THE NEUROCOGNITIVE FACTORS UNDERLYING ANOMALOUS EXPERIENCE IN THE NON-CLINICAL POPULATION

by

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Abstract

Anomalous experiences (such as hallucinations) are known to occur in healthy, non-clinical groups. Despite this, the neurocognitive mechanisms underlying such experiences in these groups has received little attention. This thesis therefore aimed to explore the relationships between anomalous experience and one candidate neurocognitive mechanism, cortical hyperexcitability, in non-clinical samples.

Chapters 2 and 3 explored the contribution of visual cortical excitability to anomalous experiences in multiple modalities, by investigating the relationship between trait (questionnaire) and state (pattern glare) anomalous experiences under transcranial direct current stimulation (tDCS) of different areas of extrastriate cortex; Brodmann's areas 5 and 7, and 17-19 (targeted with electrode sites Pz and POz respectively). These chapters evidenced differential relationships between visual trait and state measures. Chapter 2 revealed a trait-state relationship a relationship that was influenced by anodal tDCS brain stimulation, but only in those predisposed to pattern glare (indicating cortical hyperexcitability). Chapters 2 and 3 evidenced significant interactions between state experiences of pattern glare and tDCS condition, suggesting that these anomalous experiences vary depending on baseline excitability.

Chapter 4 explored whether the trait-state relationships observed within the visual modality in the previous chapters could be extended to auditory cortex. Trait and state anomalous experiences were again measured using questionnaires and pattern glare respectively. EEG-based sensory gating was used to index state

auditory cortex inhibition. Chapter 4 tentatively suggested a cross modal relationship, with greater trait predisposition to anomalous visual experiences associated with greater suppression of the auditory P2 component. Greater P2 suppression may lead to source labelling errors and so perceptual distortions.

Overall, this thesis indicates intriguing subtleties in the relationships between trait and state measures of anomalous experience and cortical excitability, that are also modality-dependent.

Main argument

The main argument of this thesis is that cortical hyperexcitability is a possible “bottom-up” mechanism underlying anomalous experiences in the healthy non-clinical population (see Figure A1). Predisposition to these experiences may depend on baseline cortical excitability states, with those with heightened baseline excitability being more likely to have anomalous experiences. In contrast, those low to normal baseline excitability may be less predisposed to these experiences. If the heightened excitability occurs in visual cortex, individuals are more likely to have visual anomalous experiences – particularly those analogous to “positive” elementary hallucinations (see Figure A2). Considerable further work is needed to fully understand these relationships, such as teasing out the relationships between trait (predisposition to) and state (ongoing experience of) anomalous perceptions. Cortical hyperexcitability may also interfere with “top-down” forward processing to produce anomalous experiences in healthy groups. It is possible that cortical hyperexcitability within e.g. the visual network can spread to or influence

processing in other sensory networks, e.g. auditory. To move this research area forward, there is need to test and establish more precise measures or indicators of state cortical excitability in healthy groups.

Visual abstract – Core concepts

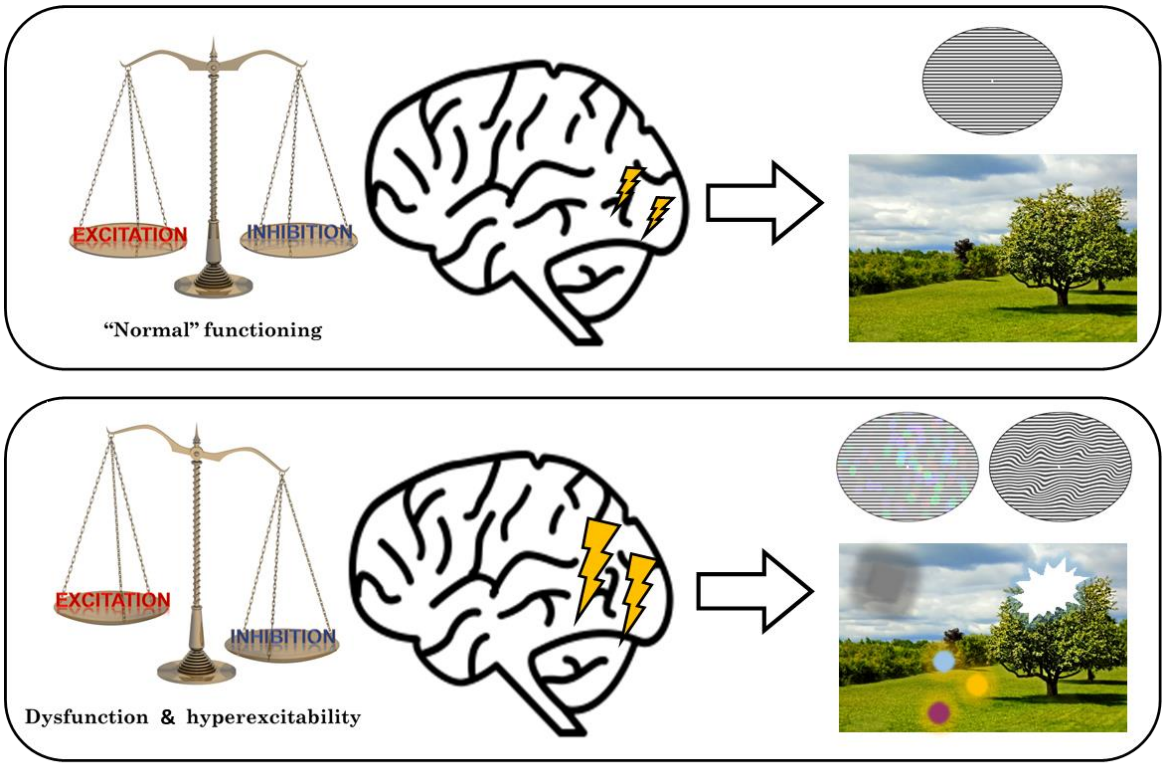

Figure A1 – Visual abstract of the proposed relationship between cortical excitability and perception. The top panel shows "normal" neuronal functioning, with balanced excitation and inhibition. This is associated with "normal" excitability in visual cortex and veridical everyday perception, and so little to no pattern-glare-type visual distortions. The bottom panel shows cortical hyperexcitability, where excitation and inhibition are not balanced. This is associated with increased excitability in visual cortex, and so increased pattern glare and anomalous experiences.

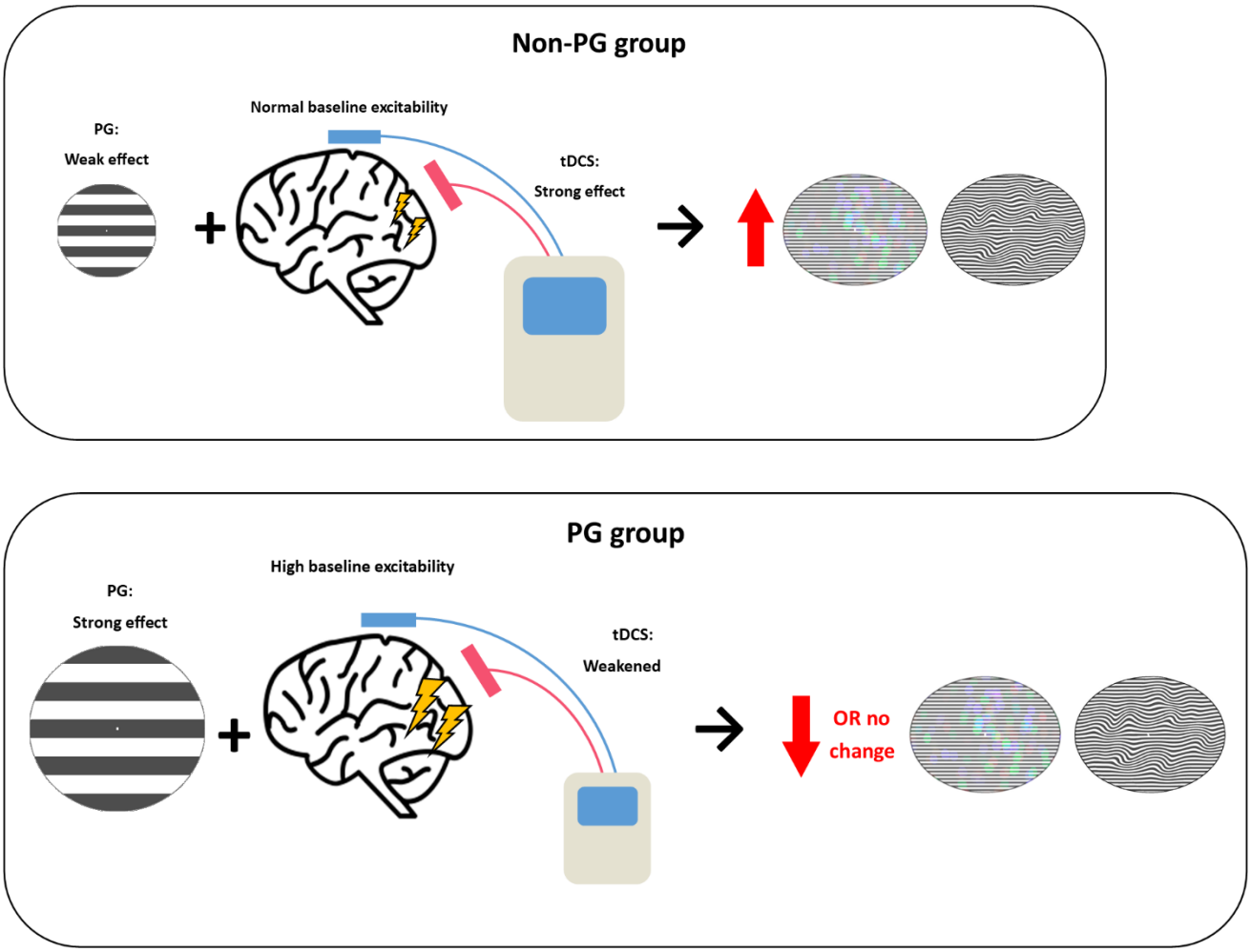

Figure A2 – Visual abstract of the proposed relationship between cortical excitability, pattern glare (PG), and transcranial direct current stimulation (tDCS). It may be that baseline excitability interacts with tDCS to produce different effects. The top panel shows proposed relationships for the "non-PG" groups studied here, with low to "normal" visual excitability (scoring <1 on the PG task). Here, anodal tDCS excites visual neurons and increases PG experiences, whilst cathodal tDCS may prime visual neurons to also increase PG experiences. The bottom panel shows proposed relationships for the "PG" groups (with high visual excitability, scoring 1 or more on the PG task). In contrast to the non-PG groups, here anodal tDCS may not be able to excite visual neurons or may cause reversal effects (due to combining tDCS and PG stimulation), leading to no change or decreases in PG experiences. Cathodal tDCS may not be able to exert inhibitory effects due to deficient inhibition, leading to no change in PG experiences.

Dedication

This thesis is dedicated to anyone who has struggled with their mental health.

You can do anything you set your mind to. I have, and I did.

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Publications and Presentations

During the course of my PhD in the School of Psychology, University of Birmingham, the following were submitted for publication or presented at conferences. Where listed, secondary authors contributed to the work through advice on study design, data analysis, and paper editing.

Papers submitted for publication

An edited version of Chapters 2 and 3 has been submitted as:

Marchant, R., Mevorach, C., and Braithwaite, J.J. (*Under review*). Examining individual predisposition to anomalous experiences in the non-clinical population using transcranial direct current stimulation (tDCS) of extrastriate cortex. *Cognitive, Affective, and Behavioral Neuroscience*.

Conference presentations

Marchant, R. & Braithwaite, J. (2017, April). *Using the Cortical Hyperexcitability index (CHi) to predict anomalous experience in psychologically-healthy young people.* Oral presentation at **the International Association for Youth Mental Health 2017**, Dublin, Ireland.

Marchant, R. & Braithwaite, J. (2017, April). *Stimulating the mind: Exploring predisposition to anomalous visual experiences using transcranial direct current stimulation (tDCS)*. Poster presented at the “Of mice and mental health: Facilitating dialogue between basic and clinical neuroscientists” scientific meeting**, Royal Society**, London, UK.

Marchant, R. & Braithwaite, J. (2017, April). *Stimulating the mind: Exploring predisposition to anomalous visual experiences using transcranial direct current stimulation (tDCS)*. Poster presented at the **British Neuroscience Association Festival of Neuroscience**, Birmingham, UK.

Marchant, R. & Braithwaite, J. (2017, March). *Stimulating the mind: Exploring predisposition to anomalous visual experiences using brain stimulation*. Poster presented at the second **Midlands Medical Academy of Sciences Research Festival**, Warwick University, UK.

Marchant, R. (2016, October). “Predisposition to anomalous experiences: An investigation using tDCS brain stimulation methods.” Invited presentation, Department of Psychology, **University of Lancaster.**

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List of Abbreviations

AHE	Aura-like Hallucinatory Experiences
AVD	Anomalous Visual Distortion
BOLD	Blood Oxygenation Level Dependent
CAPS	Cardiff Anomalous Perceptions Scale
CBS	Charles Bonnet Syndrome
CHi	Cortical Hyperexcitability index
CHi-II	Cortical Hyperexcitability index II
CPD	Cycles Per Degree
CSD	Cortical Spreading Depression
DVP	Distorted Visual Perception
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
HVSD	Heightened Visual Sensitivity and Discomfort
M-HΔ	Medium-High Difference
MUSEQ	Multi-modal Unusual Sensory Experiences Questionnaire
PG	Pattern Glare
tDCS	Transcranial Direct Current Stimulation
TLE	Temporal Lobe Experience
TMS	Transcranial Magnetic Stimulation
VEP	Visual Evoked Potential

1 Foreword to Chapter 1

Chapter 1 provides an overview of the theoretical concepts and empirical literature relevant to this thesis. The first section discusses the definition of “anomalous experiences”, arguing that terms such as “hallucination” and “misperception” exist along a spectrum of experience that cannot be clearly defined into such discrete categories. Therefore, the term “anomalous experience” is used to refer to unusual sensory experiences. The second section gives an overview of anomalous experiences in clinical and non-clinical groups, evidencing considerable variation in the phenomenology of these experiences in non-clinical individuals that is often comparable to anomalous experiences in clinical groups. This is followed by a brief review of the different neurocognitive mechanisms that have been suggested to underlie anomalous experiences across clinical and non-clinical groups. This section concludes that cortical hyperexcitability is a promising and well-evidenced mechanism for anomalous experiences, and may provide a mechanistic bridge between such experiences in clinical and non-clinical groups. Following is a brief explanation of cortical hyperexcitability, including how it differs from normal synaptic function and its definition as used in this thesis. The evidence for cortical hyperexcitability in anomalous experiences across clinical and non-clinical groups is then considered. Finally, the aim of this thesis and questions to be answered are outlined.

1 General Introduction

1.1 What are “anomalous experiences”?

“Anomalous experiences” (AEs) are perceptual experiences that deviate significantly from usual, everyday experience (Cardeña, Lynn, & Krippner, 2014). Anomalous experiences can occur in any sensory modality; they can be visual, auditory, gustatory, olfactory, tactile, somatic, proprioceptive, interoceptive, thermoceptive, nociceptive, mechanoreceptive, and chronoceptive (time) (Bell, Halligan, Pugh, & Freeman, 2011; Braithwaite, Samson, Apperly, Broglia, & Hulleman, 2011; Cardeña et al., 2014; Larøi et al., 2012). They can also be uni- or multi-modal (Braithwaite et al., 2011). The term “anomalous experience” covers a wide range of experience types, including hallucinations and distortions. These different types of experience are defined and explored below.

“Hallucinations” are perceptions in any sensory modality that are not elicited by a corresponding external stimulus (Waters et al., 2016). Some definitions of “hallucinations” are unclear, such as “waking experiences which have the character of veridical perceptions, but are elicited in the absence of a *relevant* external stimulus” (Mitchell et al., 2017)(emphasis added). It is difficult to say what “relevant” means here. David (2004) provides a more detailed definition that resolves this:

> *"A sensory experience which occurs in the absence of* ***corresponding external stimulation*** *of the relevant sensory organ, has a sufficient sense of reality to resemble a veridical perception, over which the subject does not feel [they have] direct and voluntary control, and which occurs in the awake state."*
>
> p108 of David (2004), as quoted on p15 of Aleman & Larøi (2008), emphasis added

Importantly, because this definition includes the phrase "corresponding external stimulation", it accommodates hallucinations that are caused when a hallucination in one modality is caused by external stimulation of the same modality but does not *directly* correspond to the experience; i.e. where the hallucination is qualitatively different to the stimulus. For example, some hallucinations involve hearing voices when the vacuum cleaner is turned on (Kern, 2014). In this situation, although the auditory sense is being stimulated by an external source, the quality of the source (noise) does *not directly correspond* to the quality of the actual experience (voices).

Aleman & Larøi (2008) also suggest an additional caveat to be included in David's (2004) definition; that to be classed as a hallucination, the experience should be accompanied by a strong "conviction that one perceives [something]… even though one can be aware that [it] does not exist independent of the observer" (Aleman & Larøi, 2008, p. 18); in other words, having a vivid and seemingly veridical experience whilst potentially also having clear insight that the experience is not real. However, the latter suggestion is problematic because insight can change with the course of diseases. This occurs in Charles Bonnet Syndrome

(CBS), where hallucinations are sometimes not immediately recognised as hallucinations by the person experiencing them (Eperjesi & Akbarali, 2004; Kester, 2009), and in schizophrenia, where insight into the unreality of experiences is often lacking (Chaudhury, 2010). Therefore retained insight is a problematic caveat that cannot be consistently applied.

Further to the definitions above, hallucinations are often categorised as being either “simple” or “complex”. Simple hallucinations are experiences of rudimentary or geometric phenomena such as dots, shapes, lines, patterns such as grids, and flashes of light or colour, which are unformed or have intermediate corporeality. In contrast, complex hallucinations consist of images with definite form, such as people, objects, and animals (Mosimann et al., 2008).

In contrast to hallucinations, “distortions” are defined as misperceptions of existing external sensory stimuli (and are also sometimes unhelpfully referred to as illusions[1]) (Collerton et al., 2015). For this reason, some researchers refer to “misperceptions” as covering distortions and other changes to existing visual experience. For example, Mitchell et al. (2017) define misperceptions as

[1] Although attempts at classifying distortions and illusions and their different types have been made since the 19th century, the validity of these classifications remains under intense debate even today (Collerton, Mossimann, & Perry, 2015; Notredame, Pins, Deneve, & Jardri, 2014). Further, although generally thought to involve changes in visual lateral inhibition, the mechanisms underlying illusions vary widely (Eagleman, 2001). The relationship between illusions and anomalous experiences (such as in schizophrenia) is unclear (King, Hodgekins, Chouinard, Chouinard, & Sperandio, 2017), and how (if at all) these are connected to cortical hyperexcitability or pattern glare is not known. Therefore, a full discussion of illusions in relation to the current topic is outside the scope of this thesis.

“experiences whose relationship to stimuli in the outside world is distorted or changed in some way”. Similarly, Aleman & Larøi (2008) suggest that the distinction between a distortion and a hallucination should perhaps lie in how rare or unlikely the “perceptual mistake” is. They propose, for example, that mishearing a loud drilling sound as a scream might be a rather common mistake and therefore be classed as a distortion, but that hearing voices when the vacuum cleaner is on may be rarer and so would be termed a hallucination.

However, to apply such a distinction consistently, we would need to systematically characterise a potentially infinite variety of anomalous experiences to determine the frequency of each in the population, and so this distinction is not practical. Further, this definition blurs with that of hallucinations outlined above, as some hallucinations can be the result of a stimulus which is distorted so much that it seems to the experiencer to be a different perception altogether.

For example, for some susceptible individuals, looking at visually-irritating, achromatic striped patterns (such as escalator treads or venetian blinds - see **Figure 1.1**) can induce visual “distortions” such as bending, movement, or seeing coloured geometric shapes moving across the visual field (Haigh et al., 2013). These patterns can also induce somatic experiences such as pain, nausea, and dizziness. Some of these experiences could be understood as “misperceptions” (e.g. bending), however some are very different to the original stimulus and may be more accurately classed as “hallucination” (e.g. coloured shapes). Additionally, in susceptible individuals a wide range of experiences can be had, from simple to more complex. Some of these experiences seem completely different from, and

unrelated to, the original perception, despite the fact that they were indeed triggered by the original perception. This variation in reactions to the same stimuli makes it difficult to classify such experiences as definitely being either hallucinations or misperceptions, based on current definitions.

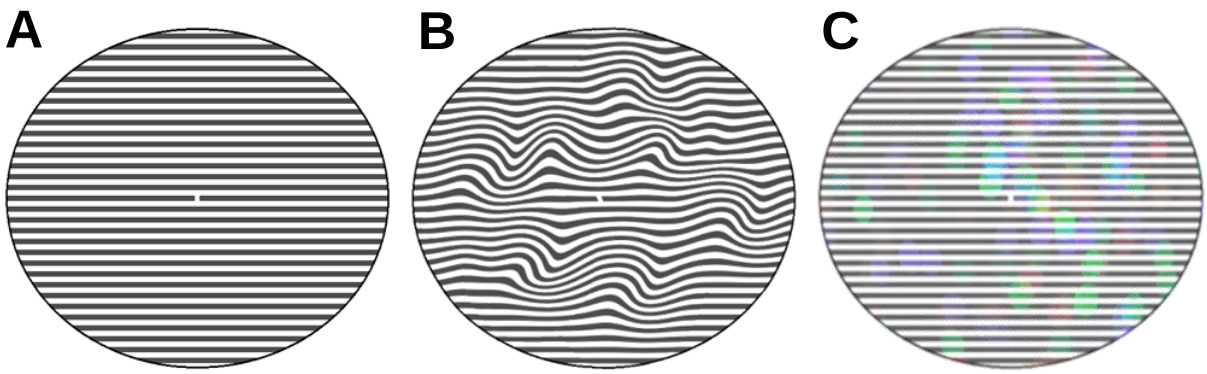

Figure 1.1 – Visually-irritating stimuli and example distortions. (A) Example of a striped grating that can induce visual (colours, movement) and somatic (nausea, dizziness) symptoms in susceptible individuals, known as “pattern glare”. (B) Example of a “bending” visual distortion experienced as part of pattern glare. (C) Example of “blurring” and “colour” visual distortions. These are examples only, as pattern glare experiences vary widely between individuals.

Overall, there is no clear distinction between misperceptions and hallucinations in the literature. Therefore, creating precise definitions that clearly demarcate these categories of experience is difficult.

It is also difficult in real clinical cases to definitively categorise anomalous visual experiences as either misperceptions or hallucinations (ffytche, 2014). Such

distinctions may not be practically helpful when exploring the neurocognitive correlates of conscious experience. Additionally, clear boundaries between different types of subjective perception do not exist (ffytche, 2014; Waters et al., 2016). Instead, sensory experiences can be placed on a continuum or spectrum from clear, veridical vision to complex hallucination, with misperceptions and voluntary imagery occurring somewhere in between (Waters et al., 2016) (see **Figure 1.2**). As Collerton et al. (2012) point out, within a constructivist model of visual perception (which can also be applied to other senses), “there is no sharp boundary around any visual phenomenon” (p78) and no clear division between veridical perception and hallucination “both conceptually and in practice” (p84).

Figure 1.2 – “Fuzzy forms of visual experience” (Waters et al., 2016). There are no clear boundaries between different experiences. Rather, these “categories” of perception all overlap to some degree.

Therefore, the terms “anomalous experience” or “anomalous perception” will be used throughout this thesis as an umbrella term. In line with current research, this approach takes a “spectrum” view of these experiences. “Anomalous experience” as used here includes misperceptions, distortions, and hallucinations, but does not include voluntary imagery (imagination) or dreams, as these types of experience are not within the scope of this thesis. Although the qualities of dreams and hallucinations overlap in places, there are “key differences that differentiate [dreams] from hallucinations” (Waters et al., 2016, p. 1102). Voluntary imagery also differs from anomalous experience in both phenomenological and neurophysiological terms[2].

