to explore this effect in a controlled manner. In the original study, Braithwaite and colleagues (2020) found no difference in autonomic activity in the perspective taking task, however, the design here (where all body-threat videos from each perspective were grouped together) may further reveal biases in perspective mediating cognitive affective responses.

In addition to autonomic activity measured by SCRs, FRRs were also gathered in the current study as a second objective measure of psychophysiological response to viewing

aversive body-threat stimuli. Previous research has evidenced facial expressions to be indicative of affective states (Dimberg, 1986; Levenson et al., 1990; Dimberg et al., 2000; Meng & Huang, 2014; Leppanen et al., 2017). The objectivity in facial expression reading from the FaceReader is based purely on movement of facial muscles relating to various expressions with no human observer bias (Suhr, 2017). The present study sought to assess if responses from the FaceReader are influenced by the aversive body-threat stimuli and furthermore may vary in some sympathy with established measures (SCRs) in delineating between the two types of stimuli (Baseline and Threat). This study is the first to our knowledge to employ the FaceReader as a salient tool in assessing biases in cognitive affective states as part of the multi-sensory experience.

The present sample was screened for their predisposition to aberrant perceptual experience and aberrant perceptual belief. Note – some (but not all) aberrant beliefs can indeed result from aberrant perceptions so there can be some overlap here. However, the two concepts can also be dissociated and exist independent of each other. Therefore, it was felt prudent to quantify both for the present purposes. Stratification of the population (reflecting predisposition) is a useful technique in assessing variability in cognitive processes underlying aberrant experiences. Given that various conditions can be associated with aberrant experiences, we sought to explore if other trait-based measures (namely, Multi-sensory Unusual Experiences Scale / MUSEQ and Community Assessment of Psychotic Experiences / CAPE) could also reflect biases in cognitive affective states. It was hypothesised that susceptibility to aberrant visual experiences (as measured by the visual factor of the MUSEQ) may reflect variability in autonomic activity associated with affective states. In contrast, predisposition to aberrant beliefs, as measured by the positive factor of the CAPE (which is primarily derived from the Peters et al. Delusions Inventory (Peters et al., 2004) may or may not reflect underlying biases associated with cognitive affective states.

Method & Procedure

Participants

One hundred and one participants (aged between 18 – 25 years) took part in the present study and were recruited from Lancaster University, Department of Psychology, UK. The safety and exclusion criteria excluded participants with any fitted electrical / medical devices, debilitating fear of blood / gore / needles and a history of epilepsy / fainting / seizures as well as psychiatric / dissociative diagnoses. The study was approved by Lancaster University Ethics Committee (FST17039) and participants were compensated for their time with course credits.

Out of the 101 participants, 14 participants did not complete the study (due to technical issues¹) and had incomplete data. In line with published procedures and accepted protocols, 8 participants were excluded from analysis as they were classified as SCR hypo-responders (Dawson et al., 2007; Boucsein, 2012, Braithwaite et al., 2013(a), 2020 (b)). The final analysis was based on 79 remaining participants, 19 males and 60 females (Mean age = 18.9 years, SD = 1.29).

Measures

Screening Measures

Multi-Modality Unusual Sensory Experiences Questionnaire (MUSEQ). This is a 43-item self-report measure that evaluates ‘unusual sensory experiences’ (USE) across six modalities (Mitchell et al., 2017). The six factors identified in this scale showed good internal consistency and reliability with Cronbach’s Alpha reported as: Auditory = 0.82, Visual =

¹ On rare occasions the FaceReader software did not identify the participants face.

0.88, Olfactory = 0.87, Gustatory = 0.88, Bodily Sensations = 0.88 and Sensed Presence = 0.77. For the present study the Visual factor was used to indicate susceptibility to aberrant perceptual experiences, and to correlate with the psychophysiological measures of the BTAB. The Visual factor consists of 8 items (see Table 2.1 below) that were rated by the participants on a five-point Likert Scale judging the frequency of the occurrence of the USE from 0 (Never Happened) to 4 (Frequently).

Table 2.1

Item questions and level of aberrant experience from the Visual Factor from MUSEQ (as in Mitchell et al., 2017)

Question	Experience
1 My eyes have played tricks on me	Broad sensory experience
2 Lights / Colours seem brighter / more intense than usual	Change in perceptual intensity
3 People / Objects / Landscapes can be seen in front of eyes when I thought of them	Internal events → Externalised
4 A figure / face emerging from a patterned object (e.g., wallpaper, curtain etc.)	Misperception
5 Lights / Flashes / Other shapes other people could not see	Hallucination
6 Object transformed to something else in front of my eyes	Hallucination
7 Image of person / object / animals in my peripheral vision but not there when I looked	Hallucination
8 Saw people / face / animals but not there	Hallucination

Community Assessment of Psychic Experiences (CAPE). This measure is a 42-item self-report questionnaire studying signs of schizotypy and psychotic experiences in the non-clinical populations (Hanssen et al., 2003; Stefanis et al., 2002). The three factors identified within this scale are positive (e.g., “Do you ever feel as if some people are not what

they seem to be”), negative (e.g., “Do you ever feel sad”) and depressive symptoms (e.g., “Do you ever feel that you have no interest to be with other people?”). In the current study, the positive factor from the CAPE (weighted frequency and distress averaged) was selected for predisposition to aberrant beliefs (typical of Schizotypy). Note, these beliefs may or may not reflect the co-presence of aberrant experience and this will be explored later.

The Body Threat Assessment Battery (BTAB)

The BTAB is a novel tool consisting of 15 high-definition short clips depicting simulated aversive threats carried out to a human body or baseline clips showing threats carried out to non-human objects (e.g., fruits, rolling pin etc, see Figure 2.1) (Braithwaite et al., 2020 and see Chapter 2). Of the 15 video clips in high definition which include 6 threat videos from an Egocentric perspective (first person), 6 threat videos are taken from an Exocentric perspective (third person) with no perspective manipulation for baseline clips. In the original task, each clip was shown individually (as a 30 second event) followed by self-report psychological ratings on four dimensions (emotional arousal, emotional valence, sense of illusory pain and realism of threat) and psychophysiological responses (in the form of Threat-related SCRs) were measured (Braithwaite et al., 2020). The task also included a 5 second setup shot preceding each video showing a torso only to avoid startle responses / artefacts in skin conductance measurement from the onset of body stimuli (Figure 2.1).

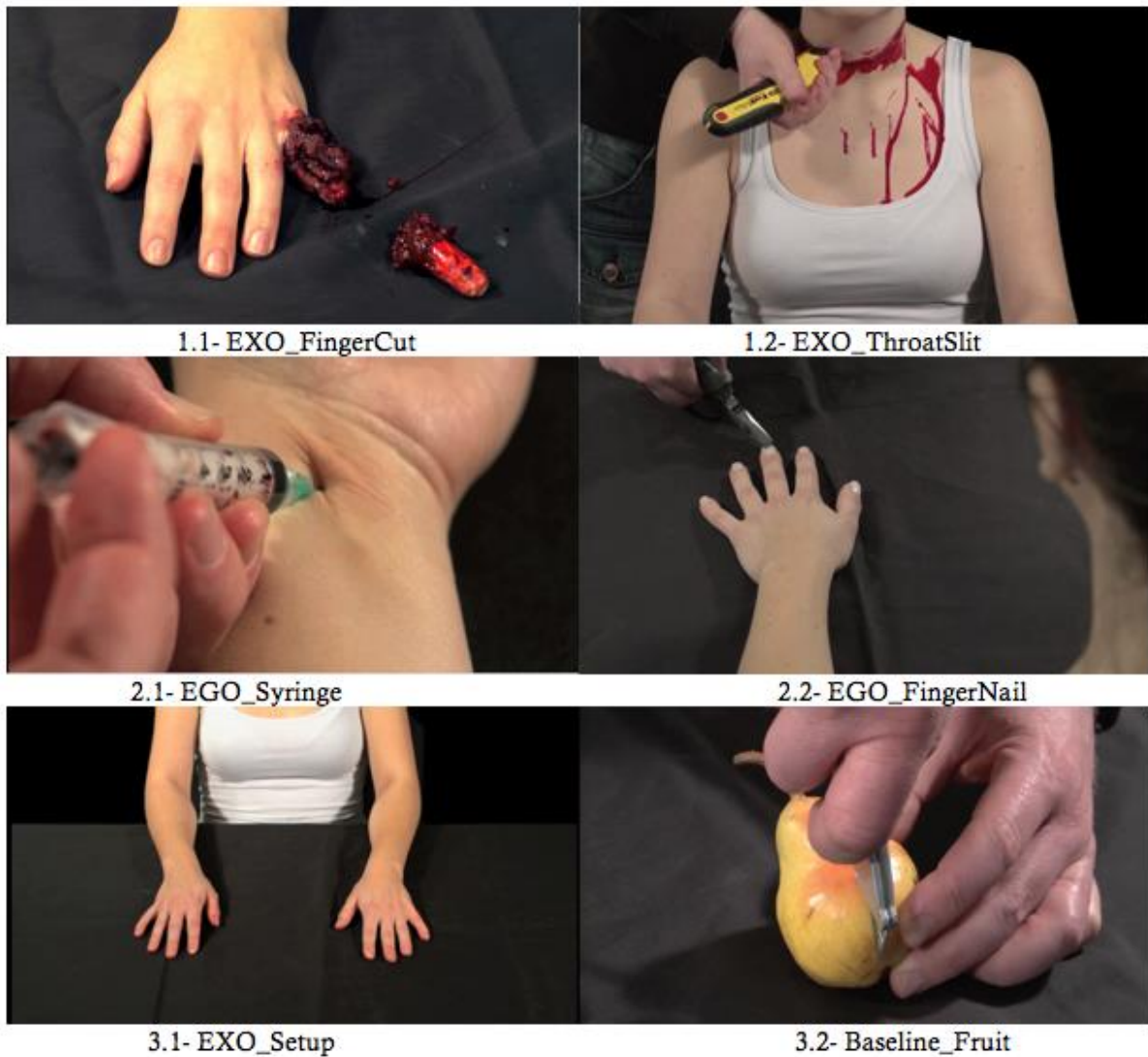
In contrast to previous work, and as a new development, the current study adopted a blocked design for the presentation of BTAB stimuli where a series of Egocentric Threats, Exocentric Threats and Baseline clips were grouped together, and the psychological ratings were presented after each series of clips (block) were shown. The underlying rationale (discussed in depth above) here was to provide a more reliable indicator of autonomic responding and psychological evaluation based on a more stable of response to a series of

consistent clips (not just one) that represent highly similar events². The task was programmed in E-Prime 3.0 and were presented on a 16:9 monitor at 1920 x 1080 resolution in a darkened room. Additionally, to avoid startle responses or unfamiliarity to procedure, participants completed a practice trial whereby a neutral video clip (body-based setup with a non-threatening stimulus; brush stroking arm) as well as the psychological response window were shown.

² At the time of this study, this had not been examined with these stimuli.

Figure 2.1

Screenshot captures showing different facets of the BTAB tool (Braithwaite et al., 2020)



Note: Row 1 (from left) are examples of threat stimuli from the exocentric view, Row 2 are threat stimuli from the egocentric view, and in Row 3 - Image 3.1 is of the setup shot preceding the block and finally, 3.2 is of the non-body threat stimuli

Psychological Responses

Following each set of video clips, participants were asked to report their experiences from viewing the stimuli. A Likert-type scale was utilised for four dimensions, emotional arousal (0 to 9), emotional valence (-5 to 5), experience of illusory / sensory pain (0 to 9) and realism of threat (from 0 to 9).

Skin Conductance Responses (SCRs)

All skin conductance responses were collected using a Biopac MP36R data-acquisition unit (Biopac Systems Inc., Goleta, CA, USA) connected to a 64-bit CPU running Windows 10 Home OS. The signals were recorded with a 0.05 Hz high-pass filter and sampled at 2000 Hz. Data was acquired by connecting two disposable pre-gelled electrodes (EL507) to SS57L sensor leads and applying a low continuous current (0.5 V). The electrodes and leads were attached to the distal phalanges of the index and middle finger of the participant's non-dominant hand to avoid movement artefacts when the participant was interacting with the task (reporting psychological experiences). The electrodes were attached 10 minutes prior to recording as this would achieve the highest / clearest quality signal.

SCRs were gathered and processed in Biopac AcqKnowledge v5.0. As per standard practices, in the current study an SCR was defined as a magnitude delta function (μS) between the peak value and SCR onset value and SCR threshold (for the signal) was set at $0.01 \mu\text{S}$ (for further detail, see Braithwaite et al., 2013). When no SCRs were detected, a zero value was used (magnitude data). For the present study, the SCR of interest was specified as the largest / strongest response within each block of stimuli (that is, Egocentric threat, Exocentric threat and Baseline). All other SCRs occurring during the presentation of each block were classified as non-specific SCRs (NS-SCRs) which were analysed for their magnitudes and frequency (F-SCR) and strength as additional measures of autonomic arousal

(Nikula, 1991; Braithwaite et al., 2013). To summarise, SCR indicators in the present study were (i) the maximum SCR magnitude occurring during any given presented series of clips (a block), (ii) the mean magnitude of Non-Specific SCRs (NS-SCRs) occurring during the block and (iii) the frequency of NS-SCRs occurring during the block (how many / count per minute).

Firstly, all signals were subject to artefact removal using visual inspection. Where an artefact was recognised, the section was down sampled by 200 samples / sec to remove them. SCR and NS-SCR magnitude data was normalised [$\text{SCR} (\text{Log} + 1)$] and standardised (Z-score conversions) as per recommended practices (Dawsen et al., 2007; Boucsein et al., 2012, Braithwaite et al., 2013(a), 2017(b), 2020(c)). Frequency of NS-SCRs were standardised by dividing the number of NS-SCRs within each block by total number of minutes of presentation of that block (count per minute). In the original published study (Braithwaite et al., 2020) there were no differences between the Egocentric and Exocentric Threat stimuli and so magnitudes of SCRs, NS-SCRs and frequency of NS-SCRs for the two Threat blocks were combined to create a general factor for the Threat stimuli³.

FaceReader Responses (FRR)

Facial expressions were recorded in real time with Noldus FaceReader software v7.0 (Noldus, Wageningen, Netherlands) via a Logitech HD Pro webcam (1920 x 1080 resolution, 30 frames / sec) which exceeded the requirements by the software. Participants were sat 80 cm from the camera and the face was indirectly illuminated using a lamp facing the wall for standard detection. Based on distinct expressions described by Ekman (1992), seven facial expressions of neutral, happy, angry, sad, surprised, scared and disgusted are recognised by

³ A preliminary analysis of the Threat SCRs for the current data set also revealed no reliable differences between the two perspectives. Therefore, the decision to pool across this dimension is further warranted for parsimony in the current analysis.

the software (see example in Figure 2.2). In addition, valence and arousal are calculated by the software based on intensity of facial expressions that are detected. As the focus of the current study was generally to detect negative affective states and so the expression ‘happy’, ‘surprised’ and ‘neutral’ were excluded from analysis (surprised and neutral were considered dual valence). Therefore, the FRR data comprised of an arousal and valence dimension and a singular average negative emotion category (including angry, sad, scared and disgusted).

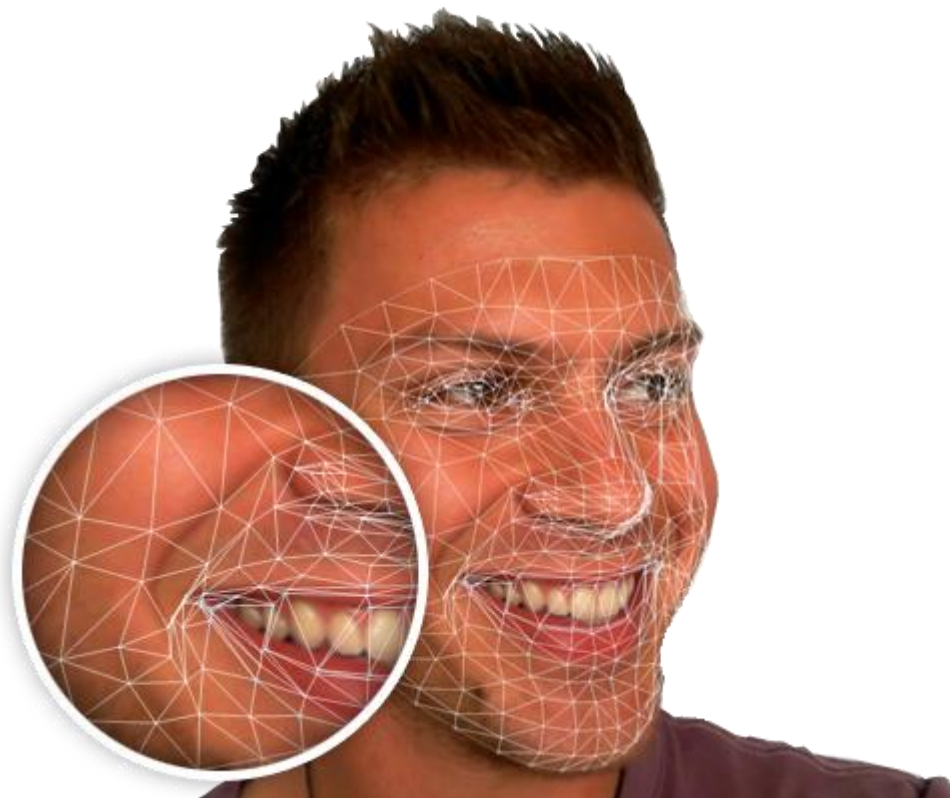
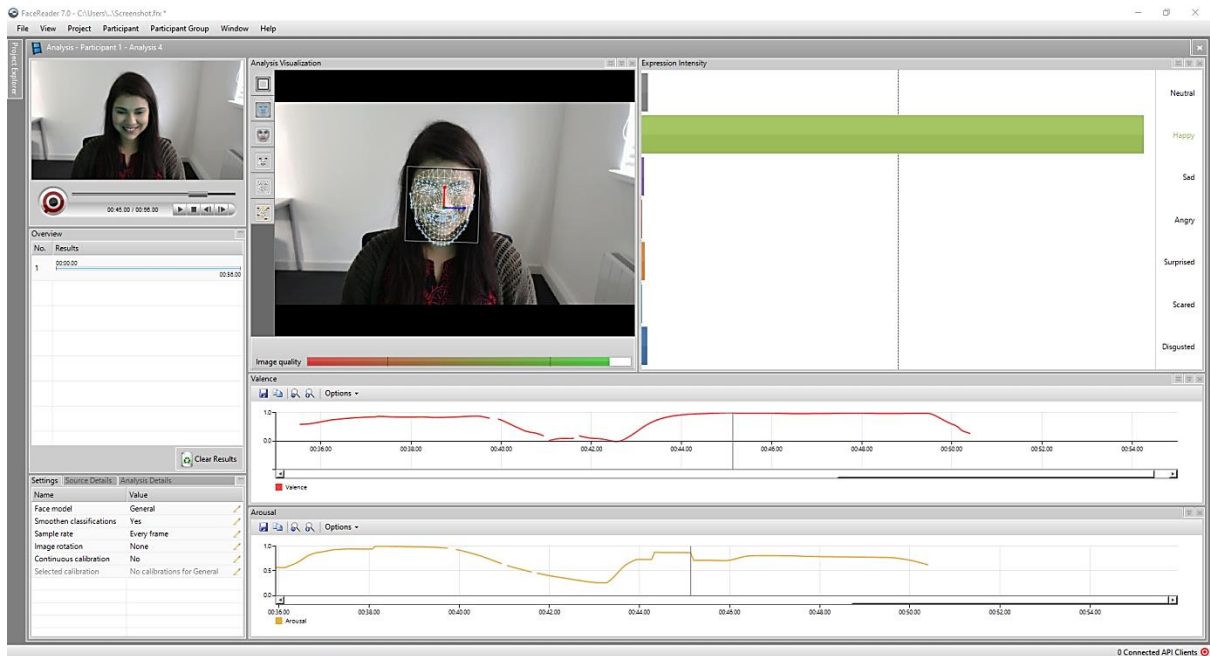
Analysis of FRRs were processed through Biopac AcqKnowledge v5.0. Each facial expression (and arousal) is calculated as continuous signal data at each time point (per second) and measured with a vector between 0 and 1 (valence values range from -1 negatively valenced to +1 positively valenced) (Loijens & Krips, 2018). FRR of interest here was defined as the maximum value for arousal and valence (minimum for this factor only) and negative emotions within each block of stimuli.

Standardisation of FRRs was achieved by dividing measures as a proportion of the maximal response from the participant. All data from a given participant were pooled and a maximum response was identified. All other values were standardised as a ratio (proportion) of this maximal response to facilitate an individual differences approach. Note – in terms of valence measures, the maximal response is the strongest negative response (ostensibly the largest ‘minimum’ response) – but the principle and procedure are the same. This resulted in three main variables that were used in the final analysis: FRR_Arousal, FRR_Valence and FRR_Negative.

Figure 2.2

Top: Showing FaceReader capture and experimental setup with 'happy' expression. Bottom:

VicarVision (n.d.) shows FaceReader realtime 3D modelling technique (expression happy)



Procedure

Each participant was asked to complete a screening questionnaire and consent form that determined their eligibility to take part in the study. The electrodes used to measure SCR were then attached to the participants index and middle distal phalanx on the non-dominant hand 10 mins prior to recording. The experimenter then ensured that the FaceReader could detect the face continuously to ensure accurate recording during the task. Participants were then taken through a practice trial to familiarize them with the procedure of the BTAB task (with a neutral stimulus that was not part of the main task, brush stroking arm). Following this, the main task was conducted where SCRs, FRRs and psychological ratings were recorded. Finally, participants completed two trait-based screening measures (order randomised) and were verbally debriefed. The entire session took approximately 1 hour per participant.

Results

Overall Statistics

All analyses were conducted using a combination of SPSS v27 (Frequentist statistics) and JASP v0.14.1 (Bayesian analysis). For normal data, paired t-tests, and Pearson's two-tailed r correlations were conducted. Non-parametric tests including Wilcoxon's signed rank tests and Kendall's Tau (τ) correlations were used when data did not follow normality. In addition, all multiple testing (for Frequentist analysis) was corrected using False Discovery Rate (FDR) method, where p values of each test conducted were ranked in ascending order (1,2,3...), then the formula $[(I / n) \times Q]$ was applied where I = original p value rank, n = total number of tests conducted and Q = false discovery rate (0.05) to give a corrected B&H p value for each test (Benjamini & Hochberg, 1995; Braithwaite et al., 2020). If the corrected B&H p value was greater than the original p value, the comparison was considered significant by this method.

Furthermore, where appropriate, Frequentist statistics (p values) were supplemented with Bayesian statistics. Bayes Factor (BF) analysis provides the strength of findings for the null hypothesis ($BF_{10} < 1$) as well as alternative hypothesis ($BF_{10} > 1$). For example, if a BF_{10} value is 10, this implies that the alternative hypothesis is 10 times more likely to occur than the null hypothesis which provides a more accurate interpretation of the data. Typically, BF_{10} values between 1 and 3 indicate inconclusive data, between 3 – 10 indicative good evidence, 10 – 100 as strong evidence and > 1000 as decisive evidence (Jarosz & Wiley, 2014; Dewe et al., 2016(a), 2017(b); Braithwaite et al., 2020). If BF_{10} was < 1 , BF_{01} values are presented alongside to evidence the strength of support for the null findings in the same manner described above.

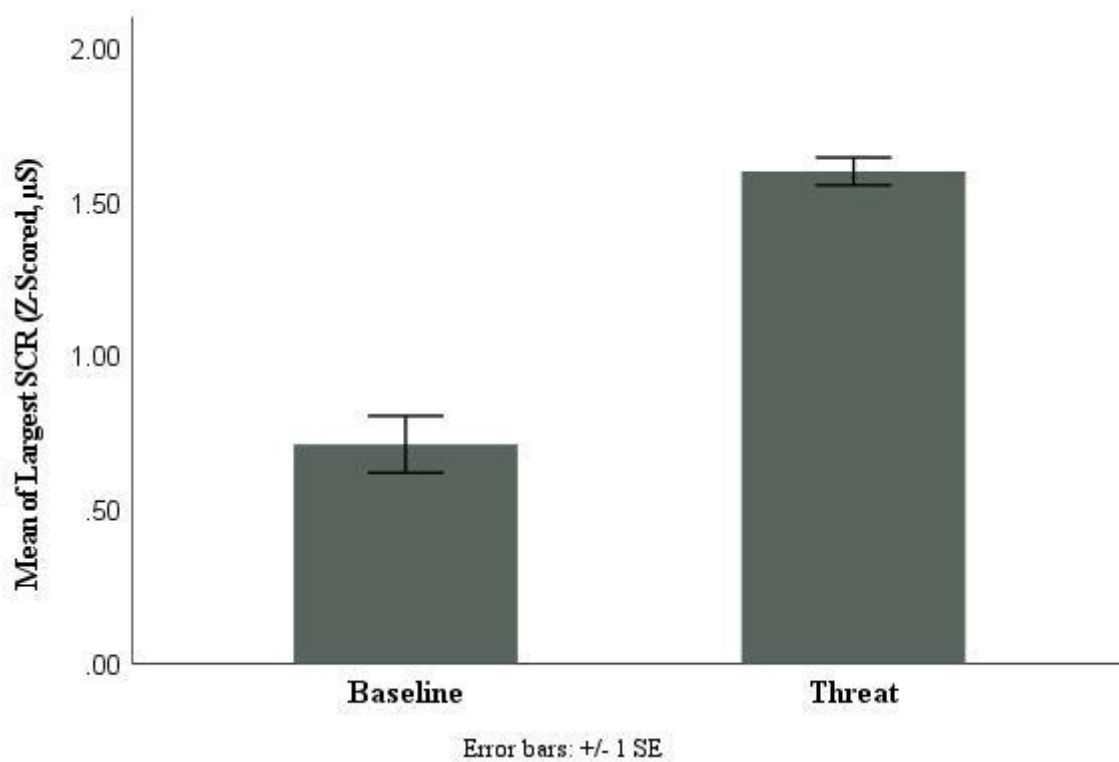
Skin Conductance Responses

BTAB SCRs

Initially, a paired t-test was conducted to compare the magnitudes of SCRs between the Baseline stimuli and the Threat stimuli (Figure 2.3). Results showed that the Threat stimuli elicited significantly stronger SCRs than the Baseline stimuli, $t(79) = 8.795$, $p < 0.001$, $d = 0.989$, $BF_{10} > 1000$ (Bayes interpretation: Decisive Alternative Hypothesis (AH)).

Figure 2.3

Comparison of SCRs (Largest, Z-scored) between Baseline (non-body stimuli) and Threat Stimuli

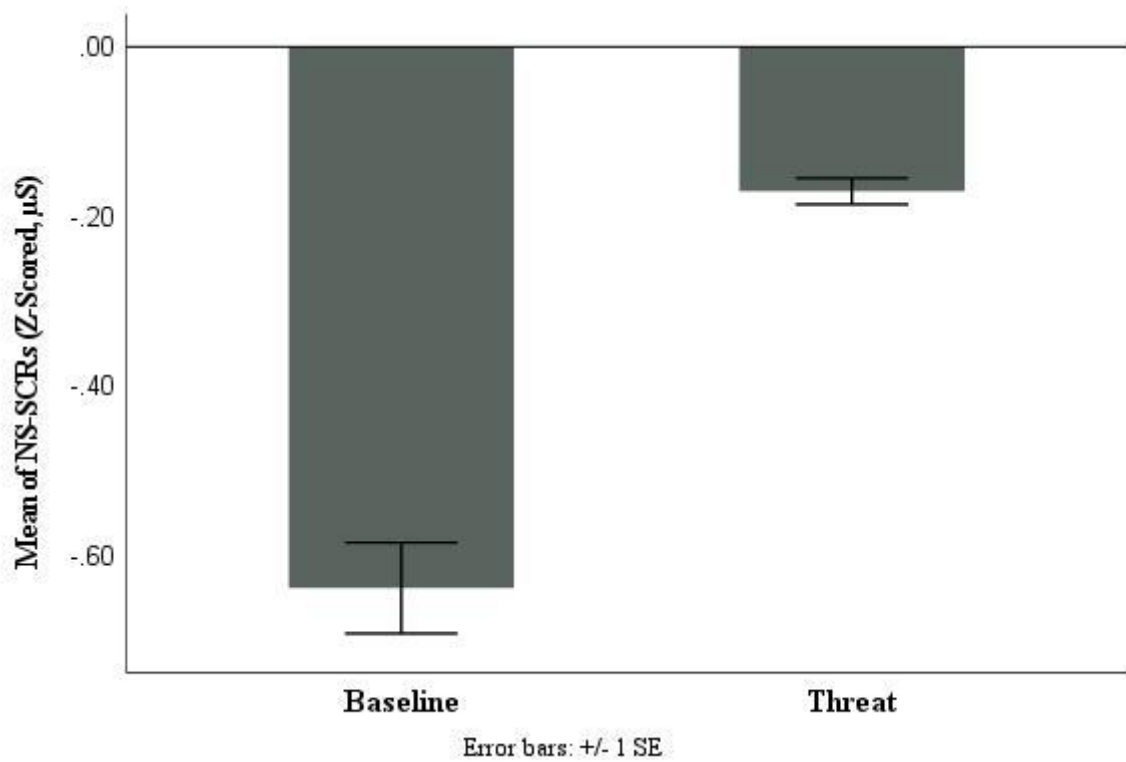


BTAB Magnitudes of NS-SCRs

As above, a paired t-test was conducted to compare the magnitudes of NS-SCRs between the Baseline stimuli and the Threat stimuli (Figure 2.4). Results showed that the Threat stimuli elicited significantly stronger NS-SCRs than the Baseline stimuli, $t(79) = 7.916$, $p < 0.001$, $d = 0.891$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Figure 2.4

Comparison of NS-SCR magnitudes (Z-scored) between Baseline and Threat stimuli

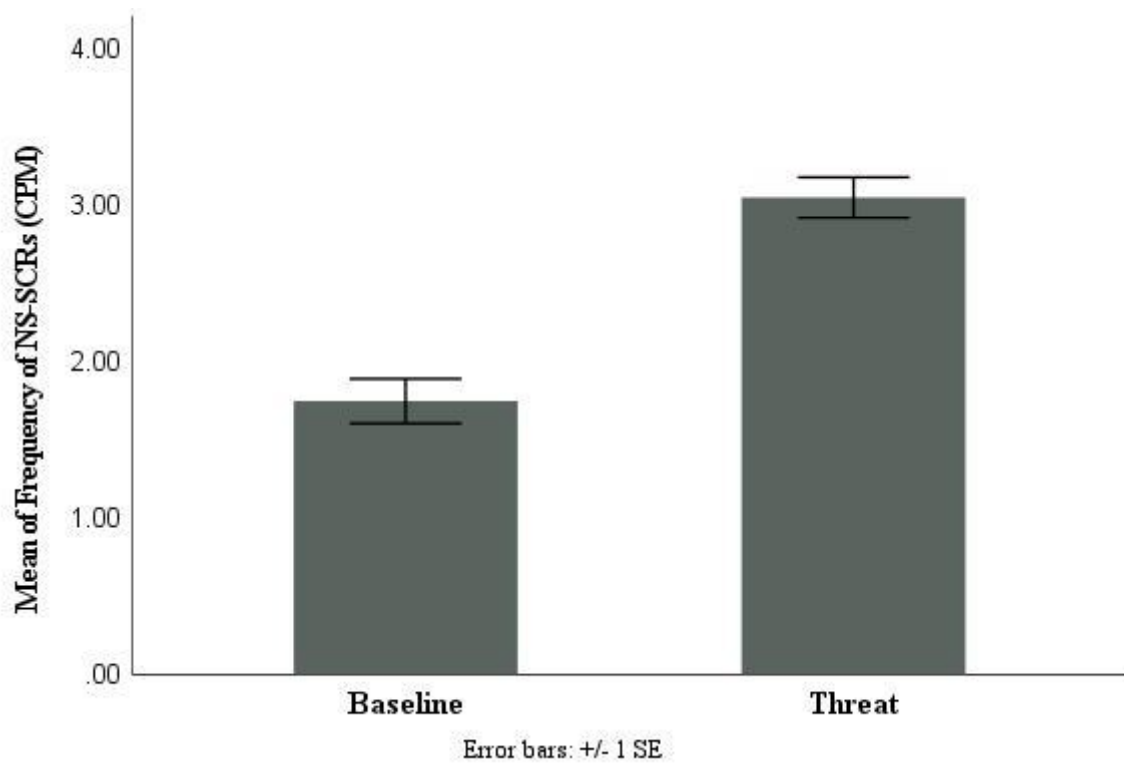


BTAB Frequency of NS-SCRs

Similarly, a paired t-test was conducted to compare the frequency of NS-SCRs between the Baseline stimuli and the Threat stimuli (Figure 2.5). Results showed that the Threat stimuli significantly elicited a greater number of NS-SCRs than the Baseline stimuli, $t(79) = 9.781$, $p < 0.001$, $d = 1.110$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Figure 2.5

Comparison of frequency of NS-SCRs (CPM) between Baseline and Threat Stimuli



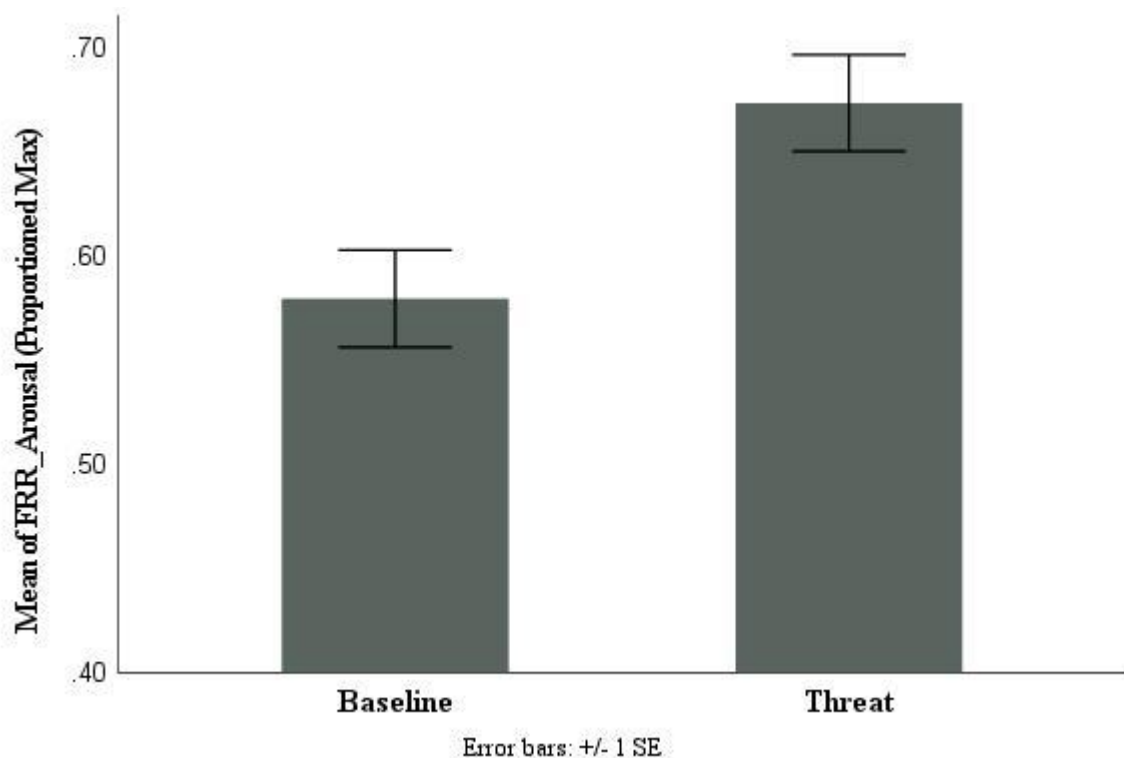
FaceReader Responses (FRR)

BTAB FRR_Arousal

The maximum scores (proportions) of Arousal factor obtained from FRR (FRR_Arousal) was compared using a Wilcoxon's signed rank test for within-subjects (as this data set did not follow normality) between the Baseline and Threat stimuli (Figure 2.6). A significant effect was noted between the two types of stimuli, $Z = 4.696$, $p < 0.001$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH). This means that the Threat stimuli elicited proportionally more arousal than the Baseline stimuli.