The term “anomalous experience” is also useful in non-clinical research for replacing terms such as “hallucination” that can be problematic due to associated stigma and clinical implications. It also covers a wide variety of experiences that are of interest for this thesis and associated with similar neurocognitive mechanisms (discussed in detail further below). The term “anomalous experience” has now been in use for several years and is gaining popularity in the literature,

[2] In contrast to hallucinations, dreams are generally separable from waking reality (Waters et al., 2016). Voluntary imagery and anomalous experience can be further distinguished by differences in phenomenology and brain activity. Auditory hallucinations are associated with activation in fronto-temporal networks related to language, whereas imagining auditory hallucinations activates these networks as well as supplementary motor areas (SMA) (Raij & Riekki, 2012). During voluntary imagery of voices, SMA activation occurs before fronto-temporal activation, whereas these co-occur during voice hallucinations (Linden et al., 2011). SMA activation is thought to underlie the process of recognising self- versus externally- generated experiences (Raij et al., 2012). Similarly, Trojano et al. (2004) observed that prefrontal activity was prominent during active imagining, whereas prefrontal activity was absent in Oertel et al.’s (2007) study of a hallucinating patient with psychosis. This may contribute to lack of perceived control over hallucinations (Linden et al., 2010; Oertel et al., 2007).

being used to describe both clinical and non-clinical experiences (Brett, Heriot-Maitland, McGuire, & Peters, 2014; Cardeña et al., 2014; Pechey & Halligan, 2012).

1.2 Who can have anomalous experiences?

Anomalous experiences are typically thought of as occurring in psychosis, however they are experienced by a wide range of clinical and non-clinical groups, for example in migraine, epilepsy, mood disorders, borderline personality disorder, dissociative disorders, delirium, dementia (e.g. neurodegenerative conditions such as Parkinson's), schizotypy (predisposition to psychotic-like experiences in the absence of any medical condition), due to drug use or sensory deprivation, during delirium, or indeed in the absence of any clear neurological or psychological condition (Baumeister, Sedgwick, Howes, & Peters, 2017; ffytche, Blom, & Catani, 2010; Johns et al., 2014; Larøi et al., 2012; Preti et al., 2014).

Despite the fact that past literature has evidenced that hallucinations occur in these wide-ranging groups/conditions, very few studies have reviewed hallucinations trans- or extra-diagnostically – likely due to the relative infancy of this research area. This section gives a very brief overview of some of this work for context.

Recent reviews have explored experiences and qualities of auditory verbal hallucinations, but specifically in bipolar disorder (Smith, Johns, & Mitchell, 2017) or bipolar and major depressive disorder (Toh, Thomas, & Rossell, 2015); from a

trauma-centred perspective (Luhrmann et al., 2019); in healthy voice-hearers only (Baumeister et al., 2017); in the context of bereavement (Castelnovo, Cavallotti, Gambini, & D'Agostino, 2015); as a function of sleep (Reeve, Sheaves, & Freeman, 2015); and as a function of age in the general population (Badcock, Dehon, & Laroi, 2017; Maijer, Begemann, Palmen, Leucht, & Sommer, 2018). Due to the novelty of this research area and the resulting paucity of research that includes clinical and non-clinical groups, the only review to compare the similarities and differences in auditory and visual hallucinations across clinical and non-clinical groups was recently published by Waters and Fernyhough (2017). This review found that, of the 21 hallucination characteristics usually associated with schizophrenia, “95% were shared with other psychiatric disorders, 85% with medical/neurological conditions, 66% with drugs and alcohol conditions, and 52% with the nonclinical groups” (Waters & Fernyhough, 2017). One excellent review by Upthegrove et al. (2016) explored the current clinical auditory verbal hallucination literature across phenomenology, psychopathology, psychological aspects, cognitive neurobiology, and neuroimaging.

However, because hallucinations are traditionally considered as indicative of psychopathology or another clinical condition, very little comparative work has been done in non-clinical voice hearers. So, whether the process of auditory verbal hallucination generation is similar between voice-hearing groups remains to be explored (Upthegrove et al., 2016). Further, whether auditory hallucinations represent a true continuum of experience also remains to be established (Upthegrove et al., 2016), and considerably more data from non-clinical groups is needed for comparison (Waters & Fernyhough, 2019). Iudici et al. (2019) found

many similarities between clinical and non-clinical experiences, with healthy individuals experiencing auditory verbal hallucinations in the absence of psychopathology. However, this research, like much of the above, does not address the detail of possible neurocognitive mechanisms underlying hallucinations and whether these are similar between groups. Despite hallucinations in certain groups/conditions previously being thought of as unique to these populations (as has been the case historically with psychosis), recent research demonstrates that this is not the case (reviewed below). Hallucinations across these populations share several phenomenological – and mechanistic – similarities.

To illustrate this, a brief review of anomalous experiences in non-clinical groups, and the clinical conditions that have contributed most significantly to our basic understanding of anomalous experience, is given below (but see Aleman & Larøi, 2008, Chapter 3 for an extensive review).

1.2.1 Anomalous experience in non-clinical groups

1.2.1.1 The term "non-clinical"

In the current context, "non-clinical" groups are those that comprise members of the general population that have not been diagnosed as having a mental, neurological, or other physical health condition that would classically be associated with anomalous experiences. The term "sub-clinical" is sometimes used interchangeably with "non-clinical", referring to individuals that are members of non-clinical groups who nevertheless report symptoms or experiences that are

consistent with certain health conditions. However, several authors suggest that "sub-clinical" is misleading, as it appears that many healthy people that have these experiences are truly healthy with no need for intervention or care (Baumeister et al., 2017; Brett et al., 2014; Nelson, Seal, Pantelis, & Phillips, 2013). As the current thesis is concerned with the occurrence of anomalous experiences in healthy groups, and predisposition to such experiences has not to date been evidenced as necessarily clinically-relevant, this thesis will use "non-clinical" to refer to anomalous experiences in healthy groups.

Although anomalous experiences are a common feature of many psychological and neurological conditions, research on these experiences provides substantial evidence that hallucinations are also experienced by many people from the general population in the complete absence of any mental or physical health conditions, or use of substances, that would necessarily predispose them to such experiences (Aleman & Larøi, 2008; Aleman, Nieuwenstein, Bocker, & De Haan, 2001; Allen et al., 2005; Block, 2012; Johns, 2005; Laroi & Van der Linden, 2005). Overall, a large body of experimental research has evidenced a higher prevalence and wider variety of anomalous experiences in non-clinical groups than might be expected.

1.2.1.2 General anomalous experience prevalence

Studies exploring anomalous experiences in the general population tend to focus on hallucinations exclusively, with auditory and visual modalities being the most commonly-studied (Mitchell et al., 2017). In 1894, the Society for Psychical Research carried out some of the first systematic research into anomalous

experiences in the general population and produced the *International Census of Waking Hallucinations in the Sane*. More than 10% of respondents said they had experienced a sensed-presence or auditory hallucination at some point in their lives. Modern surveys of thousands of individuals from the general British population put the frequency of hallucinatory experiences – seeing or hearing things when others could not – at ~4-6% (Johns, 2005; Linscott & van Os, 2013). A review of several studies from different countries found that 7-30% of children and adolescents have experienced hallucinations (Boksa, 2009). Additionally, hallucinations of a lost loved one can occur in one-third to one-half of bereaved spouses (Boksa, 2009). Recent investigations in non-clinical populations estimate a lifetime prevalence for visual and auditory hallucinations at 3-15% and 2.5-15% respectively (Mitchell et al., 2017). One study that estimated the prevalence of psychotic-type experiences in the general population across the globe reported a sex-standardised prevalence of 2.4% in mid-to-high income countries and 5.5% in low-income countries (Nuevo et al., 2012).

Some research has also demonstrated significant overlap in anomalous experience ratings between healthy control and psychosis groups, with Kao et al. (2013) finding that 14% of a non-clinical group had a higher total number of anomalous experiences as compared to a psychosis group. Similarly, Bell et al. (2011) also observed a significant overlap between 90 clinical (non-affective psychosis) and 193 non-clinical participants on the Cardiff Anomalous Perceptions Scale (CAPS; Bell, Halligan, & Ellis, 2006), which measures a range of anomalous experiences across sensory modalities. They found that 11.9% of the non-clinical sample scored above the mean of a psychosis inpatient group on the CAPS (which

closely matches the 11.3% of non-clinicals scoring above the psychosis mean observed in the original 2006 CAPS study). There were no significant relationships between age or sex and CAPS scores.

Bell and colleagues also conducted a hierarchical analysis of CAPS scores to examine whether endorsing one particular item predicted a higher total CAPS score. This analysis revealed that endorsement of rarer items was associated with a greater overall CAPS score. That is, endorsing the rarest experience ("Have you ever heard two or more unexplained voices talking with each other?", endorsed by only 1.6% of the sample) predicted endorsement of 18.3 additional items, whereas endorsing the most common experience ("Do you ever find that your experience of time changes dramatically?", endorsed by 45.1% of the sample) predicted endorsement of only 10.1 additional CAPS items (Bell et al., 2011). However, generally this also suggests that the more experiences endorsed, the greater the variety of anomalous experiences overall.

1.2.1.3 Visual anomalous experience

Various studies have placed the prevalence of visual hallucinations in the general population, in the absence of physical or mental health problems or other predispositions, at between 3.2-6% (Johns, 2005; Preti et al., 2014), although this percentage varies widely between samples. For example, one study exploring non-clinical visual hallucinations in detail found that 29% of participants had experienced at least one visual hallucination, and that 17% experienced them very frequently (Laroi & Van der Linden, 2005). However, complex visual hallucinations have been estimated to occur in as many as 30% of healthy individuals with no

pre-existing or predisposing physical or mental health conditions (Block, 2012). In a study that followed-up and surveyed the same area as the 1894 *Census,* visual hallucinations were the most commonly reported in the general population (Aleman & Larøi, 2008). Visual hallucination prevalence seems to decrease with age, which is surprising given that hallucination risk factors increase with age (e.g. sensory and cognitive impairment (Badcock et al., 2017)). Although low levels of perceived control and more negative content have been cited as hallmarks of clinical hallucinations (Baumeister et al., 2017), Larøi and van der Linden (2005) evidenced low perceived control and more negative than positive emotional reactions in their non-clinical participants. Importantly, and in contrast to some earlier studies (such as Ohayon et al., 2000), Larøi and van der Linden (2005) specifically recorded alcohol and/or narcotics use in their non-clinical samples and found that the hallucinations reported were not associated with use of these substances. As compared to auditory hallucinations, however, there is a relative dearth of studies on visual hallucinations in strictly non-clinical groups (i.e. the absence of any diagnosed condition or status that may predispose groups to anomalous experiences), making estimates of prevalence difficult. Studies tend to explore general population samples without controlling for potentially confounding factors such as substance use (including nicotine), medication, or medical status / physical illness, and so there is limited data on non-clinical groups that is useful for discerning possible neurocognitive mechanisms.

1.2.1.4 Auditory anomalous experience

Research has also shown that individuals from non-clinical groups experience auditory hallucinations that would traditionally be thought of as

indicative of psychosis – such as voices that are externalised, vivid, involuntary, and negative – more often than might be expected (Longden, 2017). A review by Johns and colleagues (2014) found that auditory verbal hallucinations had many similar characteristics across groups regardless of clinical status, including the volume, location, number of voices heard, and the underlying brain activity. Although relatively few studies have specifically explored auditory hallucinations in the general population that are not related to lifestyle factors (such as substance use) or health problems (e.g. sleep disorders), reviews have suggested a prevalence of around 13% (Johns et al., 2014). Interestingly, a recent review found that, overall, the subjective experience of hearing voices (e.g. vividness, negative valence) does not appear to differ significantly between clinical and non-clinical groups (Bauermeister et al., 2017).

1.2.1.5 Other modalities of anomalous experience

Ohayon (2000) found that olfactory, bodily, and gustatory hallucinations were experienced at least once per week by a quarter or more of individuals with no associated diagnoses or other health issues. Multi-sensory hallucinations are rarer than single sense hallucinations, although prevalence has been estimated to be ~19% in healthy samples (Preti et al., 2014). Sensed-presence hallucinations are studied less often, however a recent review found that 30-60% of adults had post-bereavement hallucinatory experiences, such as hearing, seeing, being touched by, or feeling the presence of the deceased (Castelnovo et al., 2015). Short-term sensory deprivation is commonly used to reliably induce temporary, psychotic-like experiences in healthy individuals, including auditory and visual hallucinations (Daniel, 2017; Daniel, Lovatt, & Mason, 2014).

It is important to note that estimations of hallucination prevalence vary widely depending on the population studied; factors such as sex, age, culture, time frame, stigma, and personal circumstances may influence prevalence statistics (Badcock et al., 2017). For example, older adults frequently convey concerns around disclosing hallucinations for fear of upsetting relatives or being labelled as "mad" or cognitively incompetent (Badcock et al., 2017). Further, many estimates of hallucinations rely on self-report measures, which may be subject to reporting or other experimental biases – although reports of hallucinations in student populations do not seem to be related to measures of social desirability (Laroi & van der Linden, 2005). Although DeVylder and Hilimire (2015) found that pre-psychotic experience endorsement is affected by social desirability bias, this was with the exception of subthreshold auditory hallucinations, the only hallucinatory item included in the measure used (with the remaining questions linked to interpersonal difficulties or social anxiety, negative symptoms, and suspiciousness) (Liu et al., 2013). Therefore these factors must be taken into consideration when assessing hallucination prevalence estimates. Overall, research indicates a surprising, well-evidenced prevalence of anomalous experiences in those with no related clinical diagnosis or condition – and this is likely a conservative estimate, considering the many factors that may discourage individuals from disclosing such experiences.

1.2.1.6 Psychosis continuum / schizotypy

The frequency of anomalous or "psychotic-like" experiences in the general population has led many researchers to propose the "psychosis continuum"; the

idea that psychotic-like symptoms and traits (such as hallucinations) can occur in those who are otherwise healthy, and also vary along spectrums or dimensions (such as vividness, duration, and associated distress) in clinical and non-clinical groups (Park, Lim, Kirk, & Waldie, 2015; Waters & Fernyhough, 2019). Under this view, such a spectrum has two extremes; symptoms experienced without distress, dysfunction, or the need for intervention at one end, and symptoms being so severe that they require treatment at the other (Waters & Fernyhough, 2019). A predisposition to having psychotic-like experiences (including certain personality traits traditionally associated with psychosis) in the absence of any medical condition has been described as “schizotypy” (Teufel et al., 2015). An emerging body of evidence suggests that schizotypal features are present throughout the general population, supporting the idea that psychosis may lie on a continuum with “normality” (Teufel et al., 2015). Schizotypy studies evidence a psychosis continuum and the occurrence of anomalous experiences in the general population, and suggest that anomalous experiences can occur outside of “formal” psychosis.

1.2.2 Anomalous experiences in clinical groups

1.2.2.1 Migraine

Migraine is an intense, pulsating headache that affects approximately 10-15% of people worldwide (Coppola, Pierelli, & Schoenen, 2007; Cui, Kataoka, & Watanabe, 2014; NHS, 2019). The visual system is central in migraine pathophysiology, and so many migraine triggers are visual in nature (Bridge et al., 2015; Harle, Shepherd, & Evans, 2006; Shepherd, Hine, & Beaumont, 2013). The most common visual triggers of migraine found in everyday environments

include glare, flicker, and geometric patterns such as stripes, amongst others (see Harle et al., 2006; Shepherd et al., 2013) (see **Figure 1.3**).Such stimuli are similar to those that are epileptogenic in photosensitive epilepsy (Shepherd et al., 2013).

Figure 1.3 – Environmental sources of visual irritation. (A) escalator tread texture (sourced from flickr.com); (B) computer screen glare (sourced from flickr.com); (C) venetian blinds (sourced from ebay.co.uk).

In accordance with this visually-centred pathology, large prevalence studies have suggested that migraine is accompanied by “aura” in ~4.4 to 22.5% of migraine cases. Aura denotes visual symptoms that tend to precede migraine, such as seeing simple shapes (such as spots), flashing lights (phosphenes) or zig-zag patterns (scintillations), and blind spots (scotoma) which move across the visual field (Aiba et al., 2010; Evans & Aurora, 2012; Hadjikhani, 2008; Hadjikhani et al., 2001). These visual symptoms occur in 94% of aura cases (Hadjikhani, 2008). Rarely, aura can also occur without migraine (Evans & Aurora, 2012). In addition to these relatively simple hallucinations, migraine can be associated with highly

complex anomalous experiences, such as auditory hallucinations (Miller, Grosberg, Crystal, & Robbins, 2015), Alice-in-Wonderland syndrome, hemianopic blindness, and out-of-body / abduction experiences (Silberstein & Young, 1995).

1.2.2.2 Epilepsy

Epilepsy is a seizure disorder, with seizures being the abnormal, excessive, and synchronous discharge of cortical neurons that occur when these neurons become hyperexcitable (Bromfield, 2006). Anomalous experiences, from small flashing coloured spots or shapes to complex hallucinations, occur at a rate of approximately 3% in epilepsy generally, and at a much higher rate of 14% in "temporal lobe epilepsy" (TLE) (see **Figure 1.4**). In TLE, the initial discharges can alter affect and perception, resulting in a variety of anomalous experiences such as time distortions, déjà vu, depersonalisation, sensed presence hallucinations, and out-of-body experiences (Persinger & Makarec, 1987; Stafstrom, 1998), with auditory hallucinations being the most common (and nearly exclusive to TLE) (Hug, Bartsch, & Gutschalk, 2011). Occipital seizures occur in around 4.6% of those with epilepsy and are almost always accompanied by visual hallucinations (Teeple, Caplan, & Stern, 2009). As one quarter of hallucinations in epilepsy are experienced not during but after seizures, and as anomalous "psychosis-like" symptoms often present before and after seizures, epilepsy can sometimes be mistaken for psychosis (Larøi et al., 2012). Frequent headaches and anomalous experiences are common to both epilepsy and migraine (Bigal, Lipton, Cohen, & Silberstein, 2003), and the medications used to treat these conditions overlap, suggesting a common neurophysiological mechanism (Bigal et al., 2003).

Figure 1.4 – Example of a complex visual hallucination experienced as part of epileptic aura. This was interpreted by the patient as being Puss in Boots with large colourful plumes in his hat (from Schulz, Woermann, & Ebner, 2007).

1.2.2.3 Psychosis

Hallucinations are a core feature of the diagnostic criteria for psychosis (Oertel et al., 2007; Upthegrove et al., 2016), and so it is unsurprising that 40-80% of individuals with a diagnosis of schizophrenia experience hallucinations (Larøi, 2012). Because the prevalence of psychosis is thought to be approximately 0.2-0.7%, and the percentage of the general population that experiences hallucinations is approximately 2-15% (likely a conservative estimate), it is clear that many more people experience anomalous perceptions than receive treatment for psychosis, and that “psychotic-like” experiences are more common in the general population than psychotic disorders (Kao et al., 2013; Longden, 2017; Waters et al., 2014).

Hallucinations in psychosis are often verbal, but can also take non-verbal forms such as whistling or animal sounds (Larøi et al., 2012). Verbal hallucinations occur in an estimated 70% of patients with schizophrenia, as compared to in 10-20% of the general population (Upthegrove et al., 2016). Visual hallucinations are experienced by approximately 27-32% of those with psychosis (Oertel et al., 2007; Solesvik et al., 2016; Zmigrod, Garrison, Carr, & Simons, 2016), as compared to 6% of non-clinical individuals (Zmigrod et al., 2016). The visual hallucinations are usually complex and corporeal (Oertel et al., 2007; Waters et al., 2014) (see **Figure 1.5**).

Figure 1.5 – Art created by Kate Elisabeth (2017), diagnosed with schizophrenia at age 17. Of this image, Kate says: “This is a self-portrait. I looked in the mirror and my eyes did this thing. I painted it.”

1.2.2.4 Other clinical conditions

Hallucinations are also common to several other clinical conditions, including Charles Bonnet Syndrome (CBS), delirium, and neurodegenerative conditions. CBS is characterised by experiencing vivid visual hallucinations due to decreased visual input (often caused by eye disease, such as macular degeneration (O'Farrell, Lewis, McKenzie, & Jones, 2010)), and people with CBS experience both simple and complex visual hallucinations (Block, 2012; Sacks, 2012). Delirium is a syndrome that involves disturbed consciousness and attention, and can have many different causes (such as medication, alcohol withdrawal, or infections) (Teeple et al., 2009). “Psychotic symptoms” such as hallucinations affect ~43% of those with delirium, and visual hallucinations are the most common (Teeple et al., 2009). Because of this, delirious individuals in hospitals are commonly (but mistakenly) referred for psychiatric assessment (Teeple et al., 2009). Visual hallucinations are very common in neurodegenerative diseases, occurring at a rate of ~30-80% in Dementia with Lewy Bodies (DLB), ~22-50% in Parkinson’s disease, and 13% of Alzheimer’s cases (Carter & ffytche, 2015; Teeple et al., 2009).

1.2.3 Co-correlates of anomalous experience in non-clinical and clinical groups

1.2.3.1 Sex

There is conflicting evidence related to sex differences in anomalous experiences. In one of the first major reviews of hallucinations in the general population, Tien (1991) found that visual hallucinations were more common in

males. However a recent study suggested that there are no significant differences between the sexes in hallucination prevalence (Preti et al., 2014). In a revalidation of the CAPS questionnaire (measuring psychotic-like perceptual distortions), Bell et al. (2011) also found no differences between the sexes. Due to this, sex was recorded to characterise samples, but not controlled for, in the experimental chapters.

1.2.3.2 Age

In non-clinical groups, research also suggests that hallucination characteristics are generally invariant across age, with a slight decrease in prevalence as age increases (with the exception of bereavement hallucinations, which increase with age) (Bell et al., 2011; Preti et al., 2014). However one multi-national study suggested that age was unrelated to hallucination prevalence (McGrath et al., 2015). As the current studies recruited student samples, which had the effect of constraining age to within a somewhat limited range, age was recorded to characterise samples, but not controlled for, in the experimental chapters.

1.2.4 Summary

Surprisingly, the above evidence suggests that there appears to be little to no difference in the actual characteristics of anomalous experience – their general phenomenology – between non-clinical and clinical groups. Is it clear that hallucinations can be experienced by individuals regardless of their clinical status, and calls into question whether these experiences are necessarily "psychopathological" (as has been historically assumed in psychiatry (Upthegrove et al., 2016)). For example, in one of the only published trans-diagnostic reviews,

Waters and Fernyhough (2017) state that, as hallucinations occur across such a wide number of clinical and non-clinical conditions, they are “non-specific for psychotic disorders”, and therefore a categorical approach that relies “solely on the presence of hallucinations is not useful as a diagnostic aid” (Waters & Fernyhough, 2017, p.33). Other work has also suggested that auditory verbal hallucinations, for example, are now known not to necessarily be disease-related, and that making a distinction between “pseudo-hallucinations” (non-clinical) and “true hallucinations” (clinical) may not be “robust or valid” (Upthegrove et al., 2016). Such categorical models of anomalous experiences are inconsistent with current research, which instead suggests a continuum of anomalous experience prevalence and intensity (Bauermeister et al., 2017). However, until recently very little research has explored the mechanistic similarities and differences between clinical and non-clinical hallucinations. We cannot move forward in our understanding of how these experiences are generated without addressing this gap. This will help us to understand whether there are specific mechanisms that are unique to psychopathology, or whether a “true” continuum model is applicable (i.e. where the aetiological mechanisms of hallucinations are the same across clinical and non-clinical groups) (Upthegrove et al., 2016). Therefore, it is important to explore the mechanisms of anomalous experiences both trans- and extra-diagnostically.[3]

[3] The jury is still out as to whether cognitive processes such as negative emotional states and appraisals, coping style, and biases such as “jumping to conclusions”, necessarily contribute to increased “risk” for psychopathology (Johns et al., 2014). However, many individuals who have anomalous experiences will not seek help, because these experiences may not cause significant distress or interference in daily life (Baumeister et al., 2017; Johns & van Os, 2001). As recent changes to the DSM centre hallucinations as “almost definitional of psychosis”, it is vital that any differences in anomalous experiences between clinical and non-clinical groups are identified in future work to improve the accuracy of category boundaries and need-to-

The following section reviews the various neurocognitive mechanisms associated with anomalous experiences, in clinical and non-clinical groups.

1.3 Neurocognitive mechanisms underlying anomalous experiences

Although the idea of hallucinations as brain-based was identified as early as 1838, there does not yet exist a unified theory of hallucinations that encompasses our knowledge at multiple levels of explanation (from cellular to behavioural)[4] (Weiss & Heckers, 1999; Zmigrod et al., 2016). This persistent problem is "amplified by the lack of unified theories that account for hallucinations in multiple modalities" (Zmigrod et al., 2016), with different contents (Garrison et al., 2017), and across different groups (Waters et al., 2012).

Various iterations of **top-down and bottom-up process models** have been proposed to explain hallucinations at a cognitive level of description (Allen, Larøi, McGuire, & Aleman, 2008; Hugdahl, 2009). The main cognitive models are memory and thought intrusion, and source misattribution (but these are not mutually exclusive), reviewed in more detail below. These explanations are sometimes complemented by discussing associated brain areas, but beyond this,

treat decisions (Upthegrove et al., 2016). These questions were not explored here due to the limited scope of this thesis. This work is outlined to acknowledge that there are other areas that are lacking in non-clinical data and that will need to be explored, in addition to the question of neural mechanisms explored here, to answer the bigger questions of what exactly contributes to psychopathology development and so differentiates clinical and non-clinical groups.

[4] For example, Huang and colleagues (Huang, Zhuo, Xu, & Lin, 2019) recently published the first molecular-to-connectivity perspective on auditory verbal hallucinations in schizophrenia.

specific neural processes are not often addressed. Neural explanations mainly focus on exploring changes to **activity levels or excitation-inhibition balances in specific sensory areas** during hallucinations (most often in clinical groups) (Allen, Larøi, et al., 2008; Hugdahl, Løberg, & Nygård, 2009). Specifically, nearly all current models of auditory and other modality hallucinations in schizophrenia, several other clinical conditions, and healthy groups emphasise **hyperactivity of auditory sensory cortex** (Allen, Larøi, et al., 2008; Badcock & Hugdahl, 2012; Carter & ffytche, 2015; Huang, Zhuo, et al., 2019; Huang, Datta, Bikson, & Parra, 2019; Jardri et al., 2016; Jardri, Pouchet, Pins, & Thomas, 2011; Tranulis, Sephery, Galinowski, & Strip, 2008; Waters et al., 2012; Zmigrod et al., 2016). The perceptual content of hallucinations across modalities is likely determined by the location of activity in the cortex (Pang, 2016), regardless of clinical grouping (Allen, Larøi, et al., 2008; Carter & ffytche, 2015), i.e. hyper-activity within primary visual cortex generates simple visual hallucinations, related to the function of this area. However, explanations that go beyond this to the neural network or cellular level in humans are rare, and it is not yet known whether neurocognitive models of hallucinations are applicable across clinical and non-clinical groups (Rollins et al., 2019)(Upthegrove et al., 2016). Some models are beginning to incorporate multiple brain areas and/or functional connectivity to provide a network perspective, which will be outlined below.

This section will give a brief overview of these cognitive and neural explanations across clinical and non-clinical groups, and attempt to integrate them where possible. It is not possible to discuss all theories of hallucinations in depth here due to space limitations, but see (Blom & Sommer, 2011) and (Aleman &

Larøi, 2008) for detailed discussions. Overall, the evidence summarised below suggests that some mechanisms appear related to hallucinations in clinical groups only, whereas hyperactivation of sensory cortices appears related to hallucinations in both clinical and non-clinical groups.

1.3.1 Top-down / bottom-up processing

Abnormalities in both top-down and bottom-up processes are a central feature of several hallucination models (see Aleman & Vercammen, 2013 for a review). “Top-down” processing controls and influences perception using contextual information (such as previous experience), whereas “bottom-up” processing processes raw sensory information (such as sounds) (Aleman & Vercammen, 2013). These top-down and bottom-up processes are also now commonly discussed in terms of “predictive coding” models, which further suggest that accurate perception depends on ongoing interaction between top-down expectations, producing “predictions”, and bottom-up sensory information, sometimes producing “prediction error”. Influential models of hallucinations can all be interpreted within this top-down/bottom-up processing framework to some degree, which is becoming a common approach, particularly with the advent of predictive coding perspectives.

The predictive coding model has been successfully applied to hallucinations in psychosis by Frith and colleagues (Fletcher & Frith, 2009) and most recently to hallucinations across clinical and non-clinical groups by Corlett et al. (2019). Corlett et al. (2019) outline an “active inference” model of hallucinations, which suggests that hallucinations are simply an “exaggeration of normal non-hallucinatory

perception, to which we are all sometimes prone" – thus characterising hallucinations as not inherently indicative of psychopathology and supporting continuum theory.

These top-down/bottom-up models of hallucinations intersect with neural models emphasising the excitation/inhibition balance. Generally, a balance between bottom-up prediction errors "feeding forward" and top-down prior expectations "feeding back" is thought to be achieved through carefully maintained ratios of excitation and inhibition (Sterzer et al., 2018)(Aleman & Vercammen, 2013), perhaps through cholinergic signalling (e.g. acetylcholine; Corlett et al., 2019). Therefore, hallucination theories emphasising imbalances in top-down and bottom-up processes suggest that their respective neural substrates are decreased inhibition and/or increased spontaneous activity in executive control brain areas (interfering with source monitoring and volition), and aberrant activation of sensory cortices (producing the vivid perceptions) (Aleman & Vercammen, 2013; Zmigrod et al., 2016)(Allen, Larøi, et al., 2008; Hugdahl, 2009). For example, auditory hallucinations are thought to be driven by aberrant "bottom-up" activity in left temporal lobe, which is hyperactive due to failures of "top-down" inhibitory control (due to impaired functioning of prefrontal and anterior cingulate cortex, for example) (Hugdahl, 2009). Models suggest that hallucinations cannot be fully explained without attention to both of these perceptual and cognitive control aspects, which come together to give the experience of a vivid perception that is external and not self-generated (Hugdahl, 2009).

The key models of hallucinations are reviewed below, and can be broadly categorised into (1) aberrant or hyperactivation of sensory cortex, (2) memory and thought intrusion, and (3) source misattribution or self-recognition errors (Jardri et al., 2011; Waters, Woodward, Allen, Aleman, & Sommer, 2010; Zmigrod et al., 2016). These will be contextualised within this top-down/bottom-up context where possible. Importantly, although top-down and bottom-up mechanisms can be conceptualised separately to some degree, they are concurrently active and interactive, and so their integration is probably necessary to satisfactorily explain hallucinations (Zmigrod et al., 2016).

1.3.1.1 Hyperactivation of sensory cortex

Spontaneous activation of sensory cortices in the absence of external stimulation is thought to underlie hallucinations in both clinical (Allen, Larøi, et al., 2008; Diederen et al., 2011; Griffiths, 2000; Horga, Schatz, Abi-Dargham, & Peterson, 2014; Hugdahl, 2009; Hunter et al., 2006; Jardri et al., 2011; Kompus et al., 2013; Linden et al., 2011; Waters et al., 2012; Waters et al., 2014; Waters & Fernyhough, 2019; Zmigrod et al., 2016) and non-clinical groups (Allen, Larøi, et al., 2008; Diederen et al., 2011; Jardri et al., 2011; Waters et al., 2012; Waters & Fernyhough, 2019; Zmigrod et al., 2016). For example, direct external electrical stimulation of healthy temporal cortex can produce a variety of auditory hallucinations commonly seen in schizophrenia, such as single and multiple voices, music, and environmental sounds (Jones, 2010). A large meta-analysis of neural activation during clinical hallucinations demonstrated that increased activity above baseline in specific sensory cortical areas was associated with hallucinations in the corresponding modality, across clinical and non-clinical groups (Zmigrod et al.,

2016). Specifically, hyperactivity in secondary auditory cortex during auditory hallucinations, and in secondary and association visual cortices during visual hallucinations, was a common finding across studies (Zmigrod et al., 2016). This hyperactivation of sensory cortex in the absence of external stimulation appears sufficient for generating these vivid but false perceptual experiences, with the contents determined by the sensory area activated (Carter & ffytche, 2015; Jones, 2010; Payne, 2009; Vercammen, Knegtering, Bruggeman, & Aleman, 2011).

This increased activation of brain regions over and above normal or expected levels is often termed “cortical hyperexcitability”. Cortical hyperexcitability explains hallucinations by focusing on aberrations in the excitation/inhibition (E/I) balance in the cortex (Blom & Sommer, 2011, pp. 43-44). A delicate E/I balance is necessary for all brain functioning, and each cortical area maintains its own specific E/I balance that supports its function (Jardri et al., 2016). Therefore, an imbalance in excitation/inhibition may lead to increased excitability (and/or decreased inhibition), and resulting hyper-activation of sensory cortices may lead to hallucinations (Allen, Laroi, McGuire, & Aleman, 2008; Rollins et al., 2019). From a predictive coding perspective, although prior expectations cannot themselves induce supra-threshold activity, they may instead “modulate, prime, or sensitize” neurons to respond more robustly to certain types of sensory information (Aleman & Vercammen, 2013).

The involvement of cortical hyperexcitability is further supported by a unique transdiagnostic review of the possible causal mechanisms of visual hallucinations (covering schizophrenia, Alzheimer’s disease, dementia with Lewy bodies,

Parkinson's disease, and eye disease), which concluded that occipital and parietal atrophy across all patients – regardless of specific condition – could mark local hyperexcitability within these regions (Carter & ffytche, 2015). This is because atrophy may reflect changes to "internal cortical architecture" that reduce inhibitory control within and beyond visual areas, producing hallucinations through increased/decreased excitatory/inhibitory output from areas connected to visual processing, or increased excitation within visual areas themselves (Carter & ffytche, 2015). In support of this, Waters and Fernyhough (2019) reviewed the limited literature available that compared clinical and non-clinical auditory hallucinations, and concluded that whilst several mechanisms for hallucinations have been identified that appear discontinuous between clinical groups (such as dopamine synthesis, which is reduced in psychosis but not non-clinical groups (Upthegrove et al., 2016)), a unique candidate for a continuous mechanism between clinical and non-clinical groups is increased spontaneous cortical activation in sensory cortex corresponding to the modality of the hallucination (Waters & Fernyhough, 2019). Particularly, activation of auditory structures (such as superior temporal gyrus and bilateral inferior frontal gyri) in the absence of appropriate external stimulation is common to these experiences in both groups (Diederen et al., 2011; Kompus et al., 2013; Linden et al., 2011). This fits with Carter and ffytche's suggestion that variations in the location and/or distribution of this hyperexcitability within the cortex likely account for variations in the content and complexity of visual hallucinations across conditions (Carter & ffytche, 2015). The authors noted that this result was surprising given the considerable methodological variation across the sampled studies.

Another line of evidence for a link between cortical hyperexcitability and hallucinations in both clinical and non-clinical groups comes from sensory deprivation research (where bottom-up input from the senses is reduced or completely removed). There is a well-established relationship between sensory degradation or deprivation and hallucinations in the corresponding modality (Aleman & Vercammen, 2013; Blom & Sommer, 2011). For example, visual hallucinations are common in blindness (such as in CBS, outlined above), and auditory hallucinations in deafness (Block, 2012; Sommer, Koops, & Blom, 2012; Yuksel, Kisa, Aydemir, & Goka, 2004). Several studies have also evidenced occurrence of simple and complex visual and auditory hallucinations in healthy individuals during sensory deprivation (Daniel et al., 2014; Mason & Brady, 2009; Merabet et al., 2004). The proposed neural explanation for this is that degraded or absent sensory input leads to increased compensatory activity within the deprived sensory area/s, generating hallucinations (Beniczky et al., 2002; Daniel, 2017; Pang, 2016).

This model suggests that our everyday experience is “controlled” by incoming, bottom-up sensory information, with this information acting in an inhibitory manner to “constrain” perception. Loss of this input (or the areas that process this information) may therefore promote hyperexcitability in these sensory pathways (Daniel, 2017; Pang, 2016). This is also known as “release theory”, whereby a lack of inhibitory control over sensory cortex activity causes experiences (any priors, e.g. memories) to be “released” from the subconscious into the conscious (Pang, 2016). Integrating with predictive coding theory, if signals from external stimuli / bottom-up processing become weakened or are removed entirely,

internal experiences and priors (top-down processing) may become more salient and too strong. This may impair reality monitoring and allow internal priors to “win out”, causing hallucinations (Aleman & Vercammen, 2013; Corlett et al., 2019; Upthegrove et al., 2016)(Reichert et al., 2013).

Indeed, research using deep learning artificial neural networks to model hallucinations in CBS has demonstrated that input degradation (equivalent to sensory impairment) initially leads to a decrease in neuronal activity, which is then compensated for by homeostatic regulators significantly increasing unit excitability above baseline in order to restore “balance”, causing hallucinations (Reichert, Series, & Storkey, 2013).

Although there may be differences in patterns of hyperexcitability between groups or types of experiences (as suggested by Carter & ffytche, 2015), this would not undermine the involvement of hyperexcitability in non-clinical hallucinations per se, but simply mean that even hyperexcitability is a quasi-continuous mechanism (and so call into question fully continuous spectrum models). There is a need to understand the mechanisms that lead to hyperexcitability – but this issue is beyond the scope of this thesis. Research has evidenced hyperactivation of common brain networks between clinical and non-clinical groups (Diederen et al., 2011; Kompus et al., 2013; Linden et al., 2011), and so the concept of cortical hyperexcitability is an intriguing (if general) starting point from which to identify similarities and differences between groups.

Therefore, hyperactivation of sensory cortex is a common bottom-up aberration highlighted by models of hallucinations, particularly in the auditory modality. Several authors suggest that bottom-up hyperactivation in sensory cortex is sufficient to elicit vivid hallucinations that are experienced as involuntary and external (Jones, 2010; Vercammen et al., 2011). For example, hyperactivation in areas such as superior frontal gyri, inferior parietal lobe, and Wernicke's could contribute to externality, as these areas are responsible for spatial localisation (Badcock, 2008; Cruz, Del Pozzo, Zar, & Hansen, 2019) and are active during hallucinations in both clinical and non-clinical groups (see "**Network perspective**"). A lack of local inhibition may also allow any hyperactivity to "propagate to higher levels of processing", contributing to the hallucination's perceived uncontrollability and "externality" (Kompus et al., 2013). Alternatively, other top-down impairments that have been evidenced in schizophrenia, such as imprecise prediction errors leading to reduced top-down control or missing efference copies, may also be linked to hallucinations in healthy groups (Garrison et al., 2017; Horga et al., 2014) – these are discussed below.

However, what is missing from the literature are studies specifically exploring possible measures and manipulators of hallucinations and cortical hyperexcitability spefifically, in large, healthy samples, and in different modalities (Zmigrod et al., 2016). For example, although Hunter and colleagues (Hunter et al., 2006) found that spontaneous activation in auditory cortex during silence was associated with activity in anterior cingulate cortex in a healthy sample – an area thought to be involved in attention and the "behavioural drive to produce speech" (Boksa, 2009) – this study did not include any hallucination measures to further

probe this relationship. This is a key issue with many studies in this area, and will be returned to in the "**Integrated perspective and outstanding issues**" section.

1.3.1.2 Memory and thought intrusion

This perspective highlights the role of disinhibited memories and thoughts (including fragments of stored representations such as words), which may "intrude" into conscious experience and be experienced as hallucinations (Badcock & Hugdahl, 2012; Zmigrod et al., 2016). Although a popular model in the past, more recent work has suggested that intrusive memory approaches can only explain a fraction of hallucination content; those including fragments of traumatic event memories (Jones, 2010). Outside of trauma, memory intrusions do not seem able to account for the majority of common auditory hallucination content, such as hearing voices narrating the individual's day-to-day life, dynamic dialogues between the individual and voice/s (Jones, 2010), or multiple voices conversing (Upthegrove et al., 2016). Whilst some studies have observed activation of memory-related areas during hallucinations (Jardri et al., 2011), others have not (Diederen et al., 2011).

What is also not clear in this explanation is how intrusive memories or thoughts (experienced as unwanted but internal, and generally caused by the agent) are perceived as truly hallucinatory (i.e. external, and not caused by the agent). Intrusive thoughts are common in many clinical conditions (such as obsession compulsive disorder) (Seli, Risko, Purdon, & Smilek, 2017), but are clearly not synonymous with hallucinations. Therefore, for intrusive memories or thoughts to be experienced as hallucinations, the intrusions must be labelled as

other-generated and external – which does not seem to be sufficiently explained by intrusion models. Source misattribution perspectives may offer an explanation.

1.3.1.3 Source misattribution and self-recognition errors

"Source attribution" is a specific top-down process that allows us to distinguish between internal and external sensory information (or "sources"). Deficits in this source (or reality) monitoring process may lead to non-recognition of or misattributions about the source of stimuli or events, such that inner experiences are labelled as externally-sourced and experienced as hallucinations (Zmigrod et al., 2016). Most proposed mechanisms of auditory verbal hallucinations in schizophrenia address some aspect of these inaccurate "self/other" distinctions or self-recognition failures (Waters et al., 2012) and highlight misattribution of inner speech to the external environment (Hugdahl et al., 2009; Upthegrove et al., 2016).

These explanations provide a possible mechanism by which memory and thought intrusions could be mislabelled as other- and externally-generated, rather than self- and internally-generated (Kinderman, 2011). A strength of these explanations is that the usual contents of inner speech – focused on the control or regulation of action – are similar to common contents of auditory verbal hallucinations, such as commenting on day-to-day life and issuing commands ("Go to the hospital") (Jones, 2010).

Misattribution of inner speech to the external environment may be caused by increased top-down processing enhancing the influence of our expectations on

experience, such that inner signals are stronger than bottom-up external sensory signals (Aleman & Vercammen, 2013). It is also possible that weakened top-down processing can contribute to misattribution, for example through decreased inhibitory control from dorsolateral prefrontal cortex and weakened activity in source monitoring areas (dorsal and ventral anterior cingulate, supplementary motor area, and cerebellum) (Allen, Larøi, et al., 2008).

Additionally, some work suggests that dysfunctional connectivity between sensory cortices, and monitoring and volition areas, reduces the ability of these monitoring areas to modulate or inhibit e.g. auditory cortex activity (Jones, 2010). Hyperactivity of sensory cortex may contribute to increased perceived loudness and externality of the inner voice, and so non-recognition or misattribution of inner speech (Jardri et al., 2011; Jones, 2010; Vercammen et al., 2011). This may occur in healthy but hallucination-prone individuals in the absence of any general source monitoring deficits (Garrison et al., 2017).

However, inner speech models face several problems. It is unclear how misattribution of one's own inner speech to the environment could produce hallucinations experienced as the voice of another person or multiple or conversing voices (Jones, 2010; Upthegrove et al., 2016), or non-voice hallucinations, which are common and include music, whistling, blowing, clicks, and bangs, for example (Jones, 2010). Neuroimaging studies generally give solid support for defective source monitoring (of inner speech) as central to auditory verbal hallucination generation in schizophrenia (Jones, 2010), but the evidence is limited and mush less consistent for non-verbal and non-clinical hallucinations. Some research has

observed reality-monitoring deficits in healthy participants predisposed to visual hallucinations (Aynsworth, Nemat, Collerton, Smailes, & Dudley, 2017), whereas other work has not observed deficits in either reality monitoring or internal source monitoring in healthy participants predisposed to auditory hallucinations (Garrison et al., 2017; Kompus et al., 2013; Thoma et al., 2017).

Therefore current evident suggests that hallucinations in patients are driven by both bottom-up hyperactivation of sensory cortex and top-down impairments, such as source or reality monitoring. In contrast, there is good evidence that hallucinations in healthy individuals are at least partly driven by the same bottom-up aberrations (Garrison et al., 2017; Kompus et al., 2013), but mixed evidence for involvement of generalised top-down impairments (Waters & Fernyhough, 2019). These ideas are returned to in the "**Integrated perspectives**" section below.

1.3.1.4 Forward/efference copy models

"Efference copies" are copies of action or motor signals (such as inner or prepared speech) that allow self/other distinctions to be made. These efference copies are sent from planning to sensory brain areas, allowing the agent to compare predictions with sensory information or consequences, and so distinguish between intended/self-generated and external/other-generated events. The link between efference copies errors, self/other distinctions, and hallucination generation has been applied to schizophrenia by many researchers (Backasch et al., 2014; Blakemore, 2017; Pynn & DeSouza, 2013). For example, efference copies sent from speech production systems may act to control auditory cortex activity in a top-down manner, labelling prepared speech as self-generated and

suppressing activity of auditory cortex in response to the sound of the uttered speech or inner voice (Chen et al., 2011).

However, there is a lack of direct evidence for this theory, in any group (Garrison et al., 2017). Further, as described above, evidence for self-other distinction deficits in non-clinical groups experiencing hallucinations is mixed (Waters et al., 2012), and current evidence suggests that these deficits are a feature of specific clinical groups such as schizophrenia (Garrison et al., 2017).

1.3.2 Network perspective

Although the neural networks involved in hallucinations have been studied in patients, design flaws (e.g. lack of hallucinating but healthy control group, not controlling for medication or patient age (Jardri et al., 2011)) and other common confounds mentioned above mean that these networks have not been specifically linked to hallucination generation or experience (rather than other clinical variables or symptoms, or general syndromes) in most studies. However, Diederen et al. (Diederen et al., 2011) evidenced a cortical network of activity during auditory hallucinations ("hallucinations-on" state) that was common to both clinical (psychosis) and non-clinical hallucinators (see **Table 1.1**). This network constituted significantly increased activation (as compared to the baseline "hallucinations-off" state) in frontal and temporoparietal regions involved in speech perception and production, and emotion. Importantly, there were no significant differences in this activation between the groups (Diederen et al., 2011). These findings are supported by other work exploring auditory hallucination networks in non-clinical groups (Linden et al., 2011).

In schizophrenia and schizophrenia spectrum disorders, auditory hallucination networks also involve frontal and temporoparietal areas (Allen, Modinos, et al., 2012; Jardri et al., 2011) (see **Table 1.1**). However the involvement of orbitofrontal cortex, hippocampus, and para-hippocampal region appear unique to schizophrenia (Allen, Modinos, et al., 2012; Jardri et al., 2011). This may be because hallucinations in clinical groups have been clearly linked with self-monitoring deficits (Jones, 2010) and are more likely to contain intrusive or traumatic memories (as outlined above, and given that emotional distress and trauma are key in clinical diagnosis)(Gershuny & Thayer, 1999; Heriot-Maitland, Knight, & Peters, 2012). Therefore, Jardri et al.'s (2011) suggestion that hallucinations are generated through a combination of unbidden memories (that activate sensory cortex) and misattributions appears applicable to clinical groups only.

Bottom-up sensory cortex hyperactivity could be caused by prediction error deficits (Horga et al., 2014). Horga and colleagues (Horga et al., 2014) demonstrated that increased activity in left auditory cortex (in the absence of external auditory stimuli) correlated strongly with weaker speech-based prediction error signals[5] during active auditory verbal hallucinations, and greater hallucination severity (in patients with schizophrenia as compared to healthy controls). These weakened prediction error signals were "not better explained by any behavioural, neuropsychological, or sociodemographic variables, or by illness duration or

[5] Prediction error signals were calculated using a complex BOLD-based model that compared activity associated with speech versus no-speech decision trials. See (Horga et al., 2014) for full details.

medication status" (Horga et al., 2014). Weakened prediction errors may cause imprecise information to be spread/fed forward to "higher" cortical areas, such that top-down processes then cannot accurately attenuate activity in sensory cortex, leading to sustained cortical activation. However this is just one possibility, and it is not yet clear what factors produce the initial hyperactivity or influence its spread (if any), i.e. from local to wider brain areas – particularly in healthy but hallucinating samples. This issue will be further discussed in the empirical chapters.

Top-down control processes may also be important, but these have received limited attention in non-clinical groups. For clinical groups, Allen et al. (Allen, Larøi, et al., 2008) highlight decreased top-down inhibitory control of perception (mediated by decreased activation of dorsolateral prefrontal cortex and anterior cingulate), increased influence from emotion and attention areas (increased activation in orbitofrontal cortex), and decreased influence of source monitoring and volition areas (decreased activation of middle temporal gyrus, dorsal and ventral anterior cingulate, supplementary motor area) (Vercammen et al., 2011).

Aberrations in top-down control may be further exacerbated by dysfunctional or decreased connectivity between hyperactive sensory cortices (such as left temporal) and monitoring and volition areas (such as anterior cingulate) in hallucinators, which could contribute to misattribution errors (Allen, Larøi, et al., 2008; Mechelli et al., 2007).