Figure 2.6

Comparing FRR_Arousal (Proportioned Max) between Baseline and Threat stimuli

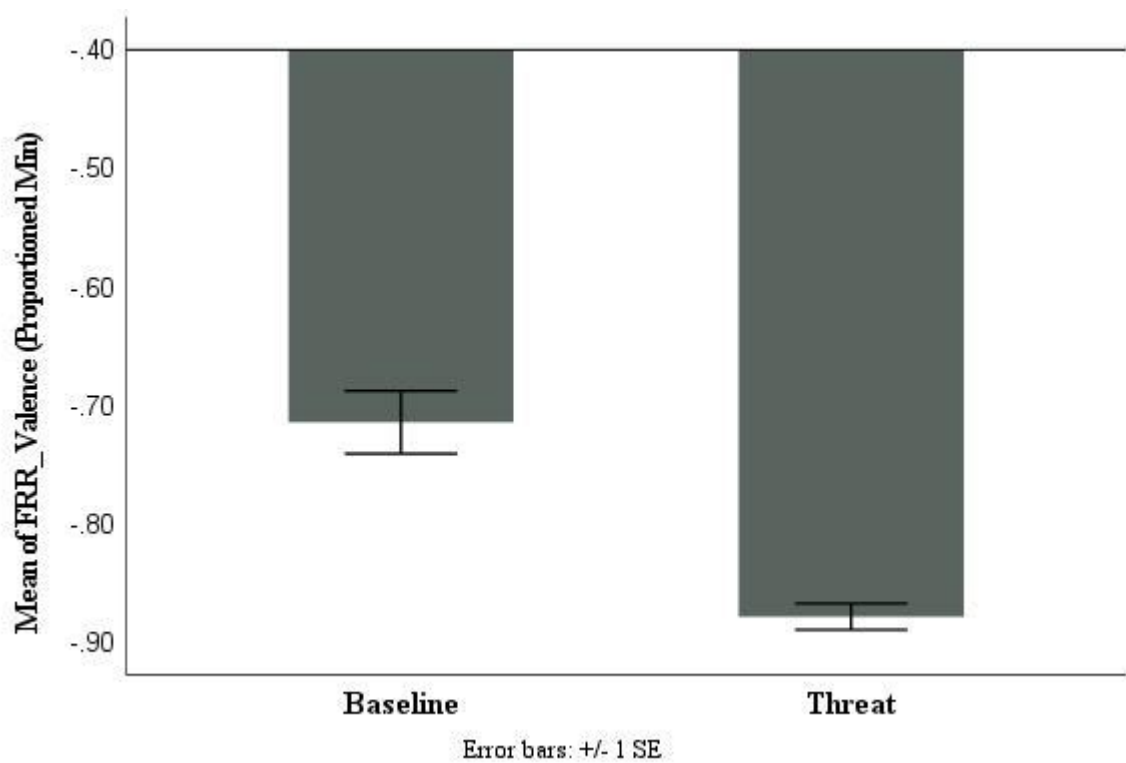


BTAB FRR_Valence

Similarly, the minimum (as Valence values lie between -1 and 1) proportions of Valence factor derived from FRR (FRR_Valence) were compared via a Wilcoxon signed rank test between the Baseline and Threat stimuli (Figure 2.7). A significant difference was observed between the two stimulus types, $Z = 4.755$, $p < 0.001$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH). This means that the Threat stimuli elicited proportionally more negative responses than the Baseline stimuli.

Figure 2.7

Comparing FRR_Valence (Proportioned Min) between Baseline and Threat stimuli

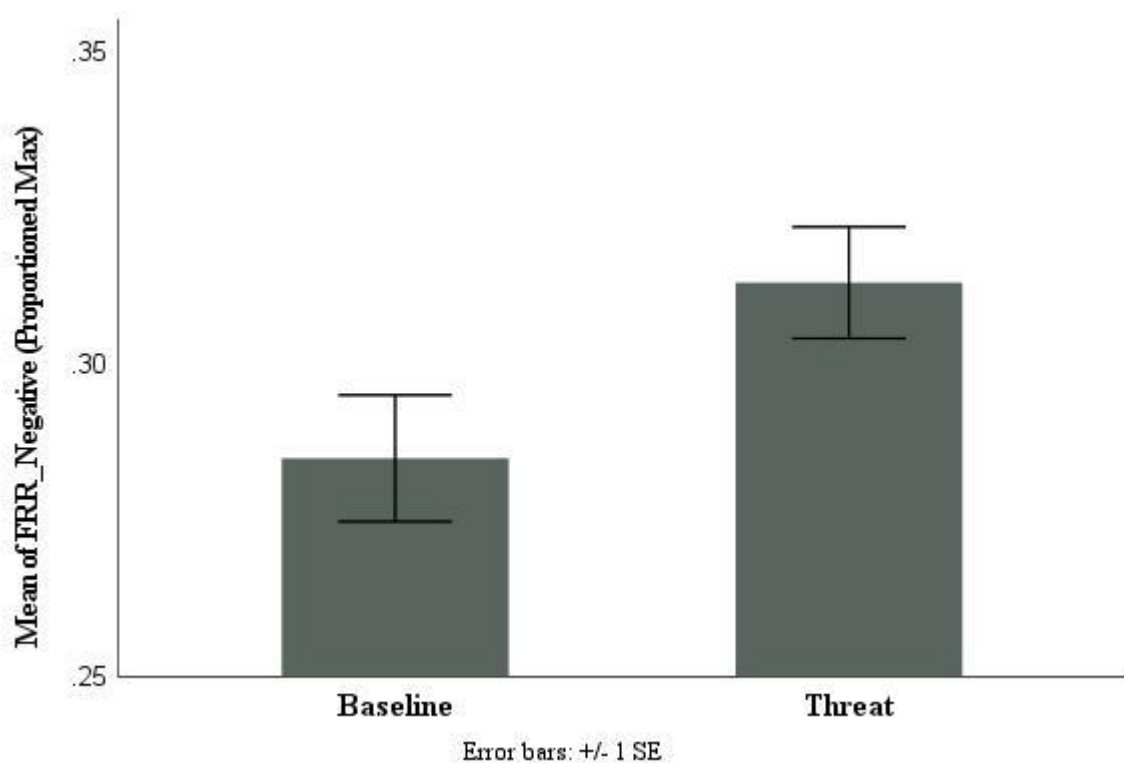


BTAB FRR_Negative

The responses from the facial emotion dimensions were pooled into one Negative Facial Emotions category (FRR_Negative). A paired t-test was conducted for the maximum proportions of Negative facial emotions calculated from the FRR between Baseline and Threat stimuli (Figure 2.8). The results showed that the Threat stimuli elicited significantly more negative expressions than the Baseline stimuli, $t(79) = 5.542, p < 0.001, d = 0.624, BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Figure 2.8

Comparing FRR_Negative (Proportioned Max) between Baseline and Threat stimuli



The findings from FRR for all three factors (FRR_Arousal, FRR_Valence and FRR_Negative Emotions) were consistent with the findings from the magnitudes of SCRs, NS-SCRs and frequency of NS-SCRs. In all cases, the Threat stimuli induced significantly stronger

responses relative to baseline stimuli. This evidences the view that the intended purpose of the BTAB was reflected in the current sample – at least for psychophysiological measures and FRR.

SCRs vs. FRRs

The magnitudes of SCRs, NS-SCRs and frequency of NS-SCRs were compared with the Arousal, Valence and Negative Emotions factors from FRRs. However, no reliable associations were noted between the measures for the Baseline or the Threat stimuli, all p 's > 0.5, $BF_{10} < 1$ (see Appendix for correlations between the measures for the Threat stimuli as an example).

BTAB and Psychological Ratings

To further measure the efficacy of the BTAB task, the baseline stimuli (non-body threat) were compared to the threat stimuli across all four psychological rating dimensions (emotional valence, emotional arousal, sense of illusory / sensory pain and realism of threat). The psychological ratings data did not follow a normal distribution and so non-parametric analysis was employed.

Emotional Arousal

Wilcoxon's signed rank tests revealed that participants rated the Threat stimuli as significantly more emotionally arousing than the Baseline stimuli (Figure 2.9a), $Z = 7.539$, $p < 0.001$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Emotional Valence

Similarly, Wilcoxon's signed rank tests were conducted to compare participants Valence ratings between the Baseline and Threat stimuli (Figure 2.9b). Results showed that participants experienced the Threat stimuli to be more negative than the Baseline stimuli, $Z = -7.460$, $p < 0.001$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Sense of Pain

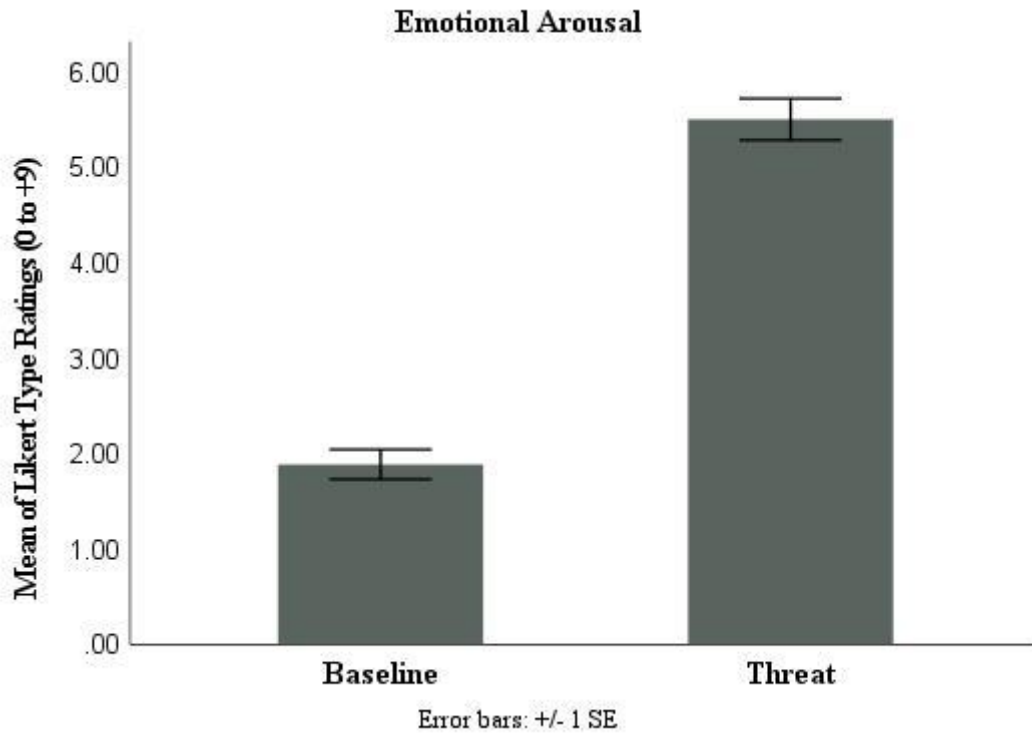
Like above, Wilcoxon's signed rank tests revealed that participants experienced significantly more sense of illusory pain in the Threat stimuli than the Baseline stimuli (Figure 2.9c), $Z = 5.814$, $p < 0.001$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Realism of Threat

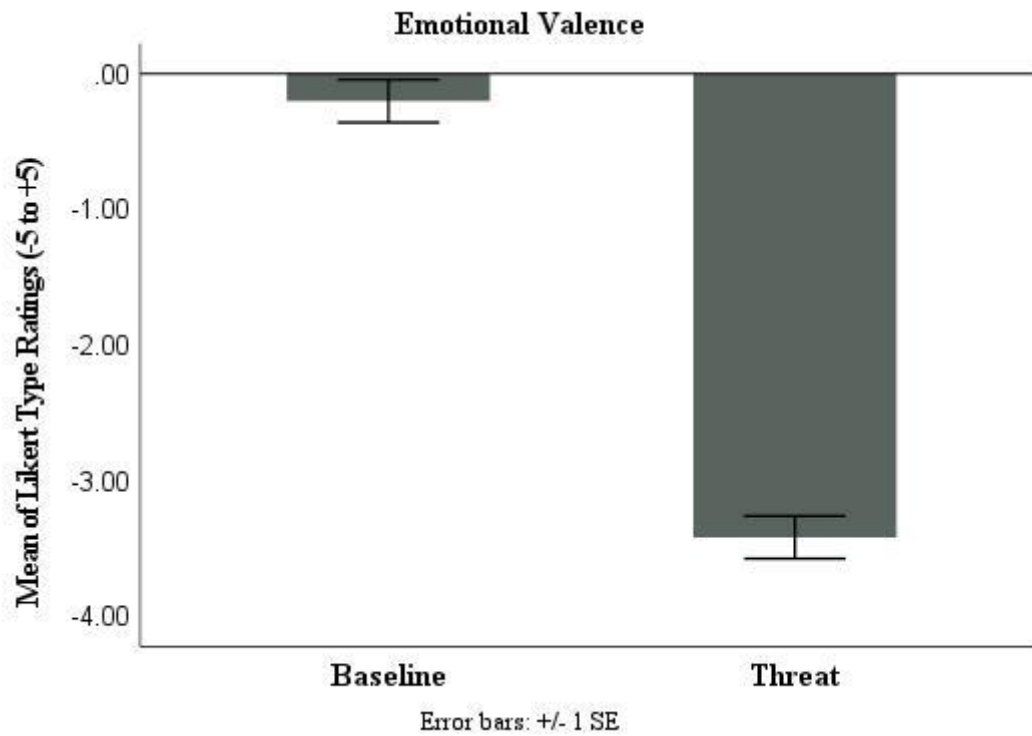
As above, Wilcoxon's signed rank tests showed that participants experienced the Threat stimuli to be significantly more threatening than the Baseline stimuli (Figure 2.9d), $Z = 7.379$, $p < 0.001$, $BF_{10} > 1000$ (Bayes interpretation: Decisive AH).

Figure 2.9

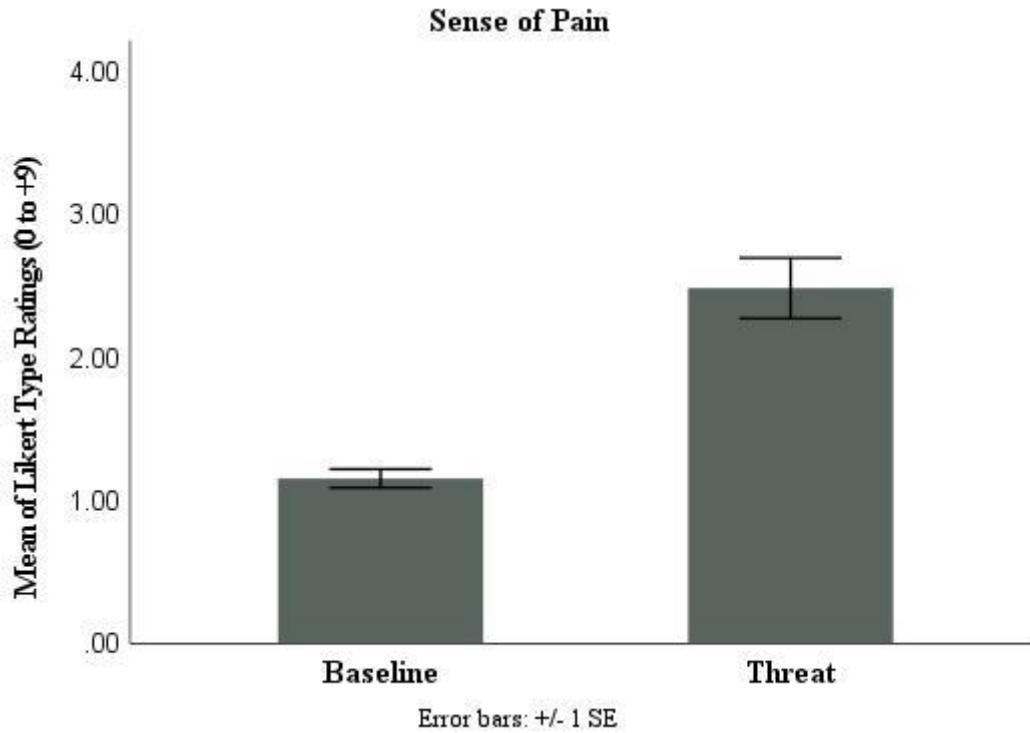
Differences between Baseline and Threat stimuli for the four psychological rating dimensions



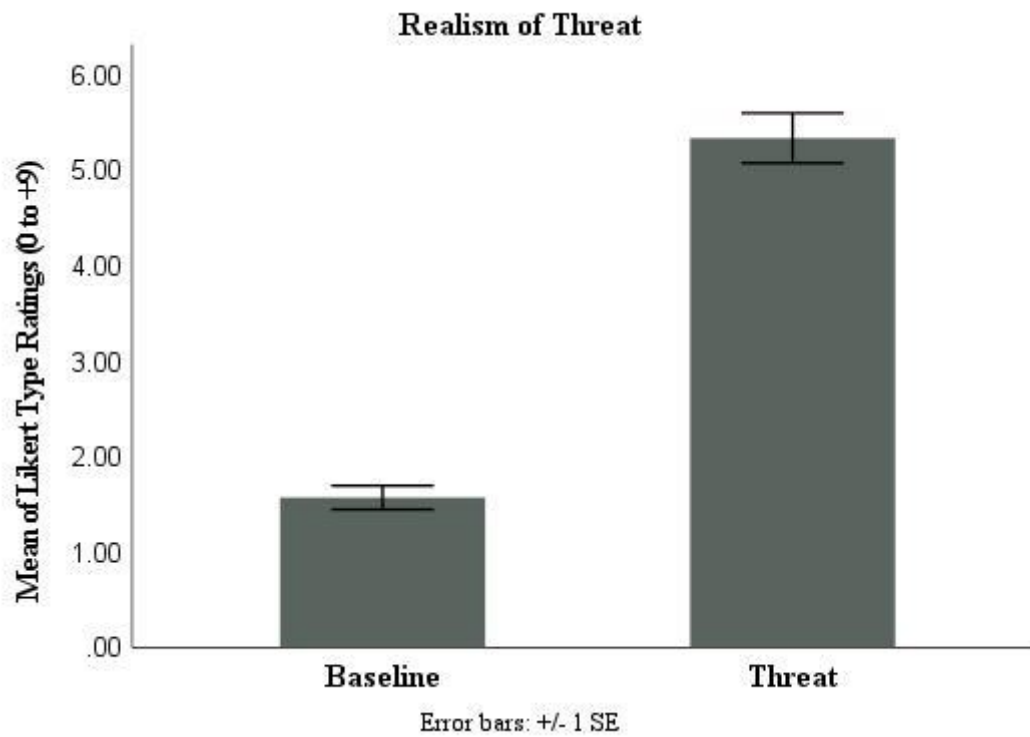
(a)



(b)



(c)



(d)

Note: In the above figure, the four psychological ratings taken after viewing each block of the BTAB and are illustrated for (a) emotional arousal, (b) emotional valence, (c) sense of illusory pain and (d) realism of threat

Psychological Ratings vs. FRRs

The psychological ratings (all four dimensions, emotional arousal, emotional valence, sense of illusory pain and realism of threat) were compared with maximum FRRs (Arousal, Valence and Negative). The correlations between the measures for the Baseline or Threat stimuli did not show any reliable associations, all p 's > 0.05, $BF_{10} < 1$ (the correlations between the Threat stimuli are presented in the Appendix as an example)

Aberrant Visual Experiences

Skin Conductance Responses (Threat Stimuli) and Aberrant Visual Experiences (AVE)

Pearson's two-tailed r correlations were conducted between the magnitudes of SCRs, NS-SCRs, and frequency of NS-SCRs (F-SCRs) of the Threat stimuli and aberrant visual experiences (Visual factor from the MUSEQ measure – AVE). However, no correlations were observed (Table 2.2).

Table 2.2

Pearson's correlation coefficients (FDR corrected) and Bayes values between SCR_T, NS-SCR_T, F-SCR_T and AVE

Correlation Pair	r	p value	B&H value	BF_{10} **	BF_{01} **	Bayes Value Interpretation**
SCR_T vs. AVE	0.122	0.284	0.017	0.247	4.046	Good Null
NS-SCR_T vs. AVE	-0.120	0.290	0.033	0.243	4.110	Good Null
F-SCR_T vs. AVE	0.039	0.732	0.050	0.149	6.717	Good Null

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

FaceReader Responses (Threat Stimuli) and Aberrant Visual Experiences (AVE)

Pearson’s two-tailed *r* correlations were conducted between the FRRs from the Threat stimuli (FRR_T_Arousal / Valence / Negative) and the AVE. However, no reliable associations were noted (Table 2.3).

Table 2.3

Pearson’s correlation coefficients (FDR corrected) and Bayes values between FRR_Arousal / Valence / Negative and AVE

Correlation Pair	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁**	Bayes Value Interpretation**
FRR_T_Negative vs. AVE	-0.214	0.059	0.017	0.812	1.231	Inconclusive Null
FRR_T_Arousal vs. AVE	0.122	0.286	0.033	0.246	4.065	Good Null
FRR_T_Valence vs. AVE	0.105	0.355	0.050	0.214	4.677	Good Null

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

Psychological Ratings (Threat Stimuli) and Aberrant Visual Experiences (AVE)

Kendall’s τ correlations were conducted between all dimensions of psychological ratings (Valence, Arousal, Pain and Threat) from the Threat stimuli and the AVE. Results showed that increasing ratings of emotional arousal, emotional valence (in this case more negatively rated) and realism of threat for the threat stimuli of BTAB were associated with lower scores on aberrant experiences (Table 2.4).

Table 2.4

Kendall's correlation coefficients (FDR corrected) and Bayes values between

Ratings_T_Arousal / Valence / Pain / Threat and AVE

Correlation Pair	τ	p value	B&H value	BF₁₀ **	BF₀₁	Bayes Value Interpretation**
Ratings_T_Valence vs. AVE	0.218	0.008*	0.013	7.791		Good AH
Ratings_T_Threat vs. AVE	-0.214	0.009*	0.025	6.780		Good AH
Ratings_T_Arousal vs. AVE	-0.199	0.015*	0.038	4.054		Good AH
Ratings_T_Pain vs. AVE	-0.003	0.968	0.050	0.147	6.813	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.

Aberrant beliefs

Skin Conductance Responses (Threat Stimuli) and Proneness to Aberrant Beliefs (AB)

Pearson's two-tailed r correlations were conducted between the magnitudes of SCRs, NS-SCRs, and frequency of NS-SCRs (F-SCRs) of the Threat stimuli and proneness to aberrant beliefs (Positive factor from the CAPE measure – AB, weighted frequency and distress scores averaged). The skin conductance responses did not associate with aberrant beliefs (Table 2.5).

Table 2.5

Pearson's correlation coefficients (FDR corrected) and Bayes values between SCR_T, NS-SCR_T, F-SCR_T and AB

Correlation Pair	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁**	Bayes Value Interpretation**
NS-SCR_T vs. AB	-0.070	0.540	0.017	0.169	5.917	Good Null
F-SCR_T vs. AB	-0.022	0.846	0.033	0.143	6.984	Good Null
SCR_T vs. AB	0.008	0.942	0.050	1.141	7.096	Good Null

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

FaceReader Responses (Threat Stimuli) and Proneness to Aberrant Beliefs (AB)

Pearson's two-tailed *r* correlations were conducted between the FRR_Arousal / Valence / Negative from the Threat stimuli and proneness to aberrant beliefs (AB). Similar to above, there were no correlations of note between the FRRs and aberrant beliefs (Table 2.6).

Table 2.6

Pearson's correlation coefficients (FDR corrected) between FRR_T_Arousal / Valence / Negative and AB

Correlation Pair	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁**	Bayes Value Interpretation**
FRR_T_Arousal vs. AB	0.197	0.082	0.017	0.621	1.611	Inconclusive Null
FRR_T_Valence vs. AB	0.130	0.255	0.033	0.265	3.767	Good Null
FRR_T_Negative vs. AB	-0.126	0.268	0.050	0.257	3.894	Good Null

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

Psychological Ratings (Threat Stimuli) and Aberrant Beliefs (AB)

Kendall's τ correlations were conducted between all dimensions of psychological ratings (Valence, Arousal, Pain and Threat) from the Threat stimuli and proneness to aberrant beliefs (AB). As above, psychological ratings from the BTAB showed no associations with aberrant beliefs (Table 2.7).

Table 2.7

Kendall's correlation coefficients (FDR corrected) and Bayes values between Ratings_T_Arousal / Valence / Pain / Threat and AB

Correlation Pair	τ	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁	Bayes Value Interpretation**
Ratings_T_Threat vs. AB	0.109	0.169	0.013	0.396	2.532	Inconclusive Null
Ratings_T_Valence vs. AB	-0.056	0.490	0.025	0.191	5.234	Good Null
Ratings_T_Arousal vs. AB	0.047	0.557	0.038	0.176	5.676	Good Null
Ratings_T_Pain vs. AB	-0.024	0.770	0.050	0.154	6.492	Good Null

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

General Discussion

The present study examined cognitive affective processing underlying predisposition to aberrant experience and belief in the neurotypical population. A host of measures including psychophysiological and psychological were utilised to explore responses to aversive body-threat images in a sample screened for predisposition to aberrant visual / perceptual experience and aberrant beliefs. Both methodological and theoretical factors were examined.

Both the SCR and the FRR measures produced significantly stronger responses for Threat stimuli than for Baseline stimuli. This was the case for the magnitudes of Threat SCRs (a phasic measure of autonomic activity) and the magnitude of NS-SCRs (a tonic measure of autonomic activity), - both of which were significantly stronger for body-threat stimuli relative to baseline stimuli. The frequency of NS-SCRs was also significantly increased for body-threat stimuli. The frequency of NS-SCRs is known to be a reliable tonic measure of negatively tuned cognitive states (Nikkula, 1991; Dawson et al., 2007; Boucsein, 2012).

The FRR data were analysed as a second objective measure of autonomic activity. The same pattern was seen for the independent FRR measure as was observed for SCRs. Here, measures of Arousal were significantly stronger for threat stimuli, as were the responses for the combined Negative Emotions factors (relative to baseline stimuli). In addition, for measures of Emotional Valence, the body-threat stimuli induced significantly more negative responses than those seen for baseline stimuli.

On the whole, psychological ratings (Emotional arousal, Valence, illusory pain, realism) were all consistently rated higher (i.e., more emotionally negative, more emotionally arousing etc.) for the Threat stimuli when compared to the Baseline stimuli.

Collectively, the SCR data and psychological ratings replicated the findings from those reported from the first study from Braithwaite et al., (2020) however, here the effects

were observed under conditions when individual clips were integrated into a short series of clips (Blocks) and those separate blocks of threats were matched on measures of potency. Furthermore, the present findings showed new effects in that a novel FRR measure also provided clear evidence of stronger responses for body-threat stimuli relative to baseline stimuli – providing an independent objective verification of the underlying autonomic processing.

These results provide evidence on two important aspects. First, by replicating the findings from the original study, this study provides additional utility to the modified block design of the BTAB in reliably increasing autonomic activity to body specific threat stimuli. Second, the findings from the FRR provide evidence for a new methodological tool that can be utilised alongside skin conductance and self-report ratings in studies of this type.

Interestingly, although both the SCR and FRR data showed consistent responses to threat versus baseline stimuli, they did not show any reliable association with each other. This was surprising given the initial success in all these factors delineating between the Threat and Baseline stimuli. The lack of correlation between these factors might be explained, at least in part by the following observations. Firstly, of note, the SCR data were Z-scored from a time-series of integrated signals whereas FRR data were corrected as a proportion of maximal response with the raw data being overall summary data from the series of clips (it is not advisable to Z-score nominal data – Boucsein, 2012; Braithwaite et al., 2013). While both approaches are accepted, reliable and valid in the standardisation of data, they do not work in the same way. Going forward utilising a moving window approach (i.e., FRR measures taken every couple of seconds through the entire series of clips) may be more accurate / sensitive for comparing more discrete FaceReader responses to other measures.

When the psychophysiological measures were correlated with predisposition to aberrant visual experiences (measured by the visual factor from the MUSEQ), there were no reliable outcomes on any dimension. All SCR and FRR measures failed to correlation with both screening measures. The psychological ratings, particularly for emotional arousal, emotional valence and realism of threat correlated negatively with aberrant visual experiences which suggests a sort of suppression of affect to aversive body-threat, however, as this was not echoed by the psychophysiological data, these findings require further examination in future studies. Perhaps, the generalised aberrant visual experiences assessed in the MUSEQ measure (see Table 2.1) whilst suggesting some overlap with the psychological ratings, may need to be more specific on the type of aberrant experience (illusion, distortion, simple / unformed hallucinations, complex hallucinations etc.) to accurately examine the overlap between cognitive biases underlying aberrant perceptual and aberrant body experiences, if any. In addition, the original study by Mitchell et al. (2017) showed significant differences between clinical and non-clinical groups with some overlap of frequency distributions which was consistent with a continuum of aberrant experiences. However, the sensitivity metrics within the non-clinical group remained underexplored even though the measure was intended for non-clinical use. This would suggest that in the present study, predisposition to these experiences (as a screening measure) could not be accurately characterised.

In the case of predisposition to aberrant beliefs (Positive factor from the CAPE) we found no correlations with the SCRs. This was also supported by no associations with the strength and frequency of NS-SCRs. Although some delusions are considered to be rationalisations of perceptual aberrations, neurocognitive biases underlying delusions may indeed reflect distinct neural networks. Additional support for this finding was provided with FRRs and psychological ratings that did not correlate with proneness to aberrant beliefs.

Theoretical Implications

Attenuated affect / dulled emotion has been shown to occur due to a dysfunction in the inhibitory processes in the pre-frontal regions (specifically the rVLPFC) propagating to the insula regions (AI) and anterior cingulate cortex (ACC) (Hunter et al., 2004; Jay et al., 2014(a), 2016(b); Critchley, 2005; Craig, 2009; Seth, 2013; Seth & Critchley, 2013). Co-activation of these regions has been considered to be essential in integrating and processing interoceptive / physiological states with exteroceptive / environmental states for stable multi-sensory integration (Craig, 2009; Seth, 2012(a); 2013(b), Suzuki et al., 2013). A dysfunction in these processes has been shown to occur due to over estimation of incoming threat signal that inappropriately triggers the suppression mechanism resulting in suppressed autonomic responses (Philips et al., 2001; Sierra et al., 2002(a), 2006(b); Lemche et al., 2007; Sierra & David, 2011; Dewe et al., 2016(a); 2018(b) also see Horn et al., 2020 for a review). The findings of the present study, support and further validate the use of the BTAB as a salient tool in assessing cognitive affective biases specific to aberrant body experiences. The newly modified design of the BTAB was indeed shown to provide a stable and reliable method of presenting the body-threat and non-body threat as blocks which would be useful in future studies incorporating brain stimulation / brain imaging studies. The efficacy of the BTAB in increasing autonomic responses is further validated in this study. In addition, the present study did not find differences in perspective manipulation. These findings were in line with the original study (Braithwaite et al., 2020) further suggesting that spontaneous perspective taking does not affect biases in underlying aberrant body experiences.

In essence, many conditions in the clinical and non-clinical populations are linked with both aberrant perceptual experiences and aberrant body-experiences such as out-of-body experiences, Heutoscopy and Autoscopy (Brugger et al., 1997; Brugger, 2002; Blanke et al., 2004; Blanke & Mohr, 2005; Arzy et al., 2006; Blanke & Castillo, 2007; Braithwaite et al.,

2011). This suggested that there may be a functional overlap between the two types of experiences and so predisposition to aberrant perceptual experiences would also reveal cognitive-affective biases that are more commonly seen with aberrant body experiences (flattened affect / dulled emotional experiences). However, the findings from the psychophysiological measures in current study did not lend to this notion. It could be considered that the majority of the self-report questions on the visual factor from the MUSEQ were related to complex visual hallucinations. Typically, aberrant body experiences are considered to be distortions in perception as opposed to hallucinations. For example, in depersonalisation, patients are aware of the bizarreness of their aberrant body experiences, (its “as if” my arm did not belong to me) (Sierra, 2009; Sierra & David, 2011). Given this, perhaps a measure assessing aberrant distortions may be a better indicator in examining if the cognitive affective biases underlying aberrant visual and aberrant body experiences overlap.

Aberrant beliefs / delusionary beliefs are thought to be rationalisations arising out of perceptual aberrations and aberrant self-experiences (Maher 1974; Maher, 1988; Maher 1992; Bentall et al., 2001). Furthermore, the threat anticipation model that is theorised in aberrant beliefs suggests that experiences of threat, heightened arousal, hallucinations, perceptual anomalies, depersonalisation, illusions etc. give rise to aberrant beliefs and therefore are critical part in understanding underlying mechanisms that lead to delusions (Maher, 1974; Freeman, 2007; Salvatore et al., 2012). This suggests that there may be an overlap in the neurocognitive biases underlying aberrant body experiences and aberrant beliefs however not many studies have evidenced this (Bentall et al., 2001; Blackwood et al., 2001; Gilleen & David; 2005; Bell et al., 2006; Salvatore et al., 2012). For example, Phillips et al., 2000 found that schizophrenic patients with persecutory delusions identified threats quicker than schizophrenic patients without delusions, however, those with delusions spent less time reappraising the threat. The current findings from SCRs, FRRs and psychological ratings did

not find any reliable association indicating that belief evaluation and aberrant body experiences have distinct neural networks as well as providing evidence that aberrant beliefs are not linked aberrant body experiences.

Limitations and Future Studies

FaceReader is a promising and commercially viable tool that can be used in this research however in its infancy. Despite this, the current findings, the FaceReader data were capable of delineating between baseline and threat stimuli. Future studies could examine the factors identified in this study as a time-series data which may associate with established measures (SCRs and psychological ratings).

Given the utility of the BTAB in successfully elevating autonomic activity to viewing aversive body-threat stimuli, future studies can examine this effect with brain stimulation of the prefrontal regions implicated in the atypical threshold triggering of inhibitory regions (rVLPFC) which project to the insula and anterior cingulate regions.

Although the findings from the present study with regards to predisposition to aberrant visual experiences was not present, future work can consider using other trait-based measures to assess aberrant visual experiences or cortical hyperexcitability to further improve our understanding of cognitive biases underlying aberrant experiences.

Conclusion

This is the first study to our knowledge that has utilised the FaceReader in assessing cognitive affective biases in the non-clinical population predisposed to aberrant experiences. The present study provides evidence that FaceReader responses are capable in distinguishing

between body-threat and baseline stimuli. The current study successfully replicated the previous findings (see Braithwaite et al., 2020) in eliciting elevated autonomic arousal to body-threat stimuli. The findings also further validate the usefulness of specific body-threat / non-body threat in research understanding the cognitive affective biases underlying aberrant experiences.

Chapter 3

Optimised Multi-channel Transcranial Direct Current Brain Stimulation (MtDCS) Reveals Differential Involvement of the Right Ventrolateral Pre-frontal Cortex (rVLPFC) in those Predisposed to Aberrant Experiences.

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Abstract

A growing number of studies have shown a prominent role for cortical hyperexcitability underlying aberrant perceptions, hallucinations, and distortions in human conscious experience – even in neurotypical groups. In addition, the right-ventrolateral prefrontal cortex (rVLPFC: and its inferred functional relationship with the insula complex) 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 screening 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. Each participant experienced all stimulation conditions 1 week apart. Stimulation was applied at 2mA across 7-channels for 10 mins. On completion of each stimulation session, participants completed a newly devised body-threat Task (BTAB) while skin conductance responses and psychological responses were recorded. Participants showing signs of increasing cortical hyperexcitability showed significant suppression of SCRs in the cathodal stimulation relative to the anodal and sham conditions. Those scoring high on the trait-based measures of depersonalisation-like experiences failed to show reliable effects. These findings support the notion that baseline brain states can mediate the effects of neurostimulation which would be missed without appropriate screening measures - though now extended to measures of aberrant experiences. Theoretical implications and methodological improvements are discussed.

Introduction

Cortical hyperexcitability is defined as a heightened activation of neural activity in particular systems which is above expected levels (Haigh et al., 2012). Aberrant levels of such neural excitation have been identified with the co-existence of both elementary and complex hallucinations in visual and other sensory systems (de Boismont, 1853; Siegal, 1977; McGuire et al., 1993; Panayiotopoulos, 1994(a), 1999(b); Manfred & Andermann, 1998; Bien et al., 2000; Bressloff et al., 2001(a), 2002(b); Braun et al., 2003; Sass & Parnas, 2003; Taylor et al., 2003; Allen et al., 2008; Elliot et al., 2009(a), 2009(b)). Consequently, elevated levels of cortical hyperexcitability are now seen as having a pivotal role in many striking distortions of human conscious experience.

Typically, these observations occur in concert with the presence of underlying neurological disorders and clinical conditions. Examples of these include; (i) migraine with aura patients, (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; Siegal, 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 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 in sympathy 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 hallucination (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; Diederer et al., 2012; Braithwaite, 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 & Renninghaus, 2016; Baumeister et al., 2017). The emerging view is one of a continuum of cortical hyperexcitability / predisposition to aberrant perceptions along which people 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 self-consciousness.

Depersonalisation-like experiences (DLEs)

Our typical daily experience of self-consciousness, of being the agent of one's thoughts, feelings, and actions, of stable embodiment and having a salient sense of 'presence' (of being in the here and now) 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(a), 2013(b); Blanke, 2012; Seth et al., 2012; Clark, 2013; Suzuki et al., 2013; Braithwaite et al., 2014; Kessler & Braithwaite, 2016).

Depersonalisation disorder (DPD) is a particular form of dissociative experience where the patient typically describes a feeling of unreality for the bodily self (depersonalisation), their surroundings (derealization), or both (Sierra & David, 2011; see Sierra 2009 for a review). Patients report feelings of estrangement from themselves;

remoteness from their bodies, thoughts, and actions, coupled to a profound altering in the sense of ‘presence’ (being in the here and now) 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; Sierra, 2001(a), 2009(b); Sierra et al., 2005; Sierra & David, 2011; Medford, 2012; Seth, 2012 (a), 2013 (b); Clark, 2013).

Importantly, unless occurring co-morbidly with other conditions or disorders, DPD is not typically associated with sensory hallucination or delusion (reality-testing is 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. DPD patients are generally aware of the bizarreness of their experiences and the shift in consciousness that has taken place.

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(a), 2018(b); Sierra & David, 2011; Braithwaite et al., 2020). Accordingly, these experiences reflect many of the thematic components of DPD, albeit in somewhat 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 (a), 2013 (b); Clark, 2013; Jay et al., 2014 (a), 2016 (b)).

Several studies have demonstrated a suppression of autonomic arousal (skin conductance responses / SCRs) to aversive stimuli in DPD patients and those prone to aberrant DLEs in neurotypical samples (Sierra et al., 2002 (a), 2005(b); Dewe et al., 2016 (a), 2018 (b); Braithwaite et al., 2020).

To account for these observations, researchers have posited a role for a dysfunctional fronto-limbic suppressive network where inhibitory networks housed in the right ventrolateral prefrontal cortex (rVLPFC) have become over-active and inappropriately inhibit 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; Oschner & Gross, 2004 (a), 2005 (b); Medford et al., 2006; Critchley, 2005; Eippert et al., 2007; Lemche et al., 2007 (a), 2008 (b); 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 and prevented 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.

As well as behavioural and brain-imaging research (discussed above) evidence from neurostimulation studies 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 in DPD patients and healthy controls and found that low-frequency rTMS has an inhibitory effect on neural processes. The underlying rationale here was to inhibit the brain networks thought themselves to be inhibitory – thus liberating other brain regions receiving major projections from it (the AIC) from becoming overly-inhibited.

Previous studies examining autonomic responding in DPD groups have typically used stimuli that can be described as generally aversive from collections such as the International Affective Picture System (Lang et al., 1997). Despite the fact that aberrant body experiences

are a central and core component of DPD, until recently body-based aversive imagery or threats had not been used to determine how such stimulation interacts with autonomic responding in such groups. Accordingly, the role of these networks in neurotypical levels of DLEs awaits clarification. Dewe and Colleagues (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 SCRs and autonomic responding to such threats and the magnitude of the suppression was associated with the strength of the DLEs reported. Such findings support the idea that autonomic suppression does appear to be present even in neurotypical groups predisposed to DLEs and may well provide a tractable neural substrate for the reported phenomenology.

tDCS 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 and neurotypical / non-clinical samples (Antal et al., 2003(a), 2004(b), 2007(c), 2011(d); Nitsche et al., 2008; Nitsche & Paulus, 2011; Vallar & Bolognini, 2011; Jacobson et al., 2012; Braithwaite et al., 2015).

Although numerous demonstrations of the efficacy of tDCS have been reported, the underlying biophysics of tDCS remain somewhat unclear. 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 depolarizing cell membranes making it more likely that they fire. In contrast, cathodal (inhibitory) stimulation attenuates cortical excitability by hyperpolarizing cell membranes making them less likely to fire (Lauro et al., 2014).

However, recent findings and discussions argue for a somewhat more complex account than this (Nitsche & Paulus, 2000; Nitsche et al., 2008; Bikson, 2016; Parkin et al., 2019; Masina et al., 2021; Lerner et al., 2021). The emerging view suggests that the individual differences in the baseline neural state is important for mediating the influence of brain stimulation and hence has implications for examining effects and their subsequent interpretation (Hsu et al., 2016; Romei et al., 2016; Silvanto et al., 2018).

Hence in tDCS work, it is now becoming increasingly important to measure and take into account potential differences in baseline excitability (Benwell et al., 2015; Hsu et al., 2016; 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; 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. Therefore, future research should consider the influence of participants' latent background baseline excitability, where the effects of brain stimulation may also benefit from individual-difference stratification and help determine more complex interactions between individual brains and fixed stimulatory montages.

However, despite this, 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, tDCS effects.

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; DaSilva et al., 2018; Fox et al., 2014; Ruffini et al., 2014; Kunze et al., 2016). The emerging prediction is that optimised multi-electrode arrays consisting of several anode and cathode configurations can be used to simultaneously modulate regions of a distributed functional network (Miranda et al., 2013; Ruffini et al., 2014; Fischer et al., 2017; Ruffini et al., 2018). The critical advantages from this approach are of both methodological and theoretical importance. From a methodological perspective, modelling the optimal electrode sizes, electrode location (including reference electrodes), current flow, stimulation intensity, and duration will lead to superior focality and spatial resolution in helping to ensure the stimulation occurs maximally within the target networks (Ruffini et al., 2014).

Purpose of the Present Study

The present study examined the role of the right-ventrolateral prefrontal cortex (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 screened for: (i) predisposition to aberrant experiences known to reflect increased degrees of visual cortical hyperexcitability, and (ii) proneness to depersonalisation-like aberrant experiences (DLEs). The role of the rVLPFC (and by proxy, the insula) was assessed via a targeted optimised multi-channel transcranial direct current brain stimulation (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 delineated (stimulation current and location of all electrodes) to directly identify the optimal targets and parameters for accurate brain stimulation (Ruffini et al., 2014) 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 on 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 skin conductance responses (Critchley, 2005; Medford et al., 2006; Lemche et al., 2007 (a), 2008 (b); Jay et al., 2014; Xia et al., 2017; Vinberg et al., 2021) and this would become primarily manifest in autonomic SCR responses to body-threat stimuli.

In addition, and in line with contemporary findings on tES brain-stimulation (Horvath et al., 2015; Hsu et al., 2016; Romei et al., 2016; Medina & Cason, 2017; Silvanto et al., 2018), we 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 current study explored the notion that these brain regions may also be implicated in mediating DLEs in neurotypical samples in line with what has been reported for clinical depersonalised patients (Jay et al., 2014(a), 2016(b)). More specifically, we sought to quantify trait-based factors pertaining to aberrant experience (reflecting cortical hyperexcitability) by screening participants on a recently devised measure (the CHi_II - Fong et al, 2019; Braithwaite 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 from our laboratory on the CHi_II measure revealed a 3-factor solution; “Aura-like Hallucinatory Experiences” (AHE), “Distorted Visual Perception” (DVP) and “Heightened Visual Sensitivity and Discomfort” (HVSD) (Fong et al., 2019). Neurophysiological investigations (EEG / VEP) and behavioural work (Pattern-glare tasks) have validated its (CHi_II) underlying assumptions with migraine patients and neurotypical samples showing differential performance patterns as a function of the different factors (Fong et al., 2019 (a), 2020 (b)). This work additionally demonstrated that the factor “AHE” best predicted underlying aberrant degrees of cortical hyperexcitability. Therefore, this factor was taken 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 brain-stimulation procedure.

It should be noted that the CHi_II is a measure centred on aberrant visual experiences that likely occur due to aberrant processes within primary and associative visual systems (Wilkins, 1995; Huang et al., 2003(a), 2011(b); Braithwaite et al., 2013(a), 2015(b); Fong et al., 2019, Fong, 2020, Merchant 2021). However, it is not known if indicators of visual cortical hyperexcitability also reflect some broader component of cortical hyperexcitability

extending beyond visual regions (i.e., more medial and frontal regions) and thus have a meaningful relationship with rVLPFC. Therefore, the use of the CHi_II here is to provide a proxy measure of general cortical hyperexcitability that may exist beyond this region.

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

In summary, we 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 / insula complex. 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 brain stimulation conditions.

Method & Procedure

Participants

Thirty-five participants were recruited from Lancaster University, Department of Psychology, UK. Participants' ages were between 18 – 25 years (Mean = 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 from taking part. The study was approved by the Lancaster University Ethics Committee (FST19024). All volunteers were compensated for their time with course credits.

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 et al., 2013(a), 2020(b), Boucsein, 2012). The final sample used for analysis consisted of 27 participants, 10 male and 17 female participants (mean age = 19 years, SD = 1.53).

Measures

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). 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 (a), 2020 (b)). 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) work particularly 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 et al., 2013; Dewe et al., 2016 (a), 2018 (b); Braithwaite et al., 2020 for a similar approach). The combined maximum score of the DLE factor (which contain 13 items in total) is 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).

Multi-Channel Transcranial Direct Current Stimulation (MtDCS)

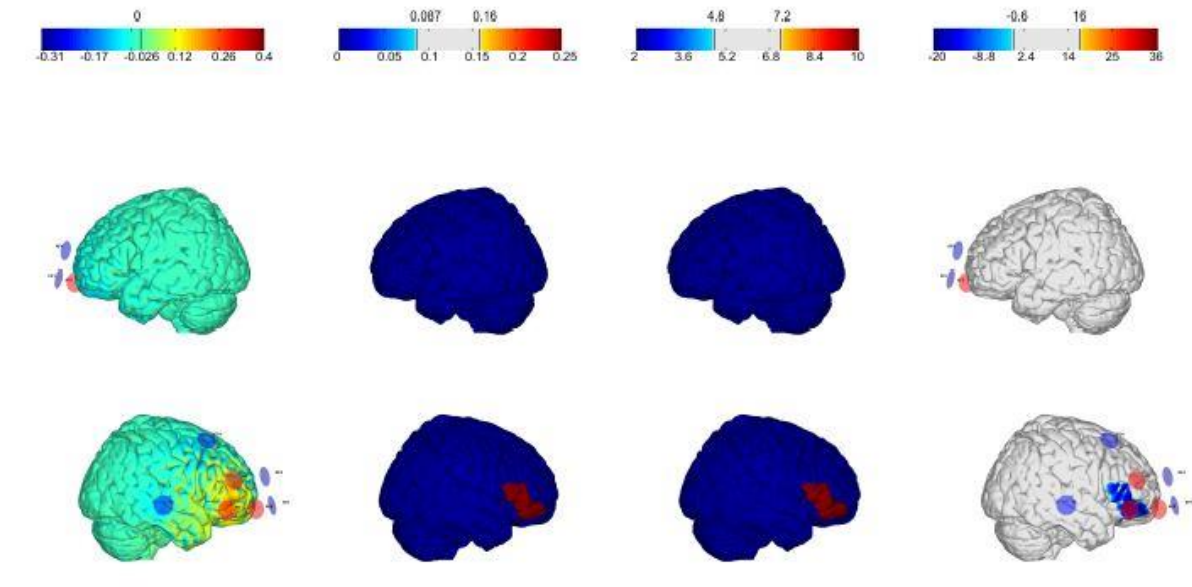
An optimised 7-channel montage was modelled to specifically target the right-ventrolateral prefrontal cortex (rVLPFC). This was done initially by highlighting the region via the Stimtargeter tool (Neuroelectronics, Barcelona, ESP) and montage optimization performed by the Stimweaver multi-focal algorithm which revealed an optimized solution for the target area (Ruffini et al., 2014). The solutions were modelled on a standard generic reference brain, which was also used to determine the optimized montage.

The efficacy of this montage was based on three competing models. The final optimization chosen was a montage with the best goodness of fit metrics for focusing on the target required to be stimulated ($WCC=0.53$ and $ERNI=-4245 \text{ mV}^2/\text{m}^2$ – Figure 3.1). The high definition headcap had 64 points based on a subset of the 10-10 EEG system (Seeck et al., 2017). The electrodes identified were AF8, F6, F8, AF4, FC4, FP1, T8 for stimulation (see Figure 3.2 and Table 3.1). The polarity of the electrode combination was determined by the condition (Anodal or Cathodal). For safety, the total output was calculated to not exceed 2mA and each stimulation electrode was capped at a maximum current of 1mA. The stimulator used was Starstim 8 controlled by the NIC2 Software (Neuroelectronics).

Stimulation occurred for 11 mins in total per session which included a ramp-up (30secs) and ramp-down period (30secs) of electrical current. In the Sham condition, the stimulator only used the ramp-up and ramp-down protocol (total active stimulation time of 1 minute) to mimic the experience of stimulation. Each participant completed three neuromodulation sessions (Anodal, Cathodal and Sham) in a randomised order and were blind 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. Each participant attended all three stimulation conditions (one week apart).

Figure 3.1

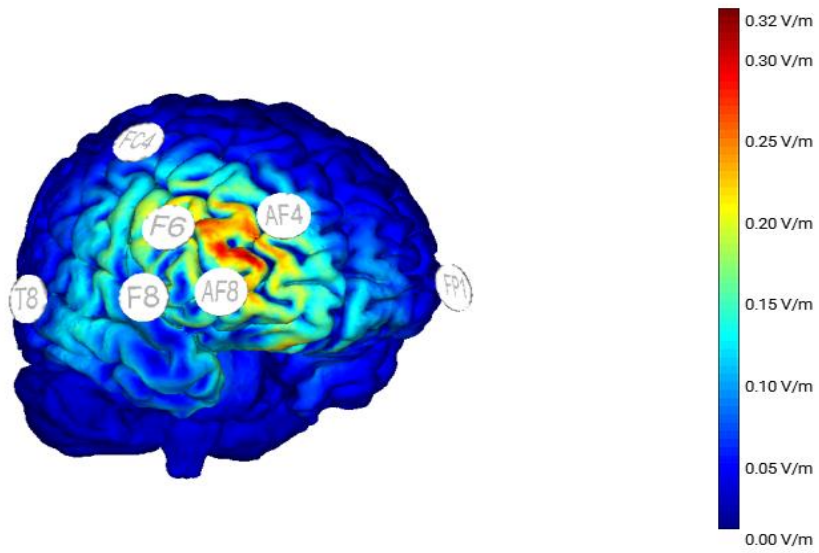
Optimisation Montage for Anodal Condition: $I_{Max,total} = 2mA$, 7 electrode montage, $I_{Max} = 0.973 mA$



Note: From left to right: Normal component of the E-field E_n (V/m), target E-field (V/m), target weight and ERNI (mV^2/m^2) for grey matter

Figure 3.2

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 3.1

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

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 SCRs and non-specific SCRs) were determined (Braithwaite et al., 2020). Additionally, 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.

In the present study, a blocked design (programmed in E-Prime 3.0) was implemented in which 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} = difference between SCR onset and its maximum peak) described in Braithwaite et al. (2020) so that they were matched in terms of autonomic potency. The 3 blocks were randomised within E-Prime 3.0.

Stimuli were presented on a 16:9 aspect ratio monitor at 1920 x 1080 resolution, in a darkened room. Additionally, to avoid unfamiliarity to 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 Figure 3.3).

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).

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 0.05Hz high-pass filter and sampled at 2000 Hz. Data were collected by applying a small continuous low voltage current (0.5 V) through two disposable pre-gelled

electrodes (EL507) 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. An SCR was defined as a magnitude delta function (μS), between the peak value and SCR onset (for more detail, see Braithwaite et al., 2013). 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 $0.01 \mu\text{S}$. The SCR of interest was defined as the largest / strongest response that occurred in each block of stimuli. 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; Braithwaite et al., 2013).

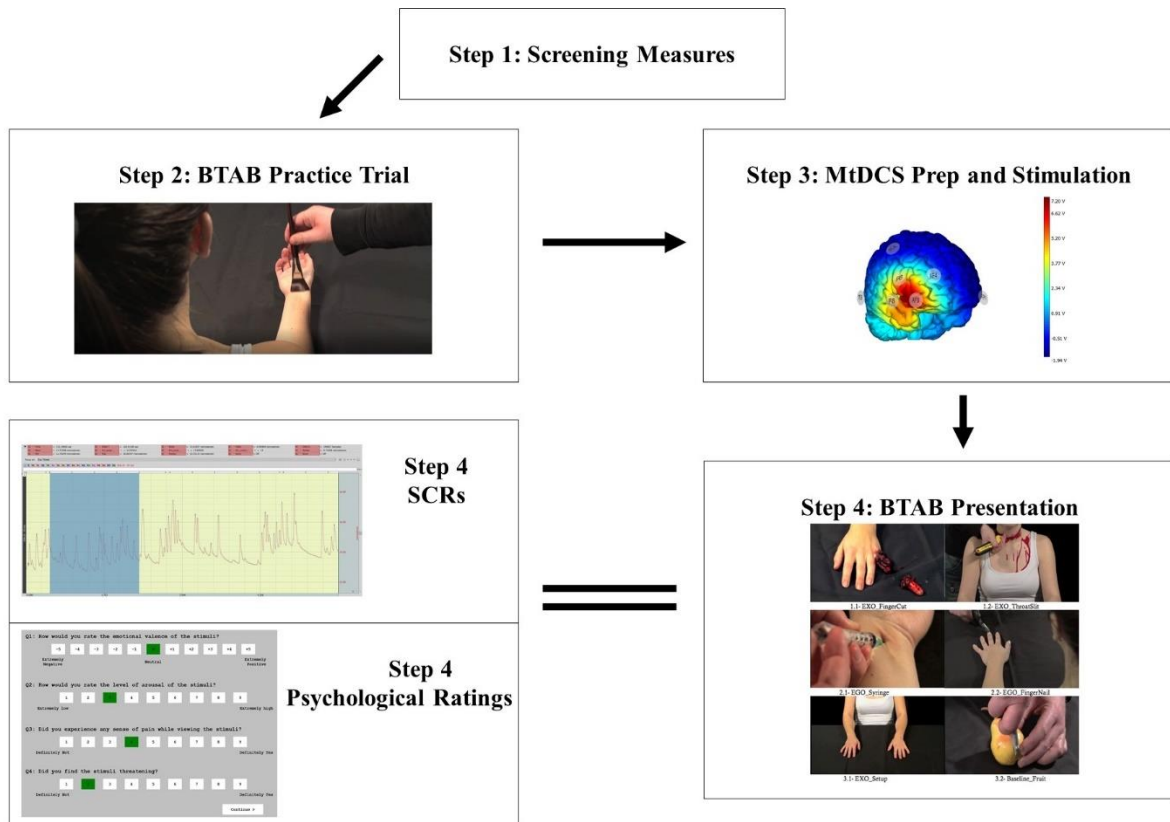
All signals were visually inspected for artefacts and if / when encountered the signal was down sampled by 200 samples / sec (iteratively) to remove them in that section of the signal. In line with recommended practice, SCR magnitude and NS-SCR magnitude data were normalised by using $[\text{SCR} (\text{Log} + 1)]$ transformations and standardized by converting to Z-Scores (Dawsen et al., 2007; Boucsein et al., 2012; Braithwaite et al. 2013(a), 2017(b), 2020(c)). Previous research (Braithwaite et al., 2020; Joshi et al., (Chapter 2)) showed that the two video perspectives (Ego and Exo) were equally efficient at eliciting strong responses and so both were combined (average of the largest SCR in each block) to make one composite Threat block per stimulation condition. Additionally, the Baseline block SCRs, NS-SCRs and F-SCRs were merged into a single Baseline value for analysis.

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, this 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). 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 k Ω). In addition, the electrodes for the SCRs were attached. Once completed, the stimulator was turned on and stimulation was delivered for 11 mins (including 30 seconds 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. This was followed by an exit-questionnaire to ensure that participants did not experience any severely adverse effects during the stimulation. This was repeated for each participant across all sessions (see Figure 3.3). Each session took approximately 1.5 hours per participant.

Figure 3.3

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.

Results

Overall Statistics

Analyses were conducted using a combination of SPSS v27 and JASP v0.14.1. Non-parametric tests (Mann-Whitney U independent samples t-tests, Friedman'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 ANOVA's, within-subject ANOVA's and Pearson's two-tailed r correlations were used with the questionnaire and 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, Braithwaite et al., 2020).

Comparisons between trait-based predisposition to cortical hyperexcitability (CHi_II) and aberrant body experiences (DLE) and responses based on stimuli 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.

Finally, where appropriate, Bayesian statistics are also 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 evidence for the alternative, 10 - 100 as strong and > 100 as

decisive evidence. Where BF_{10} was <1 , BF_{01} values (the reciprocal of BF_{10} values) are presented alongside to ascertain the strength of support for the null hypothesis.

Psychophysiological Responses

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

BTAB maximum SCRs

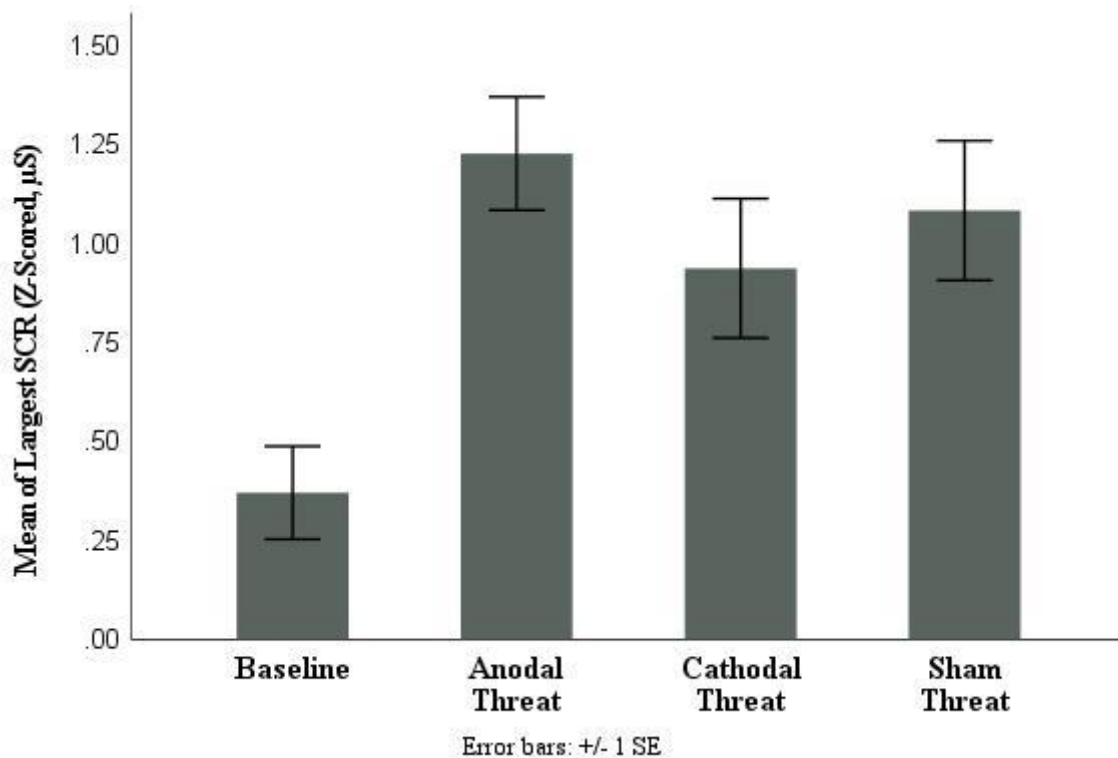
The baseline stimuli (non-body threat) maximum SCRs and the body-threat stimuli (Threat) maximum SCRs were compared across the three experimental conditions (Anodal, Cathodal and Sham) (Figure 3.4). A within-subject ANOVA (with 4 levels, Baseline, Anodal Threat, Cathodal Threat, and Sham Threat) revealed a significant main effect of stimuli type $F(3,78) = 5.587, p < 0.001, \eta^2_p = 0.177, BF_{10} = 60.108$. 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, $BF_{10} = 270.707$), Cathodal (MD = 0.565, SE = 0.191, $p = 0.006$, B&H = 0.033, $BF_{10} = 6.981$) and Sham (MD = 0.711, SE = 0.201, $p = 0.002$, B&H = 0.05, $BF_{10} = 23.36$).

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 rm-ANOVA; $F(2,52) = 0.663, p > 0.05, BF_{10} = 0.204, BF_{01} = 4.906$. To summarize, 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.

Figure 3.4

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)



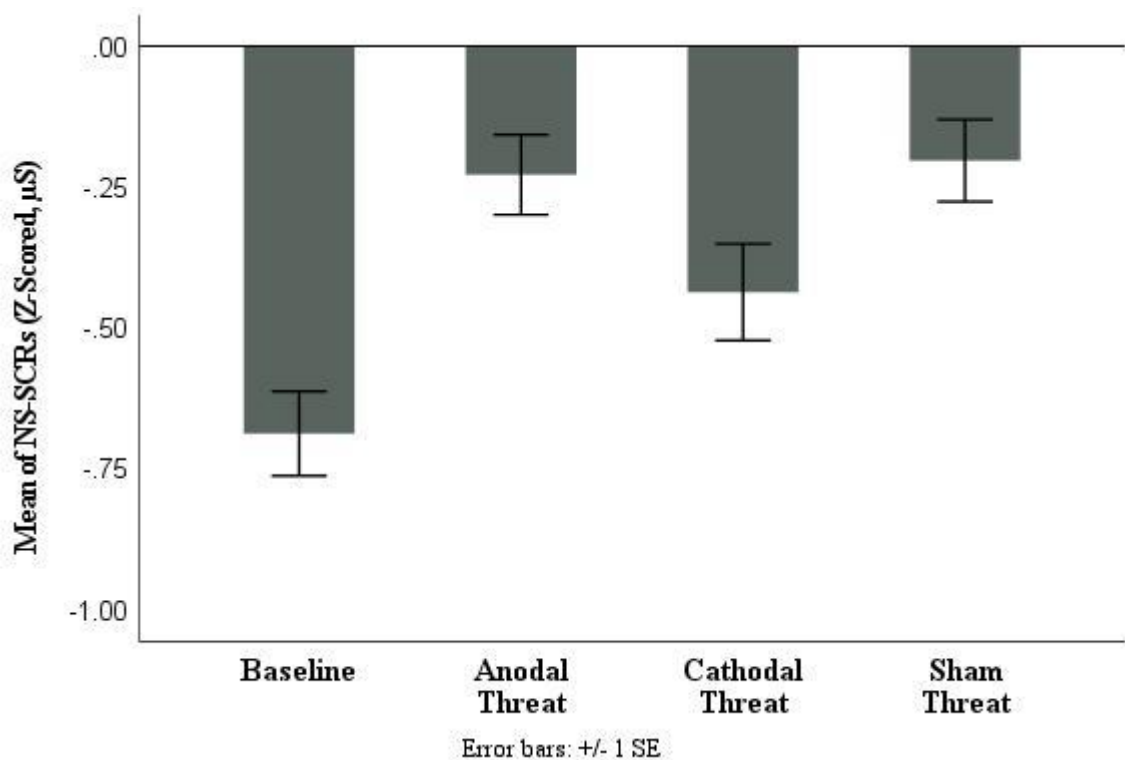
BTAB Magnitudes of NS-SCRs

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 also provide an index of autonomic arousal, was conducted using a within-subject ANOVA at 4 levels (Baseline, Anodal Threat, Cathodal Threat and Sham Threat) (Figure 3.5). There was a significant main effect of stimuli type $F(3,78) = 7.524, p < 0.001, \eta^2_p = 0.224, BF_{10} > 1000$. 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, $BF_{10} = 86.549$), Sham (MD = 0.484, SE = 0.118, $p < 0.001$, B&H = 0.033, $BF_{10} = 81.713$) and Cathodal (MD = 0.251, SE = 0.114, $p = 0.036$, B&H = 0.05, $BF_{10} = 1.611^4$). However, a rm-ANOVA comparison between just the threat blocks did not reveal any significant differences in the Frequentist analysis at the whole sample level; $F(2,52) = 2.388$, $p > 0.05$, $BF_{10} = 1.094$.

Figure 3.5

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)



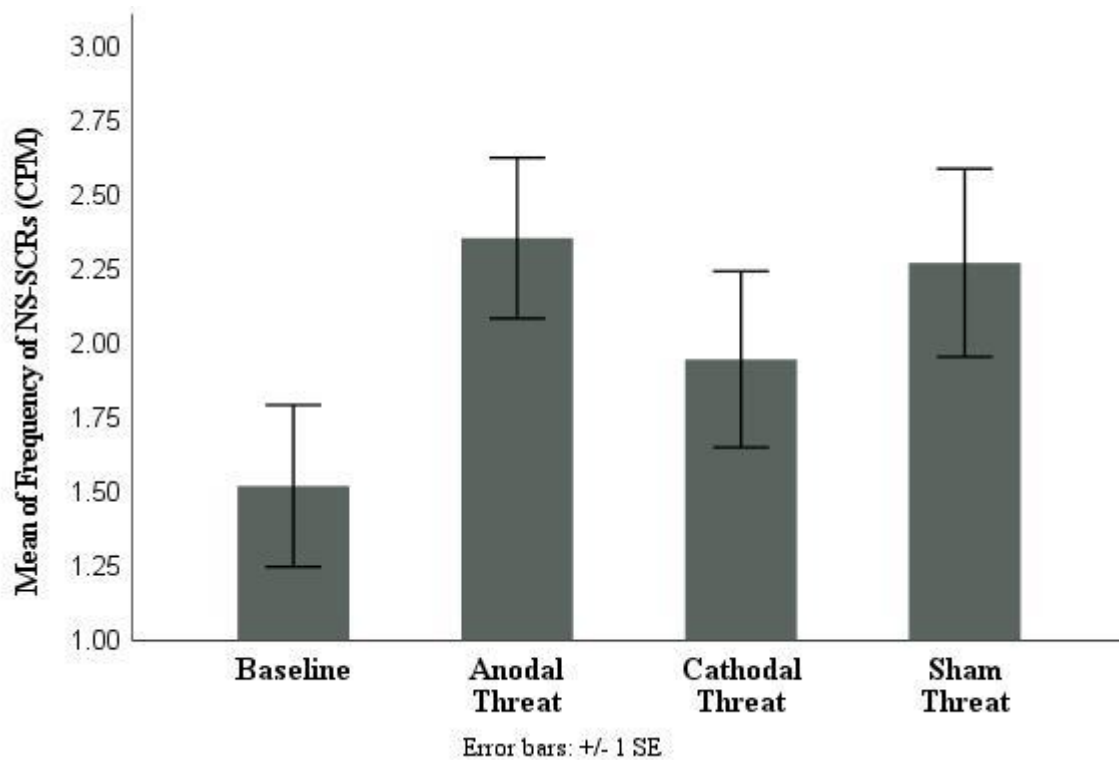
⁴ Note – The p value and BF_{10} here result from a two-tailed test. However, a one-tailed test *may* also be appropriate (Baseline NS-SCRs < Cathodal NS-SCRs) to consider. In this case the resulting $BF_{10} = 3.152$.

BTAB Frequency of NS-SCRs

The frequency of NS-SCRs was counted as the total number of NS-SCRs occurring in each block divided by the duration of the block (count per minute or CPM) (Figure 3.6). A within-subject ANOVA was conducted with 4 levels (Baseline, Anodal Threat, Cathodal Threat, Sham Threat) which produced a significant effect of stimuli type - $F(3,78) = 5.300, p < 0.01, \eta^2\rho = 0.169, BF_{10} = 14.861$. 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, $BF_{10} = 338.401$) and Sham (MD = 0.750, SE = 0.276, $p = 0.012$, B&H = 0.033, $BF_{10} = 4.083$) 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; $F(2, 52) = 1.700, p > 0.05, BF_{10} = 0.389, BF_{01} = 2.567$.

Figure 3.6

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)



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

The CHi_II and Optimised MtDCS Brain Stimulation

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 3.2). 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 (Figure 3. 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.

Table 3.2

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

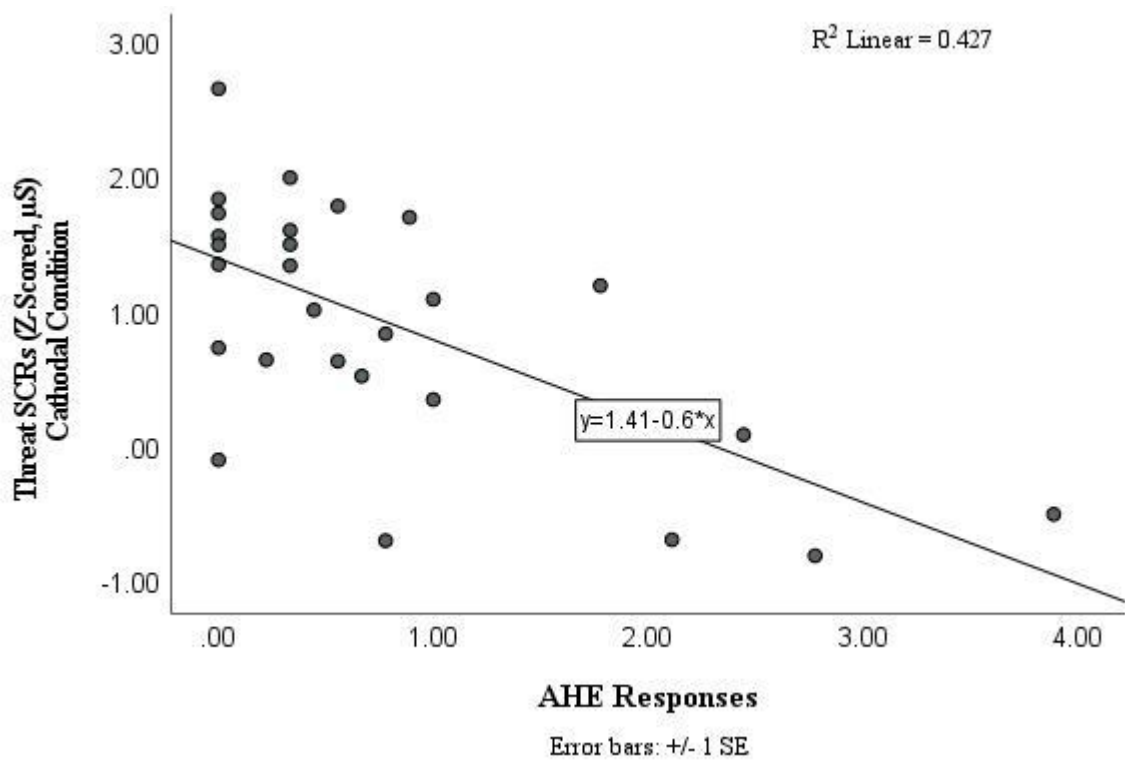
Correlation Pair	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁ **	Bayes Value Interpretation**
AHE vs. Cathodal	- 0.654*	0.000	0.017	155.880		Decisive AH
AHE vs. Anodal	0.225	0.260	0.033	0.437	2.288	Inconclusive Null
AHE vs. Sham	0.035	0.861	0.050	0.242	4.124	Good Null

* 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.