	MODALITY	LOBE	AREA	FUNCTION
CLINICAL AND NON-CLINICAL GROUPS[1-5, 7]	Auditory	Temporal lobe	Primary and secondary auditory cortex	Auditory processing
			Superior temporal gyri and sulci (Auditory association cortex, overlaps with Wernicke's area)	Sound and speech perception, processing human voices
			Superior temporal pole	Semantic processing and memory
			Insula	Inner speech production, emotional cognition
		Parietal lobe	Inferior parietal lobe (part of Wernicke's)	Speech processing, emotion
		Frontal lobe	Left precentral gyri (primary motor cortex, overlaps with Broca's)	Voluntary movement, including speech
			Bilateral inferior frontal gyri (including Broca's)	Speech production and processing, verbal imagery
	Visual		Primary and secondary visual cortex	Visual processing
			Visual association cortex	Visual processing
CLINICAL GROUPS ONLY (SCHIZOPHRENIA, SCHIZOPHRENIA SPECTRUM DISORDERS)[3,6, 8]	Auditory	Temporal lobe	Middle temporal gyri (Auditory association cortex)	Speech production
		Frontal lobe	Orbitofrontal cortex	Executive control, integrates information from sensory and limbic areas
		Limbic lobe	Hippocampus, parahippocampal region	Memory, recall
		Basal ganglia	Right internal globus pallidus	Voluntary movement

Table 1.1 – Brain areas implicated in hallucinations in clinical and non-clinical groups. There is considerably more detail for auditory versus visual areas due to the focus of previous research on auditory hallucinations. No areas unique to non-clinical groups have

yet been identified. References: (1) Diederen et al., 2011; (2) Linden et al., 2011; (3) Jardri et al., 2011; (4) Barkus et al., 2007; (5) Vincent et al., 2005; (6) Allen et al., 2012; (7) Kompus et al., 2013; (8) Zmigrod et al., 2016.

1.3.3 Integrated perspective and outstanding issues – A focus on cortical hyperexcitability

Despite considerable previous research, a unified theory does not yet exist that uses specific neural mechanism/s to explain the various cognitive and perceptual features of hallucinations (Jones, 2010; Zmigrod et al., 2016). What is clear from the literature is that out of the multiple mechanisms and explanations for hallucinations that exist, some appear discontinuous and some continuous between clinical and non-clinical groups. Hallucinations in patient groups appear to be driven by both bottom-up spontaneous hyperactivation of sensory cortices and top-down impairments, but in healthy individuals appear to be primarily driven by these bottom-up aberrations (Hugdahl, 2009). Therefore, bottom-up cortical hyperexcitability may represent a continuous mechanism across groups (Allen, Modinos, et al., 2012; Waters & Fernyhough, 2019; Zmigrod et al., 2016), whereas top-down changes may be restricted to certain clinical categories (Hugdahl, 2009; Kompus et al., 2013). Research that explores practical measures and manipulators of cortical hyperexcitability (that could also be applied across groups) is lacking. The growing evidence for such experiences in healthy people requires the investigation of mechanisms that can explain these experiences. Therefore, this thesis works to bridge some of these gaps in our knowledge and models of hallucinations by exploring the contribution of cortical hyperexcitability to anomalous experience, in large non-clinical samples.

It is important to again note here that this thesis limits its focus to cortical hyperexcitability for the above theoretical reasons (and due to practical constraints), however this is of course only one possible mechanism and additional

work will need to explore whether the other mechanisms outlined above are also applicable to healthy groups (and other possible continuous factors).

Although Waters and Fernyhough (2019) suggest that continuity of experience does not equal continuity in mechanism, it appears that cortical hyperexcitability is certainly a possible exception and may very well bridge clinical and non-clinical experiences. Although brain activity associated with simple hallucinations in medical conditions such as acquired deafness appears localised, whereas activity associated with complex hallucinations in schizophrenia is widespread (Waters & Fernyhough, 2019), this may be due to the relative simplicity or complexity of anomalous experience in these groups. Elliot et al. (2009) found that the localisation of seizure activity in epilepsy predicted the modality of simple hallucinations (seizure activity in visual cortex produces visual percepts), but that as the complexity of the hallucinations increased, localisation became more difficult (Elliott, Joyce, & Shorvon, 2009). However whether such patterns also apply to non-clinical experiences is not yet known, and further research is required to determine whether the relative localisation or spread of hyperactivity is associated with hallucination modality and phenomenology.

1.4 What is cortical hyperexcitability?

1.4.1 Current definition of cortical hyperexcitability

Cortical hyperexcitability is a form of aberrant neural activity. During normal functioning, a delicate balance of inhibition and excitation is usually maintained by homeostasis, to ensure appropriate refractory periods and neuronal firing rates and

so support accurate perception and appropriate functioning (Isaacson & Scanziani, 2011; Jardri et al., 2016; Stafstrom, 1998). As excitatory processes are also normally modified by inhibitory processes across neuronal networks, inhibition "sculpts" excitation in a dynamic manner (Stafstrom, 1998). From this it follows that aberrations in these carefully maintained balances and processes could result in hyperexcitability.

Cortical hyperexcitability can be defined in several ways depending on the level and detail of the description, and whether it is attached to a specific disorder. For example, hyperexcitability can occur "at one or more levels of brain function", such as at the network level, at the level of the neuronal membrane or intracellular messenger cascades, and via changes to neurotransmitters and their receptors (Stafstrom, 1998, p.342). For the purpose of this thesis, however, cortical hyperexcitability is defined as **excessive excitability of cortical neurons over and above expected levels, as determined by brain homeostasis and normal functioning.** Importantly, significant activation in a specific region that would be expected during normal sensory stimulation or functioning, but that *occurs spontaneously in the absence of that sensory stimulation*, is here classed as hyperexcitability. This is because this activation is occurring above the expected level, where there is insufficient sensory stimulation to explain that level of activity (Hunter et al., 2006; Kompus et al., 2013). For example, auditory hallucinations have been consistently associated with activation in brain areas involved in processing external speech, in the absence of this speech (Allen, Larøi, et al., 2008; Kompus et al., 2013; Shergill et al., 2001).

This definition was selected to be as neutral as possible (i.e. not referencing any specific condition or disorder) whilst also encompassing the essential criteria of hyperexcitability listed in the literature across conditions, disorders, and diagnoses. The current definition is also purposefully removed from the specific mechanisms that can potentially cause the hyperexcitability itself, as these are not the focus of this thesis, and the specific data gathered during this research also cannot determine which mechanism/s are causing the hyperexcitability. Even when removed from specific causative mechanisms, “it is useful to think about [hyperexcitability] as a disruption in the normal balance between excitation and inhibition in part or all of the brain” (Stafstrom, 1998, p.343). Although cortical hyperexcitability is associated with many different conditions and disorders (discussed below), it can occur in the brain of *any* person.

1.5 Overview of evidence for cortical hyperexcitability as a mechanism underlying anomalous experiences

This section gives a more detailed overview of evidence for the association between cortical hyperexcitability and anomalous experiences, in clinical groups (briefly, for context) and in healthy samples.

1.5.1 Migraine

Research has indicated that migraine aura clearly has a cortical origin (Coppola et al., 2007), and the idea that the brains of migrainers are hyperexcitable is a leading theory of migraine and aura pathophysiology (Bridge et al., 2015; Coppola & Schoenen, 2012; Cosentino, Fierro, & Brighina, 2014a; Datta, Aguirre, Hu, Detre, & Cucchiara, 2013; Eikermann-Haerter & Ayata, 2010; Hadjikhani,

2008)[6]. Cortical spreading depression (CSD) is thought to be the electrophysiological correlate of migraine aura (Block, 2012; Charles & Baca, 2013; Goadsby, 2001). CSD involves an initial wave of glial depolarisation that spreads across the cortical surface, followed by reduced or suppressed cortical activity in the wake of the depolarisation (Block, 2012). Aberrant neuronal excitability may predispose individuals with migraine to CSD, with the initial wave of excitation in occipital cortex producing the aura (Evans & Aurora, 2012). A generalised imbalance in the levels of excitation and inhibition may also exist in migraine (Bridge et al., 2015). This imbalance may be due to, for example, deficits in glutamatergic (excitatory) and GABAergic (inhibitory) signalling, which may also increase cortical vulnerability to CSD (Bridge et al., 2015; Zielman et al., 2017).

1.5.2 Epilepsy

In epilepsy, a disruption to the balance of excitation and inhibition in the brain leads to hyper-excitability and hyper-synchronisation of neurons, which generates seizures (Devinsky, Vezzani, Najjar, De Lanerolle, & Rogawski, 2013;

[6] There remains some debate in the literature as to whether the cortex is hyper- or hypo-excitable in migraine generally, or whether there is an overall condition of "hyper-responsiveness" (Consentino et al., 2014; Coppola et al., 2012). Migraine has distinct stages; prodromal or pre-ictal, ictal, post-ictal, and inter-ictal, with each stage presenting unique electrophysiological features (Aurora & Wilkinson, 2007), and so it is likely that the state of the cortex varies from hypo- to hyper-excitable across stages (Coppola et al., 2007) with excitation-inhibition imbalances (Bridge et al., 2015) varying accordingly. Of interest to this thesis is the state of the visual cortex during aura specifically, and whether the underlying neural mechanisms evidence a continuity of mechanism for hallucinations across different populations. Therefore, the debate surrounding this issue will not be expanded upon here (but see Aurora & Wilkinson (2007), Consentino et al. (2014), and Coppola et al. (2007) for reviews).

Stafstrom, 1998). Early research suggested that spontaneous neuronal firing may cause epileptic hallucinations (Russell & Whitty, 1955). Accordingly, artificial stimulation of temporal lobe seizure foci are associated with various anomalous experiences, such as auditory misperceptions, complex visual hallucinations (e.g. of complete scenes), déjà vu, and sensed presence and out-of-body experiences (Elliott et al., 2009; Heydrich, Marillier, Evans, Blanke, & Seeck, 2015; Persinger & Makarec, 1987; Schulz et al., 2007).

Both migraine aura and epilepsy are thought to be caused by hyperexcitability, and can present with similar clinical symptoms and comorbidities (Belcastro, Striano, & Parisi, 2013; Bigal et al., 2003). It is well known that stimulus-induced ("reflex") seizures can occur as a consequence of viewing epileptogenic visual stimuli (the "photoparoxysmal response"), most commonly flicker and high contrast striped patterns – and this is caused by cortical hyperexcitability of primary visual cortex (Ferlazzo, Zifkin, Andermann, & Andermann, 2005), as in migraine (see **Figure 1.1** above). Further evidencing this overlap, the term "migralepsy" has been coined to refer to epileptic seizures with migraine-like features (Belcastro et al., 2013). For example, in a case of migralepsy, visual aura was experienced along with déjà vu and olfactory hallucinations (fresh laundry) followed by seizure (Belcastro, 2013). Other recent work has also demonstrated a common hyperexcitability syndrome in epilepsy and migraine (De Simone et al., 2007; Mantegazza & Cestèle, 2018; Zarcone & Corbetta, 2017).

1.5.3 Psychosis

Hallucinatory experiences associated with various psychoses, such as schizophrenia, are also related to “excess excitability” in sensory areas (Block, 2012, p.85; Jardri et al., 2016). Numerous studies have evidenced a relationship between sensory cortex hyperactivity and hallucinations within corresponding senses in psychosis (Allen, Larøi, et al., 2008; Dierks et al., 1999; Homan et al., 2014; Oertel et al., 2007; Silberstein & Young, 1995; Silbersweig et al., 1995; Waters et al., 2014). Other research has suggested that visual hallucinations in psychosis may be caused by an underlying generalised cortical hyperexcitability[7] (Csaszar, Kapocs, & Bokkon, 2019), which may interfere with bottom-up sensory processing by increasing system noise, and so lead to increased focus on or responsiveness to internal stimuli and reduced responsiveness to external stimuli (Spencer et al., 2004; Upthegrove et al., 2016).

The role of hyperexcitability in hallucinations in schizophrenia is supported by a number of meta-analyses finding significant reductions in auditory hallucinations using low-frequency repetitive transcranial magnetic stimulation (rTMS) over Wernicke’s area in left temporo-parietal cortex (Cole, Green Bernacki, Helmer, Pinninti, & O'Reardon, 2015; Slotema, Aleman, Daskalakis, & Sommer, 2012; Slotema, Dirk Blom, Hoek, & Sommer, 2010; Tranulis et al., 2008). This type of stimulation is thought to reduce excitability of targeted cortex, and so Tranulis et

[7] This hyperactivity may arise due to dysregulated GABAergic, glutamatergic, and serotonergic signalling (Jardri et al., 2016). Interestingly, hallucinations are typically induced in healthy individuals using drugs that target the functioning of these same neurotransmitters, suggesting their dysregulation may be responsible for hallucinations generally (Rolland et al., 2014).

al. (Tranulis et al., 2008) suggest these findings strongly support abnormal hyperactivity models of hallucinations.

However, there are several other possible functional mechanisms for hallucinations in psychosis, including erroneous self-monitoring processes (as discussed above) and increased activity in deep brain structures in addition to sensory cortices (Allen, Larøi, et al., 2008). It has been suggested that deep structure hyperactivity generates or modulates hallucinations, whilst sensory cortex hyperactivity determines their perceptual content (Allen, Larøi, et al., 2008; Silbersweig et al., 1995). The influence of these other mechanisms may explain why the duration of hallucination-reducing rTMS effects appears to be less than one month (which is surprising given that rTMS treatment involves intensive daily treatments for two to four weeks (Slotema et al., 2012)). This could suggest that even intensive treatment is not sufficient to alter system excitability long-term, and/or that the factors mentioned above are not addressed by this rTMS treatment and so continue to influence hallucination generation. So, although cortical hyperexcitability plays a key role, addressing this alone will not offer a complete mechanistic explanation (or treatment solution).

1.5.4 Other clinical conditions

There are also several mechanistic similarities for other clinical conditions. Hyperactivation of visual areas above baseline during visual hallucinations in CBS has been evidenced by ffytche et al. (1998) and others (Coltheart, 2018; Painter, Dwyer, Kamke, & Mattingley, 2018; Reichert et al., 2013). Across CBS, schizophrenia, and neurodegenerative disease, atrophy of visual areas (occipital,

parietal, and temporal cortices) may give rise to hyperexcitability through loss of inhibitory neurons or modulatory control (de-afferentation) between network areas (Carter & ffytche, 2015).

1.5.5 Non-clinical groups

1.5.5.1 Behavioural studies

Several studies have linked cortical hyperexcitability to anomalous experiences in non-clinical groups. This section provides an overview of some of the key and most recent contributions to this literature.

Behaviourally, several studies have evidenced a relationship between cortical hyperexcitability and aberrant perceptions in non-clinical samples, using psychophysical experiments (Braithwaite, Broglia, Bagshaw, & Wilkins, 2013; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite, Marchant, Takahashi, Dewe, & Watson, 2015; Braithwaite, Mevorach, & Takahashi, 2015; Fong, Takahashi, & Braithwaite, 2019; Georgeson, 1976; Pearson et al., 2016). For example, it is possible to induce hallucinations and distortions in non-clinical participants using achromatic, square-wave striped "pattern glare" stimuli, which are thought to irritate the visual cortex and induce hyperexcitation of visual neurons[8] (Bargary, Furlan, Raynham, Barbur, & Smith, 2015; Evans & Stevenson, 2008; Huang et al., 2003; Wilkins, 1995; Wilkins et al., 1984). Patterns presented at 3 cycles per degree (cpd) of visual angle are the most visually irritating and can induce epileptiform

[8] Although there is good empirical evidence that pattern glare induces hyperexcitation of visual neurons (Huang, Cooper, Santana, Kaufman, & Cao, 2003; Huang et al., 2011), it should be noted that pattern glare is an indirect indicator / correlate of cortical hyperexcitability only.

discharges (as measured by electroencephalogram) in those with photosensitive epilepsy (Evans & Stevenson, 2008). According to Meldrum and Wilkins (1984, as cited in Evans & Stevenson, 2008, p. 297), these striped gratings “should produce a concentrated excitation... compromising the shared inhibitory processes... Patterns of stripes may therefore cause a high level of cortical stimulation leading to a breakdown in cortical inhibition... the neural excitation could be responsible for visual perceptual distortions”. This has been supported by other work suggesting that hyperexcitation is due to dysfunctional inhibition in visual cortex, both in primary cortex and beyond to areas responsible for processing motion and colour (Georgeson, 1976; Wilkins et al., 1984). Additionally, work on pattern glare by Fong et al. (2019) evidenced a significant positive relationship between state pattern glare scores and trait predisposition to aura-like hallucinatory experiences in a healthy group.

A possible criticism of pattern glare and the claim that it indicates hyperexcitability of visual cortex, is that pattern glare stimuli can cause non-visual somatic sensations such as pain and nausea (Fong et al., 2019). However, in a study comparing migrainer and non-clinical groups, Fong et al. found a relationship between pattern glare experiences and trait measures of heightened visual sensitivity and discomfort in the migrainer group only. It is possible that the visual hyperexcitability induced by the stimuli impacts on vestibular and trigeminovascular networks to produce somatic experiences (Fong et al., 2019; Noseda, Jakubowski, Kainz, Borsook, & Burstein, 2011). Therefore rather than suggesting that pattern glare is unrelated to visual hyperexcitability, these findings indicate that the effects of the induced hyperexcitability can be widespread.

Similarly to Fong et al. (2019), Pearson et al. (2016) demonstrated that it is possible to induce simple visual hallucinations in healthy participants using simple visual stimuli. Presenting a flickering white ring imposed over a black background induces the experience of hallucinatory pale grey blobs rotating around the ring (with these also spontaneously switching direction) in all participants. This study also used monocular versus binocular stimulus presentations to demonstrate that these effects were cortically- rather than retinally-mediated, and computational neural field modelling to suggest that spontaneous activity in primary visual cortex was the most likely mechanism (Pearson et al., 2016).

1.5.5.2 Brain stimulation studies

Various brain stimulation paradigms have been used to explore the relationship between cortical excitability and anomalous experiences, including transcranial direct current stimulation (tDCS) and TMS. One study that combined the pattern glare task with tDCS over primary visual cortex found evidence of increased excitability in a non-clinical sample – that is, as the efficacy of anodal stimulation increased, the efficacy of cathodal stimulation decreased (Braithwaite, Mevorach, et al., 2015). Moreover, increased trait predisposition to anomalous experience (as measured by questionnaire) was specifically associated with increased pattern glare scores under excitatory stimulation only, suggesting that the trait of being predisposed to hallucinations is associated with brains that are more easily excitable and more difficult to inhibit due to dysfunctional inhibitory mechanisms (Braithwaite et al., 2015b).

However only a small number of studies have explored pattern glare in non-neurological samples (Braithwaite et al., 2015b), or the relationship between pattern glare and anomalous experience using tDCS, and so these results are tentative. Further, as Braithwaite and colleagues point out, both tDCS and pattern glare stimuli can be viewed as stimulating the visual system. Therefore, additional work that explores different manipulations of these variables is needed to fully clarify these relationships (such as different stimulation durations, and online versus offline stimulation). Additionally, this study stimulated primary visual cortex, and so further iterations of this study should look to stimulate other visual areas to determine whether the relationships observed here are replicable. These issues will be addressed in this thesis.

Several studies have linked cortical hyperexcitability and anomalous experience by successfully reducing phosphene thresholds (making their occurrence more likely) by using tDCS, TMS, or combined tDCS-TMS to excite visual cortex in healthy groups (Antal, Kincses, Nitsche, & Paulus, 2003a; Antal, Kincses, Nitsche, & Paulus, 2003b; Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004; Antal, Nitsche, & Paulus, 2001; Battelli, Black, & Wray, 2002). Inducing perception of phosphenes using TMS has often been used “as a measure of visual cortex excitability”, and “a reduced threshold for phosphene perception... implies greater excitability and vice versa” (Ekkert, Noreikaitė, Valiulis, & Ryliškienė, 2019). Accordingly, inhibitory rTMS over visual cortex has been successfully used to suppress both visual and auditory hallucinations (Lefaucheur et al., 2014).

1.5.5.3 Brain recording studies

Electroencephalography (EEG) has mainly been used to explore visual hallucinations in healthy participants after inducing these experiences using hallucinogens targeting serotonergic signalling (such as psilocybin) (daSilva Morgan, Elder, ffytche, Collerton, & Taylor, 2018). A common correlate of visual hallucinations in these cases is decreased occipital alpha-band power, indicating increased excitability (daSilva Morgan et al., 2018). However, in addition to changes in cortical excitability, decreased occipital alpha-band power and increased gamma-band power during hallucinogen-induced visual hallucinations suggest the involvement of increased selective attention and "formation of conscious perceptions via access to attentional processes" respectively (daSilva Morgan et al., 2018). The neural mechanisms behind these are not yet known. This also highlights the limited explanatory power of cortical hyperexcitability alone.

Vivid and complex visual and auditory hallucinations can also be induced in healthy individuals using sensory deprivation (Aleman & Vercammen, 2013; Block, 2012; Boksa, 2009), which is thought to produce hallucinations through increasing excitability of sensory cortex (as discussed above; see Daniel, 2017). As sensory deprivation can produce transient "psychotic-like" experiences in non-clinical populations (such as perceptual distortions), it has been used as an experimental model of psychosis (Daniel, 2017). Daniel (2017) suggested that elevated cortical hyperexcitability may play a role in this hallucination proneness, with decreased baseline theta, alpha, and beta activity (as measured by EEG) observed in those highly prone to hallucinations thought to reflect poor inhibitory processing and weakened homeostatic control, as compared to a low hallucination prone group. Those most prone to hallucinations also reported significantly more experiences

associated with cortical hyperexcitability (as indexed by the Cortical Hyperexcitability index; Braithwaite, Marchant, et al., 2015).

Similarly, a decline in auditory functioning is associated with auditory hallucinations in otherwise healthy older adults with hearing loss (Badcock et al., 2017). Cortical hyperexcitability is the most common explanation for the observed increases in cortical activity observed during hallucinations associated with sensory decline (Badcock et al., 2017). Although there are other possible explanations, these are not at the neural level. Genetics may play a role, but there is currently insufficient evidence that predisposition to hallucinations specifically is heritable; cognitive inhibitory and reality-monitoring processes (as discussed above) are important, but there is little evidence for these in healthy groups or work that relates these to underlying neural mechanisms; and cognitive dysfunction may not be sufficient to explain hallucination generation specifically (Badcock et al., 2017).

1.5.5.4 Brain imaging studies

Interestingly, recent neuroimaging work has found activation of similar auditory networks during auditory verbal hallucinations in individuals with psychosis and non-clinical voice hearers, with no significant differences in activation patterns between the groups (Badcock & Hugdahl, 2012; Diederen et al., 2011; Larøi et al., 2012; Linden et al., 2011). Increased predisposition to spontaneous auditory activity may be the neural substrate of such experiences in both clinical and non-clinical groups (Badcock & Hugdahl, 2012). Recently, Abid et al. (2016) induced hallucinatory experiences of “magnification” (stimuli seeming

enlarged) in healthy participants using two types of static concentric circle stimuli; one set in grey, and one with checkerboard borders. Abid et al. observed significant activations in extrastriate cortex (Brodmann's areas 17, 18, and 19) concordant with experiences of hallucinatory magnification when these stimuli were presented (as compared to viewing baseline stimuli), suggesting increased excitation of visual neurons (Abid et al., 2016).

Further evidence comes from "signal detection tasks", which are often used to explore auditory hallucination proneness in non-clinical groups. These involve participants listening to white noise imbedded with snippets of clear or at-threshold (difficult to detect) speech or with no speech at all. Scheper et al. (2016) found that speech "misperceptions" – hearing speech in white noise where none exists – are associated with decreased alpha-band activity over temporal regions, indicating high excitability. This is consistent with findings on auditory hallucinations in clinical groups (Maran, Grent-'t-Jong, & Uhlhaas, 2016).

However, there is still too little research that explores the mechanisms underlying non-clinical hallucinations to make any firm conclusions (Diederen et al., 2011; Larøi, 2012). Further work is needed that explores the neural mechanisms of hallucinations in non-clinical groups specifically – particularly in visual and other modalities. Diederen and colleagues (2011) suggest that the contributing mechanisms may be "pathophysiological", however there is not currently enough evidence to confirm this – especially as similar mechanisms and experiences have been identified in both clinical and non-clinical groups.