Figure 3.7

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



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, $n = 13$, Mean = 1.48, SD = 1.04) and low predisposition group (low AHE, $n = 13$, Mean = 0.12, SD = 0.16) by a median-split approach to identify the pattern of effects on brain stimulation (Figure 3.8).

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, however, the interaction between group and condition on SCR's was significant, $F(2,48) = 6.209$, $p = 0.004$, $\eta^2\rho = 0.206$, $BF_{10} = 40.310$.

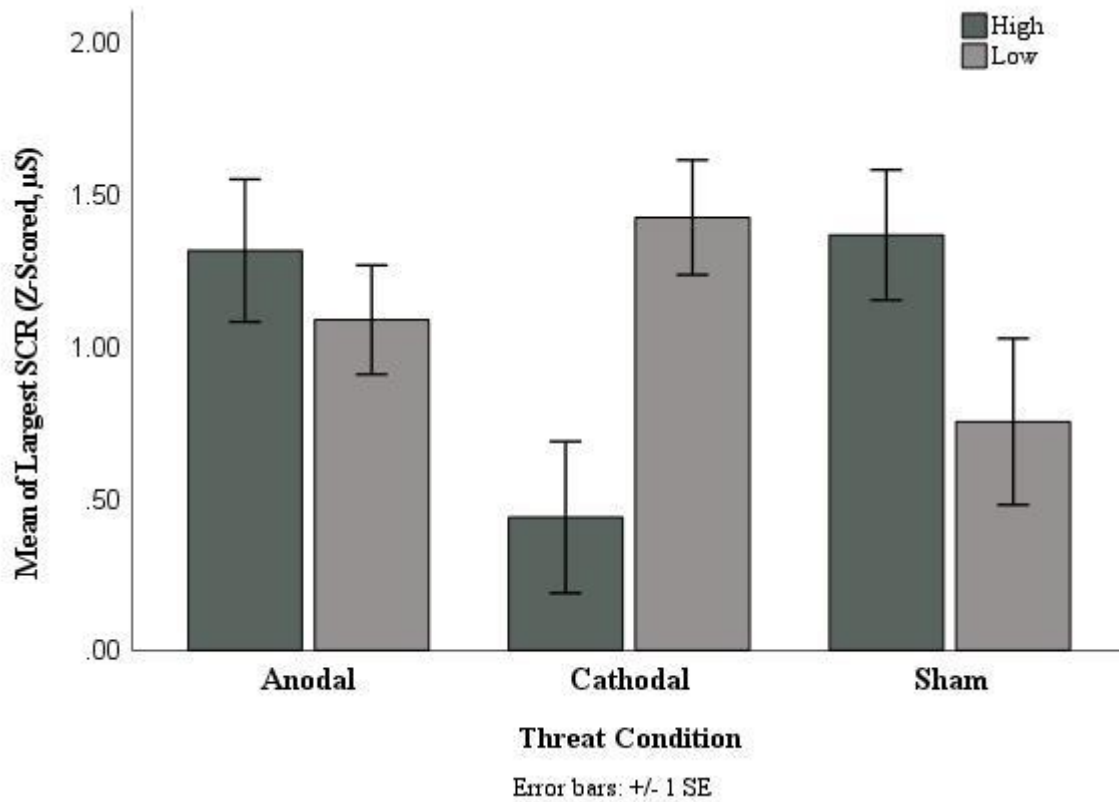
To investigate the interaction effect, within-subject ANOVAs were conducted on the high AHE and low AHE groups separately. The high AHE group revealed a significant effect of condition, $F(2,24) = 4.719$, $p = 0.019$, $\eta^2\rho = 0.282$, $BF_{10} = 7.461$. Pairwise comparisons using FDR corrections in the high AHE group showed that under cathodal stimulation SCRs were significantly weaker relative to the Sham threat block ($MD = 0.929$, $SE = 0.257$, $p = 0.004$, $B\&H = 0.017$, $BF_{10} = 13.592$) and Anodal threat block ($MD = 0.878$, $SE = 0.362$, $p = 0.032$, $B\&H = 0.033$, $BF_{10} = 2.269$). However, the low AHE group did not show any significant effect in the Frequentist analysis [$F(2, 24) = 2.067$, $p > 0.05$, $BF_{10} = 1.048$].

Furthermore, independent sample t-tests comparing the high AHE group and low AHE group showed a significant effect in the Cathodal condition [$t(24) = 3.157$, $p = 0.004$, $d = 1.238$, $BF_{10} = 9.777$] but not in the Anodal condition [$t(24) = -0.772$, $p > 0.05$, $BF_{10} = 0.452$, $BF_{01} = 2.212$] or the Sham condition [$t(24) = -1.766$, $p > 0.05$, $BF_{10} = 1.109$].

Collectively 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 (Figure 3.8).

Figure 3.8

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



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). There 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 suggestions it is inconclusive (Table 3.3).

Table 3.3

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	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁ **	Bayes Value Interpretation**
AHE vs. Cathodal	- 0.404	0.036	0.017	1.910		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.

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 (Figure 3.9). 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 SCR's was found to be borderline significant, $F(2,48) = 3.268, p = 0.047, \eta^2\rho = 0.120, BF_{10} = 3.188$.

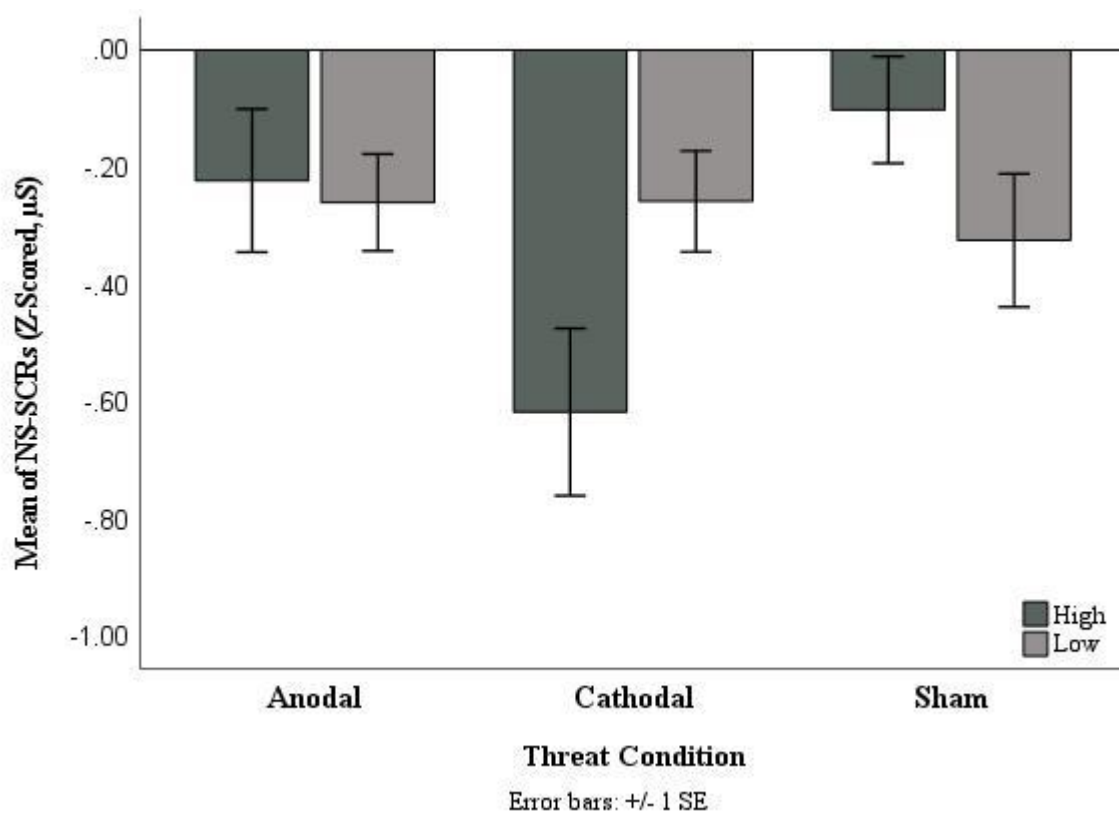
As the interaction was borderline significant, further analysis in terms of within-subject ANOVA on the high AHE and low AHE groups was conducted. In the high AHE group, a significant main effect $F(2,24) = 4.182, p = 0.028, \eta^2\rho = 0.258, BF_{10} = 6.205$ was revealed. Pairwise comparisons using FDR corrections in the high AHE group showed that under Cathodal stimulation NS-SCRs were significantly weaker relative to the Sham threat block ($MD = 0.516, SE = 0.167, p = 0.009, B\&H = 0.017, BF_{10} = 6.163$) but no significant differences were noted between the Anodal condition and Cathodal condition ($MD = 0.395, SE = 0.217, p > 0.05, BF_{10} = 1.005$) 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 were equivalent [$F(2,24) = 0.153, p > 0.05, BF_{10} = 0.208, BF_{01} = 4.815$]

Independent sample t-tests showed a borderline significant effect between the high AHE and low AHE groups only in the Cathodal condition [$t(24) = 2.164, p = 0.041, d = 0.849, BF_{10} = 1.881$] but not in the Anodal condition [$t(24) = -0.250, p > 0.05, BF_{10} = 0.371, BF_{01} = 2.693$] or Sham condition [$t(24) = -1.531, p > 0.05, BF_{10} = 0.847, BF_{01} = 1.181$].

Figure 3.9

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



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 3.4).

Table 3.4

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	BF₁₀ **	BF₀₁ **	Bayes Value Interpretation**
AHE vs. Cathodal	- 0.427	0.026	0.017	2.482		Inconclusive AH
AHE vs. Anodal	- 0.364	0.062	0.033	1.251		Inconclusive AH
AHE vs. Sham	- 0.107	0.597	0.050	0.273	3.666	Good Null

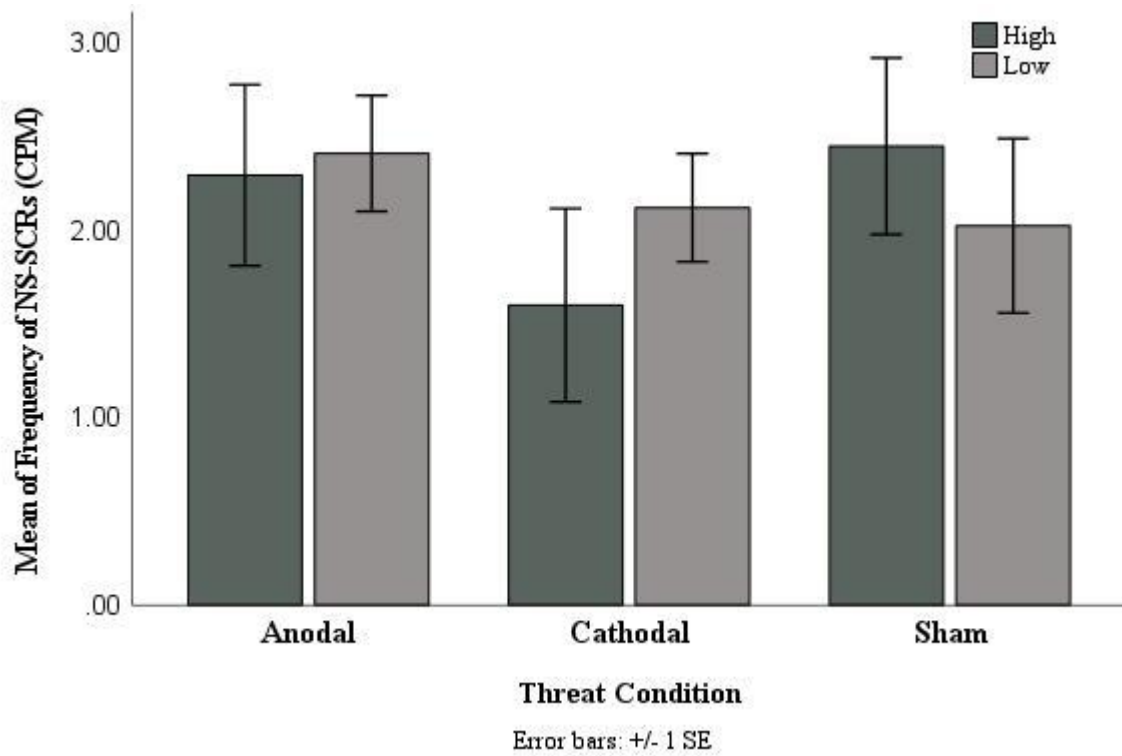
** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

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 (Figure 3.10). 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 did not show any differences in any of the condition: Anodal [$t(24) = 0.202, p > 0.05, BF_{10} = 0.368, BF_{01} = 2.715$], Cathodal [$t(24) = 0.880, p > 0.05, BF_{10} = 0.483, BF_{01} = 2.071$] or Sham [$t(24) = -0.641, p > 0.05, BF_{10} = 0.422, BF_{01} = 2.367$].

Figure 3.10

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



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 3.5).

Table 3.5

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	BF₁₀ **	BF₀₁ **	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.

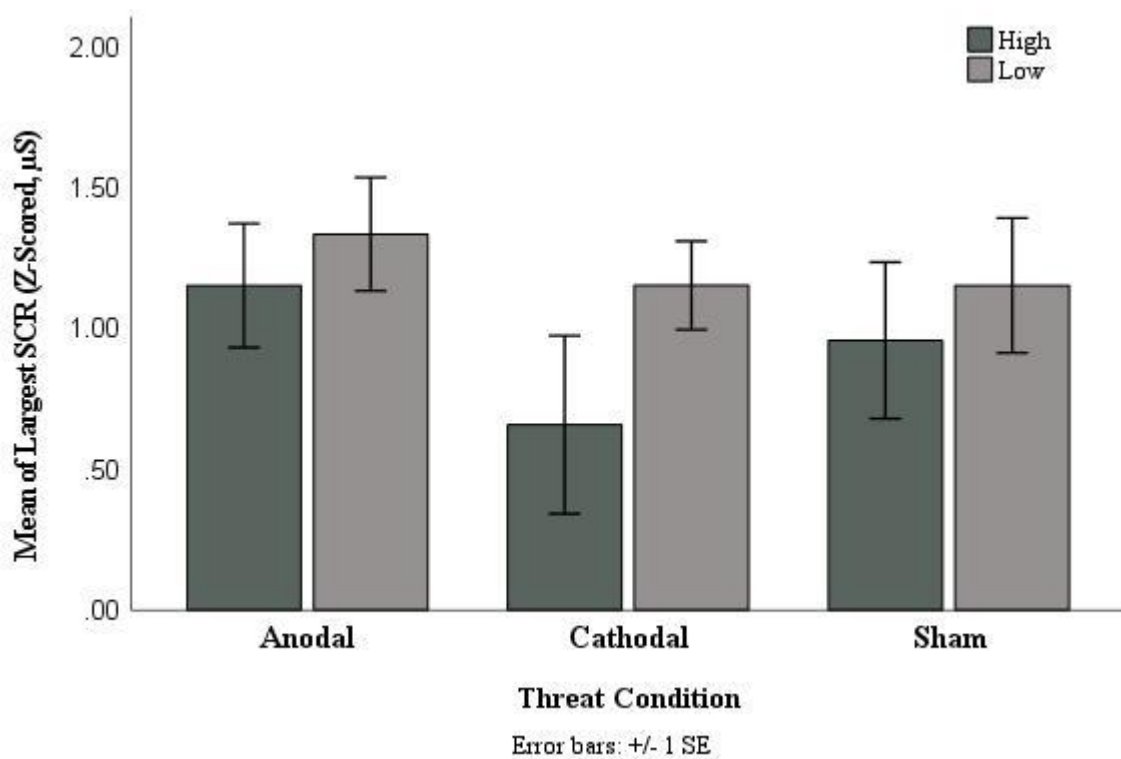
The DLE factor was then split using a median to identify a high DLE group ($n = 13$, mean = 3.32, SD = 0.82) and a low DLE group ($n = 13$, mean = 0.85, SD = 0.56) to observe the pattern of effects on brain stimulation (Figure 3.11).

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, no pairwise comparisons were 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 [$t(24) = -0.532, p > 0.05, BF_{10} = 0.404, BF_{01} = 2.478$].

Figure 3.11

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



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 3.6).

Table 3.6

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	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁ **	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.

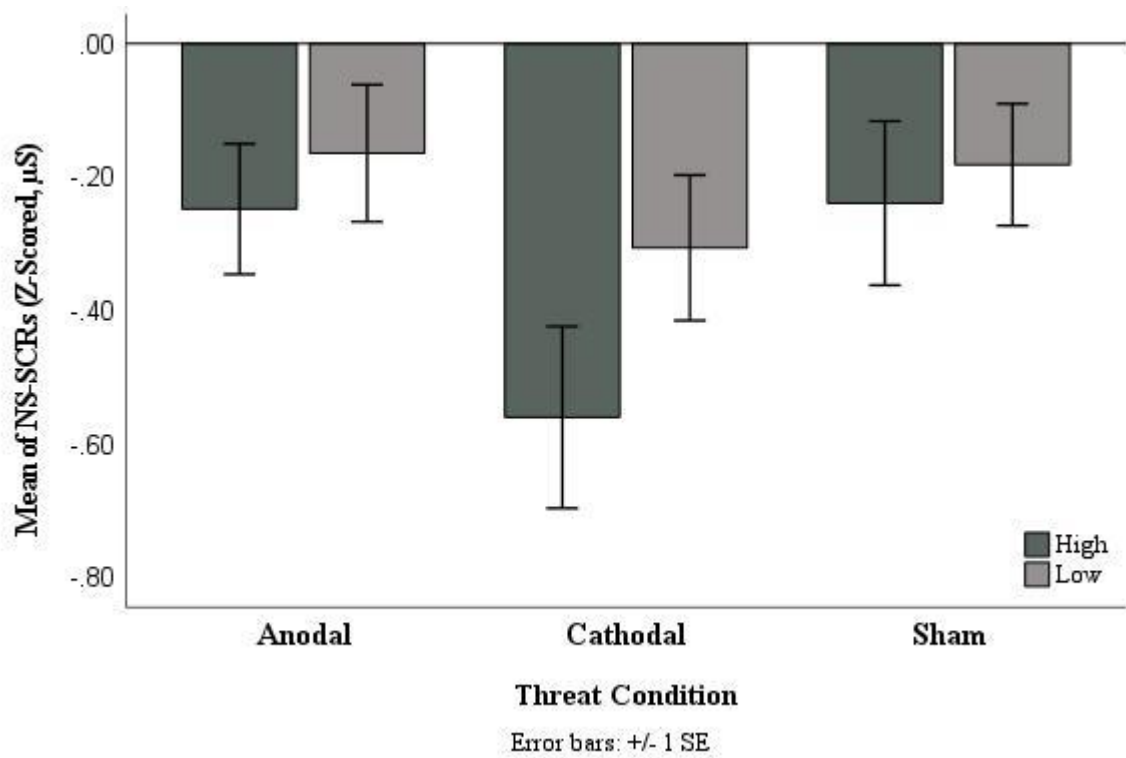
A 2x3 ANOVA with two variables of group (Between-subjects: high DLE vs. low DLE) and condition (Within-subjects: Anodal, Cathodal and Sham) was conducted on NS-SCRs in the threat blocks (Figure 3.12). However, no significant main effect of condition [$F(2,48) = 2.288, p > 0.05, BF_{10} = 1.059$] or group [$F(2,48) = 3.463, p > 0.05, BF_{10} = 0.505, BF_{01} = 1.980$] 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.

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 [$t(24) = -0.377, p > 0.05, BF_{10} = 0.383, BF_{01} = 2.611$].

Figure 3.12

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



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 3.7).

Table 3.7

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	<i>r</i>	<i>p</i>	B&H	BF₁₀ **	BF₀₁ **	Bayes Value
		value	value			Interpretation**
DLE vs. Cathodal	- 0.391	0.044	0.017	1.650		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

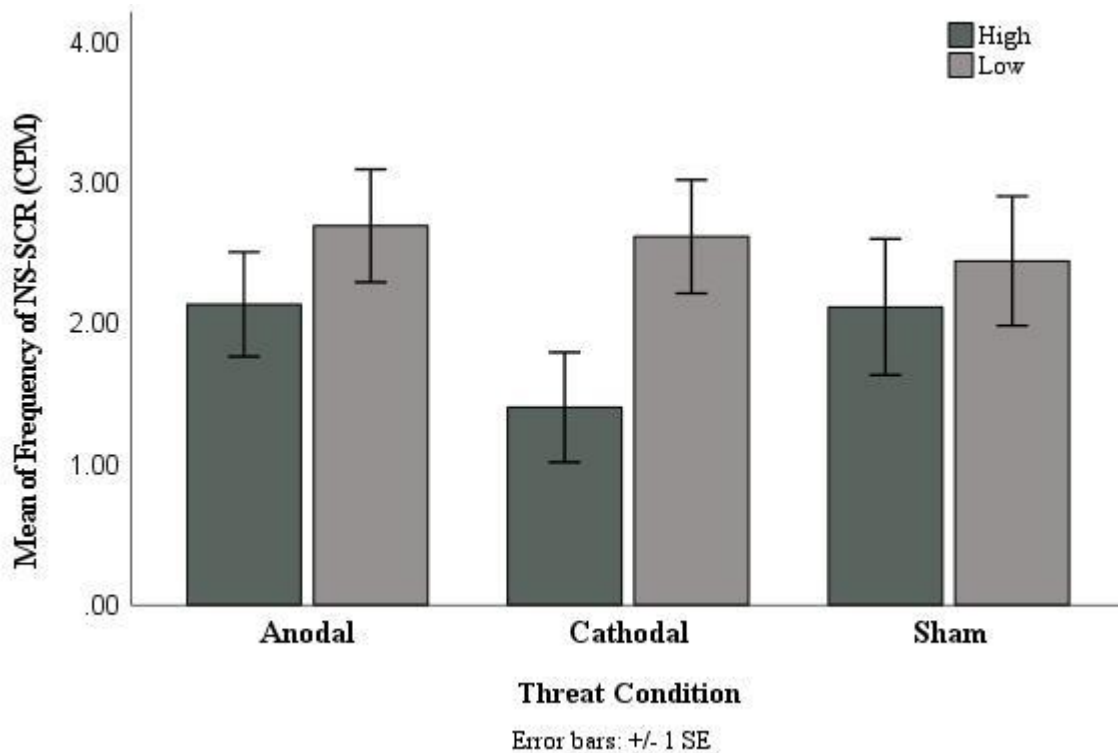
** Bayes values and interpretation according to (Jarosz & Wiley, 2014). AH = Alternative Hypothesis.

A mixed 2x3 ANOVA with two variables of group (Between-subjects: high DLE vs. low DLE) and condition (Within-subjects: Anodal, Cathodal and Sham) (Figure 3.13) 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 [$F(2,48) = 1.921, p > 0.05, BF_{10} = 0.659, BF_{01} = 1.518$].

The independent sample t-tests between the two groups showed a significant effect between the high DLE and low DLE groups only in the Cathodal condition [$t(24) = 2.161, p = 0.041, d = 0.401, BF_{10} = 1.873$] but not in the Anodal condition [$t(24) = 1.022, p > 0.05, BF_{10} = 0.533, BF_{01} = 1.878$] or Sham condition [$t(24) = 0.490, p > 0.05, BF_{10} = 0.397, BF_{01} = 2.521$]. However, the Bayes analysis suggests that the evidence here is relatively weak or inclusive.

Figure 3.13

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



Psychological Ratings

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 $\chi^2 = 12.617$, $p = 0.006$ (Figure 3.14a). 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 ($Z = -2.809$, $p = 0.005$, B&H = 0.017), Cathodal ($Z = -2.961$, $p = 0.003$, B&H = 0.033) and Sham ($Z = -2.881$, $p = 0.004$, B&H = 0.05).

Emotional Valence. A Friedman's test revealed an overall difference between the different blocks (Baseline, Anodal Threat, Cathodal Threat and Sham Threat) $\chi^2 = 42.082$, $p < 0.001$ (Figure 3.14b). 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 ($Z = -4.346$, $p < 0.001$, B&H = 0.017), Cathodal ($Z = -4.283$, $p < 0.001$, B&H = 0.033) and Sham ($Z = -4.410$, $p < 0.001$, B&H = 0.05).

Sense of Pain. This dimension did not reveal any significant effects between the baseline stimuli and the threat stimuli ($\chi^2 = 3.472$, $p = 0.324$) or the threat blocks in the three stimulations conditions (Anodal Cathodal and Sham), all p 's > 0.05 (Figure 3.14c).

Realism of Threat. Similar to the sense of pain dimension, a Friedman's test revealed no significant main effect between the baseline stimuli and threat stimuli in all three stimulation conditions $\chi^2 = 4.833$, $p = 0.184$ (Figure 3.14d). However, 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 ($Z = -2.357$, $p = 0.018^5$, B&H = 0.017), Sham ($Z = -2.178$, $p = 0.029$, B&H = 0.033), and Anodal ($Z = -2.139$, $p = 0.032$, B&H = 0.05).

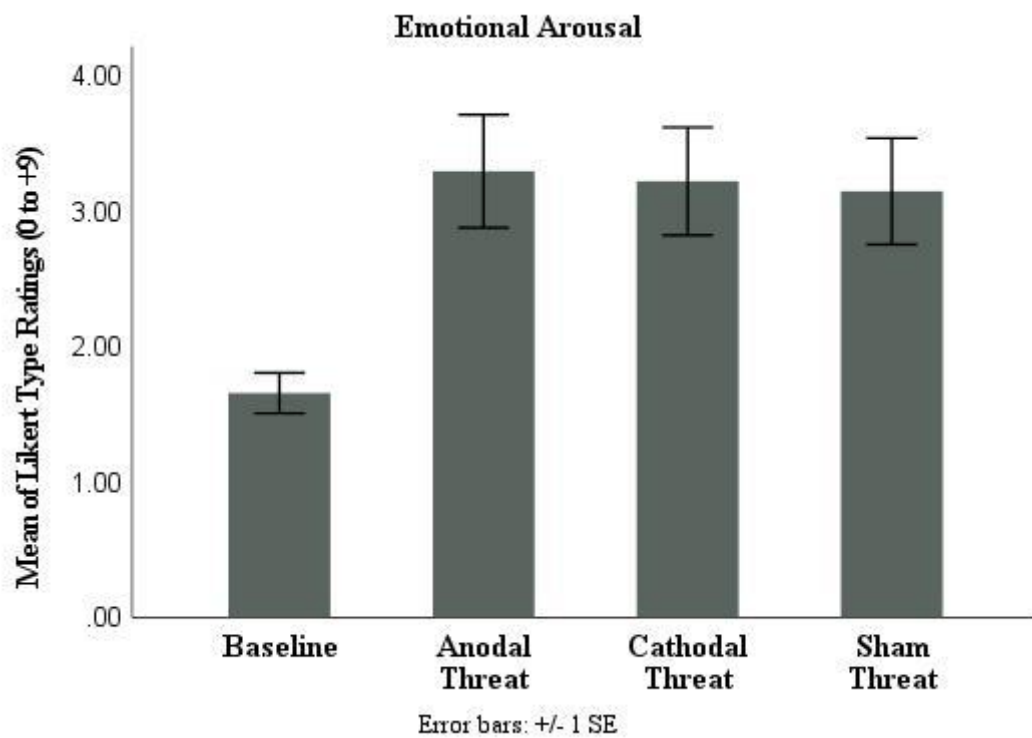
However, when only the threat blocks from all conditions (Anodal, Cathodal and Sham) were compared, no reliable differences were noted (all $p > 0.05$). These data showed consistency

⁵ This interaction is significant under the FDR corrections (see Benjamini & Hochberg, 1995)

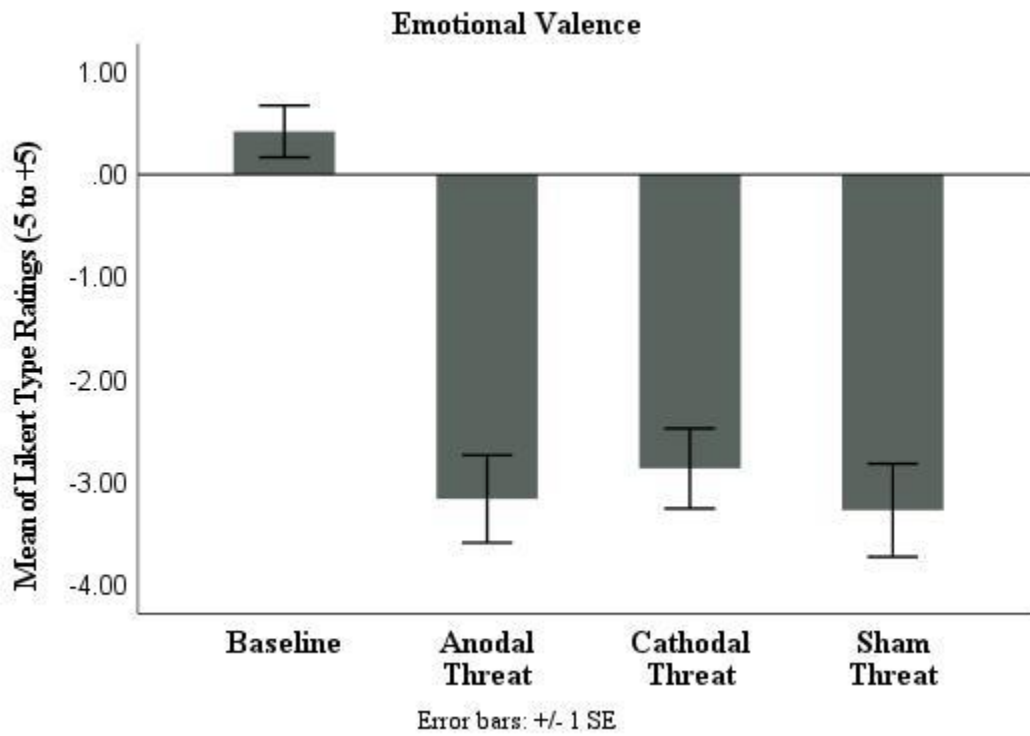
with the psychophysiological findings in that the baseline stimuli were rated as less aversive/arousing/threatening than the threat stimuli.

Figure 3.14

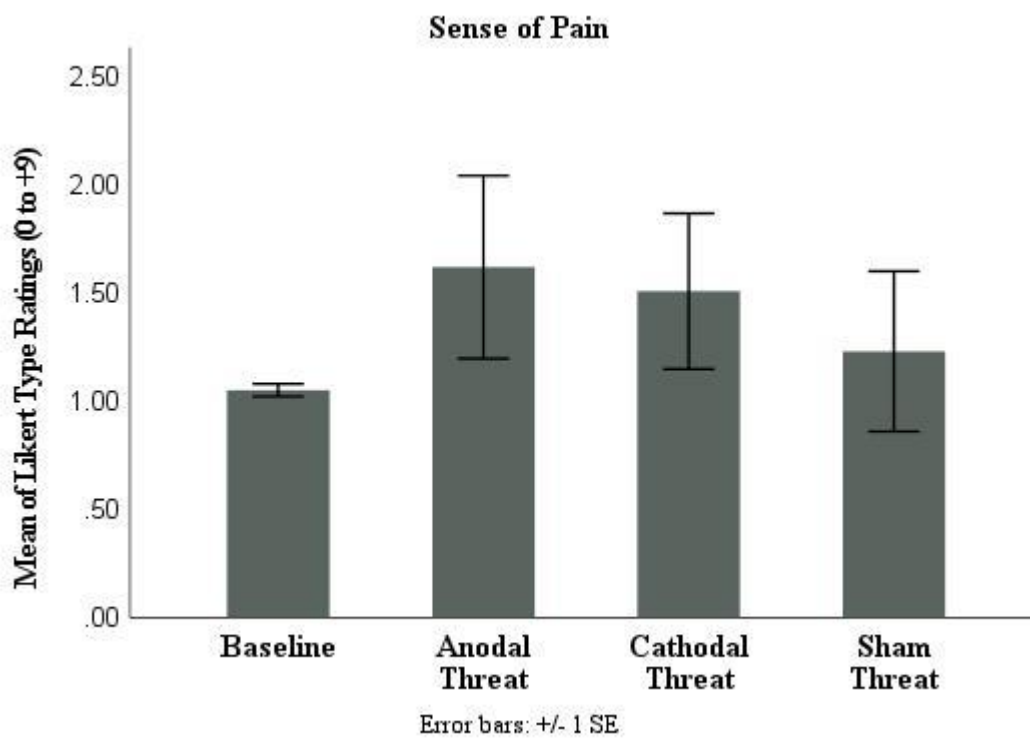
Differences between Baseline and Threat blocks in each stimulation condition (Anodal, Cathodal and Sham) for the four psychological rating dimensions



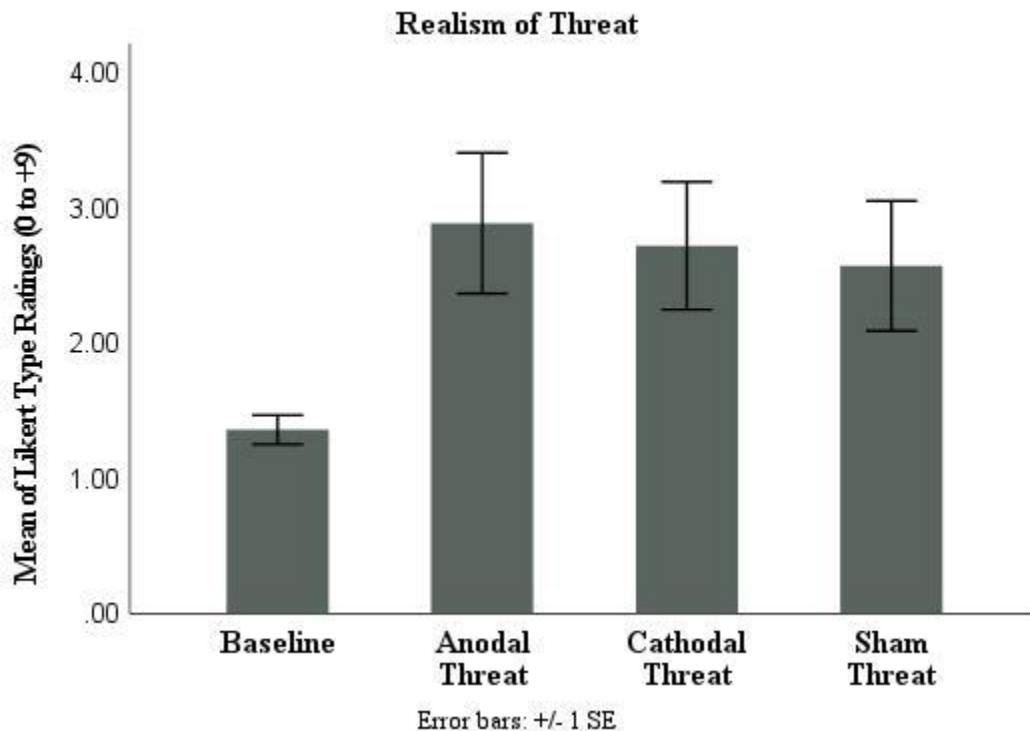
(a)



(b)



(c)



(d)

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

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,

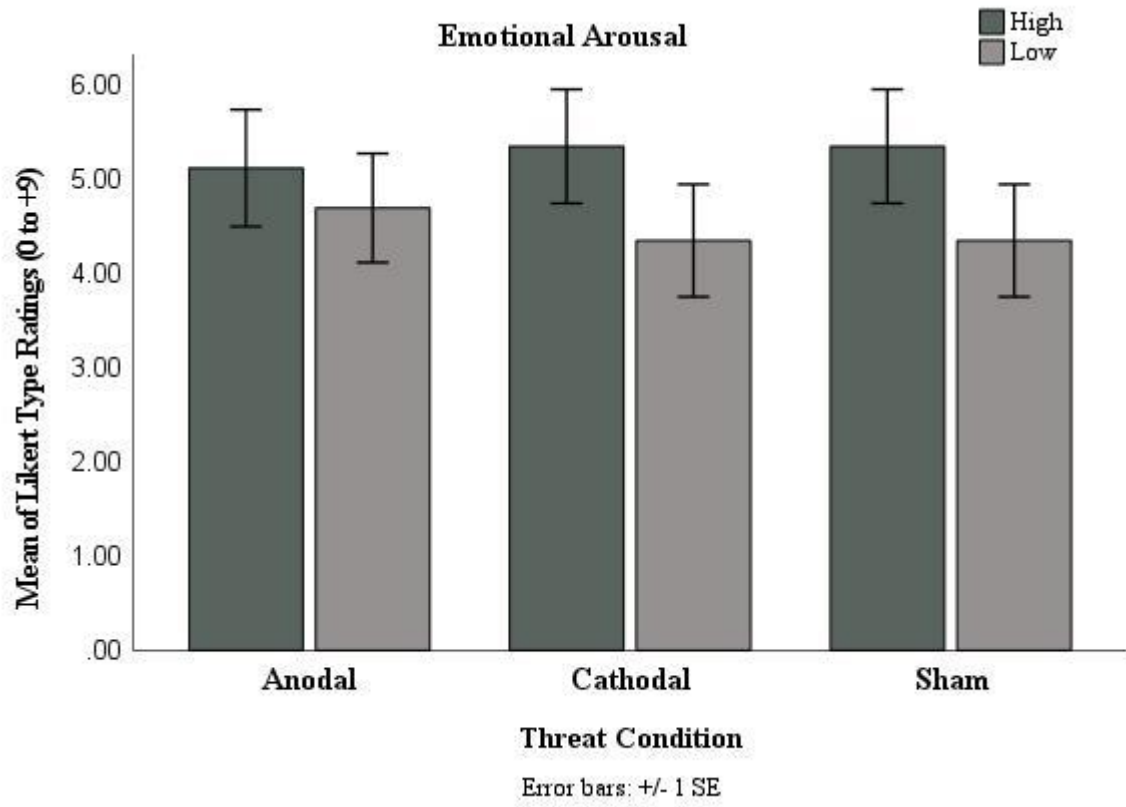
$BF_{10} < 1$) between the two groups in the three stimulation conditions (see Figure 3.15 a, c and d).