Overall, these findings support cortical hyperexcitability as one potential neural substrate for anomalous experiences in non-clinical populations. Indeed, in a review of auditory hallucinations in schizophrenia and healthy populations, Waters et al. (2014) suggest abnormal, spontaneous activation of auditory networks as the first step of auditory hallucination generation across groups.

1.5.6 Schizotypy

The anomalous perceptions experienced as part of schizotypy have also recently been linked to hyperexcitability, although there are far fewer studies exploring this as compared to schizophrenia. For example, Ferri et al. (2017) explored the relationship between schizotypy (focusing on unusual perceptual experiences) and excitability, using spectroscopy to measure Glu/GABA concentrations and indexing the E/I balance using gene variants associated with GABA and glutamate signalling, in a healthy sample. The “temporal binding window” (TBW) was also measured. This provides an indication of the time window within which external and internal stimuli are “bound” together, and abnormally large TBWs are thought to contribute to erroneous integration and so abnormal perceptual experiences in both psychosis and schizotypy (Ferri et al., 2017). Evidence strongly suggests that this process depends on balances in excitatory and inhibitory neurotransmission (Ferri et al., 2017). It was found that higher glutamate concentrations combined with E/I balances shifted towards inhibition were associated with narrower TBW and fewer unusual perceptual experiences, whereas higher glutamate concentrations and E/I balances shifted towards excitation were associated with wider TBW and more unusual perceptual experiences (Ferri et al., 2017). This supports the idea of deficient inhibition and

increased excitation leading to anomalous experiences, here through decreased temporal precision and increased (but indiscriminate) saliency of both internal and external stimuli, even in healthy individuals. This also suggests that increased Glu concentration is not sufficient to increase excitation – the E/I balance must also be shifted towards excitation to influence the TBW and perception.

1.6 Conclusion and aims

Hyperexcitability may be responsible for a wide variety of hallucinatory experiences (Block, 2012). The available research linking cortical hyperexcitability to anomalous experiences generally is extensive, but still fairly limited in non-clinical groups (as this group has received little attention until recent years). Based on the research above, it may be that specific mechanisms or patterns of hyperexcitability are unique to certain types of hallucinations in certain groups – which may not match with current clinical groupings. To begin to answer these questions, it is necessary to gather more basic data on hyperexcitability and its correlates in non-clinical groups.

A key issue with previous hallucination research and theory is the strong influence of psychiatric perspectives and wide use of clinical samples, such that most models can only explain hallucinations in specific conditions or modalities. Mechanisms of auditory verbal hallucinations in schizophrenia dominate the literature. These models are difficult to reconcile with hallucinations in other conditions and in healthy groups, particularly because clinical data is confounded by illness duration and chronicity, comorbidity, medication use, and cognitive

dysfunction, for example (Allen, Modinos, et al., 2012). Due to these issues, much previous research has lacked both precision in teasing out the mechanisms underlying hallucinations specifically (as opposed to those underlying general clinical syndromes) (Rollins et al., 2019), and data on hallucinations in multiple modalities (Zmigrod et al., 2016) from large, healthy samples.

Therefore, the overall aim of this thesis was to further explore the contribution of cortical hyperexcitability to anomalous experiences in non-clinical samples. This thesis sought to answer the following questions:

- What, if any, are the relationships between trait and state measures[9] of anomalous experiences and cortical hyperexcitability?

- Are there differences in these relationships depending on whether trait-state or state-state comparisons are made?

- Are there differences in these relationships depending on whether uni-modal or cross-modal comparisons are made?

[9] Use of the terms “trait” and “state” to refer to measures and experiences, as in this thesis, is common in anomalous experience research (Dewe, Watson, Kessler, & Braithwaite, 2018; Fong, Law, Braithwaite, & Mazaheri, 2020; Fong et al., 2019; Kühn & Gallinat, 2012; Smith et al., 2013; Wright, Fowler, & Greenwood, 2018). “Trait” measures are those assessing general predisposition to anomalous experiences, usually through retrospective ratings of previous experiences, whereas “state” measures ask individuals to detail their current, in-the-moment experiences, or quantify “online” correlates or manipulations of experiences (Smith et al., 2013; Thoma et al., 2017).

- Are specific types of trait anomalous experience related to different state measures of cortical hyperexcitability?

Foreword to Chapter 2

Building on previous research, this chapter explored whether previously identified trait-state relationships between anomalous experiences and pattern glare under tDCS of primary visual cortex (Braithwaite et al., 2015b) could be extended to extrastriate visual cortex. This allowed investigation of the influence of different stages in the visual hierarchy on both trait and state experiences of aberrant perceptions. In order to investigate a wide range of non-clinical anomalous experience, questionnaires that focused on visual and multiple modalities were used.

Based on previous work (Braithwaite, Mevorach, et al., 2015), it was hypothesised that positive correlations between trait and state measures of anomalous experience and excitability would be observed in a continuous manner across the sample. Such findings would suggest that trait-state relationships are mediated in a similar way by tDCS over striate and extrastriate visual cortex. Additionally, it was expected that anodal stimulation would be facilitated by the pre-existing high baseline excitability in those with high scores on a pattern glare task (which is a reliable indicator of cortical hyperexcitability; Evans & Stevenson, 2008; Harle et al., 2006) and so increase pattern glare experiences. Further, this pre-existing excitability would decrease the efficacy of cathodal (inhibitory) stimulation

to decrease pattern glare experiences. In contrast, those with low scores on the pattern glare task (and so low to moderate excitability) would display the anodal-excitation effect to a lesser degree, and a relatively robust cathodal-inhibition effect, due to hypothesised intact inhibitory mechanisms. This would suggest that both striate and extrastriate cortex respond in a similar way to tDCS, and that the efficacy of tDCS is influenced by baseline excitability.

An edited version of Chapters 2 and 3 has been submitted as one journal article to *Cognitive, Affective, and Behavioural Neuroscience*.

Materials relevant to these chapters (consent / screening forms, and questionnaires) are presented in **Appendices A – G**. Computational current flow models of tDCS for Chapters 2 and 3, which were not included in the submitted manuscript, are presented in **Appendix H**.

2 Chapter 2

2.1 Introduction

Perceptual experiences that deviate significantly from usual, everyday experience are known as “anomalous experiences” (Cardeña et al., 2014). Anomalous experiences can occur in any sensory modality; and can also be multi-modal (Braithwaite & Dent, 2011; Braithwaite et al., 2011; Cardeña et al., 2014; Larøi et al., 2012). The term “anomalous experience” covers many types of perceptual aberration, including hallucinations and distortions. Hallucinations are perceptions in any sensory modality that are not elicited by a corresponding external stimulus (Waters et al., 2016). In contrast, distortions are misperceptions of existing sensory stimuli (Collerton et al., 2015). These experiences can be placed on a spectrum from veridical perception to complex hallucination, with misperceptions and voluntary imagery occurring somewhere in between (Bentall, 2003; Collerton, Perry, & McKeith, 2005; McCreery, 2006; Waters et al., 2016).

A wide variety of anomalous perceptions are experienced by people with various neurological and psychiatric conditions, including migraine with aura, psychosis, epilepsy, and Charles Bonnet syndrome (Braithwaite, Marchant, et al., 2015; Braithwaite, Mevorach, et al., 2015; Heydrich et al., 2015; Siddiqui & Khan, 2016; Smith, Wright, & Bennett, 2015; Waters et al., 2014). Anomalous experiences can also occur in a variety of altered states, such as during sensory deprivation and delirium, and as a result of substance use (Cowan, Dietrich, Kim, & Zald, 2015; Daniel et al., 2014; Perry, Ashton, & Young, 2002). However, even in the absence of any kind of clinical diagnosis or altered state, these strange experiences are relatively common in the general population (Baumeister et al.,

2017; Johns & van Os, 2001; Ohayon, 2000; Preti et al., 2014; van Os & Reninghaus, 2016). Studies with very large sample sizes have estimated prevalence at 7.3% for auditory verbal hallucinations (Kråkvik et al., 2015) and 5.2% for visual or auditory hallucinatory experiences unrelated to sleep disturbances, alcohol or drug use (McGrath et al., 2015). This estimate rises to 38.7% when a broader range of experiences are considered, such as olfactory, haptic, gustatory, out-of-body, and sleep-related hallucinations (Ohayon, 2000). Even complex hallucinations such as out-of-body experiences are also experienced by psychologically-healthy individuals (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite & Dent, 2011; Braithwaite et al., 2011). Overall, research indicates a surprisingly high prevalence of anomalous experiences in samples of the psychologically-healthy general population.

2.1.1 Cortical hyperexcitability and anomalous experience

Across neurological, psychiatric, and non-clinical groups, there exists a wealth of research linking increased cortical excitability to anomalous perceptual experiences, including but not limited to migraine with aura (Palmer, Chronicle, Rolan, & Mulleners, 2000), epilepsy (Panayiotopolous, 1999), Charles Bonnet syndrome (CBS) (Burke, 2002), psychosis (Baumeister et al., 2017), depersonalisation and derealisation (Schicho & Pogarell, 2014), visual stress (Braithwaite, Mevorach, et al., 2015), and miscellaneous cases of spontaneous hallucinations in healthy individuals with no clear tractable pathology (Barkus, Stirling, Hopkins, McKie, & Lewis, 2007; Braithwaite, Broglia, Brincat, et al., 2013;

Braithwaite et al., 2011). Hyperexcitability has also been related to both “positive” and “negative” anomalous experiences (such as experiencing shapes or colours imposed on the visual field and temporary blind spots, scotomas, and tunnel vision respectively) (Chen et al., 2011; Cosentino, Fierro, & Brighina, 2014b; Dobry & Sher, 2013; Eikermann-Haerter & Ayata, 2010; Lauritzen, 2001; Simpson, Goadsby, & Prabhakar, 2013). The vivid visual hallucinations experienced in CBS are thought to be the result of deafferentation and hyperexcitability of extrastriate cortex, caused by lesions to visual pathways or macular degeneration (Burke, 2002; Carter & ffytche, 2015; ffytche et al., 1998; Jang et al., 2011; Pang, 2016). Hyperactivation of extrastriate cortex is also thought to be central to the visual hallucinations experienced in dementia with Lewy bodies (Taylor et al., 2011).

Braithwaite and colleagues have evidenced signs of elevated cortical excitability in non-clinical hallucinators using both behavioural and brain stimulation methods (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite, Mevorach, et al., 2015; Braithwaite & Takahashi, 2015; Fong et al., 2019; Takahashi & Braithwaite, 2015). A recent multi-disciplinary review highlighted the central role of an imbalance in cortical excitation and inhibition in hallucinations, with increased excitation and/or decreased inhibition being consistently associated with hallucinations across the literature on schizophrenia (Jardri et al., 2016).

Brain stimulation methods such as TMS have been used to induce and manipulate hallucinatory experiences in both healthy and clinical groups. Evidence from migraine patients, for example, suggests that these individuals have a pre-

existing neural vulnerability to episodes of increased excitability, which may underlie hallucinatory aura experiences (Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998; Battelli et al., 2002). In support of this hypothesis, visual and auditory hallucinations can be successfully suppressed using inhibitory repetitive TMS (rTMS) of the primary visual cortex and temporoparietal cortex respectively (Lefaucheur et al., 2014). Collectively, research suggests that elevated levels of neural excitability are associated with increased predisposition to anomalous experiences. This is unsurprising given that stable conscious experience depends heavily on a delicate balance between inhibitory and excitatory networks, with disruptions in this balance leading to altered consciousness (Vaitl et al., 2005).

Neuro-imaging methods such as functional magnetic resonance imaging (fMRI) have also provided evidence of correlation between hyper-excitation of specific extrastriate visual areas and hallucination phenomenology (ffytche et al., 1998). Recent fMRI research has supported this relationship in other groups and modalities. In adolescents experiencing brief psychotic episodes, auditory, visual, and multi-modal hallucinations were correlated with increased blood oxygenation level-dependent signal in the corresponding sensory cortices (Jardri, Thomas, Delmaire, Pins, & Delion, 2012). Several state studies have evidenced increased activation in speech-related areas during auditory hallucinations in schizophrenia (Jardri et al., 2011), and this relationship has also been evidenced in non-clinical groups, with no significant differences between clinical and non-clinical participants (Diederen et al., 2011).

2.1.2 Behavioural measures of cortical hyperexcitability

The “pattern glare” task has been widely used as a behavioural proxy measure of visual cortical hyperexcitability (Huang et al., 2003; Huang et al., 2011; Wilkins, Huang, & Cao, 2004). Pattern glare refers to a collection of experiences (including distortions, sensitivity, pain, and elementary hallucinations) that can be induced by exposure to viewing certain visual stimuli, such as striped patterns (gratings) (Monger, Wilkins, & Allen, 2015). A high-contrast grating with approximately three cycles per degree (cpd) of visual angle can induce visual discomfort and anomalous sensory experiences in susceptible observers, these experiences include visual distortions – such as bending lines, shimmering, zooming, – hallucinations such as coloured halos, and anomalous bodily sensations such as, dizziness, and nausea (Allen, Evans, & Wilkins, 2012; Braithwaite, Mevorach, et al., 2015; Chu, Im, Chung, & Oh, 2011).

Experiencing these pattern-induced phenomena is thought to reflect an increased degree of cortical excitability. By this account, the gratings are thought to over-stimulate neurons in the visual cortex resulting in aberrant and anomalous perceptions (Braithwaite, Marchant, et al., 2015; Haigh et al., 2013; Huang et al., 2011; Monger, Shah, Wilkins, & Allen, 2016). Consistent with this, pattern glare has been observed in migrainers experiencing aura (Huang et al., 2003; Monger et al., 2015; Shepherd et al., 2013) and in individuals on the autistic spectrum who experience visual stress (Ward et al., 2017). Research by Huang and colleagues (2011) used fMRI to evidence hyperneuronal activity in the visual cortex of migrainers in response to pattern glare gratings, supporting the relationship between a generalised hyperexcitability and anomalous perceptions. Furthermore,

excess cortical activation, and so visual discomfort, was significantly reduced in migrainers through the use of tinted lenses, which are thought to reduce hyperexcitation in visual regions by redistributing the aberrant neural activity (Monger et al., 2015). Interestingly, this reduction primarily occurred in areas anterior to V1, suggesting that hyperexcitability in extrastriate areas can influence anomalous perceptions (Huang et al., 2011). Experiences of pattern glare also occur in non-clinical samples, and are associated with predisposition to experiencing complex hallucinations such as out-of-body experiences (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite et al., 2011).

Brain -stimulation and -imaging methods have also been used to index cortical hyperexcitability. TMS has been widely used to alter phosphene thresholds by manipulating excitability levels, in both clinical and non-clinical groups (Battelli et al., 2002; Boroojerdi, Bushara, et al., 2000; Brighina, Piazza, Daniele, & Fierro, 2002). Migrainers have significantly lower phosphene thresholds and more vivid/sustained phosphenes than controls (as indexed by TMS over V5) (Battelli et al., 2002), and migraine prophylaxis can increase phosphene thresholds by decreasing excitability of visual cortex (Mulleners, Chronicle, Vredeveld, & Keohler, 2002). Additionally, inhibitory rTMS is effective in neutralising the excessive cortical excitability that can result from occipital stroke, leading to a reduction in associated chronic visual hallucinations (Rafique, Richards, & Steeves, 2016). Using a combined TMS-fMRI paradigm with healthy volunteers, Boroojerdi et al. (2000) showed that light deprivation leads to significantly increased visual cortical

excitability and decreased phosphenes thresholds, again evidencing a link between excitability and anomalous perceptions even in non-clinical groups.

There exist several questionnaire measures that attempt to quantify the rate and range of trait-based anomalous experiences, such as the Cardiff Anomalous Perceptions Scale (CAPS) (Bell et al., 2006), Cambridge Depersonalisation Scale (CDS) (Seirra & Berrios, 2000), and Launay Slade Hallucinations Scale Revised (Morrison, Wells, & Nothard, 2001). Until recently, no validated multi-factor screening measure existed that sought to quantify a range of perceptual experiences that have been specifically related to visually-induced cortical hyperexcitability in the literature. To rectify these issues, the Cortical Hyperexcitability index (CHi) (Braithwaite, Marchant, et al., 2015) was developed to provide a proxy measure of predisposition to anomalous experiences thought to be associated with cortical hyperexcitability. Exploratory factor analysis of the CHi suggested a three-factor structure, with different types of anomalous experience clustering into separate but correlated factors: visual sensitivity and discomfort; “positive” aberrations (additions to visual experience, such as phosphenes); and “negative” aberrations (loss of visual experience, such as scotoma and tunnel vision) (see **Materials** for detail) (Braithwaite, Marchant, et al., 2015).

2.1.3 Transcranial direct current stimulation (tDCS)

Given the apparent relationship between cortical excitability and anomalous experience, experimental methods for manipulating excitability levels can provide valuable insight into the mechanisms underlying anomalous perceptions. One such

method is transcranial direct current stimulation (tDCS), a non-invasive brain stimulation method that can alter baseline cortical excitability levels in human cortex (Braithwaite, Mevorach, et al., 2015; Jacobson, Koslowsky, & Lavidor, 2012)The exact biophysical mechanisms by which tDCS exerts its effects are still unclear (Lauro et al., 2014). It is thought that anodal stimulation produces an excitatory effect by depolarising cell membranes and so increasing the likelihood of spontaneous neuronal firing, whilst cathodal stimulation decreases excitability by hyperpolarising cell membranes and so decreasing the likelihood of spontaneous firing (Braithwaite, Mevorach, et al., 2015; Jacobson et al., 2012; Lauro et al., 2014). TDCS may influence membrane potentials of cortical areas directly beneath electrodes as well as neural activity in adjoining regions (Lauro et al., 2014). Although the online effects of tDCS are thought to be influenced solely by changes in membrane potential, synaptic mechanisms – such as changes to NMDA receptors and modulation of GABAergic and glutamatergic synapses – and cell morphology may also contribute to the online- and offline- effects of tDCS (Miranda, Callejón-Leblic, Salvador, & Ruffini, 2018; Stagg & Nitsche, 2011).

Modulating baseline excitability through tDCS is associated with various behavioural and cognitive effects, in both clinical and non-clinical brains (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Lauro et al., 2014). In cognitive tasks, the anodal-excitation effect is regularly significant, whereas the cathodal-inhibition effect is rather weaker and less consistent (Dedoncker et al., 2016; Jacobson et al., 2012; Lauro et al., 2014). TDCS has also been used to successfully manipulate phosphene thresholds in healthy subjects, with anodal and

cathodal stimulation of visual cortex reducing and increasing thresholds respectively (Antal et al., 2003a).

Despite the success of tDCS methods for investigating the effects of excitability changes, only one study has used tDCS to investigate manipulations of cortical hyperexcitability and variations in pattern glare experiences (Braithwaite, Mevorach, et al., 2015). Here, anodal stimulation of primary visual cortex was significantly associated with increased anomalous perceptions indicated by a pattern glare task. Additionally, the greater the individual response to anodal stimulation, the smaller the response to cathodal stimulation – suggesting that excitable cortices are easier to excite and more difficult to suppress, consistent with a hyperexcitable cortex (Braithwaite, Mevorach, et al., 2015).

Similarly, recent studies have also provided evidence that baseline factors (such as habitual brain states and individual differences in excitability) interact with tDCS to modulate its behavioural effects, prompting reconsideration of the traditional anodal-excitation cathodal-inhibition assumption. Visual working memory (VWM) studies have evidenced considerable inter-individual variability in behavioural responses to tDCS, based on performance. Some participants show the expected anodal-excitation (VWM task facilitation) and cathodal-inhibition (VWM task impediment) effects (Hsu, Juan, & Tseng, 2016), however in other studies anodal tDCS enhances visual working memory capacity in low- but not high-performing participants (Juan, Liang, Miggleton, Tseng, & Hsu, 2017; Tseng et al., 2012).For others, the positive or negative impacts on task performance from anodal stimulation were associated with the same direction of effect from cathodal

stimulation (Hsu et al., 2016). These studies suggest that receptivity to, and the effects of, tDCS depend on individual baseline states (Hsu et al., 2016).

Furthermore, state-dependent effects on visual experience have been observed using TMS over visual cortex. Silvanto et al. (2007) found that adapting participants' visual systems to colour resulted in phosphenes of the same colour, which may reflect a facilitation effect in affected neurons. With no exposure to adapting colour stimuli, phosphenes appeared colourless, as all neurons were at a similar "baseline" level of activation when TMS was applied and so were activated equally. More recently, (Silvanto, Bona, Marelli, & Cattaneo, 2018) combined TMS over primary visual cortex with various visual priming tasks (which rely on changes to neural excitability) as brain state manipulators. In this study, low or high baseline performance on a visual priming task was associated with TMS-induced facilitation or impairment respectively, suggesting that baseline excitability significantly influences TMS efficacy and resultant behavioural effects. These finding suggest that baseline states vary considerably across participants and directly impact both receptivity to and the effects of brain stimulation (Hsu et al., 2016; Silvanto et al., 2018; Silvanto et al., 2007). and so it is vital to take state factors into account in tDCS application, analysis, and interpretation. Moreover, combining manipulation of both brain states and tDCS parameters moves beyond conventional approaches that assume all neurons are stimulated and respond indiscriminately, and allows a more fine-grained examination of the neuronal mechanisms underlying specific cognitive functions (Romei, Thut, & Silvanto, 2016). The current study will address this by exploring the relationships between state- and trait-based measures and

tDCS stimulation in individuals arguably displaying diverse levels of predisposition to anomalous perceptions.

2.1.4 Overview of the current study

Many pattern-glare experiences suggest the involvement of extrastriate cortex and are not restricted to what we might assume is the involvement of V1 alone (i.e., motion effects and colours). In addition, the imaging study by Huang and collegaues (2011) demonstrated that the largest reduction in heightened activation from wearing tinted lenses was principally-mediated anterior to visual cortex (extrastriate cortex; V2, V3, V3a, V4). Other findings have shown that visual anomalies experienced in migraine are likely associated with dysfunctions in visual processing that lead to a spreading wave of hyperexcitability, which extends beyond primary visual cortex to extrastriate areas (Shibata, 2007; Shibata, Yamane, Otuka, & Iwata, 2008).

By stimulating primary visual cortex (Oz), a previous tDCS investigation revealed evidence for increased cortical hyperexcitability in non-clinical groups predisposed to anomalous experiences (Braithwaite, Mevorach, et al., 2015). Although the anode was placed over Oz in this study, it is possible, based on current tDCS models, that the majority of this stimulatory field impacted on regions between the Oz and Cz electrodes (i.e. visual association cortex) in addition to those directly underneath them (Datta, Truong, Minhas, Parra, & Bikson, 2012; Miranda et al., 2018; Santhouse, Howard, & ffytche, 2000; Shibata, 2007; Shibata et al., 2008; Wurzman, Hamilton, Pascual-Leone, & Fox, 2016). If true, then this

would unite the imaging findings to the nature of pattern glare experiences, and findings from brain-stimulation studies supporting the notion that pattern-glare experiences may reflect contributions from extrastriate cortex. In addition, the development of recent new questionnaire measures now allows us to determine relationships, if any, between potential background trait-based and state-based effects.

Extending previous studies, the current investigation explored whether signs of cortical hyperexcitability exist beyond primary visual cortex and can be revealed by tDCS brain stimulation targeting higher cortical regions, and whether such experiences are associated with predisposition to anomalous hallucinatory experience. This would imply that the neural vulnerabilities underlying predisposition to pattern-glare phenomena, and anomalous elementary hallucinatory experience, do indeed extend into higher extra-striate regions – even for non-clinical groups.