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.

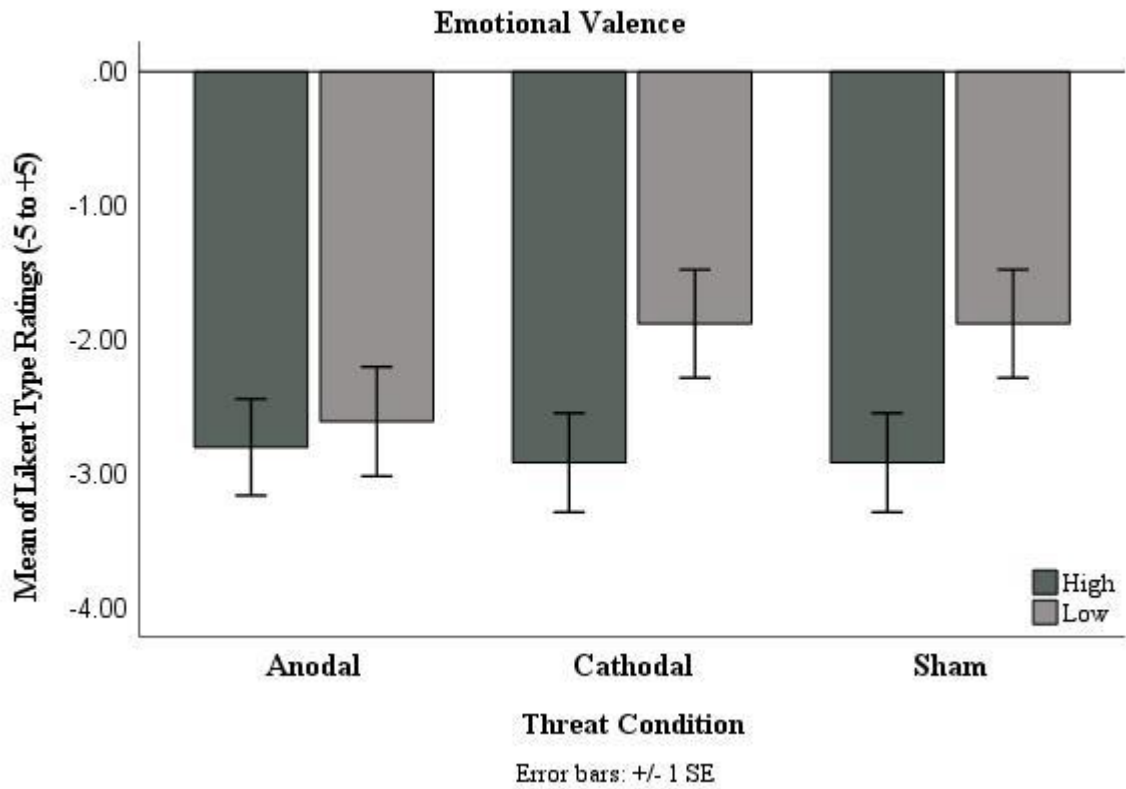
An overall 2 (high AHE group and low AHE group) x 3 (Anodal, Cathodal and Sham) ANOVA was conducted. Although the main effect of group or condition was not found to be significant ($p > 0.05$), the interaction effect between group and condition was found to be significant $F(2,48) = 3.296, p < 0.05, \eta^2 p = 0.121, BF_{10} = 7.988$ (Figure 3.15b). Further exploration using a rm-ANOVA revealed no significance in the high AHE group however, the low AHE group showed a significant difference between the different stimulation conditions $F(2,24) = 8.950, p = 0.001, \eta^2 p = 0.427, BF_{10} = 23.826$. 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, $BF_{10} = 5.268$) and Sham condition (MD = -0.731, SE = 0.244, $p = 0.011$, B&H = 0.033, $BF_{10} = 5.268$). However, one-way ANOVAs between the groups did not reveal any significant results (all p 's $> 0.05, BF_{10} < 1$).

Figure 3.15

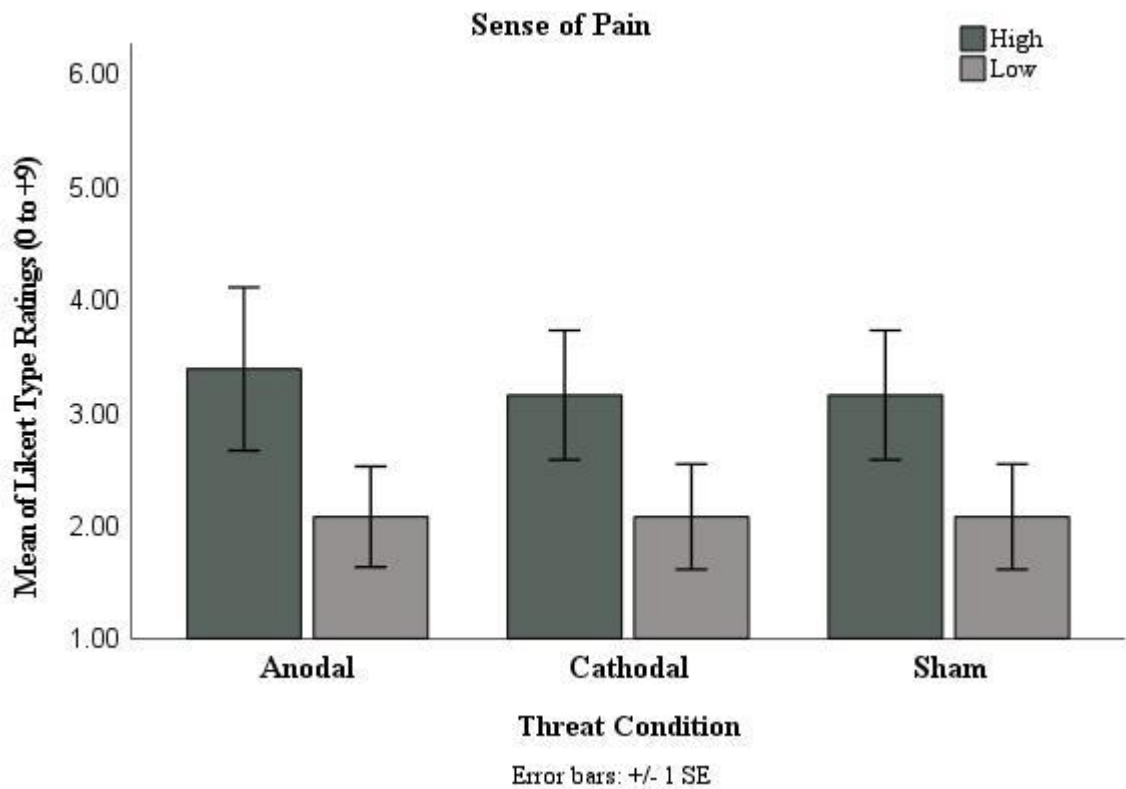
Differences between high AHE vs. low AHE groups for all stimulation conditions (Anodal, Cathodal, Sham) in the four psychological rating dimensions



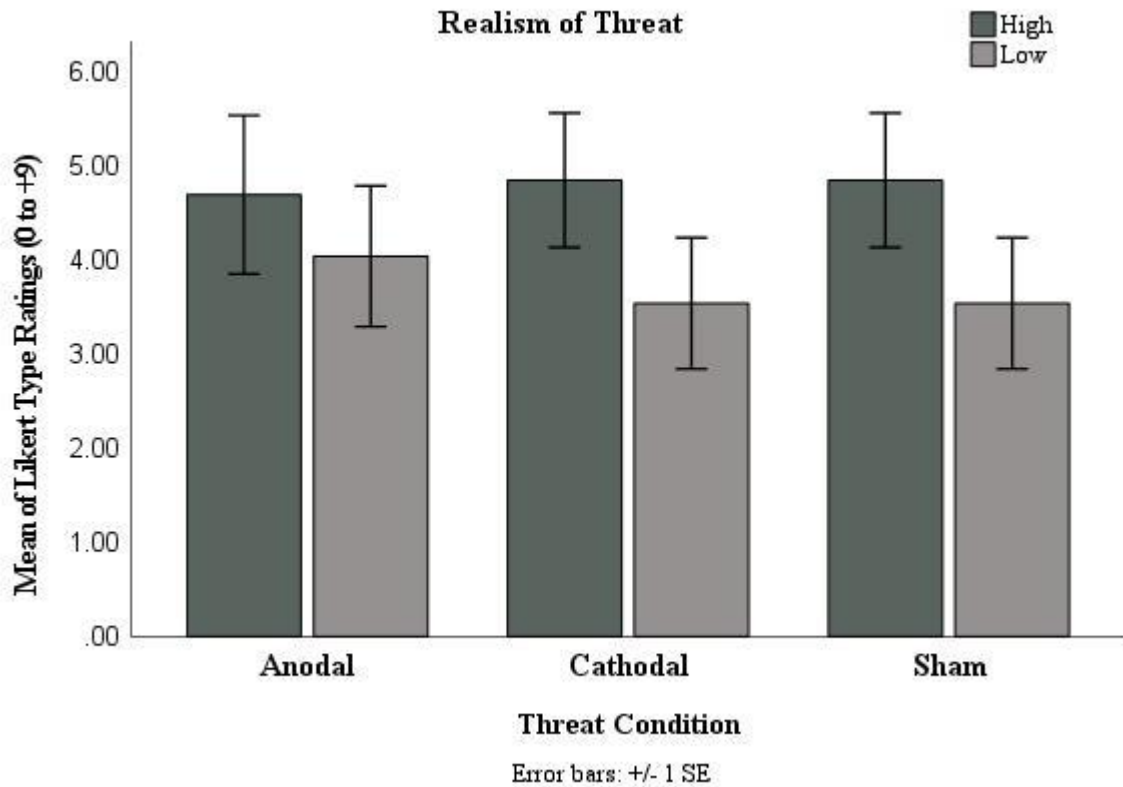
(a)



(b)



(c)



(d)

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

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 , $BF_{10} < 1$) (Figure 3.16 a, b and d).

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 3.8). 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 3.8

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} **	Bayes Value Interpretation**
DLE vs. Anodal	0.366*	0.012	0.017	7.594	Good AH
DLE vs. Sham	0.299	0.043	0.033	2.461	Inconclusive Null
DLE vs. Cathodal	0.277	0.059	0.050	1.771	Inconclusive Null

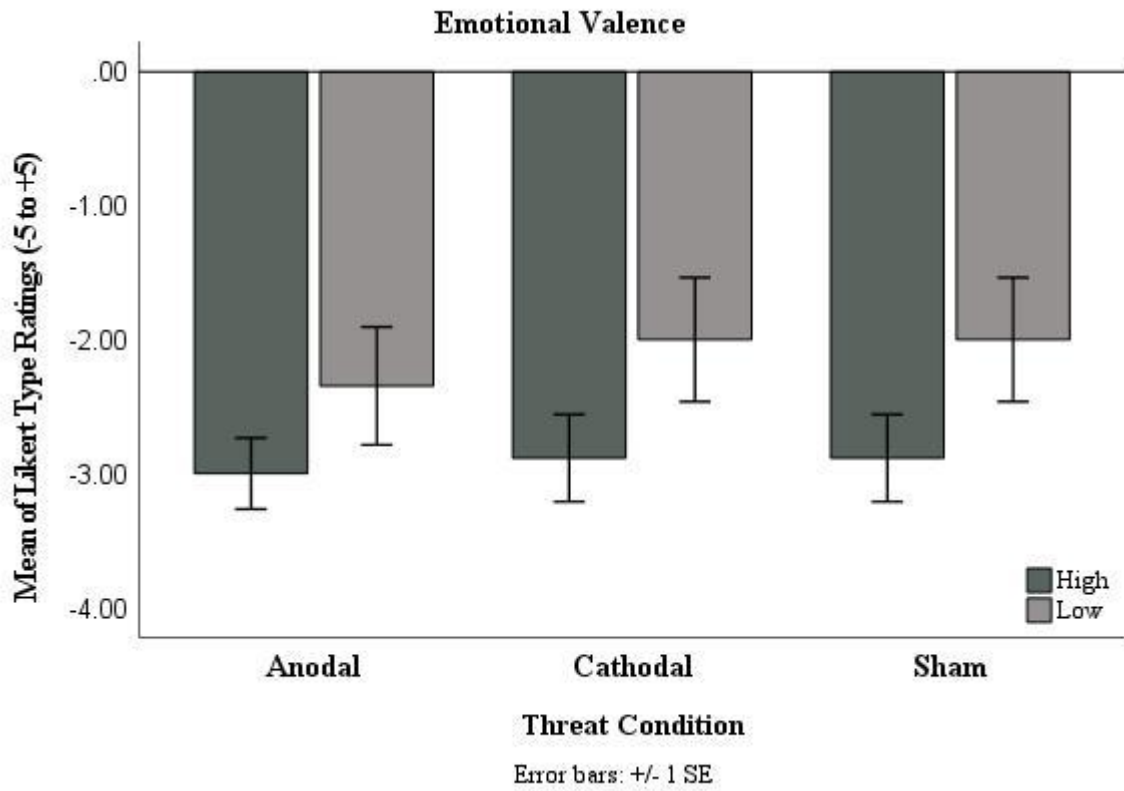
* Significant correlations after using FDR corrections, the correlation pairs are ranked in ascending order.

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

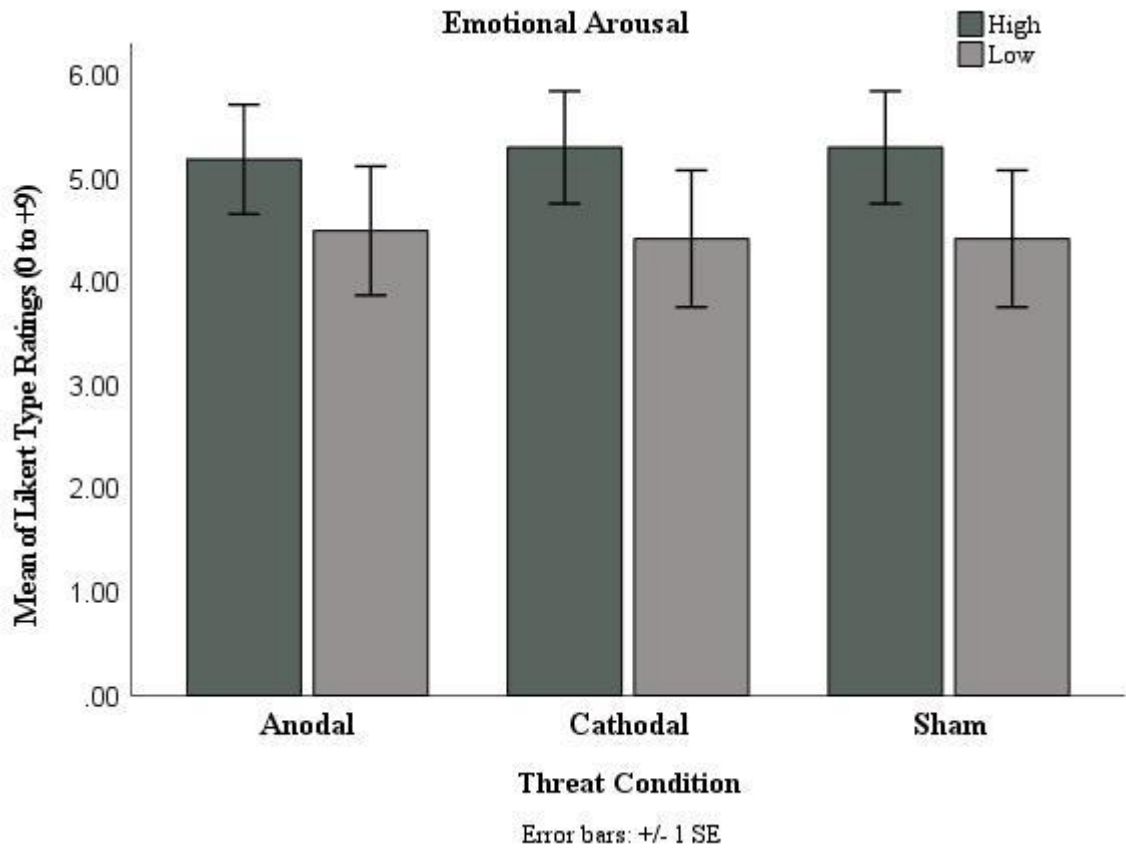
No significant differences were noted between the stimulation conditions (Anodal, Cathodal, Sham) in the high DLE and low DLE groups (Figure 3.16c). However, Mann-Whitney U independent sample t-tests revealed that participants in the high group perceived the stimuli as more painful in every stimulation condition; Anodal ($U = 141$, $p = 0.003$), Cathodal ($U = 123.5$, $p = 0.044$) and Sham ($U = 123.5$, $p = 0.044$).

Figure 3.16

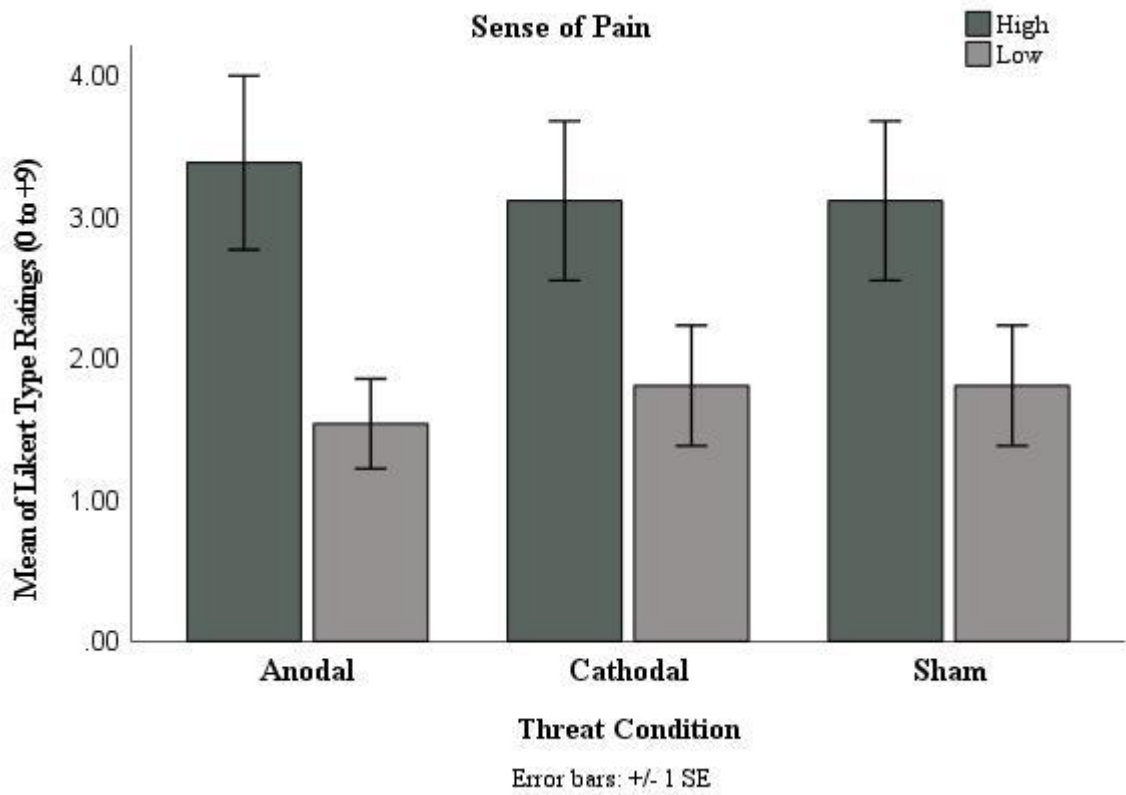
Differences between high DLE vs. low DLE groups for all stimulation conditions (Anodal, Cathodal, Sham) in the four psychological rating dimensions



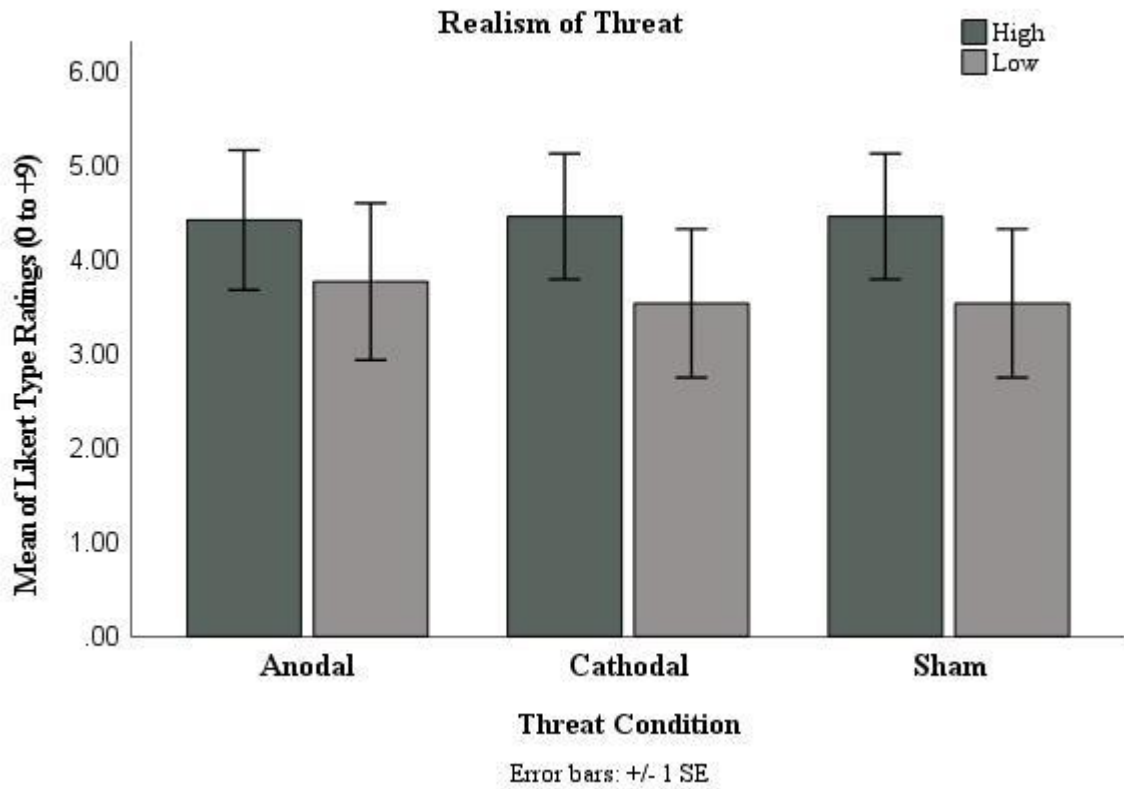
(a)



(b)



(c)



(d)

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

General Discussion

The current study, the first to our knowledge, examined the presence of trait-based predisposition to aberrant experience (reflecting increased cortical hyperexcitability and / or increased degrees of depersonalisation-like experiences) 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 dynamic aversive body-threat scenarios (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 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 (an independent 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 (though this was not conclusive).

When collapsed 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 when examined at the whole sample level. Taken together, 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 the cortical hyperexcitability measure (the CHi_II measure). This implies the overall finding that MtDCS had no effects is not entirely accepted, lending support to the notion that using such screening 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).

Cathodal stimulation of the rVLPFC via an optimised 7-channel MtDCS montage produced significantly suppressed SCR magnitudes (as per the correlation), relative to the sham and anodal condition. As scores on the cortical hyperexcitability measure increased, Threat SCR magnitudes significantly decreased for this 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 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.

Although there was more than a suggestion for anodal stimulation to increase SCR magnitudes relative to the sham condition (as cortical hyperexcitability was reduced) this was not reliable. Anodal stimulation produced no reliable effects on SCR responses (maximum SCRs or NS-SCRs) in terms of the strength or the frequency of responses relative to the sham condition. Furthermore, although there appears to be a difference in the strength of threat SCRs for the sham condition – 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. We suggest 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 (a), 2008 (b); Jay et al., 2014; Xia et al., 2017; Vinberg et al., 2021).

While we observed some novel effects in relation to proxy signs of cortical hyperexcitability, this was not the case when we examined the sample in terms of aberrant body experiences (DLEs). The DLE measure did not reveal any significant findings for either the magnitudes of maximum SCRs or NS-SCRs. However, it is important to note that the frequency of NS-SCRs significantly decreased (albeit with inconclusive Bayes factor) in the cathodal condition as DLEs increased. Although a weak effect relative to those scoring low on the DLE measure, this may indicate that there was a mediatory impact from this stimulatory condition. It has been argued previously that the frequency of NS-SCRs reliably reflects autonomic tonic arousal for negatively tuned cognitive states – and our findings here suggest that cathodal stimulation is having a suppressive effect here in relation to DLE experiences (Nikkula, 1991; Boucsein, 2012).

Although we should be cautious about interpreting the other null effects, the Bayes Factor analysis does allow for some extrapolation here and a tentative explanation can be explored. One reason for the weaker DLE effects might be that the questions on the DLE measure are more multifaceted – covering a host of mid and higher-level multisensory experiences, relative to the very specific and focused items on the CHi_II measure (which centre on aberrant visual experiences only). In addition, the random-sampling approach led to a DLE with a mean score of 3.32 out of a maximum of 13 and so this group might not be sufficiently predisposed to aberrant body experiences in order for larger effects (with less noise) to emerge (Sierra et al., 2005). Finally, it should be acknowledged that these effects

may have failed to have occurred due to the factors above coupled to a lack of power.

Interestingly, the general pattern we observed is consistent with the findings from the CHi_II measure but this was not statistically reliable in the DLE measure.

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, our results indicated that brain stimulation did not have a reliable impact on the overall psychological ratings (though they did follow in the direction of SCRs). This was also observed even when the sample was split on the basis of the screening measures (AHE and DLE). The general pattern however showed that the high groups (on the AHE and DLE measures) rated the threat videos as more negatively valenced, emotionally arousing, generating a higher sense of illusory pain, and observed them as more threatening but the three stimulation conditions did not reliably affect these ratings. 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 conscious awareness (Silvert et al., 2004; Christopoulous et al., 2019).

These findings replicate those reported previously for the BTAB measure and establish that the threat imagery was indeed inducing increased autonomic arousal and psychological ratings for the current sample (Braithwaite et al., 2020, Joshi et al., (Chapter 2)). Therefore, we can be confident that the measure was successful in eliciting greater body-based threat / fear responses in participants relative to non-threat stimuli.

Theoretical Implications

Our current study investigated the role of the rVLPFC as a direct 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 (a), 2003 (b), 2009 (c); Critchley et al., 2004; Critchley, 2005; Oschner & Gross, 2004 (a), 2005 (b); Lemche et al., 2007; Eippert et al., 2007; Klumpers et al., 2010; Gu et al., 2013; Seth, 2013; Clark, 2013). Other conditions and disorders are also associated with degrees of aberrant body-states – with many now being discussed within the broader concept of the role for rVLPFC in mediating conscious feeling states of the bodily self (e.g., Autoscopy, Heautoscopy, schizophrenic loss of body boundaries) (Blanke et al., 2000; Kaladjian et al., 2007; Leitman et al., 2011; Zhang et al., 2019). In line with this known neuronal anatomy and function, the assumption would have been that anodal and cathodal brain stimulation would have a direct impact on autonomic activity to salient aversive stimuli.

A prominent theory for many of the aberrant 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(a), 2016(b); Critchley, 2005; Craig, 2009; Seth, 2013; Clark, 2013). By this account, the inhibition emanating from rVLPFC has become aberrant and persistent towards the AIC. Jay et al. (2014) provided evidence that by suppressing the rVLPFC (using rTMS), autonomic SCR activity was significantly increased in clinically depersonalised patients, however, healthy participants did not show any differences in autonomic activity under the same stimulation condition. This also resulted in reduction of CDS state-based scores in depersonalised patients pre- and post-TMS sessions. In essence, the experimental protocol was being used to inhibit a brain network that was itself 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 DLEs (trait-based) in the current neurotypical sample go, we found low levels of these experiences overall and no differences in SCRs as a function of scores on the DLE measure. Therefore, it is unfortunate, but the present random sample is unable to speak to depersonalisation or these prior findings specifically.

It should be acknowledged that the present study differs from that of Jay and colleagues (2014) in several important ways. First, we utilised a neurotypical sample that was screened for DLEs and not patients with clinical levels of these experiences. Second, the sample was also screened for proxy signs of cortical hyperexcitability to examine the efficacy of brain stimulation as a function of differences in background trait-based indicators. Third, we utilised a form of transcranial electrical stimulation (optimised MtDCS) and not low frequency repetitive magnetic stimulation (rTMS). Crucially here, cathodal MtDCS applied to the rVLPFC did not ‘release’ the AIC and produce increased autonomic responding (SCRs). When screened for cortical hyperexcitability, signs of elevated scores on this measure were reliably associated with increased suppression of SCRs from the application of Cathodal brain stimulation (relative to anodal stimulation and sham conditions). Although the actual mechanism of interaction between MtDCS and the underlying neural processes awaits clarification some tentative suggestions can be examined.

In terms of screening groups on a proxy measure of cortical hyperexcitability, the present findings show an opposite pattern – where far from ‘releasing’ the AIC from aberrant endogenous suppression, we induced more suppression of autonomic responses, and this suppression increased in sympathy with increased proxy indicators of cortical hyperexcitability. One reason for this might be that MtDCS primarily manipulates only the more active neurons – and thus effects are manifest here for the high scoring group on proxy measures of hyperexcitability (Liebetanz et al., 2002, Nitsche et al., 2005).

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. Although we acknowledge the many differences between our work here and that of Jay and colleagues (2014) this finding is striking in that it occurred in the opposite direction – in that our attempts here to inhibit the rVLPFC significantly decreased autonomic responses.

These observations are all the more interesting when it is noted that the CHi_II measure is one focused on visual anomalies (and therefore the visual and extra striate cortices) alone (Braithwaite et al., 2015; Fong, 2019; Fong et al., 2019 (a), 2020 (b); Marchant, 2021). And yet, this measure was able to reliably differentiate performance in the cathodal condition here directed at the rVLPFC (a region considerably anterior to, but also receives projections from, visual cortex (Crick & Koch, 1995; Miller, 1999; Barcelo et al., 2000; Benchenane et al., 2011). This may imply that cortical hyperexcitability (as indexed by the CHi_II) thought to be present in one region need not be constrained by it and may reflect a more domain general component.

Our findings provide clear evidence that trait-based indicators of baseline levels of neural activity can be used to reveal important differences in the efficacy of MtDCS to influence brain processes. This is in line 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). These findings also considerably extend the utility of the CHi_II measure itself in relation to examining the efficacy of MtDCS brain-stimulation.

Based on our findings, we have highlighted that trait-based baselines are important to consider when examining brain stimulation methods. Specifically, pre-screening individuals on the basis of trait-based predisposition to cortical hyperexcitability or even the inclusion of a state-based task would provide more thorough insights into the functional interaction between brain-stimulation montages and the background latent ability of neural systems – that may otherwise be missed by general averaging approaches.

From this an additional, albeit highly speculative suggestion, could be that our study and that of Jay et al. (2014) might imply an important redescription in the functional relationships of these networks between neurotypical groups and those who have transitioned to disorder. Our findings have shown that a modifiable and malleable threshold of action in the rVLPFC results in variable autonomic responses to salient aversive stimuli. Consequently, the present findings suggest that the inhibitory function of the rVLPFC may well differ for the neurotypical population predisposed to aberrant experiences due to latent cortical hyperexcitability, relative to those diagnosed with clinical levels of depersonalisation. Such tantalizing possibilities require further investigation.

Limitations & Further study

The present work could be extended in several ways. While the use of trait-based measures is indeed 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). They 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 experience in neurotypicals could also be improved by having a larger range of scores on the DLE measures used here. Our failure to find effects in this regard may reflect the observation that our sample was not overly predisposed to DLEs. Precision in MtDCS could also be increased with montages containing more channels and based on person-specific (rather than generic) MRI head models. Nonetheless, we did observe reliable and noteworthy effects with the 7-channel solution, supporting the idea that the current approach was more than appropriate and targeted the desired brain regions.