If cortical hyperexcitability in extra-striate cortex is associated with predisposition to anomalous perceptions, then those scoring higher on the CHi measure should also experience an increased intensity of sensory distortions associated with the state-based pattern glare task (where participants rate experiences of distortions online, as they experience them, rather than retrospectively rating their trait-based predisposition). This would also provide more objective evidence that the CHi is a reliable proxy measure of anomalous experiences associated with cortical hyperexcitability. In addition, individuals whose cortices respond more readily to anodal stimulation may also display

reduced efficacy of cathodal stimulation in relation to the intensity of experiences induced from the state-based task (Study 2), as has been shown previously (Braithwaite, Mevorach, et al., 2015) – but now also extending into higher-level extrastriate cortex and with different stimulation parameters. Inclusion of a state-based behavioural measure of anomalous experiences will allow us to explore whether this state factor does indeed interact with tDCS responsiveness, as suggested by existing literature. Following traditional models of tDCS efficacy, individuals with high baseline excitability (as indicated by pattern glare ratings) would be expected to experience more intense state-based visual distortions in the anodal stimulation condition, as this stimulation may be facilitated by underlying hyperexcitability. However, given the above work on the state-dependency of tDCS, we hypothesise that high and low pattern glare scorers will respond differently to tDCS.

Several studies have successfully used brain stimulation of occipital and occipitoparietal cortices to induce visual distortions and hallucinations – including a variety of simple and complex hallucinatory experiences (Selimbeyoglu & Parvizi, 2010). Electrode site Pz (targeting Brodmann's area 5 and 7 – occipital parietal cortex) is of particular interest as the functions of BA 5 and 7 correspond to several of the visual distortions experienced in the pattern glare task. Activation in BA7 has been observed when participants view moving patterns, in addition to V5 in BA19 (Barbur, Watson, Frackowiak, & Zeki, 1993), and different types of movement are commonly-experienced distortions of pattern glare stimuli (such as shimmering, zooming, jitter). As BA7 also serves as a convergence point for visual and proprioceptive functions, it is plausible that hyperexcitability in this area may be

responsible for aberrant bodily experiences, such as distortions of perceived bodily position and nausea.

To assess state-based levels of cortical hyperexcitability, participants completed a computerised version of the pattern glare test (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite, Mevorach, et al., 2015). For a measure of trait-based predisposition to anomalous perceptions, participants also completed the CAPS (to gain a broad overview of individual predisposition to anomalous experiences in various modalities) and the newly-devised CHi questionnaire measure. Study 1 examined the effects of 20 mins of anodal tDCS stimulation (contrasted with a sham condition). Study 2 examined the effects of 10 mins of anodal, cathodal, and sham tDCS. The stimulatory montages varied in terms of active brain locations and stimulation duration across the studies (see **Materials**).

2.2 Methods

2.2.1 Participants

Eighty-six participants took part in Study 1. Of these, 68 (79%) were female and 72 (84%) were right-handed. Participant age ranged from 18 to 39 years ($\bar{x}$ = 20.1, σ = 3.0). All participants were undergraduate/postgraduate students, research assistants, or support staff from the University of Birmingham (UK), recruited through advertisements on the Research Participation Scheme and the my.bham university portal. Participants received research credits or monetary

compensation in return for participation. A self-report screening questionnaire was administered at the start of each study to ensure that participants did not meet any of the exclusion criteria, which were: a neurological or psychiatric condition, personal or family history of seizure/epilepsy/recurrent fainting; seizures of unknown origin, compromised vision or physical state (including excessive caffeine/alcohol consumption the previous night; metal or medical implants (cochlear implant, pacemaker, medication pump, surgical clips); taking any prescribed or unprescribed medication that may interfere with cognitive function; on-going anti-malarial treatment; regular sleep disruption/disorders (such as insomnia); and previous significant head injury, concussion, or eye-surgery. Individuals who may be/were pregnant, or had taken part in more than one brain stimulation study in the past six months, were also not eligible to participate. Informed consent was obtained from participants using a consent form that described the nature of the study, potential benefits and risks, and participant compensation. The study was approved by the Ethics Committee of the University of Birmingham [ERN_12-0446R].

Based on previous work estimating occurrence of anomalous experiences in the general population at 5% (McGrath et al., 2015), we used Cochran's sample size formula to calculate the needed sample size (where Z = Z value, p = estimated proportion of the population with this attribute, q = p-1, and e = α value (0.05)):

$$n_0 = \frac{Z^2 pq}{e^2}$$

This gives:

$$n_0 = \frac{(1.96)^2(0.05)(0.95)}{(0.05)^2} = 73$$

Therefore a sample of at least 73 participants was needed. Effect sizes are indicated for relevant comparisons in the Results section (as correlation coefficients, and Hedges' *g* for t-tests due to different sample sizes (Lakens, 2013)).

2.2.2 Materials

2.2.2.1 Cortical Hyperexcitability index (CHi)

The CHi (Braithwaite, Marchant, et al., 2015) is a psychometrically-validated proxy measure of cortical hyperexcitability, consisting of 27 items. All CHi questions feature two response dimensions; "frequency" and "intensity". For each item, participants give responses to these two dimensions along a 7-point Likert scale (1-7; 1 = "Never"/"Not at all", 7 = "All the time"/"Extremely intense"). CHi questions relate to the presence, intensity, and frequency of experiences from three distinct but inter-correlated factors: (1) heightened visual sensitivity and discomfort; (2) "negative" visual aberrations (decreases in or loss of visual information); and (3) "positive" visual aberrations ("additions" to visual experience) (see Braithwaite et al., 2015). Factor 1 exclusively reflects experiences of a heightened sensory sensitivity to certain environmental stimuli or properties, which can cause discomfort, irritation, and pain. Factor 1 consists of 13 items. Factor 2 (six items) largely relates to negative aura-type visual disturbances, such as narrowing of or loss of information from the visual field, blind spots (scotoma), and macropsia/micropsia (Braithwaite, Marchant, et al., 2015). Factor 3 (five items) relates to experiences of positive aura-type experiences, such as seeing shapes, lights, and colours imposed on the visual field. Such experiences are associated

with disorders that have aberrant neural activity as a core feature, such as epilepsy and migraine with aura (Badawy, Simon, Vogrin, Lai, & Cook, 2013; Belcastro et al., 2013; Eikermann-Haerter & Ayata, 2010). Factor 3 also contains a question related to out-of-body experiences (OBEs), defined in this study as a phenomenon in which the experiencer can view the world from a vantage point outside of their physical body. OBEs have been reported as part of migraine aura (Braithwaite et al., 2011; Podoll & Robinson, 1999).

Both “positive” (Factor 3) and “negative” (Factor 2) aberrations have been associated with cortical spreading depression (CSD) models of migraine aura in humans (Eikermann-Haerter & Ayata, 2010; Goadsby, 2001; Lauritzen, 2001). Specifically, CSD involves an initial wave of spontaneous depolarisation in visual cortex followed by a wave of neural suppression (Charles & Baca, 2013). Evidence suggests that the initial over-excitation of neurons is associated with “positive” visual aberrations, whilst “negative” symptoms may be caused by the following wave of neural depression (Braithwaite, Marchant, et al., 2015; Charles & Baca, 2013; Eikermann-Haerter & Ayata, 2010; Hadjikhani et al., 2001).

2.2.2.2 Cardiff Anomalous Perceptions Scale (CAPS)

The CAPS (Bell et al., 2006) is a 32-item, psychometrically-validated measure of predisposition to anomalous experiences across sensory modalities. Participants respond to each question via a binary “yes/no” response scale. If participants indicate “yes” for any question, they then rate their experience on three sub-scales – distress, intrusiveness, and frequency – all on 5-point Likert scales (1

= not at all distressing/distracting, very infrequent; 5 = very distressing/distracting/frequent).

Factor analysis of CAPS components suggested three factors, one of which was related to “temporal lobe disturbance” (including experiences linked to non-psychotic temporal lobe epilepsy and disturbances associated with seizure (Bell, Halligan, & Ellis, 2007)). This “Temporal Lobe Experience” (TLE) factor of the CAPS contains items related to anomalous perceptual experiences that are commonly reported by individuals with temporal lobe epilepsy during pre-seizure aura (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, Brincat, et al., 2013). Such experiences are not limited to clinical populations, and are known to also occur in the general population to an attenuated degree (Persinger & Makarec, 1987). Previous research has demonstrated a link between scores on the TLE component and OBEs in non-clinical samples (Braithwaite, Broglia, Bagshaw, et al., 2013). The “non-TLE” component comprises scores from all remaining CAPS items including those that loaded onto the factors of chemosensation (CS) and clinical psychosis (CP). (CAPS items that also appeared on the CHi were removed from CAPS data before analysis.)

2.2.2.3 Pattern-glare (PG) task

For the PG task, three separate types of achromatic, horizontally-striped gratings were presented in one block (with a chequerboard grating presented during the PG practice trial).

Each grating type differed with regard to its spatial frequency (SF); gratings were either non-irritating chequerboard (practice trial) (approx. 0.5 cpd both horizontally and vertically) (Braithwaite, Mevorach, et al., 2015), “low” (baseline, approx. 0.7 cpd), “medium” (critical stimulus, approx. 3 cpd), or “high” (approx. 14 cpd) (see **Figure 2.1**). The low-frequency stimulus functioned to break up presentations of the more irritating gratings (medium- and high-frequency), prevent habituation, and act as a contrast for the medium- and high- frequency gratings. The low-frequency also acts as an index of suggestibility, and so although there will inevitably be some positive responses from participants when viewing this grating, these responses should be relatively low in number and consistent across the sample (Braithwaite, Mevorach, et al., 2015). The Michelson contrast was 0.7 for all stimuli. All gratings featured a small fixation point in the centre, and were presented centrally and separately for 12s (stimulus diameter = 12cm) at a fixed distance of 80cm (visual angle = 8.53 x 11.0 degrees). In the experimental PG task, the low, medium, and high gratings were each presented three times, making a total block of 9 trials. Grating presentation order was randomised each time the experimental program was run, with the restriction that the same grating could not be presented twice in a row. Each PG trial began with the presentation of a blank grey screen for 8s. The trial stimulus was then presented for 12s. Participants were instructed to focus on the fixation point for the duration of stimulus presentation. The spacebar could be pressed to remove the stimulus from view if it was too uncomfortable to fixate and pressed again to make the stimulus reappear and allow the trial to continue. Spacebar presses were recorded as an additional measure of visual discomfort.

At the end of the viewing period, the stimulus was removed from the screen and participants were presented with various questions relating to their experiences during the viewing of the grating. Participants were asked to indicate whether they had experienced any associated visual distortions (AVDs) (such as shimmering, flickering, nausea, coloured halos, etc. – see **Table 2.1**) when viewing the stimulus, and to rate the intensity of each of these distortions along a Likert scale from 0 (“Not at all”) to 6 (“Very intense”). Each AVD was explicitly defined to participants, and a list of descriptions for all AVDs was provided for participants to ensure response accuracy. It was emphasised that participants were free to pick as few (including none) or as many AVDs as necessary. Finally, participants were asked whether they experienced the AVDs in the left or right visual fields, or equally across the visual field (if participants did not experience any AVDs, they selected “no effect”). The screen then cleared, and the above procedure repeated until the end of the block.

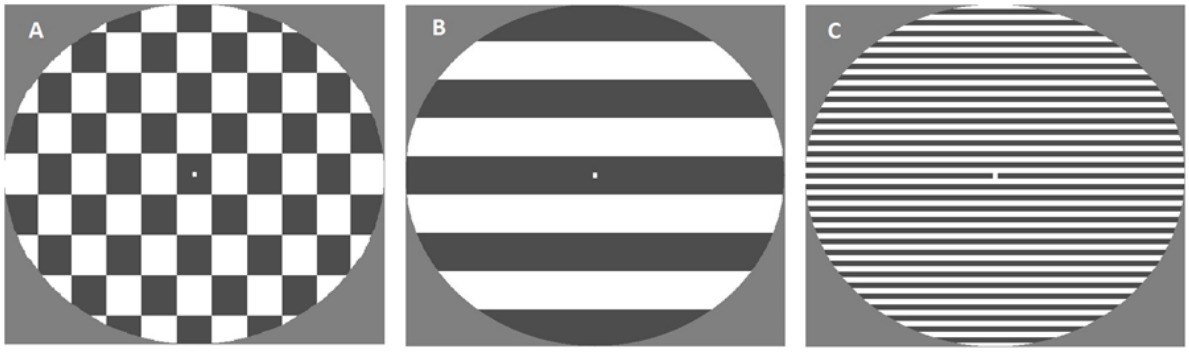

Figure 2.1 – Pattern glare task stimuli; A = checkerboard (practice trial), B = low-frequency grating (baseline), C = medium-frequency grating. The high-frequency grating is not shown, as this grating aliases on a small scale and so is difficult to faithfully reproduce here. (Images sourced from PG task program).

Question	Response	
Did you experience any of the following?	Pain	Nausea
	Shadowy shapes	Unease
	Shimmering	Dizziness
	Flickering	Faint
	Bending	Headache
	Blue	Illusory stripes
	Red	Zooming
	Green	Jitter
	Blue	Physical eye strain
	Yellow	Light-headedness
Were the effects greater in the:	Left visual field	Right visual field
	Equal	No effect

Table 2.1 – An overview of questions asked during the computerised PG task used in the present study. Each experience was rated on a Likert scale of intensity from 0-6. All questions were repeated for all stimuli.

Before completing the main PG task, participants completed two practice trials that proceeded as described above, in order to familiarise themselves with the task. Practice trials included the checkerboard grating only.

2.2.2.4 Transcranial direct-current stimulation (tDCS)

tDCS was delivered through a battery-driven constant current stimulator (Magstim DC-Stimulator Plus – Magstim Ltd., UK), via a pair of conductive rubber electrodes covered by saline-soaked (83mM or 3% NaCl) sponges (25cm^2) (see **Figure 2.2**). Electrodes of different sizes have varying effects on the stimulated sites. 5x5cm electrodes were chosen to maximise specific stimulation of the chosen areas whilst avoiding excessive stimulation of adjoining sites (i.e. from using larger electrodes) or increasing the variability of effects (i.e. by using smaller electrodes) (Nitsche et al., 2008). For example, electrodes of 35cm^2 may deliver stimulation that is not sufficiently focal (Shin, Foerster, & Nitsche, 2015). Wide strapping (3M^{TM} Coban^{TM} self-adherent wrap) was used to keep electrodes in place on the head, as narrow rubber straps can put centralised pressure on electrodes and cause the edges to rise up, decreasing contact and increasing current density (Horvath, Carter, & Forte, 2014).

Participants took part in all tDCS conditions and were blinded to the condition – a sham condition contributed towards effective blinding, and the tDCS machine display was hidden from participants throughout the experiment. tDCS conditions were randomised. Time between tDCS sessions was at least 48 hours (maximum = 1 week) to maximally reduce the likelihood of any carry-over effects between sessions.

In Study 1, to excite extrastriate cortex, the anode was placed over Pz and the cathode placed over Cz (vertex) using the standard international 10/20 electrode positioning system (TransCranial Technologies, 2012). A midline montage was chosen to target both hemispheres (TransCranial Technologies, 2012), with a Cz reference point in accordance with recommendations from tDCS literature (Antal et al., 2004; Peters, Thompson, Merabet, Wu, & Shams, 2013; Reinhart, Xiao, McClenahan, & Woodman, 2016). A bicephalic arrangement was used, as monocephalic setups have been found to produce results no different to sham, and extracephalic reference electrodes may require greater current densities to produce cognitive effects (which may have safety implications due to current passing through the brainstem, or lead to greater discomfort for participants). In the sham condition, electrodes were positioned at the same locations. All participants received offline anodal stimulation for 20 minutes (1.5mA, 0.06mA/cm^2, 30s fade in/out) or sham stimulation for <1 minute (10s fade in/out, 30s stimulation up to 1.5mA). This montage was chosen for several reasons. Previous research using tDCS over visual areas in healthy participants generally used stimulation durations of between 10-20 minutes (Antal et al., 2004; Braithwaite, Mevorach, et al., 2015; Chadaide et al., 2007; Viganó et al., 2013), with a duration of 10 minutes being sufficient to shift excitability up to 10 minutes post stimulation (Antal et al., 2003a). For the current study, stimulation duration was set at 20 minutes, in line with previous research that successfully altered pattern glare experiences using tDCS (Braithwaite, Mevorach, et al., 2015). In visual tDCS studies on healthy subjects, stimulation intensity is typically 1-1.5mA, and current density is typically 0.04-0.06mA/cm^2 (Chadaide et al., 2007; Marshall,

Esterer, Herring, Bergmann, & Jensen, 2015; Nitsche & Paulus, 2000; Walsh, 2013). These levels are sufficient to increase or decrease excitability for at least five minutes post-stimulation, whilst being safe and preventing participant discomfort (Nitsche & Paulus, 2000; Walsh, 2013). Some work has also suggested that participant blinding becomes ineffective at 2mA stimulation intensity, as at this level participants are able to accurately judge the stimulation condition above chance level (likely due to increased scalp sensations. During the sham condition, participants were stimulated for a very short amount of time (<1 min) to give the experience of tDCS-related sensations (such as tingling and heating) without also inducing any discernible cognitive effects that could alter task responses (Nitsche et al., 2008). Thirty seconds of stimulation during the sham condition ensures sufficient scalp sensations such that distinguishing between sham and active stimulation conditions is more difficult (Gandiga, Hummel, & Cohen, 2006). To maintain consistency between conditions, participants immediately completed the behavioural task 20 minutes after stimulation onset in both conditions.

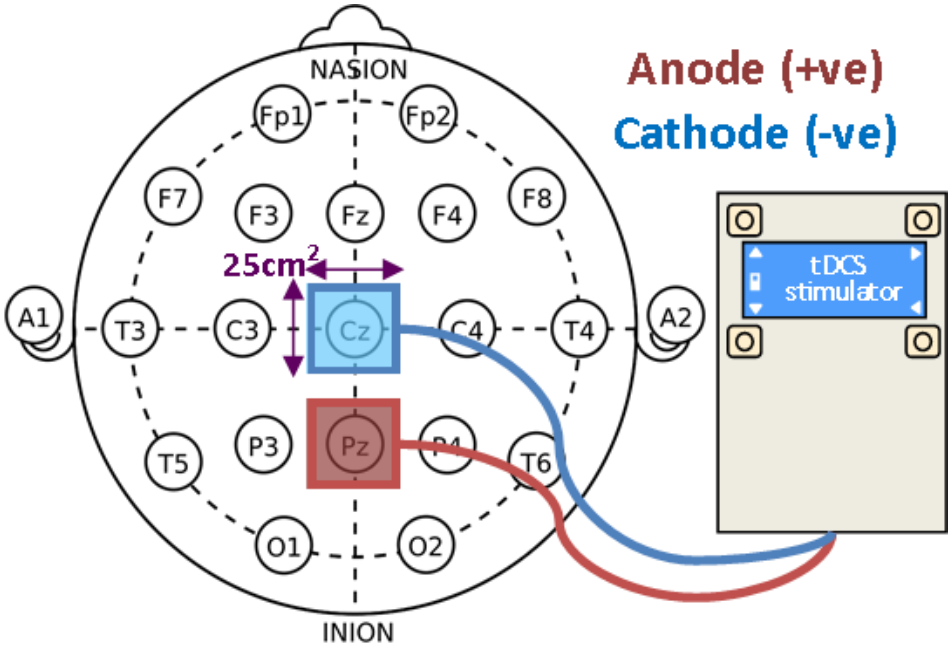

Figure 2.2 – tDCS montage from Study 1.

Only anodal and sham stimulation conditions were included in Study 1. There were two reasons for this decision. First, the most recent meta-analysis on the topic has revealed that while anodal stimulation appears to often have significant effects in cognitive studies, cathodal stimulation does not produce consistent and reliable effects (Jacobson et al., 2012). Second, in the only available study that closely resembles the current one, Braithwaite et al. (2015) found no significant differences between pattern glare effects under sham and inhibitory tDCS conditions – thus providing a sound premise for the decision here.

Pattern glare (PG) task stimuli were presented on a HP p1230, 20” monitor (30.7x40.5cm, 1600x1200 screen resolution, 85Hz refresh rate). The present study utilised the same computerised version of the PG task reported previously (Braithwaite, Mevorach, et al., 2015). The PG task was run using a custom E-Prime 2.2 program in a dimly-lit laboratory, in which the main source of illumination was the computer monitor. A small desk lamp, directed away and positioned far from participants, provided minimal background lighting. Participants used the keyboard and mouse to input task responses.

2.2.3 Design and Procedure

The current study used a within-participants repeated measures design. Current research suggests that circadian rhythms play an important role in regulating cortical excitability, and that the results of studies using transcranial electric stimulation may be unreliable if the circadian influence on excitability is not accounted for (Ly et al., 2016). Therefore, participants always took part in all

sessions of the experiment at the same time of day (± 1hr); i.e. if Participant 1 started their first session at 2pm, their remaining sessions would start from 1-3pm. In the study, participants: (i) completed the screening questionnaire, (ii) read the study information and gave consent, (iii) had the tDCS electrodes positioned on the head and tDCS started, (iv) completed selected questionnaire measures, (v) completed the PG task 20 minutes after stimulation onset, and (vi) were debriefed by the experimenter (after session 2) (see **Figure 2.3**). Experimental timings are shown in **Figure 2.4**.

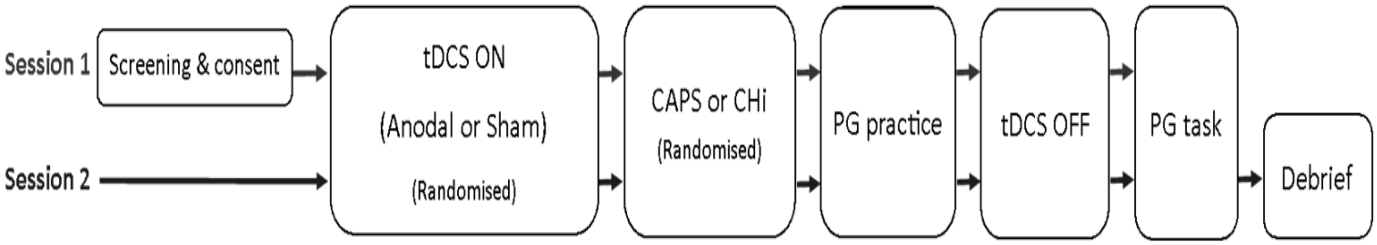

Figure 2.3 – Procedure of Study 1. In all cases, the CAPS or CHi questionnaires were completed within 20 minutes.

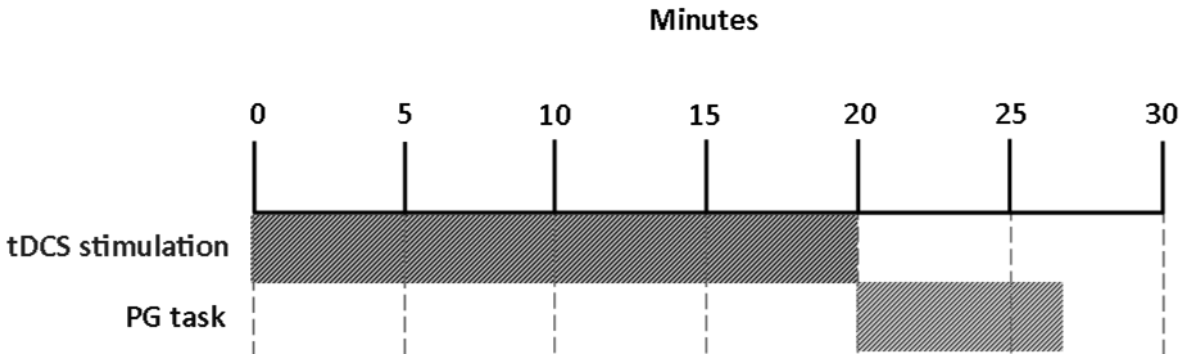

Figure 2.4 – tDCS and behavioural task timings for Study 1 (PG task mean duration = 7 mins).

2.2.3.1 Data analysis

Following the protocol from the original study, CHi scores were corrected by subtracting 1 from each response to reflect a scale from 0-6 for each response dimension (corrected CHi score range = 0 – 324). CHi frequency and intensity subscale scores were pooled across questions for analysis.

For the CAPS measure, scores were pooled across the frequency subscale for each question (CAPS score range = 0 – 160). Previously, CAPS scores have been coded as binary Yes/No responses (Braithwaite et al., 2011), however the "frequency" scale scores were used as these give information both on whether or not phenomena were experienced and also a more fine-grained rating of the frequency of that experience. For the current analyses, CAPS scores were also split into TLE and non-TLE experiences (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, & Watson, 2014; Braithwaite, Mevorach, et al., 2015).