Conclusion

The current study provides evidence that the rVLPFC (projecting to the AIC) shows differential involvement in mediating cognitive-affective responses to aversive body-threat stimuli in those neurotypical individuals predisposed to aberrant experiences. We have also shown that baseline brain states are important and trait-based stratification of the sample shows differences to the neuromodulatory paradigm that would be otherwise missed. In the present study, 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 group only. This raises difficult and exciting prospects for the field, 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. Taken together, the current study provides additional evidence to the underlying neural mechanisms mediating stable self-consciousness and that cortical hyperexcitability may be a critical variable involved in these mechanisms.

Chapter 4

The Relationship between Cortical Hyperexcitability and loss of Primary Motor Cortex Excitability in those Predisposed to Anomalous Experiences following Upper Limb Immobilisation: An Exploration

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Abstract

Multi-sensory integration is a core aspect of stable self-awareness however it known that this has a propensity to breakdown leading to aberrant experiences (such as hallucinations, distortions, aberrant body experiences). Limb immobilisation has been associated with decrease in corticomotor efficiency and atypical multi-sensory integration. The present study explored the role of predisposition to aberrant experiences and depersonalisation-like experiences in maintaining corticomotor efficiency by rTMS stimulation. Twelve healthy participants were recruited to participate in a limb immobilisation within-subject paradigm. All participants completed two trait-based measures (relating to aberrant experiences and depersonalisation experiences and a state-based measure (where skin conductance responses were measured to a fake blood-giving procedure) indexing interoceptive vulnerability. Cortical excitability was measured by motor evoked potential (MEP) responses to single-pulse TMS in a stepwise procedure for each day of immobilisation. Participants were then randomised into a treatment group ($n = 6$) who received six 1.5 seconds 50 Hz repetitive inter-pulse trains at 60s intervals and a sham group ($n = 6$) per day of immobilisation. The results indicated that although the stimulation paradigm was successful in increasing cortical excitability initially, these effects were not maintained throughout the immobilisation period and MEPs evidenced a continual decrease in amplitude over time. Stratification of the participants based on trait-based and state-based measures did not produce any reliable findings. Taken together, this indicated that the stimulation paradigm in isolation was insufficient in maintaining cortical excitability and that baseline brain states are an important consideration for future alternative therapeutic paradigms. Theoretical and methodological improvements are discussed.

Introduction

A central aspect of stable self-awareness has been associated with body ownership or embodiment (Gallagher, 2000; Aspell et al., 2009; Blanke & Metzinger, 2009). A wealth of studies within this domain have evidenced multi-sensory integration as a core mechanism by which one experiences stable sense of self (Blanke & Metzinger, 2009; Blanke, 2012; Braithwaite & David, 2016). Generally, multi-sensory integration relates to an ongoing and continuous interaction between interoceptive awareness (internal information) and exteroceptive awareness (external information) (Craig, 2003; Lenggenhager et al., 2007; Tsakiris et al., 2011; Tajadura-Jiménez & Tsakiris, 2014, Park & Blanke, 2019, Salvato et al., 2019; Fogel, 2020).

A growing body of research now shows that neurocognitive processes that underpin a stable sense of self can breakdown leading to profound distortions that are spontaneous in nature and highly variable in timing and are termed as aberrant experiences (Brugger, 2002; Critchley et al., 2004; Blanke & Arzy, 2005; Braithwaite et al., 2014; Braithwaite et al., 2016). Aberrant experiences are a common symptomology of many disorders of consciousness such as schizophrenia, depersonalisation, epilepsy etc. (Braun et al., 2003; Feinberg & Keenan, 2005; Allen et al., 2008; Sierra, 2009). However, much evidence has shown that these aberrant experiences are not limited to the clinical population but are prevalent in neurotypical samples as well and that they can occur naturally or be induced (Johns & Van Os, 2001; Verdoux & Van Os, 2002; Van Os & Renninghaus, 2016; Baumeister et al., 2017).

A common example of a break down in multi-sensory integration based on exteroceptive awareness has been shown to occur with the “rubber-hand illusion” (RHI) (Botvinick & Cohen, 1998; Tsakiris & Haggard, 2005). In this illusion, a fake hand is placed

next to the participants own hand in the exact same position and both are stroked synchronously. In the absence of visual feedback from the participants own hand, a conflict between vision and sensation results in a proprioceptive drift and participants accept the fake hand to be part of their body. Further to this, research has shown that the proprioception requires some prior knowledge of body representations as spatial mismatch of the fake hand versus own hand reduces the uptake of the fake hand as being part of the body (Tsakiris & Haggard, 2005; Constantini & Haggard, 2007). Interoceptive awareness has been categorised as a sense of internal physiological conditions informing self-awareness such as autonomic activity, cognitive affective states, homeostasis etc. (Craig, 2003; Critchley et al., 2004; Fogel, 2020). Although it is understood that these two mechanisms draw on different neural processes, a developing field of studies have shown that both types of awareness play a significant role in stable self-consciousness. For example, Tsakiris and colleagues (2011) found that individuals with lower internal sensitivities (IS) show lesser proprioceptive drift in the RHI task. Further examples have linked the activation of interoceptive neural regions (parietal, insula and premotor areas) when the rubber hand is under threat (once accepted as the own body part) (Armel & Ramachandran, 2003; Ehrsson et al., 2005; Llyod et al., 2006; Tsakiris et al., 2007; Moseley et al., 2008). Whilst lab-based short-term interventions such as the RHI allow a high amount of experimental control over the component processes of multi-sensory integration, interoceptive and exteroceptive awareness, the present study utilises observation and study of a real-life situation (upper arm immobilisation) that is extended over the scale of days, thus providing a unique opportunity for testing longer-term changes in these processes.

It is well established that limb injury and consequent immobilisation leads to corticomotor depression reflected in the motor areas (Leipert et al., 1995; Facchini et al., 2002; Avanzino et al., 2011; Rosenkranz et al., 2014). Indeed, M1 activity has also been

linked to proprioception (Ehrsson et al., 2005; Makin et al., 2008; Della Gatta et al., 2016; Fossataro et al., 2018). For example, Della Gatta et al., 2016 showed that decreased motor excitability in the M1 arm area was observed as participants accepted the fake hand in the RHI experiment using brain stimulation techniques (TMS). Typically, this corticomotor depression is alleviated by targeted active physical reuse and rehabilitation of the inactive limb (Clark et al., 2009; Furlan et al., 2016). However, in many situations, such as with stroke patients, rehabilitation is often far more difficult to achieve due to other compounding factors (Furlan et al., 2016). Therefore, alternative rehabilitation strategies to lessen muscle decline are being currently explored.

Transcranial Magnetic Stimulation

Muscle loss after limb immobilisation has been argued to be associated with a reduction in the top-down processes that maintain that muscle (i.e., those underpinning voluntary action) (Hummel et al., 2005; Fitzgerald et al., 2006; Hummel & Cohen, 2006). As a result, it has been proposed that excitation of the corticomotor pathway governing the immobilised limb should maintain these top-down processes, reducing muscle loss. Transcranial magnetic stimulation (TMS) is a non-invasive form of brain stimulation by which short magnetic pulses can be delivered through a coil to excite or suppress (the motor cortex) active neurons on the superficial areas of the brain (Hallett, 2000; Maeda et al., 2000; Wasserman & Grafman, 2005; Hummel & Cohen, 2006; Rossini & Rossi, 2007). In the case of single pulse TMS, this produces a temporary effect on the targeted area. Repetitive pulse TMS (rTMS) is a technique by which a train of pulses with short inter-pulse intervals can induce longer-lasting effects of either suppression or excitation depending on the intensity of the stimulation applied (Wasserman & Lisanby, 2001; Fitzgerald et al, 2006; Rossini & Rossi, 2007;

Hoogendam et al., 2010). Various studies have identified that rTMS applied at 20 Hz maximally increases motor evoked potential (MEP) responses to the hand area and this has been shown in the clinical (patients with stroke) as well as the non-clinical population (Maeda et al., 2000; Gangitano et al., 2002; Kim et al., 2014). Critically, whilst TMS provides a powerful tool for investigating the role of muscle loss / maintenance, it is important to note that stable and transient inter-individual variance in brain states could modulate stimulation efficacy (Hsu et al., 2016; Romei et al., 2016; Silvanto et al., 2018). Despite this evidence, few stimulation studies have assessed individual variance in stimulation (Joshi et al., (Chapter 3)). The causal efficacy of any TMS stimulation paradigm therefore would benefit from quantification of state and trait based by-participant variance.

Trait-Based and State-Based Quantification

Recently, a number of brain stimulation studies have stressed the importance of baseline brain states as a key indicator that affects the efficiency of stimulation applied (Hsu et al., 2016; Romei et al., 2016; Silvanto et al., 2018). Individual baseline stratification may reveal differences that could not be observed at the whole sample level (Boroojerdi et al., 2000; D'Souza et al., 2016; Romei et al., 2016; de Graaf et al., 2017; Silvanto et al., 2018; Yang & Sun, 2018). In the present study, we sought to explore whether a battery of state based and trait-based measures (relating to cortical hyperexcitability and aberrant body experiences) would explain the variance in efficacy of applied brain stimulation.

Cortical Hyperexcitability and Anomalous Experiences

Studies concerning interoceptive awareness show that homeostasis is an important contributing factor to stable self-consciousness (Craig, 2003; Critchley et al., 2004; Tsakiris & De Preester, 2018; Fogel 2020). Generally, this means that homeostasis maintains a

balance between excitation and inhibition within the brain and this ensures appropriate cognitive functioning. When neural excitation is elevated above and beyond what is expected, this is termed as cortical hyperexcitability (Haigh et al., 2012).

Recently, Fong et al., 2019 developed an improved trait-based measure to quantify cortical hyperexcitability in the non-clinical population. Those scoring high on this measure mainly on the anomalous subfactors have shown a propensity for cortical hyperexcitability and this has been validated in behavioural (Fong et al., 2019) and neurophysiological – VEP (Fong et al., 2020(a), 2021(b)) studies.

In the literature, cortical hyperexcitability has been associated with lower thresholds for neural activation (Aurora et al., 2003; Young et al., 2004; Braithwaite et al., 2015). Cortical hyperexcitability is a symptomology of various conditions such as Epilepsy, Migraines with aura, Charles Bonnet Syndrome etc. which are more specific to the visual brain areas (Mulleners et al., 2001; Ffytche, 2005; Badawy et al., 2007; Aurora & Wilkinson, 2007; Haigh et al., 2012; Bauer et al., 2013) Research has also shown cortical hyperexcitability can be induced in the neurotypical population prone to anomalous experiences using visual stimuli (Braithwaite et al., 2013 (a), 2013 (b), 2015(c), 2016(d); Fong et al., 2019 (a), 2020 (b)). In addition, cortical hyperexcitability has now been linked to other brain regions associated with various conditions and disorders such as amyotrophic lateral sclerosis (ALS) – motor cortex (Vucic et al., 2009), Alzheimer’s disease – motor cortex (Pennisi et al., 2011), spinal cord injury – somatosensory cortex (Yague et al., 2011), Huntington’s disease – striatum and cerebral cortex (Cepeda et al., 2019) etc. Given this evidence, the current notion is that a hyperexcitable cortex is not limited to the visual brain areas but could be a more domain general occurrence, however the extent of this is yet to be explored fully. Findings from Joshi et al. (Chapter 3) have also shown that aberrant experiences reflecting cortical hyperexcitability could be associated with the pre-frontal

cortex (rVLPFC) which is an important brain region implicated in self-awareness and emotion regulation research. In this context, this current study explored whether additional trait-based measures (more specific to aberrant body experiences / depersonalisation-like experiences) and state-based measures reflecting interoceptive vulnerability (associated atypical skin conductance responses to threat stimuli) would provide further insights into efficacy of brain stimulation with regards to the interoceptive and exteroceptive awareness.

Depersonalisation-like experiences

Depersonalisation is often associated with feelings of detachment, emotional numbing and a reduced sense of self and aberrant body experiences are a central component of this disorder (Sierra, 2009; Sierra & David, 2011; Medford, 2012). As a net consequence, patients show suppressed autonomic activity to aversive body-stimuli and this is consistent with neurotypical individuals predisposed to depersonalisation-like experiences (Sierra et al., 2002 (a), 2005(b); Braithwaite et al., 2013 (a), 2017 (b); Dewe et al., 2016 (a), 2018 (b)). It has been theorised that this occurs due to ineffective suppression of the fronto-limbic regions that are involved in inhibiting the anterior cingulate (ACC) and anterior insula regions (AI) (Craig, 2002 (a), 2003 (b), 2009 (c); Critchley et al., 2004; Critchley, 2005). Typically, perceptual networks accommodate for new incoming sensory signals with existing information of the self and surroundings. Some theoretical accounts identify subjective experiences of affect as central to this process as these actively change internal processes in response to external information (Critchley et al., 2004; Critchley, 2005). Here, the theory explains a ‘prediction error’ that occurs when the incoming information is inappropriately predicted by the fronto-limbic perceptual systems which leads to over suppression of the inhibitory systems (projecting to AI and ACC) resulting in dampened autonomic activity (Medford et al., 2006; Lemche et al., 2007 (a), 2008 (b); Jay et al., 2014 see also Dewe et al., 2018).

A commonly used trait-based measure that is indicative of depersonalisation-like experiences in the neurotypical population is the Cambridge Depersonalisation Scale (CDS) and individuals scoring > 70 on this scale are considered to be predisposed to depersonalisation (Sierra & Berrios 2000). Previous studies examining predisposition to depersonalisation-like experiences (DLE) have reported individuals to have dampened autonomic reactivity to aversive body stimuli, utilising two subscales (within CDS) that have demonstrated to be effective in identifying DLE in the neurotypical populations, namely, Anomalous Bodily Experiences and Alienation from Surroundings (Dewe et al., 2016(a), 2018(b); Braithwaite et al., 2020). These studies have used a specific task where a fake blood-giving procedure to the participants own body is performed where skin conductance responses are recorded (Dewe et al., 2016) and shown that those predisposed to aberrant body experiences / depersonalisation-like experiences exhibited weaker skin conductance responses to this threat task.

Overview of the Present Study

The current study sought to investigate if predisposition to aberrant experiences affects the loss of motor excitability during limb immobilisation in a neurotypical sample. Participants were stratified based on (i) proneness to aberrant visual experiences which reflect elevated levels of cortical hyperexcitability and (ii) predisposition to aberrant depersonalisation-like experiences. An additional measure of autonomic activity in the form of skin conductance responses to an Implied Body Threat (IBT) task was utilised to assess if variability in interoceptive vulnerability could be indicative of the degree of loss of motor excitability during limb immobilisation. In line with Maeda et al., (2000), the loss of motor excitability during limb immobilisation was assessed using repetitive 20 Hz Transcranial Magnetic Stimulation (TMS) applied to the corresponding motor brain area (M1) of the right arm that was immobilised for four days.

Aberrant experiences have been associated with loss of embodiment and a break from multi-sensory integration (Sierra et al., 2002(a), 2005(b); Braithwaite & David, 2016). Many studies have evidenced that predisposition to aberrant experiences in the neurotypical population reveals a hyperexcitable cortex and this has now been discussed not only the visual areas but as a more domain general phenomenon (other brain regions implicated as part of multi-sensory integration) (Aurora et al., 1998 (a), 2003 (b); Young et al., 2004, Braithwaite et al., 2015, Joshi et al., (Chapter 3)). It has also been shown that predisposed individuals show a suppression in autonomic responses to viewing aversive body stimuli (Dewe et al., 2018; Braithwaite et al., 2020). Additionally, within the realm of brain stimulation studies, a growing body of research has indicated that individuals' baseline brain states are an important consideration in order to assess the efficacy of the brain stimulation paradigm that is applied (Horvath et al., 2015; Hsu et al., 2016; Romei et al., 2016; Medina & Cason, 2017; Silvanto et al., 2018). A prior analysis of a larger data set (from which a subset

was drawn for the present study) suggested that the rTMS intervention did not produce a therapeutic effect (Gaffney et al., 2021). However, since body-ownership has been linked to the multi-sensory paradigm, the current study sought to explore whether predisposition to aberrant experiences and depersonalisation-like experiences would explain the variance in the efficacy of the stimulation paradigm, potentially explaining the absence of therapeutic effects in maintaining motor excitability following an upper arm injury.

To do this, two types of baseline measures were employed. Firstly, two trait-based predisposition measures were utilised; on a factor in the Cortical Hyperexcitability Index II (CHi_II) measure which assesses anomalous experiences that reflect cortical hyperexcitability (Fong et al., 2019) and on factors relating to depersonalisation-like experiences from the Cambridge Depersonalisation Scale (CDS) (Sierra & Berrios, 2000; Sierra et al., 2005). Secondly, a state-based task, Implied Body Threat (IBT) (Dewe et al., 2016) along with skin conductance responses (SCRs) was recorded to quantify participants based on their interoceptive vulnerability (IV).

Method & Procedure

Exclusion and Safety Criteria

As the current study was part of a larger collaborative project, participants were considered eligible if they met criteria requirements for all parts of the project (Gaffney et al., 2021). This included a four-stage process. Initially, volunteers were required to be male, aged 18-65 years, right-handed and had a BMI between 16-25 kg/m². If volunteers passed this requirement, they were subject to health and safety criteria for TMS as per guidelines mentioned in Rossi et al. (2009), this was also a screening measure used to ensure eligibility for SCRs. Additionally, to be able to participate in the current study, participants would be excluded if they had a debilitating fear of needles/blood. Stage three of the criteria required volunteers to participate in pre-study introductory session and were excluded if they were unable to tolerate any of the procedures (TMS, IBT task, adhering to immobilisation for 4 days etc.) during the study. In the fourth stage, volunteers were excluded from the rTMS intervention if the resting motor threshold was above 50% TMS intensity based on the protocol safety guidelines (Rossi et al., 2009).

Participants

Over seventy volunteers responded to the advertisement call at Lancaster University, UK. Of those, forty participants were rejected based on left-handedness and health and safety issues for TMS eligibility (such as, non-removable jewellery, history of epilepsy/seizures, use of medication that was a contraindication of safety for TMS protocols etc.). Of the remaining participants, 6 volunteers chose not to complete the study due to reasons including compassionate leave, uncomfortable with TMS protocol, inability to follow all study requirements etc. Finally, 12 participants completed the first session only and were

subsequently excluded due to high motor thresholds (according to safety criteria for rTMS protocols). All participants were given monetary compensation for their time and adherence to the experimental protocol.

The final sample included for were 12 Male participants aged 18 - 30 years (Mean = 21.33, SD = 2.71) with 6 participants in the Sham group (did not receive rTMS protocol) and 6 participants in the Treatment group.

Measures

Screening Measures

To determine individual susceptibility associated with cortical hyperexcitability and depersonalisation-like experiences, two pre-existing validated screening measures were implemented.

Cortical Hyperexcitability Index (CHi II). This questionnaire battery measures extent of various experiences of hallucinations in the non-clinical population that reflect degrees of cortical hyperexcitability (Fong et al., 2019). Three subfactors are identified as “Heightened Visual Sensitivity and Discomfort” (HVSD), “Aura-like Hallucinatory Experiences” (AHE) and “Distorted Visual Perception” (DVP) with a high internal consistency and reliability (Cronbach Alpha 0.90). Based on previous studies, we focussed on the “AHE” subfactor as a quantifying measure to identify effects of cortical hyperexcitability in our sample (Fong et al., 2019 (a), 2021(b); Joshi et al., (Chapter 3)). Participants were asked to report the frequency and intensity of their experiences based on Likert-type scale from 0 (Never / Not at all) to 6 (All the Time/ Extremely intense). The AHE subfactor contained 9 items with a maximum possible score of 90.

Cambridge Depersonalisation Scale (CDS). Two subfactors of the CDS, namely, “Anomalous Bodily Experiences” (ABE) and “Alienation from Surroundings” (AFS) were chosen to quantify participants for predisposition to depersonalisation-like experiences (Sierra et al., 2005, Dewe et al., 2016 (a), 2018 (b), Braithwaite et al., 2020). The scale contains 13-items which are measured on a Likert-scale from 0 to 5 based on frequency and 1 to 6 on the duration experienced for each item. The potential maximum score derived from the two subfactors pertaining to “depersonalisation-like experiences / DLE” from 13 items is 130.

To standardise the data obtained from screening measures that were used to stratify the sample, the separate factors were divided by the sum of the number of items on the factor (AHE/9, DLE/13).

Implied Body Threat Task

To measure participants affective response to threatening stimulus, we applied the Implied Body Threat Task (IBT) (Dewe et al., 2016). This task is a highly realistic (but pantomimed) blood giving procedure carried out on the participants own arm. This task involves informing the participant that they would experience a staged blood giving procedure. As part of the protocol outlined in (Dewe et al., 2016), participants were not told that this was “fake” or “pretend” as this would potentially negate the autonomic response that would be measured. Participants are then asked to place their arms palm-up on a flat surface and always look at their arm. After a short while, a dry swab is used to imitate “cleaning” the injection site. Following this, a specialised syringe is introduced in the participants view and pressed at the injection site. This syringe is a 5cc barrel and a 2.5-inch retractable needle, which would not actively penetrate the skin but retract when pressure was applied on the skin with the syringe.

The whole task was conducted for a maximum of 150 secs which included a 120 secs baseline.

Skin Conductance Responses

To assess interoceptive vulnerability, skin conductance responses (SCR) were measured to the IBT task through a Biopac MP36R data-acquisition unit (Biopac Systems Inc., Goleta, CA) connected to a Dell laptop running 64-bit Windows 10 Home OS. Data was recorded using a 0.05Hz high-pass filter and the sampling rate was set to 2000Hz. A low sustained voltage current of 0.5V was applied through two disposable pre-gelled electrodes (EL507) attached to SS57L sensor leads that were attached to the distal phalanx of the left index and middle fingers. This was placed 10 mins before data acquisition to obtain the strongest, high-quality signal.

All signals were processed using Biopac AcqKnowledge v5.0. The definition of an SCR magnitude was the difference between the peak value and onset value of the wave, which is a delta function in Microsiemens or μS , where no SCR was detected a zero value was input (Braithwaite et al., 2013). As with previous studies, threshold was set at $0.01\mu\text{S}$ from the background signal. For the present study, the main SCR of interest was determined as the SCR occurring within 20s of the presentation of the needle in the IBT. Prior to the IBT, a 120s baseline was recorded to assess the participants background autonomic activity.

Signal data from all participants were first subject to visual inspection for artefact detection. If an artefact was found, the signal was down sampled by 200 samples/sec or the section with the artefact was removed from the signal. Following standard practices, SCR magnitude data was normalised and standardised using [SCR (Log + 1)] transformations and Z-Score conversions (Boucsein et al., 2012, Dawsen et al., 2007, Braithwaite et al. 2013). SCRs in this case were utilised as a measure of “interoceptive vulnerability / IV”.

Transcranial Magnetic Stimulation (TMS)

For the current study, the hand area of the primary motor cortex (M1) on each side was targeted using a 70mm diameter figure-8 coil connected to a biphasic DuoMAG XT-100 stimulator unit (Deymed Diagnostic, Czech Republic). Single-pulse and repetitive-pulse (rTMS) protocols were applied using the same biphasic unit and the same TMS coil was used throughout the study. Following safety guidelines, participants wore earplugs (both ears) during all TMS procedures (Tringali et al., 2012). To avoid activation of the hand muscles, all TMS procedures were also conducted in resting state. Localisation was achieved through the “hot-spot” method as outlined by Möttönen et al. (2014) on the first session for each participant, and the coordinates (including coil orientation) were saved using Brainsight Neuronavigation software (Rogue Research Inc., Montreal, Canada) (see also Gaffney et al., 2021). The saved coordinates were then used for each participant for subsequent sessions (Right-hand MEP, Left-hand MEP and Right-hand rTMS, elaborated below).

To measure excitability, motor evoked potentials (MEP) were generated by placing the coil tangential to the skull at a 225° orientation to maintain posterior-anterior flow of current in biphasic stimulators (usually 45° angle is used in monophasic stimulation) (Sommer et al., 2006, Gaffney et al., 2021). In the first session, a stepwise protocol was applied on the left hemisphere (to elicit responses as Right-hand MEP) using single-pulse TMS from 5% to 75% intensity of stimulator output in increments of 5% (two MEP responses per increment) to determine the resting motor threshold (rMT) for each participant. This was defined as the intensity at which the first strongest MEP response was generated as recorded by electromyography (EMG). If rMT was determined to be $\geq 50\%$ intensity of stimulator output, participants were not allowed to continue with the study due to safety guidelines (due to the risk of seizure) (Rossi et al., 2009). Participants continuing the study

were then subject to the stepwise protocol on the right hemisphere (left-hand MEP) which was followed by the entire subsequent procedure and sessions (see Table 4.1).

To facilitate cortical excitability in the right hand which would be immobilised for the duration of the study, rTMS was applied to the left hemisphere where the coil was angled at 45° orientation (coordinates saved as right-hand rTMS). The frequency was set at 20Hz in 6 trains of 30 pulses (each 1.5 secs) with rest periods between each for 1 minute, the total time taken for this procedure was (5 mins 9 secs). The intensity of the stimulator was set to 90% of rMT of each participant. For participants in the Sham intervention group, the same rTMS procedure was applied but the coil was held roughly 5 cm above the participants head to simulate the procedure without applying current to the area. All subjects were naïve to single pulse and rTMS, and subjects in the Sham group believed themselves to be receiving rTMS. Following the rTMS, the stepwise protocol was repeated on the right-hand (left hemisphere) and left-hand (left hemisphere) to track changes in cortical excitability using MEPs. The MEP responses before rTMS were recorded as Pre-rTMS and those after were recorded as Post-rTMS

The entire procedure took about 1 hour including time for localisation (see Figure 1). All participants completed the study following the exact procedure for four sessions with 24-hour time periods in between.

Table 4.1*Schematic Representation of the Experiment Design*

Introductory Session	Session 1	Sessions 2 and 3	Session 4
1. IBT and SCR Safety Screening	1. TMS Safety Screening	1. TMS Safety Screening	1. TMS Safety Screening
2. Measures (CHi_II and CDS)	2. Localisation	2. Pre-Right-Hand MEP	2. Pre-Right-Hand MEP
3. IBT and SCR	3. Pre-Right-Hand MEP	3. Pre-Left-Hand MEP	3. Pre-Left-Hand MEP
4. TMS Safety Screening	4. Pre-Left-Hand MEP	4. rTMS (Treatment/Sham)	4. rTMS (Treatment/Sham)
5. Introduction to TMS	5. rTMS (Treatment/Sham)	5. Post-Right-Hand MEP	5. Post-Right-Hand MEP
	6. Post-Right-Hand MEP	6. Post-Left-Hand MEP	6. Post-Left-Hand MEP
	7. Post-Left-Hand MEP	7. Immobilisation (Right Arm)	7. End of Study
	8. Immobilisation (Right Arm)		

Note: Each session was conducted 24 hours later

Electromyography (EMG)

MEP responses were recorded using EMG activity. This was achieved by attaching 30 mm diameter disposable press-stud Kendall ECG pre-gelled electrodes (Henleys Medical, Hertfordshire, UK) in a tendon-belly montage on both hands. One electrode was placed on each wrist as a grounding electrode. This was connected to using a TruTrace 2 channel amplifier (Deymed Diagnostic, Czech Republic) and data was acquired and recorded using DuoMag rTMS software v6.2 (Deymed Diagnostic, Czech Republic). EMG activity was

recorded per 2 seconds and was filtered between 1-2000 Hz and sampled at 12,500 Hz (Gaffney et al., 2021)

Data was extrapolated using MATLAB (Matlab R2016a, Mathworks, Massachusetts, USA) for pre- and post-rTMS for both hands and sessions. An area under the curve (a.u.c) value was calculated for each time point, with a large a.u.c. indicating a higher motor excitability. The data was then standardised and normalised using Z-scores.

Procedure

For the present study, after participants passed the initial inclusion checks as outlined above, they were invited to attend an introductory session (Stage 3) following the procedure mentioned below.

Introductory Session

Participants were first asked to fill out the safety forms for the Implied Body-Threat task, skin conductance responses and Transcranial Magnetic stimulation. Following successful assessment of safety protocols, participants were then informed of all the tasks they would have to undergo during the study (except for which group, that is, Treatment or Sham) and signed consent was taken. Next, each participant filled out the screening measures (CHi_II and DLE). During this time, electrodes for SCRs were attached. Participants then completed the Implied Body-Threat task (IV measure). Participants were then introduced to TMS applied, firstly, to the forearm (at 30% intensity of stimulator output) and then on the M1 (50% intensity). Participants were given time to ask questions about the sessions.

Session 1

Each participant filled out the TMS safety screening as part of the safety protocol. Next, the EMG electrodes were attached to both the participants hand and TMS localisation was setup. This involved the participant wearing a headband equipped with an infrared subject tracker (also attached to the TMS coil) which would facilitate optimum headtracking and localisation using an Optical infrared sensor. Next localisation of M1 for each side was achieved using the “hot-spot” method (see above) and participants coordinates were saved in the software. Participants then were subject to MEP stepwise protocol (left hemisphere followed by right hemisphere) before the rTMS protocol. Each participant’s rMT was determined following visual inspection of the data and the intensity for the rTMS protocol was set (at 90% of rMT).

Following the rTMS protocol, the MEP stepwise protocol was repeated. Following this, each participant's dominant arm (right) was immobilised using a swathe and sling that would limit activation of the forearm muscles.

Sessions 2, 3 and 4

Participants returned to the laboratory 24 hours after each session and after completing the TMS safety screening were setup for TMS as described in session 1. During this time, all participants were instructed to not move their right arm (and continue to keep it immobilised). Researchers took every precaution in limiting the movement of the right arm and keeping the arm muscles inactive by providing an arm sling and swathe for immobilisation from the shoulder joints of the right arm. Following setup, participants took part in the TMS protocol as in session 1 (pre-Right and Left-hand MEP, rTMS, post-Right and Left-hand MEP). After sessions 2 and 3, participants right arm was again immobilised as in session 1. Following the final session 4, participants were compensated with £50 for their time, debriefed and performed some light stretching exercises of the "immobilised arm" before the study ended. The entire procedure (excluding immobilisation protocol, which was for 72 hours) including introductory session and sessions 1-4 was 7 hours.

Results

Overall Statistics

Responses from the screening measures were used to create high trait-based predisposition and low trait-based predisposition groups for (i) cortical hyperexcitability (AHE) and (ii) aberrant depersonalisation-like experiences (DLE). In addition, high and low groups were formed in terms of the interoceptive vulnerability (as measured by Threat SCRs to the IBT task).

The entire analysis was carried out using SPSS v27, JASP v 0.14.1 and MATLAB R2019a (for a.u.c data extraction). When normality was met, parametric tests were conducted using independent sample t-tests, paired sample t-tests (for within-subject comparison), two-way mixed ANOVA's and repeated measures ANOVA's (rm ANOVA). 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. Multiple testing was corrected using the False Discovery Rate (FDR) by using the Benjamini-Hochberg (B&H) procedure (Benjamini & Hochberg, 1995). First, all p -values from the multiple testing procedure were ranked in ascending order from 1,2,3... (I). Then the B&H formula $(I/n)/Q$ was used where I = the individual test's rank, n = total number of tests and Q = false discovery rate (0.5) to calculate individual B&H value for every p value. If the original p value $<$ B&H corrected p value, the comparative test was considered significant (Benjamini & Hochberg, 1995; Dewe et al., 2018; Braithwaite et al., 2020).

Additionally, Frequentist statistics (p values) were accompanied by Bayesian statistics (BF values). BF_{10} values indicate the strength of the significant findings for the alternate hypothesis, where $BF_{10} < 1$ this is an indication for the null hypothesis in which case BF_{01} values are provided to indicate the strength of the non-significant findings. According to

Jarosz and Wiley (2014), a BF value between 1 – 3 is considered inconclusive, 3 – 10 as good evidence, 10 – 100 as strong evidence and > 100 as decisive evidence.

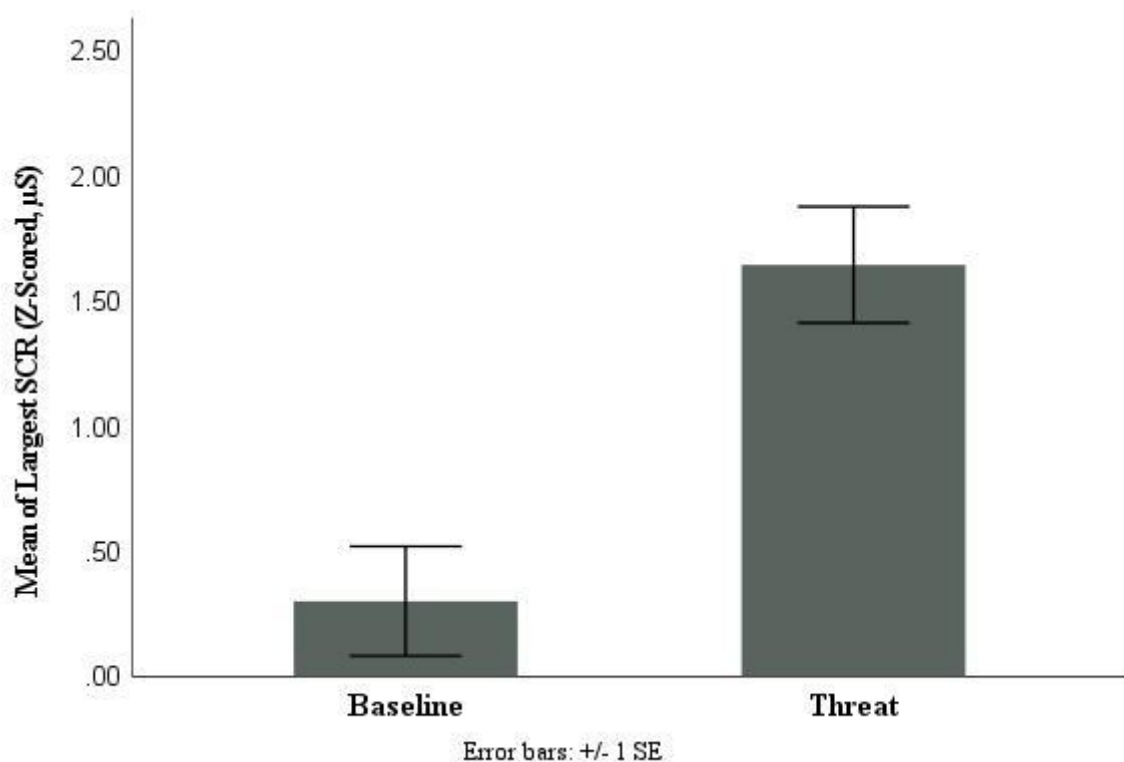
Efficacy of Implied Body Threat Task

SCRs

To assess the success of the IBT task in eliciting stronger skin conductance responses to threat paradigm, Baseline SCRs was compared to Threat SCRs for all 12 participants using a paired t-test (Figure 4.1). This revealed that the Baseline SCRs were significantly weaker than the Threat SCRs [$t(11) = 3.751, p = 0.003, d = 1.083, BF_{10} = 15.002$].