Corrected means were calculated for all questionnaire factors by dividing raw factor scores by the number of factor questions. This calculation prevents inaccurate score comparisons by accounting for the fact that there are differing numbers of questions per factor.

For PG task data, summed and mean intensity ratings for all anomalous visual distortions (AVDs) endorsed for each stimulus type were calculated by adding all intensity ratings for all visual distortion for each grating type, and dividing by the number of grating presentations (3).

The PG low-frequency (“baseline”) grating is not intended to be highly visually irritating (even for those with high visual sensitivity) and is used only as an index of suggestibility or response bias in the PG task (Braithwaite, Mevorach, et al., 2015; Evans & Stevenson, 2008; Wilkins et al., 1984), and so ratings for this grating were discarded from formal analysis. Participants with excessively high (outlier) ratings for this grating were also discarded from analysis (as this indicates some degree of suggestibility or response bias) – specifically, any participant with PG ratings greater than $\bar{x} \pm 2SD$ for the sham (baseline) condition (two-standard deviation band method) (Bloom, Fischer, & Orme, 2009).

To further compare differences in PG ratings, delta (Δ) values were calculated by subtracting mean AVD intensity ratings for high-frequency gratings from mean AVD intensity ratings for medium-frequency gratings. This is denoted as M-HΔ and provides a very conservative estimation of experiences possibly reflecting cortical hyperexcitability. This method of analysis also follows the conclusions of Evans & Stevenson (2008); that pattern glare can be indexed either by ratings for the medium-frequency grating alone (the more traditional approach), or by calculating the M-HΔ (as in the current study). The M-HΔ (or the “3-14 cpd difference”) is suggested to be a more reliable quantifier of “true” pattern glare; distortions related to visual hyperexcitability specifically. This is because, although some of the non-clinical population can experience a greater number of distortions when viewing the high frequency grating as compared to the medium frequency grating (Conlon & Lovegrove, 2001), distortions from the high frequency grating are likely to reflect optical rather than cortical processes (e.g. image appearing blurry or fuzzy) (Evans & Stevenson, 2008). It is distortions induced by the medium

frequency grating that have been strongly evidenced to reflect underlying visual cortical hyperexcitability (Evans & Stevenson, 2008; Harle et al., 2006). Subtracting high from medium grating scores therefore acts as a control for optical factors (Evans & Stevenson, 2008). The M-HΔ score further controls for order effects, as grating presentation order can influence the number of distortions seen. Presenting the medium grating before the high grating can result in seeing more distortions in the high grating (due to inducing cortical hyperexcitability with the medium grating), whereas no similar interference is found when presenting the high before the medium grating (Evans & Stevenson, 2008). Evans and Stevenson (2008) found no effect of grating presentation order on M-HΔ scores.

A M-HΔ score ≥ 1 therefore indicates a high level of general visual discomfort (with more distortions experienced when viewing medium-frequency stimuli), whereas a M-HΔ score ≤ 0 indicates low or moderate visual discomfort (Evans & Stevenson, 2008). To explore how individual baseline states influence the effects of tDCS, participants were split into “pattern glare” (M-HΔ ratings ≥ 1) and “no pattern glare” groups (M-HΔ ratings ≤ 0) using baseline M-HΔ ratings from the sham condition, in line with previous work (Evans & Stevenson, 2008; Hsu et al., 2016).

Using SPSS, Pearson’s correlation coefficients were generated from questionnaire and PG data comparisons (corrected for multiple comparisons using the False Discovery Rate (FDR) tool from SDM Project (2019)), and two-tailed student’s t-tests were also performed to assess significant differences. Bayesian analysis was also performed where relevant. Bayesian analysis determines the

predictive accuracy of the null or alternative hypotheses given the data collected, and grades the evidence in favour of these hypotheses on a continuous scale (Keuschke, 2011; Wagenmakers et al., 2018). Unlike common frequentist approaches that define probability as the limit of an event's frequency over a large number of trials, Bayesian analysis interprets probability as "the subjective experience of uncertainty" and takes into account as much prior information as possible when calculating likelihoods (van de Schoot et al., 2014). Bayesian analysis produces a "Bayes Factor" (BF_{10}), which can be thought of as indicating the "intensity" of the evidence (Wagenmakers et al., 2018). A $BF_{10} < 1.0$ reflects evidence in favour of the null hypothesis, whereas a $BF_{10} > 1.0$ reflects evidence in favour of the alternative hypothesis (Dewe, Watson, & Braithwaite, 2016). For example, a BF_{10} of 10 can be understood to mean that the data are 10 times more likely to occur under the alternative than under the null hypothesis, whereas a BF_{10} of 0.10 indicates that the data are 10 times more likely to occur under the null than under the alternative hypothesis (Dewe et al., 2016; Wagenmakers et al., 2018). Therefore, larger BF_{10} values indicate greater evidence in favour of the alternative hypothesis, with $BF_{10}>3$ being moderate, $BF_{10}>10$ being strong, and $BF_{10}>100$ being decisive (Rouder, Morey, Speckman, & Province, 2012). Bayesian analysis was performed using the JASP v0.8.6 software package (JASP Team, 2018).

2.3 Results

Data from 14 participants were excluded based on outlier ratings for the low-frequency grating. No other outliers were identified, so that the final sample

included data from 72 participants (61 (85%) female; 57 (79%) right-handed; $\bar{x}$ age = 19.8 years (σ = 2.0, range = 18-29)).

2.3.1 Questionnaires

2.3.1.1 CHi

Descriptive statistics for CHi questionnaire scores are shown in **Table 2.2.** The current sample produced an overall mean CHi score of 51.4, with endorsement of items on all three factors.

	Overall	**Heightened sensitivity & discomfort**	**Negative aberrations**	**Positive aberrations**
Mean	51.4	14.5	0.9	1.8
SEM	3.5	1.1	0.1	0.2
σ	29.7	9.3	1.0	1.3
Range	121.0	38.5	4.4	6.7

Table 2.2 – Descriptive statistics for CHi questionnaire factor scores. Each factor mean is corrected for the number of questions per factor.

The proportion of participants endorsing any of the experiences covered by the CHi was explored (i.e. any non-zero responses, so that percentages reflect

endorsement of one or more question/s per factor). Mean endorsement of items was 52%, with 44% for heightened visual sensitivity and discomfort, 14% for at least one negative aberration, and 30% for at least one positive aberration.

2.3.1.2 CAPS

Descriptive statistics for CAPS questionnaire scores are shown in **Table 2.3**. A mean total TLE score of 1.8 indicates a relatively low degree of anomalous perceptual experience associated with the anomalous experiences represented on CAPS in the current sample.

	Mean total score	
	TLE	**Non-TLE**
Mean	1.8	3.7
SEM	0.2	0.4
σ	1.6	3.2
Range	7.2	12.8

Table 2.3 – Descriptive statistics for CAPS questionnaire scores. Each factor mean is corrected for the number of questions per factor. TLE = Temporal Lobe Experience factor; non-TLE = remaining questions.

Differences in corrected CAPS factor scores were explored using a paired t-test. This suggested significant differences between CAPS TLE and non-TLE

scores (t(71)= 6.42, p<0.0001, BF_{10}>1000, Hedges' *g*=0.60), showing that participants endorsed significantly more non-TLE-type than TLE-type experiences (when corrected for the difference in the number of items on both components).

2.3.2 Pattern glare and tDCS

To explore effects of tDCS on PG ratings, delta values were calculated between the ratings for the medium frequency minus the high frequency gratings (**M-HΔ**). The PG ratings attained under the tDCS sham condition will represent PG ratings that occurred without brain stimulation. Comparing M-HΔ AVD intensity ratings between conditions (**Figure 2.5**) using a paired t-test suggested no reliable difference in PG ratings (t(71)= 0.451, p=0.65 (ns), BF_{10}=0.14, Hedges' *g*=0.05). Anodal stimulation did not significantly affect PG ratings when collapsed for the whole sample.

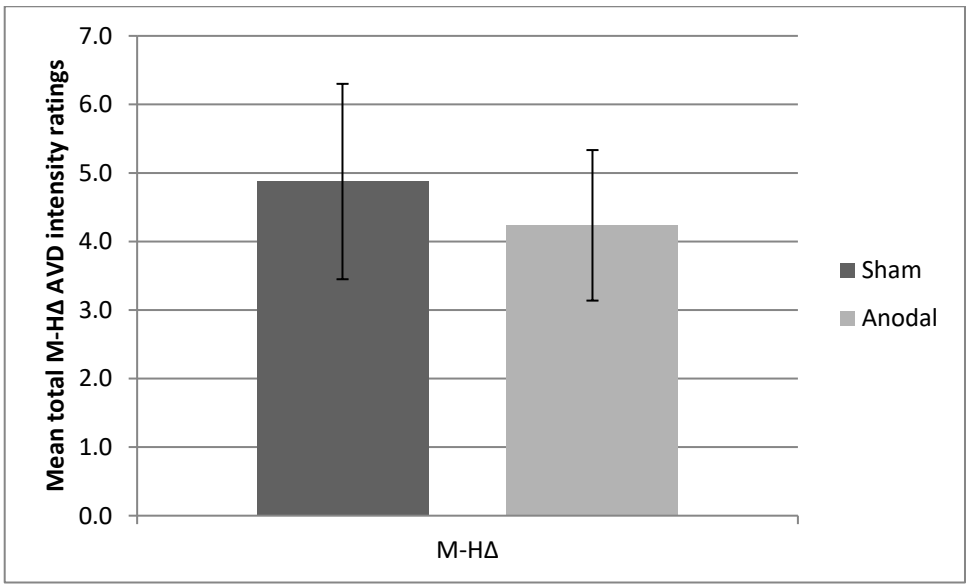

Figure 2.5 – Mean M-HΔ AVD intensity ratings under sham and anodal tDCS. Error bars = standard error of the mean.

2.3.3 Pattern glare, tDCS, and questionnaires

2.3.3.1 Trait-based analysis

The relationships between questionnaire ratings and PG M-HΔ AVD intensity ratings under sham and anodal conditions were explored using Pearson's correlations (corrected for multiple comparisons using FDR) (see **Table 2.4**). To ensure that no extreme values would overly influence a Pearson's correlation model, Cook's distances were calculated for all variables. These suggested no significant outliers in CHi or CAPS factor scores, or PG M-HΔ AVD intensity ratings (no Cook's distances ≥ 1) and so a Pearson's model was used (Field, 2013; Finch, 2012; Tabachnick & Fidell, 2001).

The positive aberrations subscale of the CHi measure correlated significantly with pattern glare M-HΔ AVD intensity ratings during anodal stimulation ($r=0.31$, $p<0.01$) (see **Table 2.4**). This was supported by a Bayes Factor giving moderate support to the alternative hypothesis over the null ($BF_{10}=4.1$). This suggests that as predisposition to report positive aberrations increased, the efficacy of tDCS to increase those experiences also increased. No correlations for other CHi or CAPS subscales were significant.

		Mean AVD intensity: M-HΔ	
		Sham	**Anodal**
CHi	Heightened sensitivity	0.20	0.16
	Negative aberrations	0.02	0.04
	Positive aberrations	0.10	0.31*
CAPS	TLE	-0.08	0.05
	Non-TLE	0.03	0.02

Table 2.4 – Pearson's correlations between mean questionnaire scores and pattern glare AVD intensity ratings (*p=0.009) (corrected for multiple comparisons using FDR, corrected p-value=0.009).

2.3.3.2 State-based analysis

To further explore this relationship, data were split into "PG" and "non-PG" groups using sham M-HΔ PG ratings (PG = M-HΔ PG ratings ≥ 1, non-PG = M-HΔ PG ratings ≤ 0) (see **Figure 2.6**). This gave 47 participants in the PG group and 25 participants in the non-PG group. (For additional information, data for the low frequency grating can be seen in **Appendix M)**.

Paired t-tests within the PG and non-PG groups suggested significant differences between sham and anodal M-HΔ PG ratings (PG: t(46) = 3.108, p=0.003, BF_{10}=10.28, Hedges' *g*=0.46; non-PG: t(24) = -3.425, p=0.002, BF_{10}=17.35, Hedges' *g*=0.78) (FDR corrected p value=0.003), suggesting that

stimulation condition significantly influenced state experience within groups. That is, anodal stimulation significantly decreased PG ratings in the PG group, but significantly increased PG ratings in the non-PG group.

Visual inspection of the data (see **Figure 2.6**) also suggested different directions of tDCS effect between groups. The PG group seemed to be more predisposed to perceptual aberrations in both sham and anodal conditions, with more positive M-HΔ scores as compared to the non-PG group. These differences could not be tested statistically due to initially using PG scores to split groups, however this pattern of opposite directions of tDCS effects between groups is interesting nonetheless.

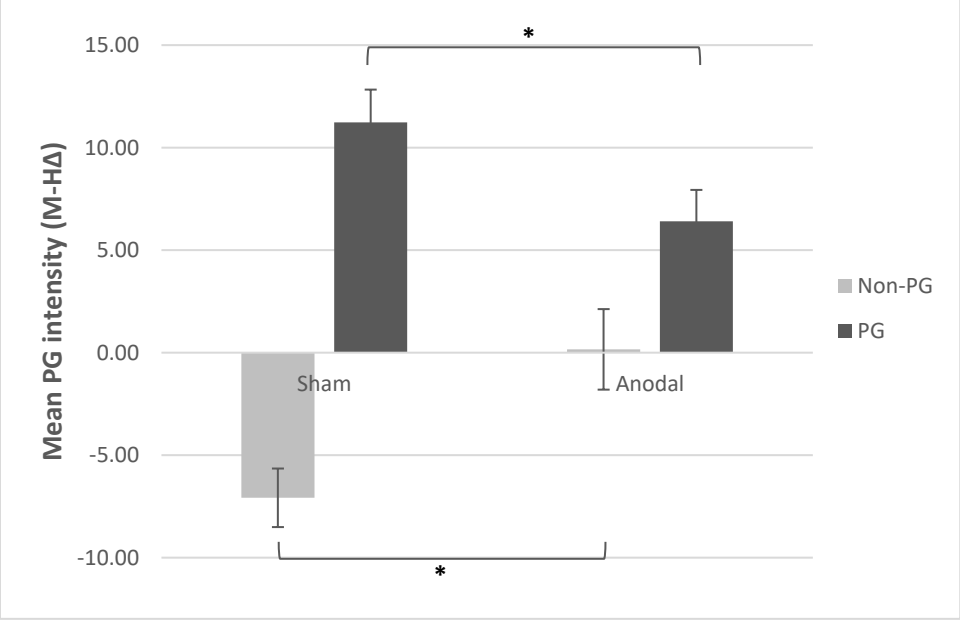

Figure 2.6 – Mean AVD M-HΔ intensity ratings split by pattern glare groups, under each tDCS condition (PG = M-HΔ PG ratings ≥ 1 (n=47), non-PG = M-HΔ PG ratings ≤ 0 (n=25)). Sham = PG baseline. Error bars = standard error of the mean. Brackets show significant differences within groups, *p<0.01.

To give further insight into the influence of tDCS on PG scores, PG intensity ratings for the medium and high gratings were graphed (see **Figure 2.7**). For the non-PG group, this suggested that the relative increase in M-HΔ PG score (towards zero) from sham to anodal stimulation seen in **Figure 2.6** was driven by a slight increase scores for the medium grating, and a decrease in scores for the high grating. For the PG group, this suggested that the relative decrease in M-HΔ PG score from sham to anodal stimulation seen in **Figure 2.6** was driven by a decrease in scores for the medium grating specifically. No formal statistical analysis was performed here, as the M-HΔ measure is the key measure for this analysis and has several strengths over analysing raw scores (see Study 1 ***Data Analysis***). This also avoids making further unnecessary multiple comparisons, as this data is already multiply compared through the PG-tDCS analysis using M-HΔ scores, which are derived from raw scores. Nevertheless, these trends are interesting and will be returned to in the discussion.

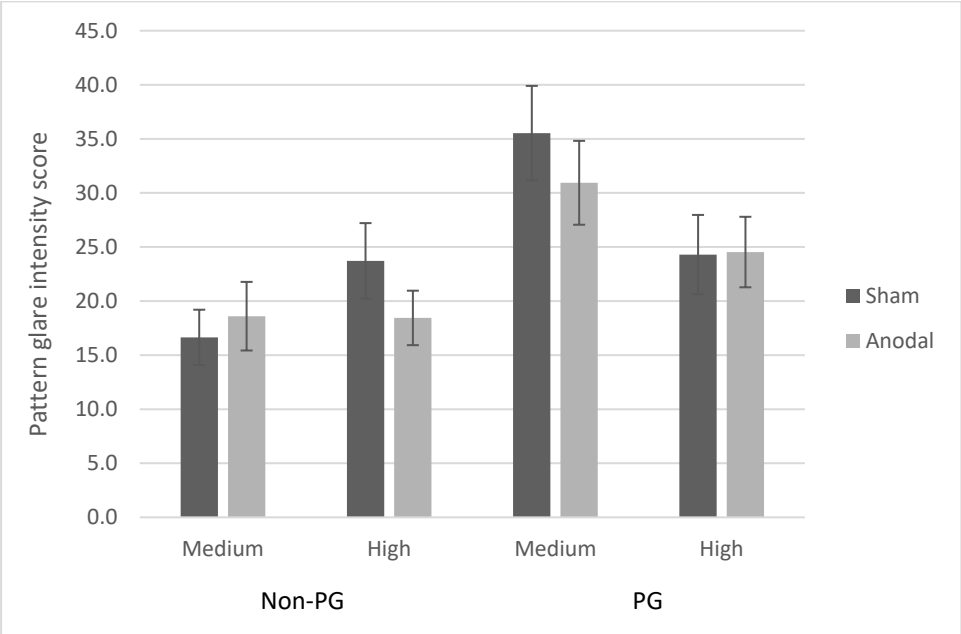

Figure 2.7 – Bar graph showing pattern glare intensity scores for each grating type (medium, high) for the non-PG and PG groups, in each tDCS condition (sham, anodal). Error bars = standard error of the mean.

2.3.3.3 State-trait sub-group analysis

Pearson's correlations between these sub-groups and CHi "positive aberrations" subscale scores suggested significant correlations between CHi and PG ratings for the PG group only (Sham: $r=0.44$, $p<0.01$, $BF_{10}=18.11$; Anodal: $r=0.41$, $p<0.01$, $BF_{10}=8.97$), with non-PG correlations insignificant (Sham: $r=-0.19$, $p=0.365$, $BF_{10}=0.37$, Anodal: $r=0.29$, $p=0.159$, $BF_{10}=0.64$) (see **Table 2.5 and Figure 2.8**). The Bayes' Factors strongly support the frequentist statistics. BF values for the PG group correlations give strong support to the alternative hypothesis over the null, i.e. that there is a correlation between these variables,

whereas BF factors for the non-PG group give support to the null hypothesis over the alternative (there is no correlation). These results suggest that the positive correlation seen for the whole sample above (**Table 2.4**) is driven by the "PG" group specifically.

	PG		Non-PG	
	Sham	**Anodal**	**Sham**	**Anodal**
CHi Positive aberrations	0.44*	0.41*	-0.19	0.29

Table 2.5 - Pearson's correlations between mean CHi "positive aberrations" scores and pattern glare AVD intensity ratings, split by PG/non-PG groups (*p<0.01, FDR corrected p value=0.02).

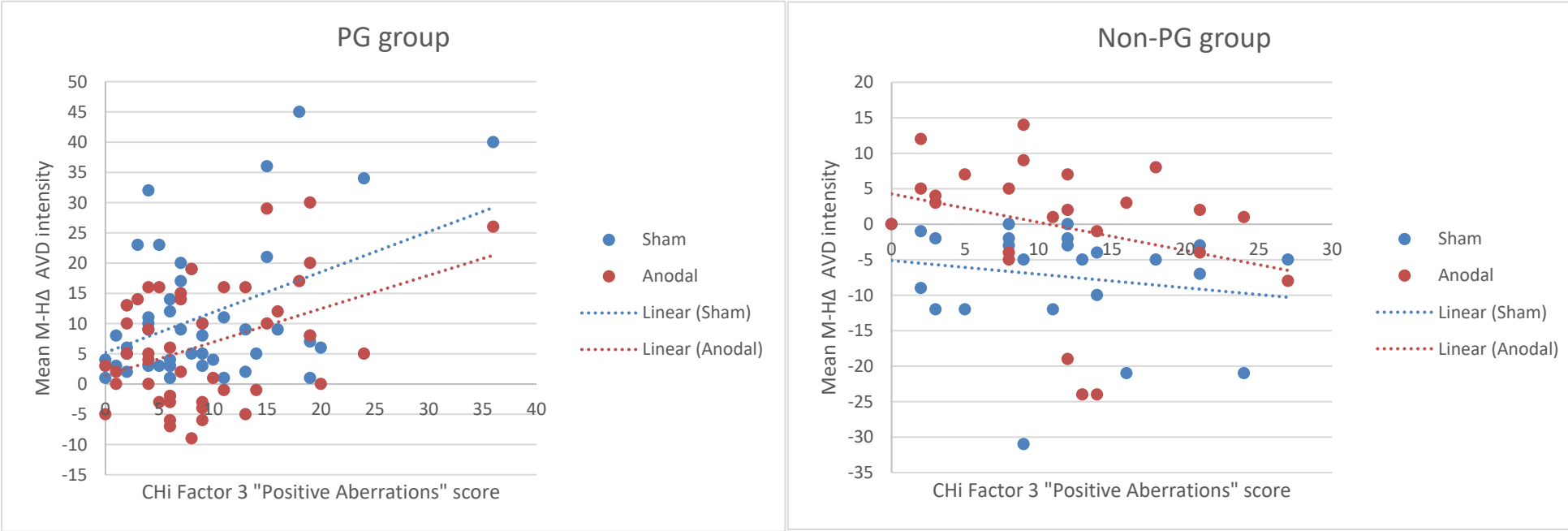

Figure 2.8 – Scatterplots of CHi Factor 3 “Positive Aberrations” scores against M-HΔ AVD intensity ratings, under sham and anodal tDCS conditions. Dotted lines show linear trendlines. It is interesting to note the opposite direction of correlation between the groups (although formal statistical comparisons cannot be made between groups).

2.4 Discussion

The present study investigated the effects of tDCS brain stimulation of extrastriate cortex on anomalous visual experiences, as indicated by a state-based pattern glare task and trait-based questionnaire measures. Experiences were assessed under sham (no stimulation) and anodal stimulation conditions.

It was hypothesised that if tDCS can sufficiently manipulate cortical activity in more anterior extrastriate cortex, and these networks are important for the generation or mediation of anomalous perceptions, then stimulation would significantly impact the intensity of the pattern-glare ratings reported. It was also hypothesised that this effect would be associated with a trait-based predisposition to anomalous perceptions, which were quantified by the CAPS and CHi measures, and state-based predisposition as quantified by pattern-glare.

There were no reliable effects of anodal brain stimulation on pattern-glare experiences (relative to the sham baseline condition) when viewed across the whole sample. While this result may suggest that tDCS did not influence pattern glare experiences, the correlation with the CHi measure and PG-subgroup analysis modifies this view. Study 1 demonstrated that the “Positive Aberrations” factor of the CHi correlated significantly with pattern-glare effects, but only under anodal stimulation conditions. PG-subgroup analysis revealed that this relationship was carried by the PG group, with this correlation observed for both sham and anodal stimulation conditions. No significant correlation was observed between this CHi factor and pattern glare for the non-PG group. This suggests that a predisposition to certain trait-based positive aberrations is associated with more intense state-

based anomalous experience at baseline (sham) and under anodal tDCS. In contrast, trait-based visual aberrations do not appear related to state-based anomalous experience in the non-PG group (with low/typical excitability). Further, anodal stimulation appears to act in the expected “excitatory” effect in the non-PG group only.

We suggest that this provides additional tentative evidence that predisposition to certain forms of hallucinatory experience appears to reflect a more excitable extrastriate cortex in non-clinical groups, such that baseline excitability influences the efficacy and effects of tDCS (returned to in the general Discussion). Therefore both trait screening and state measures may be useful for identifying individual differences and predispositions that have implications for the efficacy of brain-stimulation (see General Discussion).