Figure 4.1

Comparing SCR responses (Largest, Z-Scored) between Baseline and Threat

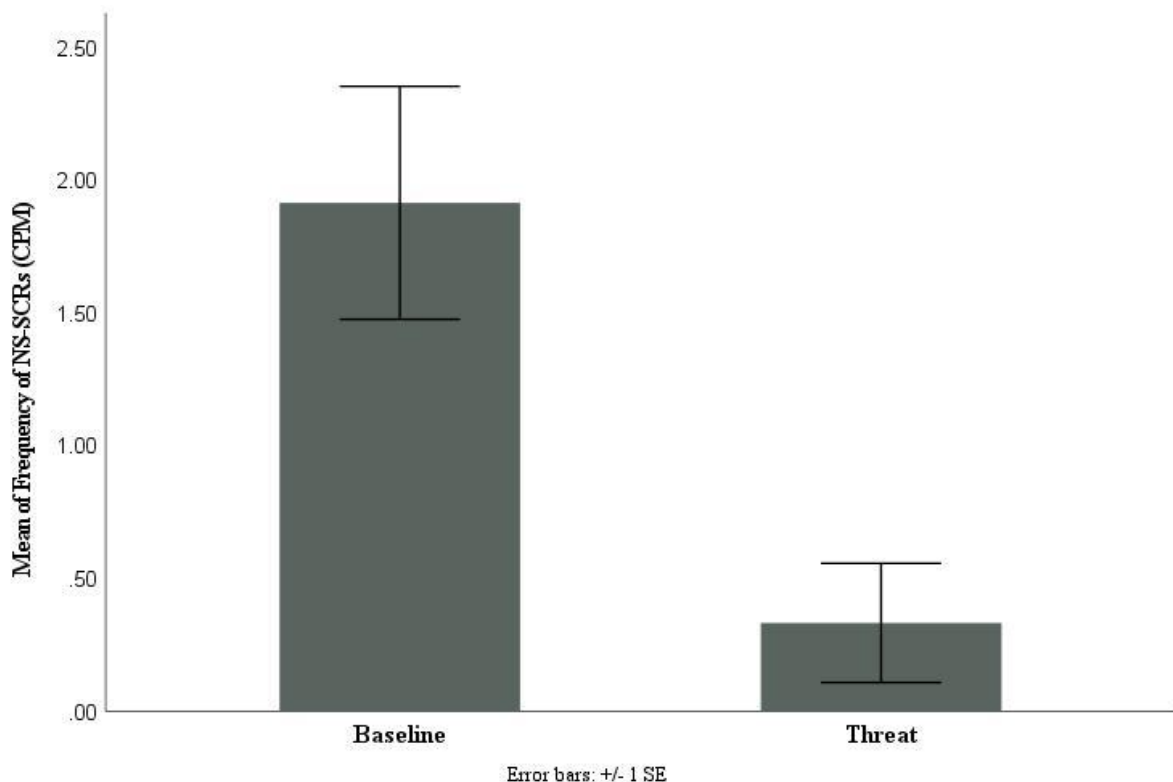


F-SCRs

Additionally, the frequency of NS-SCRs (those not tied to an event / tonic) were compared for the Baseline and Threat responses as an addition measure of autonomic activity (Figure 4.2). This has been previously shown to portray internal mental states associated with negative affect (Nikula, 1991, Boucsein, 2012, Dewe et al., 2016). As with standard practices, the frequency of NS-SCR for each period (Baseline and Threat) were divided by time (count-per-minute / CPM). A paired t-test revealed that the Baseline period had significantly higher frequency of NS-SCRs than the Threat period [$t(11) = 3.147, p = 0.009, d = 0.908, BF_{10} = 6.28$].

Figure 4.2

Comparing frequency of NS-SCR responses (CPM) between Baseline and Threat



Efficacy of Immobilisation

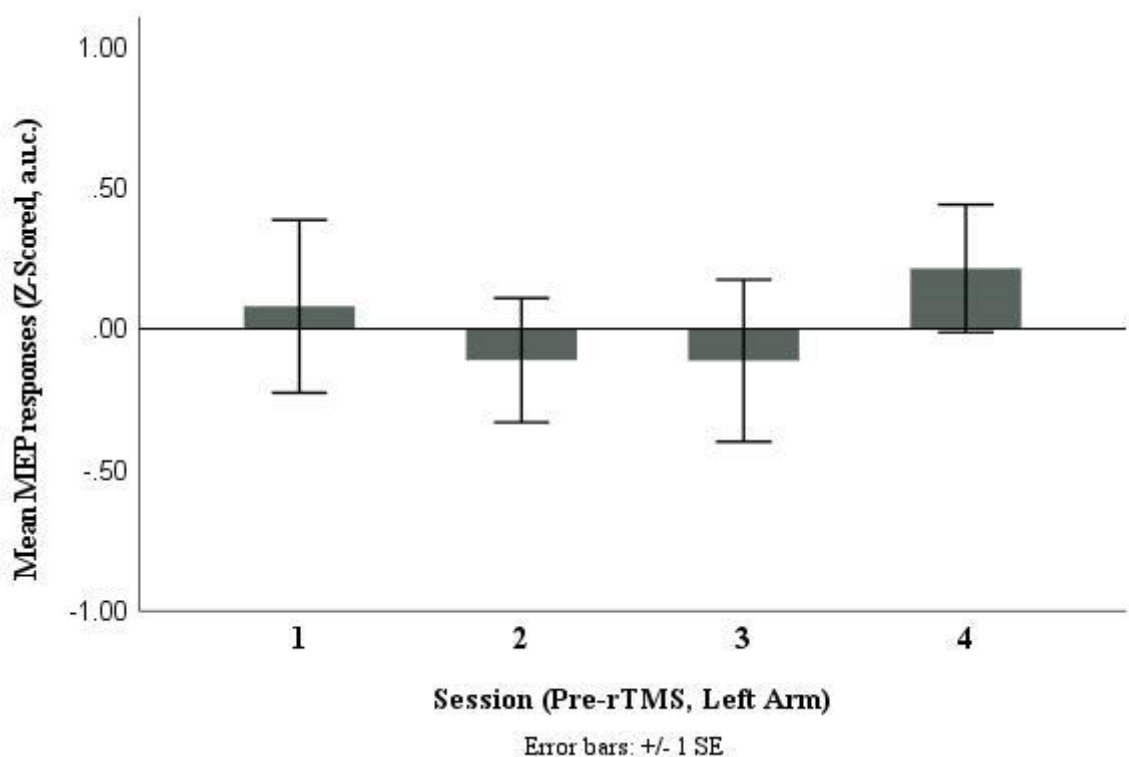
To examine the effect of immobilisation in reducing motor excitability, MEP responses gathered before the rTMS protocol were compared within each arm for all 4 sessions was compared.

Left Arm (Control)

A rm-ANOVA with 4 levels (Sessions 1-4 pre-rTMS responses) revealed no reliable differences between motor excitability [$F(3,33) = 0.340$, $p > 0.05$, $BF_{10} = 0.161$, $BF_{01} = 6.192$] (Figure 4.3).

Figure 4.3

Comparing mean MEP responses (Z-Scored, a.u.c.) for the Pre rTMS protocol in the Left arm (Control) from Sessions 1-4

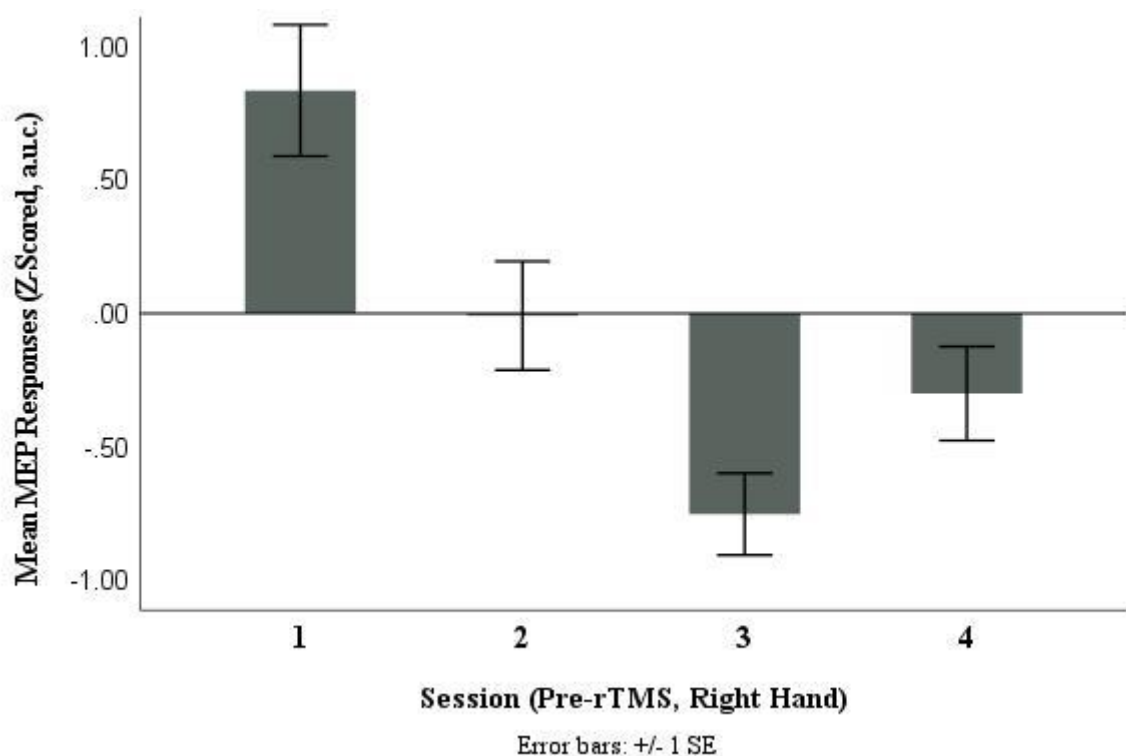


Right Arm (Immobilised)

A significant main effect of time was observed with a rm-ANOVA at 4 levels (comparing Pre-rTMS responses for Sessions 1-4) [$F(3,33) = 9.703, p < 0.01, \eta^2_p = 0.469, BF_{10} > 1000$] (Figure 4.4). Pairwise comparisons using FDR corrections for the Frequentist analysis revealed Session 3 [MD = 1.587, SE = 0.291, $p < 0.01, B\&H = 0.017, BF_{10} = 157.683$] motor excitability was significantly lower than Session 1 followed by Session 4 [MD = 1.135, SE = 0.347, $p = 0.008, B\&H = 0.033, BF_{10} = 7.468$] and Session 2 [MD = 0.843, SE = 0.361, $p = 0.039, B\&H = 0.05, BF_{10} = 1.988$]. However, overall, this indicates that the immobilisation paradigm was successful in lowering motor excitability across the four sessions.

Figure 4.4

Comparing mean MEP responses (Z-Scored, a.u.c.) for the Pre rTMS protocol in the Right arm (Control) from Sessions 1-4



Effect of rTMS protocol

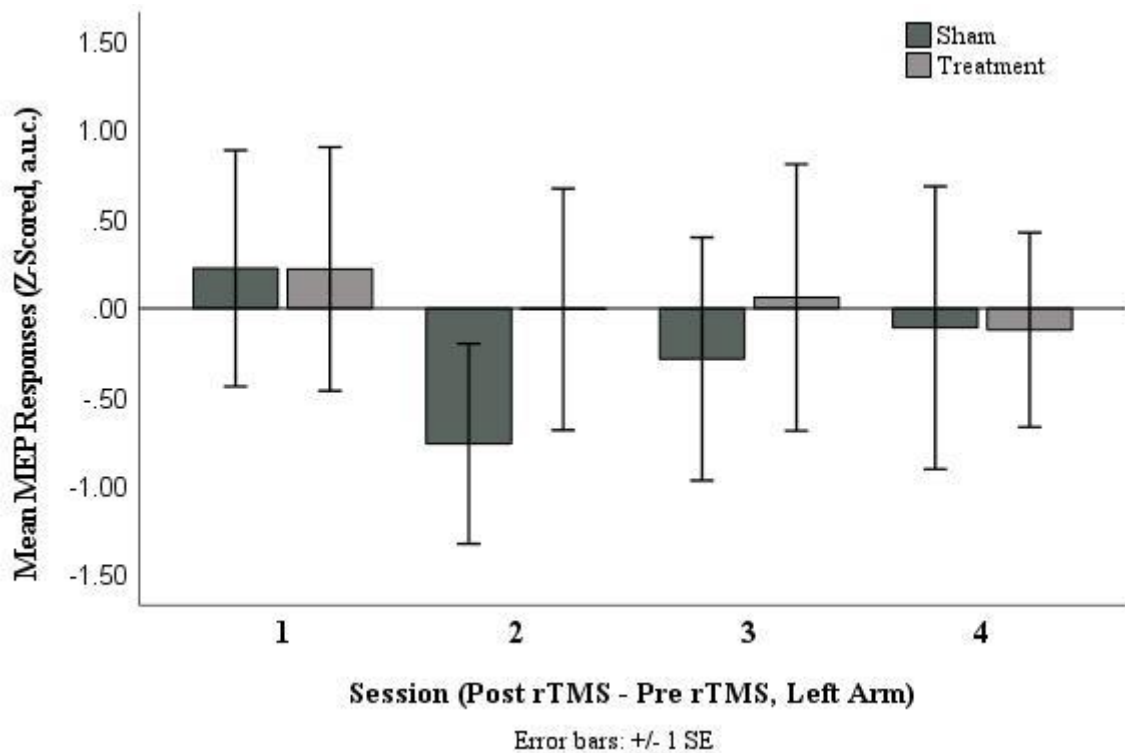
To determine the effect of the rTMS protocol in alleviating loss of motor excitability due to immobilisation, Pre-rTMS from Sessions 1-4 were subtracted from Post-rTMS responses (that is, after the rTMS protocol per session) and compared using a mixed two-way ANOVA with two variables of Time (Within-subjects variable: Session 1, 2, 3 and 4) and Group (Between-subjects variable: Sham and Treatment).

Left Arm (Control)

No significant effects of Time [$F(3,30) = 0.611, p > 0.05, BF_{10} = 0.205, BF_{01} = 4.866$] or Group [$F(1,10) = 0.120, p > 0.05, BF_{10} = 0.542, BF_{01} = 1.847$] were observed (Figure 4.5). The interaction was also non-significant here [$F(3,30) = 0.326, p > 0.05, BF_{10} = 0.255, BF_{01} = 3.919$]. Although the Group effect was found to be inconclusive with Bayesian analysis, the lack of a significant effect of Time or the interaction between the two variables suggests no reliable changes were observed in the left arm. This was consistent with the hypothesis that the control arm should not show any effects of the rTMS protocol.

Figure 4.5

Comparing MEP responses (Z-Scored, a.u.c.) from Post-Pre rTMS between Sham and Treatment Groups for the Left Arm



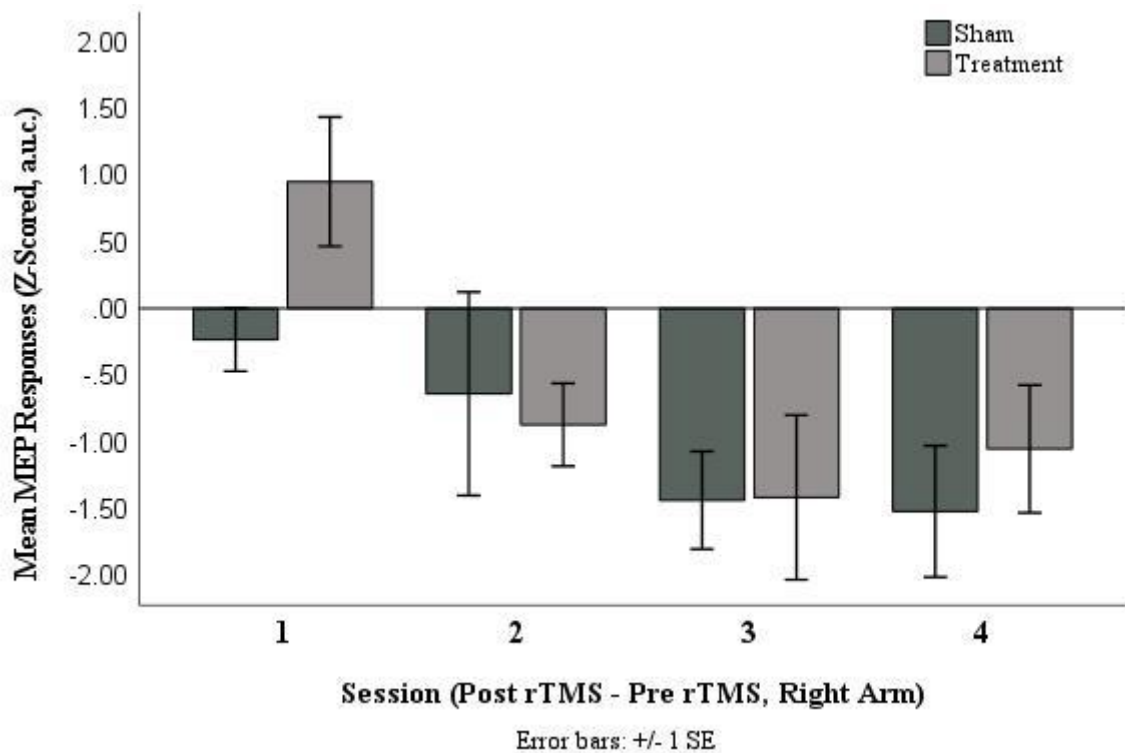
Right Arm (Immobilised)

This analysis showed that Mauchly's test of Sphericity was violated and so Greenhouse Geiser corrections were used for all effects. The main effect of Time [$F(1.660, 16.1049) = 13.576, p < 0.01, \eta^2_p = 0.576, BF_{10} > 1000$] was found to be significant (Figure 4.6).

However, the main effect of Group [$F(3, 30) = 0.377, p > 0.05, BF_{10} = 0.513, BF_{01} = 1.951$] and the interaction between Group and Time [$F(1.660, 16.1049) = 1.988, p > 0.05, BF_{10} = 0.837, BF_{01} = 1.195$] was non-significant according to Frequentist analysis suggesting that there was no effect of the rTMS protocol in maintaining motor excitability in the Treatment group. As this analysis did not support the maintenance of motor excitability, subsequent analysis was conducted only considering pre-rTMS values for Session 1 and Session 4.

Figure 4.6

Comparing MEP responses (Z-Scored, a.u.c.) from Post-Pre rTMS between Sham and Treatment Groups for the Right Arm



Chi_II and Motor Cortex Excitability

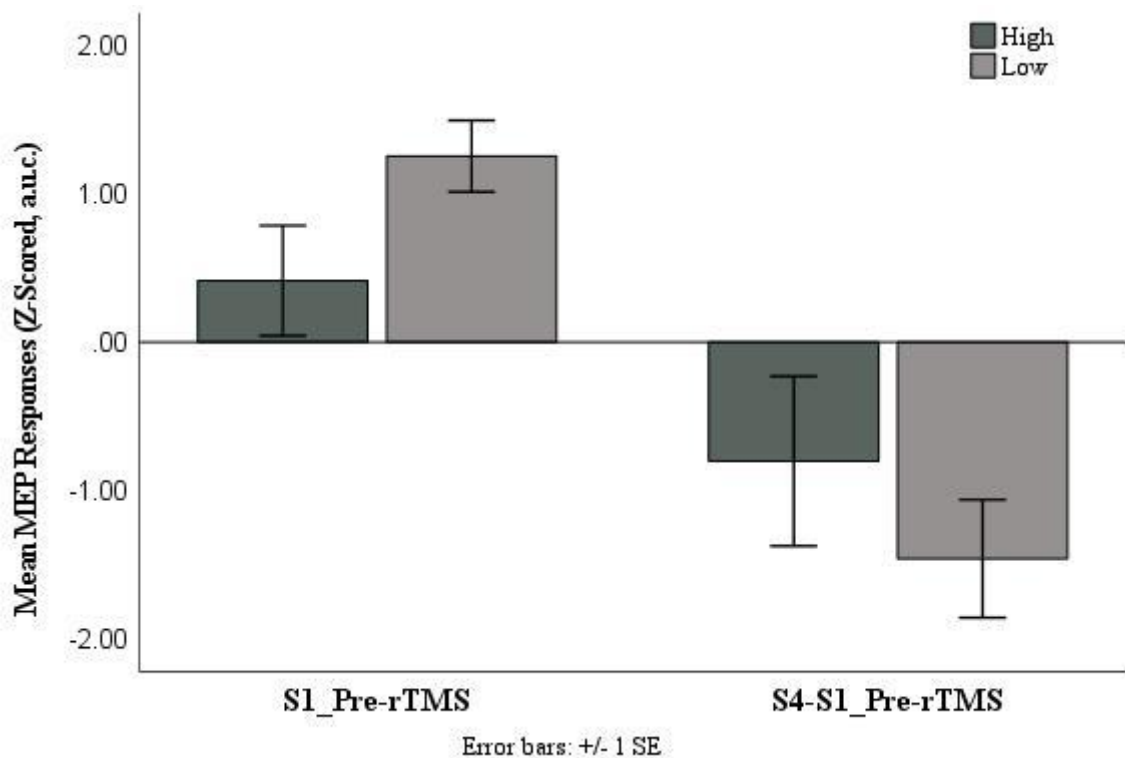
To explore the effects of predisposition to cortical hyperexcitability on (i) MEP responses before stimulation and (ii) loss of corticomotor excitability, a median split on the AHE factor responses was applied. The resultant two groups were high-AHE group (Mean = 1.11, SD = 0.64) and low-AHE group (Mean= 0.06, SD = 0.14) (Figure 4.7).

Independent samples t-tests were conducted on the Pre-rTMS Session 1 (for threshold) and the Pre-rTMS Session 4 – 1 (for the loss of motor excitability), however, these were found to be non-significant for both Pre-MEP Session 1 [$t(10) = -1.902, p > 0.05, BF_{10}$

= 1.306] and for the Pre-rTMS Session 4 – 1 [$t(10) = -0.944$, $p > 0.05$, $BF_{10} = 0.618$, $BF_{01} = 1.618$].

Figure 4.7

Mean MEP Responses (Z-Scored, a.u.c.) of Pre-rTMS Session 1 and Pre-rTMS Session 4 – 1 for the high AHE group and low AHE group



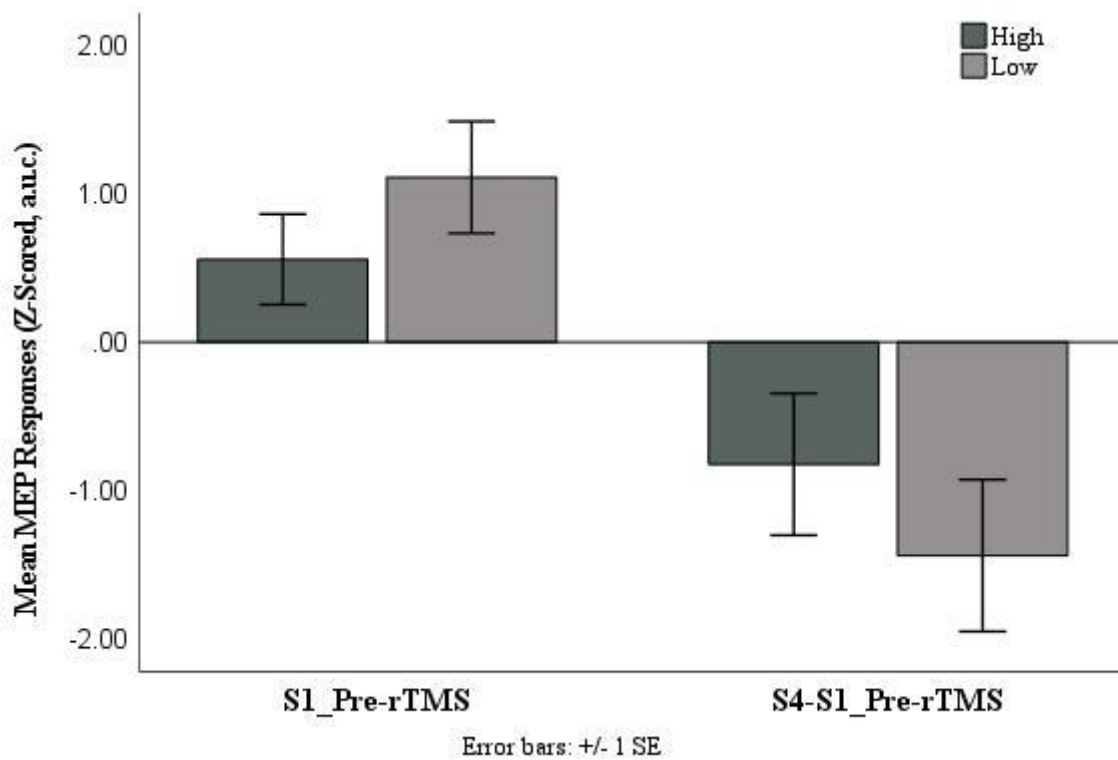
Interoceptive vulnerability (IV) and Motor Excitability

Similarly, two groups of high interoceptive vulnerability (IV) (Mean = 2.19, SD = 0.39) and low IV (Mean = 1.10, SD = 0.75) were created using a median split to explore the Pre-rTMS Session 1 responses and the loss of motor excitability Session 4 – 1 Pre-rTMS responses as a state-based baseline stratification of the sample (Figure 4.8).

Independent sample t-tests revealed that the differences between the two groups was found to be non-significant for Pre-rTMS Session 1 [$t(10) = -1.144, p > 0.05, BF_{10} = 0.698, BF_{01} = 1.433$] as well as Pre-rTMS Session 4 – 1 [$t(10) = -0.877, p > 0.05, BF_{10} = 0.596, BF_{01} = 1.679$].

Figure 4.8

Mean MEP Responses (Z-Scored, a.u.c.) of Pre-rTMS Session 1 and Pre-rTMS Session 4 – 1 for the high IV group and IV AHE group



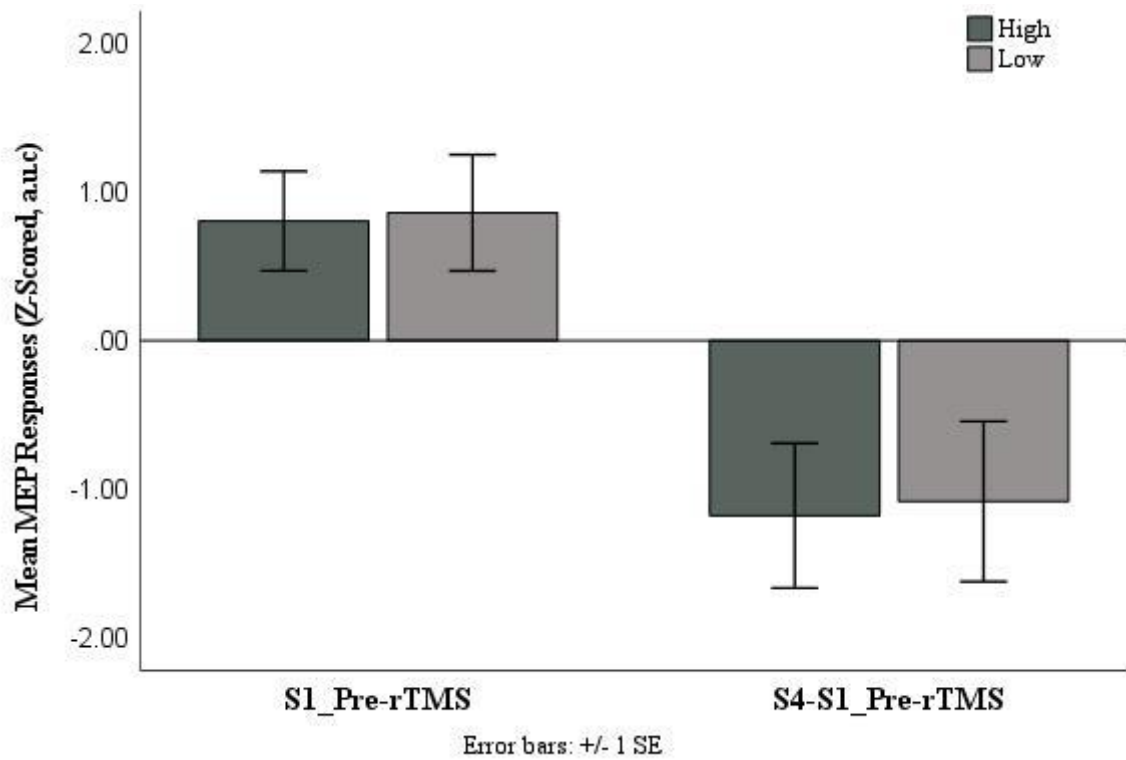
DLE and Motor Cortex Excitability

To assess if predisposition to depersonalisation-like experiences is related to variations in motor cortex excitability (Pre-rTMS Session 1) or loss of motor excitability following immobilisation (Pre-rTMS Session 4 – 1), two groups of high DLE (Mean = 1.54, SD = 1.04) and low DLE (Mean = 0.08, SD = 0.19) were created using a median split (Figure 4.9).

Independent samples t-tests revealed no differences between the two DLE groups on Pre-rTMS Session 1 [$t(10) = -0.108, p > 0.05, BF_{10} = 0.469, BF_{01} = 2.132$] or Pre-rTMS Session 4 – 1 [$t(10) = -0.131, p > 0.05, BF_{10} = 0.470, BF_{01} = 2.129$].

Figure 4.9

Mean MEP Responses (Z-Scored, a.u.c.) of Pre-rTMS Session 1 and Pre-rTMS Session 4 – 1 for the high DLE group and low DLE group



General Discussion

The aim of this study was to explore if predisposition to aberrant experiences relates to corticomotor depression following limb immobilisation. Two trait-based measures were used to quantify the neurotypical sample based on elevated cortical hyperexcitability and depersonalisation-like experiences. An additional state-based task (index of IV) was employed to measure participants' autonomic responses to an own-body threat task. Limb immobilisation occurred for three days during which participant's motor cortex threshold was measured using motor evoked potentials each day of immobilisation.

Initially, the effect of the immobilisation was measured by calculating MEP responses pre-rTMS intervention per day of stimulation. Results show that immobilisation reduced MEP amplitude each day (maximally after day 2) of immobilisation of the right arm. No differences were seen in the left arm that was not immobilised. These findings are consistent with the literature on immobilisation methods and effects (Facchini et al., 2002; Rosenkrantz et al., 2014).

There were two groups of six participants each that received either a Sham treatment protocol or Stimulation treatment protocol. The Sham participants did not receive the rTMS 20 Hz protocol (the protocol was delivered but the coil was held 3cm above the head). The Treatment group received 6 mins of rTMS at 20 Hz each day of immobilisation, which aimed to maintain corticomotor efficiency at the corresponding M1 upper-limb site. The left arm showed no reliable effect of the intervention protocol that was consistent with the hypothesis of the study, which stated that the left arm receiving no immobilisation and rTMS 20 Hz protocol will not show corticomotor differences between the Sham group and Treatment Group.

The right arm investigations in the current sample also did not show any significant differences between the two groups (Sham / Treatment). The rTMS intervention protocol did not alleviate corticomotor depression due to immobilisation. It is notable, however, that the rTMS protocol utilised in the current study did show an increase in Session 1 in the Treatment group when compared to the Sham group. This is evidenced with the strong positive change between the MEP responses recorded Post-rTMS and Pre-rTMS in Session 1. This suggests that whilst the rTMS protocol in isolation was effective at enhancing motor excitability, it was not sufficient in alleviating the corticomotor depression effects after immobilisation.

The psychophysiological responses based on the IBT task were found to be successful in terms of increasing autonomic reactivity to the threat stimuli. This was demonstrated through the higher magnitude of SCRs in the threat period than the baseline period. The baseline frequency of NS-SCRs also supported these findings as the pre-threat / baseline period contained more SCRs than the threat period. Overall, these results show that the paradigm was effective and replicated the findings from the previous studies (Dewe et al., 2016(a), 2018(b)).

When the sample was stratified according to predisposition to aberrant experiences (CHi_II) measure, the initial motor cortex activity (as measured by Session 1 pre-rTMS amplitudes) showed non-significant differences. This was also the case when we examined the loss of excitability as measured by Pre-rTMS Session 4 – 1 amplitude. Interestingly, there is a slight suggestion that the higher CHi_II group showed lower M1 threshold relative to the lower CHi_II group and this was also seen with the loss of excitability. Although these results are unreliable, Bayesian statistics in this case was inconclusive, suggesting a larger sample would be required to determine the true pattern of effects. A similar pattern was seen when the current sample was stratified based on their interoceptive vulnerability (SCRs from IBT

task). Here, the results were also non-significant as per Frequentist statistics however Bayesian statistics suggest this to be inconclusive. Finally, when the sample was quantified based on predisposition to DLE, there were no significant findings between the high and low groups for their M1 threshold as well as for the loss of M1 activity due to immobilisation.

In all three cases of stratification, we are mindful in interpreting these null findings and so we suggest possible reasons for these findings. One obvious explanation is that a much larger sample would be needed to further explore these effects. Given that aberrant experiences in the neurotypical samples occurs variably and spontaneously, a larger sample would provide for more reliable results. The second explanation for our null findings is possibly, due to random sampling, we were not able to identify participants at the higher extremes of our measures. The mean score for the high group stratified by predisposition to aberrant experiences was 1.11 / 9 and predisposition to depersonalisation experiences was 1.54 / 13 (Sierra et al., 2005). Here, utilising the pre-screening measures by way of identifying extremes in the population may provide less noisy data.

Theoretical Implications

In our current sample, corticomotor activity during limb immobilisation was not alleviated using a 20 Hz protocol. Studies have shown that increase in M1 activity has been successful under this protocol (Kim et al., 2014) and was also consistent with our initial post rTMS – pre rTMS MEP measurements. This implies that although the paradigm was effective in initially increasing motor cortex activity, this effect was not sustained throughout the immobilisation period. Perhaps utilisation of a different parameter optimisation for the TMS protocol may elicit stronger after-effects, such as longer rTMS stimulation etc. Alternatively, rTMS in isolation may not be able to alleviate corticomotor depression.

A growing body of work has shown the importance of self-generated actions in successful exteroceptive awareness, and that weakened ownership of the arm increases the proprioceptive drift that occurs with the rubber hand illusion (RHI) (Lenggenhager et al., 2007(a), 2014(b); Burin et al., 2017; Fossataro et al., 2018). Given this, research has shown that action observation (and by extension the mirror-neuron system) and motor imagery (proprioception) during immobilisation can help in maintaining corticomotor activity (Sharma et al., 2006; Zimmerman-Schlater et al., 2008, Bassolino et al., 2014; Buccino, 2014; Meugnot et al., 2015; De Marco et al., 2021). Based on our current findings, we suggest that by inducing voluntary M1 activation via motor imagery / action observation paired with rTMS may reduce corticomotor depression. Under the predictive coding framework, generally, cortical efficiency is maintained by minimising prediction error which is defined as the difference between external incoming information and prior internal information (Aitchison & Lengyel, 2017). If, there is a significant discrepancy between these two types of information, this would give rise to large prediction error. Under conditions of immobilisation, the reduction in corticomotor efficiency (as evidenced by the reduction in MEP amplitude) could indicate that the prior has updated to account for immobilisation, i.e., immobilisation is now taken as the “natural” state. The 20Hz rTMS protocol therefore induces M1 activation in the absence of a corresponding stimulus. This deviates from the immobilisation prior, resulting in a large prediction error. If this prediction error is sufficiently large, it may fail to integrate with the immobilisation prior, resulting in the after-effects of stimulation failing to be maintained. However, the magnitude of the prediction error could be reduced by creating a stimulus for M1 activation through action observation or motor imagery (or both). In turn, this may facilitate the rTMS stimulation in maintaining corticomotor efficiency during immobilisation.

In recent years, brain stimulation studies have highlighted the influence of baseline neural activity and corresponding efficacy of brain stimulation (Benwell et al., 2015; Alekseichuk et al., 2016; Hsu et al., 2016; Juan et al., 2017; Yang & Sun, 2018). As such, the reality of traditional anodal stimulation implying excitation and cathodal stimulation implying suppression is nuanced and that trait- or state-based baseline brain states are important when interpreting the data from brain stimulation studies. However, very few studies currently highlight the importance of such individual differences. A wealth of studies has shown that cortical hyperexcitability is associated with aberrant experiences and these are now being discussed beyond the visual cortex as a more domain general occurrence (Aurora et al., 2003; Young et al., 2004; Braithwaite et al., 2015; Merchant, 2020; Joshi et al., (Chapter 3)). According to the neural noise theory, if at the time of stimulation, baseline neuronal activity is high, excitatory stimulation to the target areas may not have the desired effect as excitation would reach a peak and reverse effects (Miniussi et al., 2013, Bortoletto et al., 2015). Based on this theory, the implication is that any brain stimulation protocols may have differential effects on the target brain regions. In the current study, the lack of maintaining corticomotor efficiency may be due to varying baseline states. Our current findings, although not reliable, contain a suggestion that stratification of the sample based on trait-based predisposition to aberrant experiences showed differences in M1 activity as well as the loss of excitability following immobilisation. This exploration was also extended to a state-based threat task measuring autonomic activity that yielded similar results, again not reliably so. Given this, further investigations should consider appropriate trait-based and state-based baseline stratification to ensure efficacy of brain stimulation.

Limitations and Future Studies

A much larger sample would be requisite for studies examining this effect. This would not only facilitate lower variance in the sample but be useful in investigating individual differences with regard to brain stimulation as discussed above. The sample could also be extended to include female participants in assessing interoceptive vulnerabilities and their effect of brain stimulation.

Given the findings of the current studies, we propose that future investigations regarding brain stimulation therapeutic effects into loss of immobilisation or body ownership should add additional action-observation stimuli during stimulation that could perhaps facilitate in maintaining against cortical decline following limb immobilisation. In addition, a different parameter optimisation of the rTMS protocol may be required to produce longer after-effects.

Finally, to ascertain if interoceptive vulnerabilities do indeed play a significant role in alleviating corticomotor decline, we suggest utilising appropriate pre-screening measures to identify the extremes in the sample that would help in observing the differential effects of the applied brain stimulation.

Conclusion

Short-term immobilisation of the right arm was successful in reducing cortical excitability. However, maintenance of cortical efficiency did not improve after rTMS intervention which was consistent with the findings from Gaffney et al. (2021). Trait-based and state-based stratification of the current sample suggested that the neuromodulation paradigm had differential effects based on high scores on aberrant experiences but not reliably so. Further investigations involving appropriate trait-based and state-based measures are required to

understand the neurocognitive mechanisms underlying loss of motor excitability following immobilisation and their implication on mediating stable self-awareness.

Chapter 5

General Discussion

This collection of work sought to examine the neurocognitive biases underlying aberrant experiences in the neurotypical / non-clinical populations. Critically, this thesis aimed at examining novel methodologies for investigating these biases and the role of trait- and state-based processes in mediating predisposition to such experiences. The current thesis is, in part, exploratory in that new methods that have not been previously utilised in this field were investigated here for their utility.

Novel methodological insights come primarily from; (i) being the first study to use MtDCS brain stimulation directed at the rVLPFC to examine suppressive effects in autonomic responding (ii) the work on revising the BTAB paradigm, (iii) using the latest in FaceReader technologies and, (iv) real-world manipulations as with the immobilisation study (Chapter 4). The current work additionally makes important theoretical contributions with regards the underlying neurocognition of aberrant experiences; (i) inhibition of rVLPFC lead to a suppression of autonomic activity only for those predisposed to cortical hyperexcitability (ii) clear evidence that trait-based predisposition to cortical hyperexcitability mediates effects of brain stimulation (iii) cortical hyperexcitability may be considered as a domain general occurrence (iv) aberrant beliefs have distinct neural structures to aberrant body experiences, and (v) baseline brain states may be an important consideration for alternative therapeutic strategies involving brain stimulation.

Key Findings

1. Cathodal stimulation (using optimised MtDCS) showed, for the first time, that increased trait-based predisposition to signs of cortical hyperexcitability was associated with

increased efficacy of MtDCS to suppress autonomic activity to BTAB stimuli in the neurotypical population.

2. Methodological improvements in assessing autonomic activity (magnitudes of Threat SCRs, NS-SCRs and frequency of NS-SCRs) to the novel BTAB (blocked design) is a reliable indicator in delineating between non-body threat (baseline) and body-threat stimuli. In addition to this, the use of FaceReader shows evidence of a promising tool as an additional objective psychophysiological measure in assessing aberrant body-experiences.
3. Two independent screening measures showed that predisposition to aberrant experiences or predisposition to aberrant beliefs were not reliably associated with autonomic responding on either SCR or FaceReader measures. Psychological ratings were not related to predisposition to aberrant beliefs but showed a negative correlation with aberrant visual experiences.
4. Assessment of interoceptive vulnerabilities (trait- and state-based) may be an important consideration when alternative therapeutic strategies (rTMS) are used in maintaining corticomotor efficiency following limb immobilisation (with implications for body-experiences).

Cortical Hyperexcitability and Depersonalisation-like experiences (DLEs)

The theoretical models that account for the aberrant self-experiences in DPD have implicated inappropriate inhibition of the fronto-limbic areas (specifically the rVLPFC) which have a direct role in mediating the anterior insular region (AIC) (Oschner & Gross, 2004 (a), 2005 (b); Medford et al., 2006; Critchley, 2005; Eippert et al., 2007; Lemche et al., 2007 (a), 2008 (b); Craig, 2009; Craig & Craig, 2009; Klumpers et al., 2010; Gu et al., 2013; Seth, 2013;

Seth & Critchley, 2013; Jay et al., 2014; Xia et al., 2017; Vinberg et al., 2021). The AIC has been shown to be involved in various neurobiological processes such as converting emotion into feeling states, negative affective states, response inhibition, saliency networks, interoceptive awareness, predictive-coding, and the mediation of autonomic skin conductance responses (Vergallito et al., 2018). The rVLPFC has now been studied in many areas of emotion regulation for example, social exclusion / social pain / ostracism / rejection (Chester & DeWall, 2014; Riva et al., 2014; He et al., 2018(a), 2019 (b)), aggression and impulsivity (Cohen et al., 2011; Riva et al., 2017; Chen, 2018), depression (Kober & Ochsner, 2011; Gallucci et al., 2020) in addition to Heutoscopy, Autoscopy etc. (Blanke et al., 2000; Kaladjian et al., 2007; Leitman et al., 2011; Zhang et al., 2019).

In DPD and DLE, researchers have posited that the rVLPFC overly-inhibits the AIC and thereby suppressing autonomic activity (Sierra et al., 2002 (a), 2005(b); Dewe et al., 2016 (a), 2018 (b); Braithwaite et al., 2020). This was supported by evidence from Jay et al., (2014) whereby attenuated skin conductance responses were alleviated by low frequency rTMS stimulation to the rVLPFC in depersonalised patients. And so, one of the aims of Chapter 3 was to examine the functional relationship of rVLPFC in mediating cognitive affective states in those predisposed to DLE with MtDCS stimulation.

However, the findings did not reveal any differences in the skin conductance responses across the stimulation conditions (Anodal, Cathodal and Sham). The responses from the frequency of NS-SCRs showed a slight suppression in the cathodal stimulation (however a weak effect or inconclusive) which suggests that the stimulation paradigm may have mediated skin conductance responses to a certain degree. Unfortunately, the use of random sampling to collect the sample in Chapter 3 resulted in a narrow range of scores on the DLE – and therefore one reason why the findings were not as strong here could simply be due to there not really being a strong presence of DLEs in the sample in the first place. It is

possible that targeted sampling of predisposition groups with a greater difference in scores would result in greater differences and less noise in the data, providing a stronger test of this hypothesis. Further evaluations with DPD patients under this paradigm may indeed reveal differences in network dynamics between DPD patients and neurotypical population which will provide valuable insights into the functioning of the rVLPFC.

Nevertheless, our findings from the AHE factor (indexing cortical hyperexcitability) directly addresses key questions about the role of the rVLPFC in autonomic activity. Firstly, this showed that inhibiting the rVLPFC does indeed show differences in autonomic activity. In this case, instead of the eliciting stronger SCRs when inhibiting the rVLPFC, our findings showed the opposite pattern to those from Jay et al. (2014). This implied that the inhibitory condition did not “release” responses of autonomic arousal but increased the activity in the rVLPFC which decreased the responses. The study from Chapter 3 was notably different to that from Jay et al. (2014) in that this study examined functioning of the rVLPFC in neurotypical individuals and not patients diagnosed with depersonalisation. In addition to this, participants in Chapter 3 were also screened for cortical hyperexcitability to assess the differential effects of brain stimulations as a function of background trait-based indicators. Furthermore, two different types of brain stimulation paradigms were utilised, MtDCS in Chapter 3 vs. low frequency rTMS in Jay et al., (2014). However, the opposite effects found in Chapter 3 are intriguing and may perhaps suggest that there is a functional difference and redescription required in the inhibitory performance of the rVLPFC in neurotypical individuals and those that have transitioned to a disorder.

The influence of rVLPFC as an inhibitor of the AIC may be theorised using the two prominent theories of dysfunctional fronto-limbic suppression and predictive coding (see Chapter 1) in the following way given the present findings. In the low group, assuming normal threshold for activation (Sierra & Berrios, 1998; Sierra et al., 2005; Sierra, 2009;

Sierra & David, 2011, Dewe, 2018), cathodal stimulation would increase this threshold / activity, perhaps inducing a larger prediction error whereby reducing efficiency of the rVLPFC resulting in higher autonomic activity. Meanwhile, in the high group, a hyperexcitable region would imply a lower than normal threshold for activation which would be suppressing autonomic activity naturally / aberrantly, and so, it would be assumed that cathodal stimulation would lower hyperexcitability, resulting in normal autonomic responses (from attenuated states). However, based on Bayesian inferences (statistical learning) in reducing prediction error (Lee & Mumford, 2003; Friston, 2009; Seth et al., 2012; Clark, 2013; Seth, 2013; Apps & Tsakiris, 2014; Sel, 2014; Aitchison & Lengyel, 2017; Gerrans, 2019), perhaps over time, to account for trait-based hyperexcitability, the threshold would gradually / steadily increase in neurotypical individuals. This would account for cathodal stimulation decreasing this threshold (as opposed to increasing it under normal assumption) and therefore resulting in autonomic suppression. Perhaps, with clinical levels of depersonalisation, Bayesian inferencing does not increase prior predictions which means that the lowered threshold for activation is not updated and that hyperexcitability is a persistent state. This persistent state would perhaps explain why Jay et al. (2014) found low frequency rTMS to reduce hyperexcitability in the rVLPFC that brought attenuated autonomic activity to normal levels. This would also highlight the importance of interoceptive or internal information in maintaining cortical efficiency in minimising prediction error (Seth et al., 2012; Seth, 2013; Sel, 2014) along with the importance of cortical hyperexcitability in this region.

Secondly, the DVP and the HVSD factor from the CHi_II highly correlated with the DLE factor. This is interesting because neither of these CHi_II factors include items that represent true hallucinations and depersonalisation, as a clinical disorder, is also not typified by the presence of hallucinations (Sierra, 2009; Sierra & David, 2011; Braithwaite et al.,

2015; Fong et al., 2019). Although the CHi_II measure is primarily based on hyperexcitability due to aberrant perceptual experiences, the association with the DLE to factors of the CHi_II measure that are focussed on visual distortions and anomalies provides for further understanding of cognitive biases underlying aberrant experiences as well as the utility of the CHi_II measure. Collectively, we suggest that the CHi_II measure is more sensitive with regards to identifying predisposition to aberrant experiences in the neurotypical population. Further work providing insights into the aberrant experiences may consider using the CHi_II measure in quantifying the population. Perhaps even within the DPD patients, the CHi_II measure may provide further varying responses to cathodal stimulation which will clarify the functioning of the rVLPFC in relation to aberrant experiences.

Thirdly, as mentioned above, our evidence highlights that, questions designed to quantify cortical hyperexcitability in core visual areas, might also be capable of reflecting hyperexcitability as a more domain-general component of cortical processing for some observers. Indeed, results from Chapter 3 and speculations from Chapter 4 (discussed below), show that cortical hyperexcitability can be considered as a domain general occurrence. In relation to DPD experiences, these findings provide evidence that cortical hyperexcitability mediates cognitive affective states and is an important consideration into the role of aberrant experiences.

Multi-Channel Transcranial Direct Current Stimulation

In Chapter 3, there appeared to be no reliable effects of MtDCS brain stimulation when analysed at the whole sample level. Both Anodal and Cathodal conditions were statistically indistinguishable from the no stimulation / Sham condition. However, the crucial new and key finding here showed that when the sample was stratified in terms of trait-based measures

of cortical hyperexcitability significant differences were indeed present. As scores on the AHE factor for the CHi_II measure increased, the strength of maximum threat SCRs, NS-SCRs, and their frequency were all suppressed – but only for the cathodal condition.

Although there was a trend for a mirror-opposite trend for SCRs to increase under the anodal conditions – this was not reliable. Neither the DVP nor the HVSD factors correlated with the efficacy of brain stimulation.

Specifically, Chapter 3 used a direct trait-based measure of aberrant experiences (that represent a proxy measure for cortical hyperexcitability) to assess the efficacy of optimised MtDCS brain stimulation on influencing changes in autonomic activity when participants viewed aversive body-threat stimuli. Typically, the notion of a hyperexcitable visual cortex has been established, for the most part, on the presence of aberrant visual perceptual experiences (Siegal, 1977; McGuire et al., 1993; Panayiotopoulos, 1994(a), 1999(b); Manfred & Andermann, 1998; Bien et al., 2000; Bresloff et al., 2001(a), 2002(b); Braun et al., 2003; Sass & Parnas, 2003; Taylor et al., 2003; Allen et al., 2008; Elliot et al., 2009(a), 2009(b)).

However, the findings from Chapter 3 significantly extend this notion. The items that make up the CHi_II factors are all of a visual nature with the underlying assumption being that these aberrant experiences most likely reflect cortical hyperexcitability occurring in early primary and associative visual cortex (and regions heavily involved in visual processing) – which is supported by findings from the wider cognitive neurosciences (Aurora et al., 1999(a), 2003(c); Hadjikhani et al., 2001; Bresloff et al., 2001(a), 2002(b); Huang et al., 2003; Aurora & Wilkinson, 2007; Braithwaite et al., 2013(a), 2015(b); Fong, 2019; Fong et al., 2019(a), 2020(b)). However, the findings presented here show that scores on a subset of these items (the AHE factor) were reliably associated with the efficacy of brain-stimulation to

modulate autonomic functioning when applied to regions significantly anterior to visual cortex (the rVLPFC).

This is consistent with the idea that although cortical hyperexcitability is being quantified here via the presence of aberrations in visual experience, cortical hyperexcitability itself need not be limited to visual areas but could be considered to be more of a domain general factor – extending far beyond visual areas. Future research could explore the fascinating prospect that some disorders and conditions may reflect hyperexcitability localised to certain regions, and yet other conditions and disorders may represent a more general type of hyperexcitability that may involve several cortical regions.

The findings from the trait-based measure of DLE on magnitudes of SCRs and NS-SCRs were not reliable, however, as scores on DLE increased, a significant suppression (although inconclusive under Bayesian analysis) in the frequency of NS-SCRs occurred for the Cathodal condition and this went in the same direction as the findings from the CHi_II measure. This suggests that perhaps similar effects could be observed with targeted sampling of DLE scores (in addition to better power) to identify extremes, which unfortunately the current sample did not.

Quantifying Aberrant Body Experiences

In prior research, atypical cognitive-affective responses to negative stimuli have been typically examined using the IAPS stimuli which do not contain specific standardised body-aversive threats and do not contain specific conceptualised baseline stimuli (Philips & Sierra, 2003; Ragdale et al., 2013; Braithwaite et al., 2020). The novel Body Threat Assessment Battery (BTAB – Braithwaite et al., 2020) was developed to address these (and other) concerns. The original study by Braithwaite et al. (2020) provided psychophysiological (and

psychological) normative data that the magnitudes of event-related SCRs for body-threat stimuli were stronger than for non-body threat stimuli. The potency for aversiveness was matched for the types of body-threat clips (throat cut, finger cut etc. – see Braithwaite et al., 2020 for full set of body-threat clips) across the different test blocks / series of clips used.

In Chapter 2, a new methodological improvement to the BTAB was introduced to assess psychophysiological and psychological responses to a continuous presentation of a series of clips shown in one stream (all body-threat vs. non-body threat clips). The rationale was to provide a more parsimonious experimental approach (as mentioned in Chapter 2) that did not involve a clip-by-clip assessment and could be paired with neuromodulation studies. By doing so, this provided evidence for the further utility of the BTAB tool in assessing biases underlying aberrant body-experiences with important implications for other neuroscientific investigations (i.e., brain stimulation - see Chapter 3; and brain-imaging). Additionally, Chapter 2 examined the use of FaceReader as a second objective psychophysiological measure that could potentially provide further insights into varying visceral affective responses to aberrant body-experiences.

Overall, the findings from this new continuous presentation approach were successful in that significantly increased psychophysiological activity and increased psychological ratings occurred for body-threat blocks vs non-body threat (baseline) blocks. Magnitudes of SCRs (Phasic), NS-SCRs (Tonic) and frequency of NS-SCRs (Tonic) were significantly increased for body-threat stimuli when compared to baseline non body-threat stimuli. This evidence was supported by the psychological ratings that were reported after each series of clips on all dimensions (emotional arousal, emotional valence, sense of illusory / sensory pain and realism of threat). The ratings for body-threat were significantly increased (i.e., more arousing, more negative, stronger sense of illusory / sensory pain and more threatening).

In addition, for the first-time, FaceReader responses (FRR) showed significantly increased arousal to body-threat stimuli which was comparable with the SCR – autonomic findings described above. This was also the case for significantly more negative valence factor and the negative emotions factor. However, although the FRR data independently validated and showed similar responses to the SCRs and psychological ratings, these data did not reliably correlate with each other. A potential methodological reason for this was that FRR values were considered for the whole-time frame of the series of clips (or block of clips), perhaps a time-series analysis (with bin-by-bin comparison) would be better suited to assess association with the SCR and psychological ratings.

Chapter 2 also examined if predisposition to aberrant visual experiences and aberrant beliefs reveals differences in autonomic responses in viewing the aversive body-threat stimuli. However, in contrast to expectation (only for aberrant visual experiences), the findings did not suggest any reliable associations between predisposition to aberrant visual experiences or predisposition to aberrant beliefs (at least via the measures and scales utilised in the present work) with psychophysiological responses or psychological ratings.

Aberrant visual experiences and Aberrant beliefs

As discussed above, Chapter 2 examined if predisposition to aberrant visual experiences and aberrant beliefs may reveal differences in autonomic responses to viewing the BTAB.

Aberrant perceptual experiences are thought to precede aberrant body experiences (Fletcher & Firth, 2009; Wright et al., 2020). Many conditions in the neurotypical and clinical population are associated with both aberrant visual and aberrant body experiences, for example, out-of-body experiences, Autoscopy, and Heautoscopy (Brugger et al., 1997; Blanke et al., 2004; Blanke & Mohr, 2005; Blanke & Castillo, 2007; Braithwaite et al., 2011).

This suggests that at a neural level, there may be some overlap between the aberrant perceptual and aberrant body experiences (with the latter involving multisensory integration processes). Studies have shown those predisposed to aberrant body experiences show attenuated autonomic activity to viewing aversive body-threat stimuli (Sierra et al., 2002 (a), 2005(b); Dewe et al., 2016 (a), 2018 (b); Braithwaite et al., 2020). However, the findings from Chapter 2 did not show similar attenuation when participants were screened for (non-depersonalised) aberrant visual experiences suggesting that these two types of aberrant experiences were distinct from each other and that aberrant visual experiences may not be associated with the neural networks associated with aberrant body experiences (such as prefrontal areas, AIC etc.). It is important to note here that the psychological ratings negatively associated with the scores on aberrant visual experiences. This suggests that perhaps the questions on the visual items of the MUSEQ (see Mitchell et al., 2017 and Table 2.1 from Chapter 2) were too generalised and leaned heavily on complex hallucinations in addition to lacking / limited sensitivity. This might suggest why this measure failed to capture variability in autonomic responses which are more related to distortions in aberrant body experiences.

This was also the case when participants were screened for predisposition to aberrant belief. Aberrant beliefs are thought to be rationalisations of aberrant perceptual and aberrant body experiences (Wright et al., 2020). Whilst it can be considered that there may potentially be an overlap between aberrant perceptual and aberrant body experiences, there has been limited research that have evidenced this (Bentall et al., 2001; Blackwood et al., 2001; Gilleen & David; 2005; Bell et al., 2006; Salvatore et al., 2012). There were no reliable associations between SCRs, FRRs and psychological ratings and predisposition to aberrant beliefs in our current sample. This may provide further support to the notion that the presence

of aberrant beliefs, while they can be influenced by aberrant perceptions, they also rely on distinct neural systems arguably involved in the processes of belief evaluation.

Interestingly, the lack of effects for aberrant belief is clear evidence against the notion that some of the findings presented here in this thesis can be explained by a generic response bias. Response biases (jumping to conclusions) can and do occur in some hallucinating patient populations – most notably schizophrenia and schizotypy (Dudley & Over, 2003; Holt et al., 2006; Fine et al., 2007; Moritz & Laudan, 2007; Salvatore et al., 2012; Underwood et al., 2016). Such biases influence observers to positively endorse items on questionnaire measures (as a kind of demand characteristic) rather than accurately represent the individual's conscious experience. These response biases are primarily associated with predisposition to aberrant belief, and not aberrant experience. The current findings reported in this thesis goes against the notion that response biases are present and skewing the underlying data. If they were present, they would impact on all psychological ratings equally, would not support the distinction between threat and baseline stimuli, and would be present in the brain-stimulation conditions in Chapter 3 to a similar magnitude. Clearly this did not happen.

Interoceptive Awareness

Given the findings from Chapter 3, the notion of cortical hyperexcitability as a domain general occurrence and the role of interoceptive awareness in therapeutic settings was explored in Chapter 4. As mentioned above, there was no evidence of differences in motor excitability or the loss of corticomotor efficiency in the high and low DLE groups. The obvious explanation here was that the sample size was too low. However, given the findings from Chapter 3, we speculate that a much larger sample size with selective testing of extremes would be needed to draw out the differences in DLE if indeed they are present.

The index of interoceptive vulnerability (as reflected by autonomic responses) and the AHE factor from the CHi_II measure showed a slight suggestion (although unreliable) that the high groups on these factors (IV – SCRs from the IBT task and CHi_II) exhibited higher motor excitability (or a lower motor threshold). Although these findings are based on a small dataset with limited statistical power, speculatively, the findings are in line with the understanding of cortical hyperexcitability in which a hyperexcitable cortex is related to more aberrant perceptual experiences as a result of a lower threshold in the visual cortex which means that the cortex is easier to excite (Hadjikhani et al., 2001; Huang et al., 2011; Braithwaite et al., 2015). This also extends the understanding of cortical hyperexcitability is not limited to the visual and striate areas but can be a more domain general occurrence.

The similar pattern that was seen in the high and low IV groups (again, unreliably so), suggesting that interoceptive awareness and its relationship with exteroceptive awareness is indeed interdependent (Tsakiris et al., 2011) as well as highlighting the importance of interoceptive awareness in therapeutic settings.

The causal role of loss of immobilisation and cortical hyperexcitability or IV was not known in the context of the sample from Chapter 4. The reason for this was that the Treatment rTMS group and the Sham rTMS group were not considered when the participants were stratified based on their trait- and state- based scores due to a low sample size. However, the lack of rTMS being able maintain corticomotor efficiency alone even with a larger sample and comparison between Treatment and Sham groups (as with Gaffney et al., 2021) was an indication that interoceptive awareness and cortical hyperexcitability may indeed play an important role in any therapeutic measures taken. The findings from Tsakiris et al. (2011) showed that participants with low interoceptive awareness more readily accepted the fake hand (from RHI) as their own. In conjunction with this, studies that show self-generated actions (exteroceptive awareness) are important to maintenance of motor cortex

excitability following immobilisation (Sharma et al., 2006; Zimmerman-Schlater et al., 2008, Bossolino et al., 2014; Buccino, 2014; Meugnot et al., 2015; Derbanot et al., 2020). Based on the predictive coding mechanism, the addition of motor imagery / action observation (Sharma et al., 2006; Zimmerman-Schlater et al., 2008, Bassolino et al., 2014; Buccino, 2014; Meugnot et al., 2015; De Marco et al., 2021) could increase interoceptive awareness which can be considered malleable (prior information). This would be useful in reducing prediction error (induced by rTMS to the immobilised arm) and thereby make the rTMS protocol more effective in maintaining corticomotor efficiency during immobilisation. Collectively this suggests that further work is needed in understanding the specific role of cortical hyperexcitability and aberrant body experiences (interoceptive vulnerabilities) in any therapeutic stimulation studies.

Repetitive Transcranial Magnetic Stimulation

Building on the findings from Chapter 3, Chapter 4 further explored the role of cortical hyperexcitability as a domain general occurrence in a novel ‘real-life’ simulation (of right arm immobilisation for 72 hours) as well as with a different technique of brain stimulation (rTMS).

Although the exploratory findings of Chapter 4 should be interpreted cautiously due to low sample size, the overall pattern of effects identified in Chapter 3 were indeed present here. Trait-based stratification of the sample based on cortical hyperexcitability suggested that high scorers exhibited higher motor cortex excitability (or what one might consider as lower threshold for excitation) than the low scorers (though this trend was not reliable). This was also reflected in the loss of motor excitability as the pattern suggested that high scorers exhibited less loss after the 72-hour immobilisation than the low scorers. This may suggest

that the high predisposition group was more amenable to brain stimulation from the rTMS protocol and so the degradation of corticomotor excitability was less efficient in this group. However, notably, as mentioned previously, the effects of the high frequency rTMS intervention on the loss of motor cortex excitability is not known in the findings of the present study. This was because the high and low predisposition groups did not differentiate between the Treatment and Sham groups (due to the low sample size).

The DLE trait-based measure yielded no differences between the high and low groups in Chapter 4, which resonated with the findings from Chapter 3. However, the pattern of effects obtained from stratification of participants based on the index of interoceptive vulnerability – as measured by SCRs to the IBT task (high IV vs low IV) were similar to those from the CHi_II measure (although not reliably so). It is important to note here that although this discussion is cautious in interpreting the exploratory and null findings in Chapter 4, the Bayes Factor for each of the trait- and state-based quantification measures was inconclusive, which suggests that further research to lend support to these measures is needed with more conclusive results.

The findings from both Chapters 3 and 4 suggest that the trait-based predisposition to cortical hyperexcitability can have domain-general characteristics extending across several brain regions and that this proxy measure has utility in assessing variability in individual brain states for brain stimulation studies.

Future Work

Findings from Chapter 2 showed that FRR data can indeed reliably delineate between body-threat and baseline stimuli. This suggests that the FaceReader is a promising tool that can be utilised in assessing cognitive-affective biases underlying aberrant experiences. Future

studies can consider a time-series analysis (using time-bins or segments moving through the signal) which may provide further utility in utilising the FaceReader tool in this research.

In identifying predisposition groups in the neurotypical samples, future studies can perhaps consider recruiting a larger variation in scores by selective sampling. In this thesis, whilst the findings were successful in revealing biases underlying aberrant experiences from the random-sampling method, the scores indicated that extremes of the neurotypical population were not identified. Perhaps the larger variation in scores and an increased sample size would reveal more stronger causal associations that could further the insights have been provided in the role of cortical hyperexcitability underlying aberrant experiences in the neurotypical population.

In addition, future studies can examine the role of cortical hyperexcitability in mediating cognitive affective biases with other state-based measures (e.g., Pattern Glare Task). The relationship between trait-based and state-based factors is not a clear one. It is not simply the case that increased signs on one measure are associated with similar signs on the other. This suggests that while there may be some interdependence between these processes, both also enjoy a degree of independence from each other (Basten et al., 2011; Krause & Cohen Kadosh, 2014; Hamada et al., 2013; Horvath et al., 2014). Nonetheless, there are too few studies that examine these factors, even more so in relation to aberrant experience.

Further studies can also validate the CHi_II measure with other conditions and disorders of aberrant experiences such as out-of-body experiences (OBEs).

Finally, it would be highly interesting to utilise the findings from this thesis in the depersonalised population. Given the opposite findings from Chapter 3 and Jay et al. (2014) the paradigm used in this thesis could indeed replicate or provide further insights such as a functional redescription between depersonalised patients and neurotypical individuals and the

inhibitory performance of the rVLPFC in mediating cognitive affective biases in. This would also further provide stronger evidence highlighting the role of cortical hyperexcitability as a domain general occurrence.

Conclusions

This thesis presented research into the cognitive biases in aberrant experiences in the neurotypical population and highlighting the role of cortical hyperexcitability as a domain general occurrence. Collectively this thesis provides evidence that cortical hyperexcitability is not limited to sensory domains and has important implications in interoceptive awareness, dysfunctional inhibitory networks related to DPD, emotion regulation, attentional control etc. In addition, this thesis highlighted the utility of stratification the population of trait- and state-based measures in brain stimulation which would be missed at the whole sample level. In addition, we presented the validity and use of new methodological tools in assessing the latent biases underlying aberrant experiences in the neurotypical population that await further insights from the clinical population.

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Appendix

Chapter 2

Threat SCRs (SCR_T) vs. Threat FRRs (FRR_T)

Magnitude of Threat SCR (SCR_T) vs. Threat FRR (FRR_T)

Pearson's two-tailed r correlations were conducted between magnitude of SCR_T and FRR_T (Arousal, Valence and Negative) from the Threat Stimuli. However, no significant correlations were observed (Table 6.1).

Table 6.1

Pearson's correlation coefficients (FDR corrected for Frequentist analysis) and Bayes values between SCR_T and FRR_T_Arousal / Valence / Negative.

Correlation Pair	r	p value	B&H value	BF ₁₀ **	BF ₀₁ **	Bayes Value Interpretation**
SCR_T vs. FRR_T_Negative	0.055	0.631	0.017	0.157	6.351	Good Null
SCR_T vs. FRR_T_Arousal	-0.046	0.689	0.033	0.152	6.575	Good Null
SCR_T vs. FRR_T_Valence	-0.038	0.742	0.050	0.148	6.745	Good Null

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

Magnitude of Threat NS-SCR (NS-SCR_T) vs. Threat FRR (FRR_T)

Similarly, Pearson’s two-tailed *r* correlations were conducted between magnitude of NS-SCR_T and FRR_T (Arousal, Valence and Negative) from the Threat Stimuli. However, no significant correlations were observed (Table 6.2).

Table 6.2

Pearson’s correlation coefficients (FDR corrected for Frequentist analysis) and Bayes values between NS-SCR_T and FRR_T_Arousal / Valence / Negative

Correlation Pair	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁**	Bayes Value Interpretation**
NS-SCR_T vs. FRR_T_Arousal	-0.183	0.107	0.017	0.318	1.987	Inconclusive Null
NS-SCR_T vs. FRR_T_Valence	0.124	0.277	0.033	0.144	3.980	Good Null
NS-SCR_T vs. FRR_T_Negative	-0.112	0.326	0.050	0.142	4.431	Good Null

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

Frequency of Threat NS-SCR (F-SCR_T) vs. Threat FRR (FRR_T)

Similarly, Pearson’s two-tailed *r* correlations were conducted between Frequency of NS-SCR / F-SCR_T and FRR_T (Arousal, Valence and Negative) from the Threat Stimuli. However, no significant correlations were observed (Table 6.3).

Table 6.3

Pearson's correlation coefficients (FDR corrected for Frequentist analysis) and Bayes values between F-SCR_T and FRR_T_Arousal / Valence / Negative

Correlation Pair	<i>r</i>	<i>p</i> value	B&H value	BF₁₀ **	BF₀₁**	Bayes Value Interpretation**
F-SCR_T vs. FRR_T_Valence	-0.119	0.296	0.017	0.158	4.160	Good Null
F-SCR_T vs. FRR_T_Arousal	-0.106	0.351	0.033	0.215	4.642	Good Null
F-SCR_T vs. FRR_T_Negative	-0.055	0.629	0.050	0.240	6.344	Good Null

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

Threat Psychological Ratings (Ratings_T) vs. Threat FRRs (FRR_T)

Threat FRR Arousal (FRR_T_Arousal) and Ratings_T

Kendall's τ correlations were conducted between the FRR Arousal factor from the Threat stimuli (FRR_T_Arousal) and all factors of the psychological ratings obtained from the Threat stimuli (Ratings_T_Arousal / Valence / Pain / Threat). However, no associations were observed (Table 6.4).

Table 6.4

Kendall's correlation coefficients (FDR corrected) and Bayes values between

FRR_T_Arousal and Ratings_T_Arousal / Valence / Pain / Threat

Correlation Pair	τ	p value	B&H value	BF₁₀ **	BF₀₁	Bayes Value Interpretation**
FRR_T_Arousal vs. Ratings_T_Pain	-0.097	0.243	0.013	0.342	3.085	Good Null
FRR_T_Arousal vs. Ratings_T_Valence	-0.072	0.377	0.025	0.227	4.409	Good Null
FRR_T_Arousal vs. Ratings_T_Threat	-0.051	0.521	0.038	0.182	5.487	Good Null
FRR_T_Arousal vs. Ratings_T_Arousal	-0.019	0.808	0.050	0.151	6.608	Good Null

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

Threat FRR Valence (FRR_T_Valence) and Ratings_T

Kendall's τ correlations were conducted between the FRR Valence (FRR_T_Valence) factor and all factors of the psychological ratings (Ratings_T_Arousal / Valence / Pain / Threat) obtained from the Threat stimuli. However, no significant correlations were noted (Table 6.5).

Table 6.5

Kendall's correlation coefficients (FDR corrected) and Bayes values between

FRR_T_Valence and Ratings_T_Arousal / Valence / Pain / Threat.

Correlation Pair	τ	p value	B&H value	BF₁₀ **	BF₀₁	Bayes Value Interpretation**
FRR_T_Valence vs. Ratings_T_Pain	-0.164	0.052	0.013	1.386		Inconclusive AH
FRR_T_Valence vs. Ratings_T_Arousal	-0.043	0.594	0.025	0.171	5.838	Good Null
FRR_T_Valence vs. Ratings_T_Valence	-0.011	0.898	0.038	0.148	6.755	Good Null
FRR_T_Valence vs. Ratings_T_Threat	-0.006	0.939	0.050	0.147	6.798	Good Null

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

Threat FRR Negative Emotions (FRR_T_Negative) and Ratings_T

Kendall's τ correlations were conducted between the FaceReader Negative factor and all factors of the psychological ratings obtained from the Threat stimuli (Valence, Arousal, Sense of Pain and Realism of Threat). However, no significant correlations were noted (Table 6.6).

Table 6.6

Kendall's correlation coefficients (FDR corrected) and Bayes values between

FRR_T_Negative and Ratings_T_Arousal / Valence / Pain / Threat.

Correlation Pair	τ	p value	B&H value	BF₁₀ **	BF₀₁	Bayes Value Interpretation**
FRR_T_Negative vs. Ratings_T_Threat	0.079	0.324	0.013	0.247	4.053	Good Null
FRR_T_Negative vs. Ratings_T_Pain	0.036	0.669	0.025	0.164	6.093	Good Null
FRR_T_Negative vs. Ratings_T_Arousal	-0.017	0.832	0.038	0.151	6.615	Good Null
FRR_T_Negative vs. Ratings_T_Valence	-0.007	0.934	0.050	0.148	6.715	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.