Foreword to Chapter 3

Chapter 3 further explored the limits and parameters of the effects observed in Study 1 in a completely new sample, by reducing the tDCS stimulation period before the PG task commenced, and using a new stimulatory site, POz[10]. It should be noted that presenting aversive gratings is, in and of itself, a form of stimulation, in that such gratings are thought to over-stimulate visual neurons (Wilkins & Evans, 2010). In those predisposed to elevated levels of cortical hyperexcitability, this mechanism is thought to be responsible for aberrant perceptions (Wilkins & Evans, 2010). Therefore, both tDCS and the pattern glare stimuli themselves are sources of visual neuron stimulation. This is important, as recent tDCS research suggests that tDCS effects depend more on stimulation duration than intensity (Monte-Silva et al., 2013; Vignaud, Mondino, Poulet, Palm, & Brunelin, 2018). Longer tDCS stimulation durations (>20 minutes) are associated with current polarity reversal (where anodal can become cathodal, and vice versa, which may contribute to null effects; see Paulus (2011) and Walsh (2013)), and one recent study found that 30 minutes of anodal tDCS did not increase cortical excitability at all (whilst 20 minutes did) (Vignaud et al., 2018). These findings may help to explain, at least in part, what we observed here for the PG group in Study 1.

[10] One methodological benefit of moving the site to POz is reducing the potential for scalp shunting between electrodes placed too close together (as the return electrode is at Cz) (Jackson, 2015; Santos et al., 2016). While it appears that we did not experience this in Study 1, it was prudent to make such changes here in light of other additional methodological differences.

Study 1 involved 20 minutes of tDCS followed by ~7 minutes of pattern glare (~27 minutes of total stimulation). The stimulation duration was determined primarily by a previous study which reported reliable effects when stimulating primary visual cortex (with a sample that also scored higher on trait-based measures of anomalous perceptions: see Braithwaite, Mevorach, et al. (2015)). Although a reliable effect did emerge here in Study 1, this was highly selective for one factor on one questionnaire (positive aberrations on the CHi). One possible post-hoc rationalization of this is that the stimulation duration might have been too long and worked against the potential to reveal the full impact of possible effects (as some work has suggested that stimulation durations of ≥20 minutes may result in stimulation effect reversals) (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Monte-Silva et al., 2013; Nitsche, Polania, & Kuo, 2015).

To examine this issue, stimulation time in Study 2 was reduced to 10 minutes to avoid potentially over-stimulating visual neurons and causing neuronal counter-regulation (Monte-Silva et al., 2013). Previous work on modulating visual cortex excitability has provided some evidence that seven minutes of tDCS at 1mA intensity is sufficient to induce visual changes lasting up to 10 minutes after stimulation (Antal et al., 2001). A recent fMRI study demonstrated that 10 minutes of anodal tDCS at 1mA over visual cortex, whilst participants viewed achromatic visual stimuli, was sufficient to induce a significant increase in BOLD signal (as compared to sham) localised to occipital-parietal areas (Alekseichuk, Diers, Paulus, & Antal, 2016). Work with migrainers with aura has also shown that 10 minutes of anodal stimulation over Oz is sufficient to increase cortical excitability and lower phosphene thresholds (Chadaide et al., 2007).

Additionally, some tDCS literature suggests online stimulation (ongoing stimulation during the behavioural task) can be more effective with cognitive tasks (Walsh, 2013), and so online stimulation was implemented in Study 2. This also allowed us to explore the effects of combining stimulation from two sources; tDCS, and pattern glare stimuli. A new stimulatory site was chosen to investigate whether the tDCS effects found in Study 1 would extend to another area of extrastriate cortex, BA 17-19 (targeted by stimulation site POz). Evidence from neuroimaging research suggests that extrastriate cortex can become hyperexcitable in response to pattern glare stimuli (Huang et al., 2011). Other work on the relationship between hyperexcitability and pattern-glare-type anomalous experiences suggests that diffuse effects of tDCS stimulation over primary visual cortex may propagate to extrastriate cortex (Braithwaite, Mevorach, et al., 2015).

Furthermore, given the results of Study 1, a cathodal condition was included in Study 2 to generate additional data comparison points, explore any potential "inhibitory" effects in addition to "excitatory" ones, and act as an "active control" condition, in accordance with recent literature recommendations (Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007; Parkin, Ekhtiari, & Walsh, 2015; Walsh, 2013). Previous studies have shown that while anodal stimulation can excite the primary visual cortex, cathodal stimulation (typically thought of as inhibitory) failed to produce any reliable effects (Braithwaite, Mevorach, et al., 2015; Jacobson et al., 2012; Parkin et al., 2015). In the context of the current investigation this makes intuitive sense, in that any effects of cathodal stimulation will be competing with both the stimulation from the visual presentation of an

irritative/aversive pattern *and* the potential co-presence of elevated predisposition to cortical excitability in the first place (which may itself reflect a failure of inhibitory neuronal processes). Administering a cathodal condition in Study 2 allowed for a direct assessment of this, in a new and independent large sample. A cathodal condition also allowed further exploration of the differential effects of baseline excitability on tDCS response observed in Study 1.

3 Chapter 3

3.1 Methods

3.1.1 Participants

Seventy-nine participants took part in Study 2. Of these, 73 (92%) were female and 69 (87%) were right-handed. Participant age ranged from 18 to 31 years ($\bar{x} = 20$, $\sigma = 2.4$). The participant recruitment and compensation process were the same as in Study 1. Study 2 applied the same exclusion criteria process as in Study 1, as well as excluding any potential participant with sleep disorder/s, regular users of recreational drugs, smokers (regularly smoking the equivalent of at least one cigarette every day (including vaping)), or users of nicotine products (patches, gum, vaping). These additional controls were introduced because recreational drug use (such as cocaine and ecstasy/MDMA), nicotine intake, and circadian rhythms are known to influence cortical excitability (Bauernfeind et al., 2011; Cowan et al., 2015; Hanlon et al., 2015; Huber et al., 2013; Ly et al., 2016; Thirugnanasambandam et al., 2011). Sleep deprivation is known to induce psychotic-like symptoms, and has even been suggested as an experimental model system for psychosis (Meyhofer, Kumari, Hill, Petrovsky, & Ettinger, 2017).

The same sample size calculation was used as in Study 1, such that a minimum of 73 participants were required. Effect sizes for each comparison are reported in the Results section.

3.1.2 Materials

3.1.2.1 Questionnaire measures

Study 2 used the same questionnaire measures as Study 1, the CHi and the CAPS.

3.1.2.2 Pattern-glare (PG) task

Study 2 used the same PG task as outlined and detailed for Study 1.

3.1.2.3 tDCS

The following changes to the stimulation paradigm were utilised relative to Study 1. Study 2 included three stimulation conditions; sham, anodal, and cathodal. Computational modelling of current flow also suggests that tDCS combines across all stimulation sites to produce a "net" effect across the cortex, and so it is important to include both cathodal and anodal conditions to aid identification of the source of the observed effects (Cogiamanian et al., 2007; Parkin et al., 2015; Walsh, 2013). In the anodal condition, the anode was placed over POz and cathode placed over Cz (vertex) using the International 10/20 electrode positioning system (TransCranial Technologies, 2012). In the cathodal condition, the cathode was placed over POz and anode over Cz (see **Figure 3.1**). In the sham condition, electrodes were positioned at the same locations as in the anodal condition. All subjects received anodal or cathodal stimulation for 10 minutes (1.5mA, 0.06mA/cm^2, 10s fade in/out), or sham stimulation for <1 minute (10s fade in/out, 30s stimulation up to 1.5mA). Stimulating at POz was both theoretically-and methodologically-motivated; increasing the distance between the anode and

cathode decreases the extent of current being shunted through the scalp as opposed to through the brain (Miranda, Lomarev, & Hallett, 2006). The same stimulation intensity was used, and a shorter stimulation duration of 10 minutes was chosen to decrease the possible chance of reversing the intended effect (as outlined above). Current density was unchanged from Study 1. To maintain consistency between conditions, participants now completed the behavioural task 5 minutes after stimulation onset in all conditions (see **Figure 3.2**) and so stimulation continued "online" for 5 mins during the task.

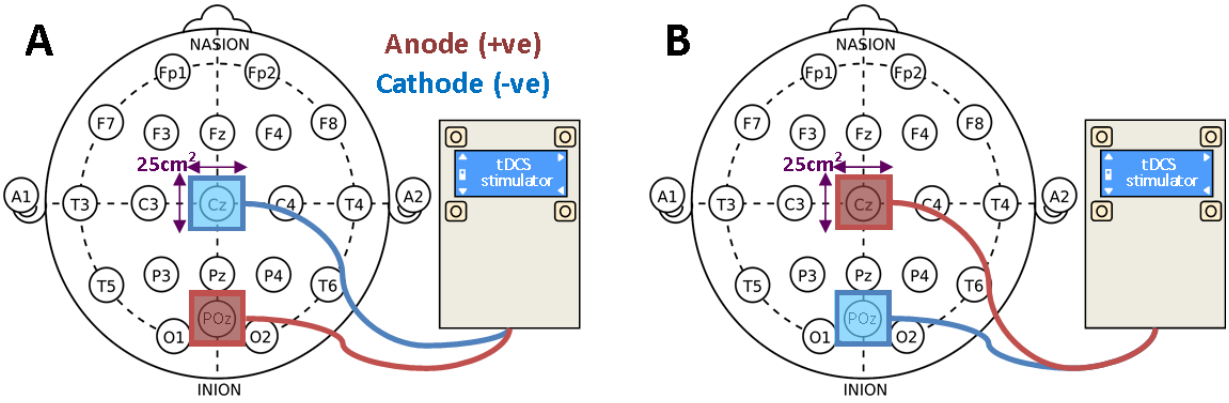

Figure 3.1 – tDCS montage used in the current study. (A) represents electrode montage during anodal and sham stimulation, and (B) represents the cathodal stimulation montage.

3.1.3 Design and procedure

A within-participants repeated measures design was used. As in Study 1, circadian influence was partially controlled for through regulating session start time. Participants: (i) completed the screening questionnaire, (ii) read the study information and gave consent, (iii) completed the questionnaires, (iv) completed the practice PG task, (v) had the tDCS electrodes placed on the head and tDCS stimulation started, (vi) completed the PG task 5 minutes after stimulation onset, and (vii) were debriefed by the experimenter (after session 3) (see **Figure 3.2**). Questionnaire order was randomised. A timeline can be seen in **Figure 3.3**.

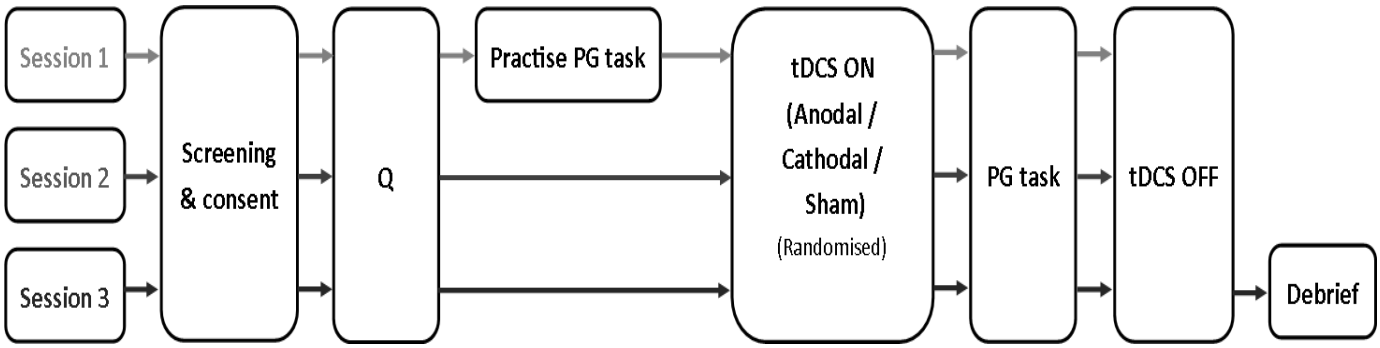

Figure 3.2 – Procedure of the current experiment. (**Q**) = one of the CHi or CAPS (randomised).

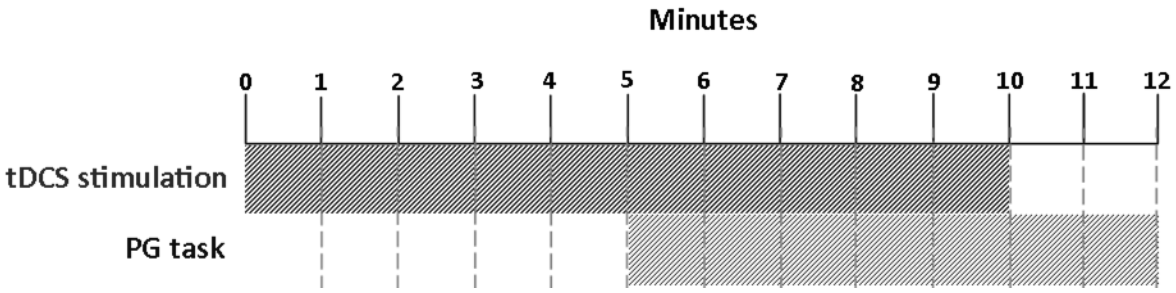

Figure 3.3 – tDCS and behavioural task timings for Study 2.

3.1.4 Data analysis

The same data analysis procedure was used as in Study 1.

3.2 Results

Outliers for the PG task were defined as any total PG ratings for the low-frequency gratings in the sham (baseline) condition greater than $\bar{x} \pm 2SD$ for the total sample (two-standard deviation band method) (Bloom et al., 2009). Data from four participants were excluded on this basis, so that the final sample included data from 75 participants (66 (88%) female; 69 (92%) right-handed; $\bar{x}$ age = 19.5 years (σ = 2.4, range = 18-31)).

3.2.1 Questionnaires

3.2.1.1 CHi

Descriptive statistics for CHi questionnaire scores are shown in **Table 3.1**. A mean total CHi score of 47.5 occurred for the present sample. Factor 1 ("heightened sensitivity") accounts for a large proportion of the overall score (68%) and positive aberrations (such as visual hallucinations) are more common than negative aberrations (losses of visual information). This descriptive pattern follows that reported for Study 1.

	Overall	Heightened sensitivity & discomfort	Negative aberrations	Positive aberrations
Mean	47.5	13.2	0.8	1.7
SEM	3.2	1.0	0.1	0.2
σ	28.0	8.8	1.2	1.4
Range	146	46.7	7.1	6.3

Table 3.1 – Descriptive statistics for CHi questionnaire factor scores. Each factor mean is corrected for the number of questions per factor.

The proportion of participants endorsing any of the experiences covered by the CHi was explored. This revealed a 48% mean endorsement of CHi items, and that 46% had experienced heightened visual sensitivity and discomfort, 13% had experienced at least one negative aberration, and 29%, at least one positive

aberration. An independent-samples t-test revealed that the total CHi scores reported here were not significantly different than those observed for Study 1 (t(145)= 0.82, p=0.42 (ns), BF_{10}=0.24, Hedges' *g*=0.14).

CAPS

Descriptive statistics for CAPS questionnaire scores are shown in **Table 3.2**. A mean total TLE score of 1.1 indicates a low degree of anomalous perceptual experience associated with this factor in the current sample.

	Mean total score	
	TLE	**Non-TLE**
Mean	1.1	0.7
SEM	0.1	0.1
σ	1.1	0.8
Range	5.5	4.5

Table 3.2 – Descriptive statistics for mean CAPS frequency scores. Each factor mean is corrected for the number of questions per factor. TLE = Temporal Lobe Experience factor; non-TLE = remaining questions.

Differences in corrected CAPS factor scores were explored using a paired t-test. This suggested a significant difference between CAPS TLE and non-TLE

scores (t(71)= 4.14, p<0.001, BF_{10}=224, Hedges' *g*=0.75), with TLE scores being higher than non-TLE scores. An independent-samples t-test showed that total CAPS TLE scores were significantly higher in Study 1 ($\overline{x}$ = 1.8) than in Study 2 ($\overline{x}$ = 1.1) (t(145)= 3.39, p=0.001, BF_{10}=30, Hedges' *g*=0.06). CAPS non-TLE scores were also significantly higher in Study 1 ($\overline{x}$ = 3.7) than in Study 2 ($\overline{x}$ = 0.7) (t(145)= 3.45, p=0.001, BF_{10}=36, Hedges' *g*=0.32).

3.2.2 Pattern glare, tDCS, and questionnaires

3.2.2.1 State-based analysis

To explore effects of tDCS on PG ratings, delta values (**M-HΔ**) were calculated. PG ratings attained under tDCS sham represent baseline PG ratings. As in study 1, when data was collapsed across the sample as a whole, there were no significant differences in PG ratings between conditions (see **Figure 3.4**).

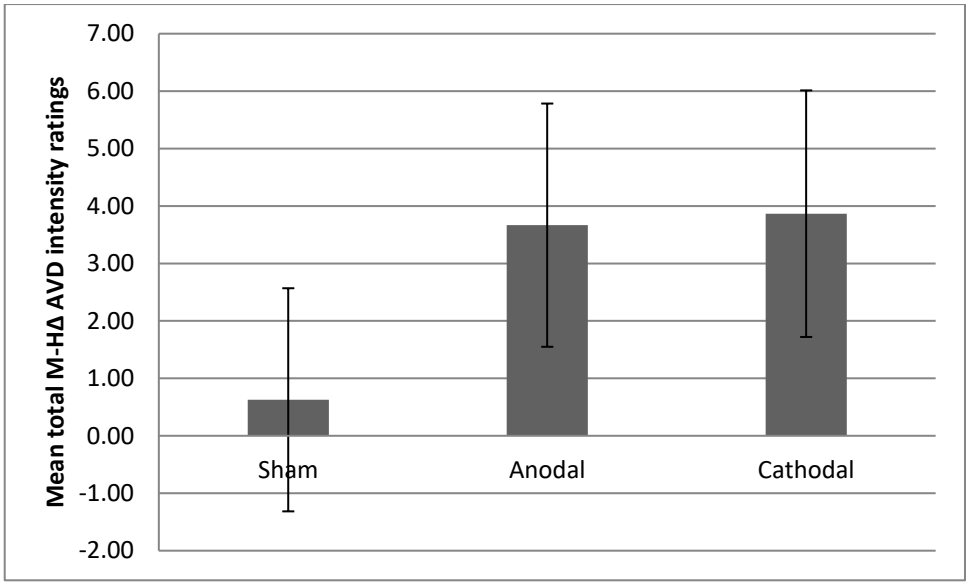

Figure 3.4 – Mean M-HΔ AVD intensity ratings under sham, anodal, and cathodal tDCS, for the whole sample. Error bars = standard error of the mean.

To explore these effects in more detail, as above, data was again split by M-HΔ PG score, with M-HΔ PG ratings ≥ 1 representing the “pattern glare” group (n=40) and M-HΔ PG ratings ≤ 0 representing the “non-pattern glare” group (n=35) (Evans & Stevenson, 2008). (For additional information, low frequency grating data split by PG group can be seen in **Appendix M**).

Differences in M-HΔ AVD intensity ratings between stimulation conditions and groups were explored using a repeated-measures ANOVA. The condition of sphericity was met (p=0.228). Results revealed a significant effect of PG group on overall M-HΔ AVD intensity ratings ($F(1, 73)=54.36$, p=0<0.001) (although this is to be expected given grouping method), and a significant interaction between PG group and tDCS condition ($F(2, 146)=4.584$, p=0.012, $BF_{10}=3.45$). Therefore,

stimulation condition significantly affected PG intensity ratings, dependent on PG group (see **Figure 3.5**).

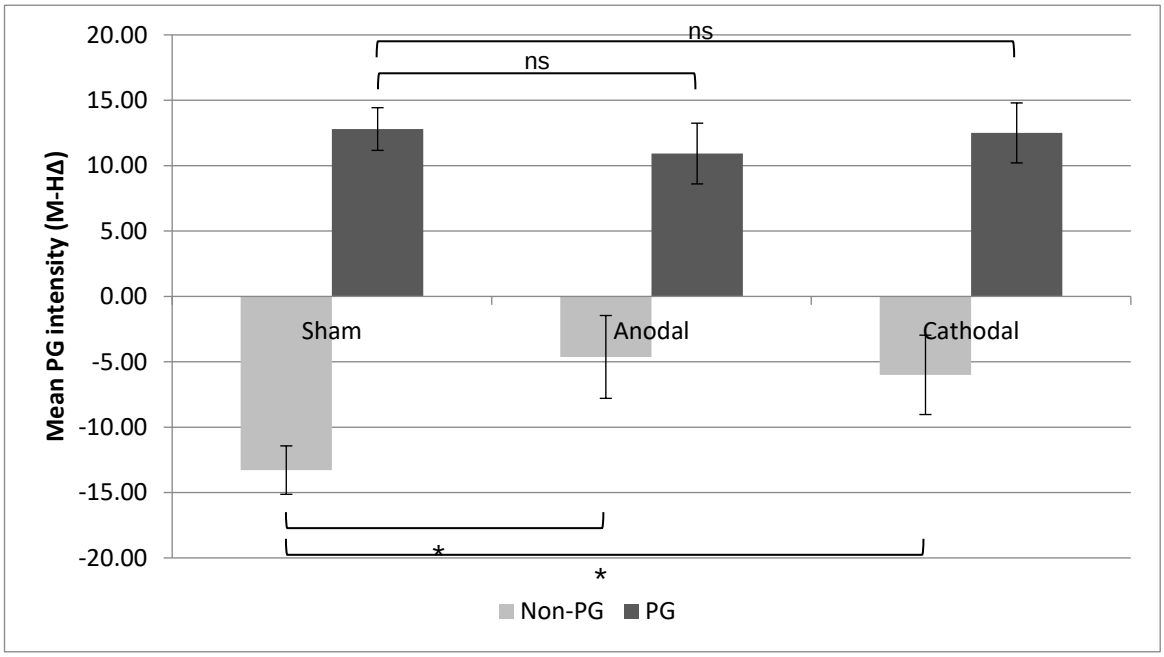

Figure 3.5 – Mean AVD M-HΔ intensity ratings split by pattern glare groups, under each tDCS condition ("PG" = M-HΔ PG ratings ≥ 1 (n=40), "non-PG" = M-HΔ PG ratings ≤ 0 (n=35)). Sham = PG baseline. Error bars = standard error of the mean. Brackets show significant differences, *p<0.01.

Within the non-PG group, post-hoc paired t-tests (p value FDR corrected to 0.01) suggested significant differences in M-HΔ ratings between the sham and anodal conditions (t(34) = -2.904, p=0.006, BF_{10}=6.23, Hedges' *g*=0.56) and between the sham and cathodal conditions (t(34) = -2.887, p=0.007, BF_{10}=6.01, Hedges' *g*=0.49), however there was no significant difference in M-HΔ ratings between the anodal and cathodal conditions (t(34) = 0.414, p=0.681, BF_{10}=0.20,

Hedges' *g*=0.08). However, within the PG group, post-hoc t-tests suggested no significant differences in PG ratings between any of the tDCS conditions (all p>0.05).

Visual inspection of the data (see **Figure 3.5**) also suggested different directions of tDCS effect between groups. The PG group seemed to be more predisposed to perceptual aberrations in general, with more positive M-HΔ scores as compared to the non-PG group in all tDCS conditions. These differences could not be tested statistically due to initially using PG scores to split groups, however this pattern of opposite directions of tDCS effects between groups is nevertheless interesting.

To give further insight into the influence of tDCS on PG scores, PG intensity ratings for the medium and high gratings were graphed (see **Figure 3.6**). For the non-PG group, this suggested that the relative increase in M-HΔ PG score (towards zero) from sham to anodal and cathodal stimulation seen in **Figure 3.5** was driven by a small increase in scores for the medium grating specifically. For the PG group, this suggested that the null effect of stimulation condition on M-HΔ PG scores seen in **Figure 3.5** was driven by lack of change in scores across medium and high gratings equally. No formal statistical analysis was performed here, as the M-HΔ measure is the key measure for this analysis and has several strengths over analysing raw scores (see Study 1, ***Data Analysis***). This also avoids making further unnecessary multiple comparisons, as this data is already multiply compared through the PG-tDCS analysis using M-HΔ

scores, which are derived from raw scores. Nevertheless, these trends are interesting and will be returned to in the discussion.

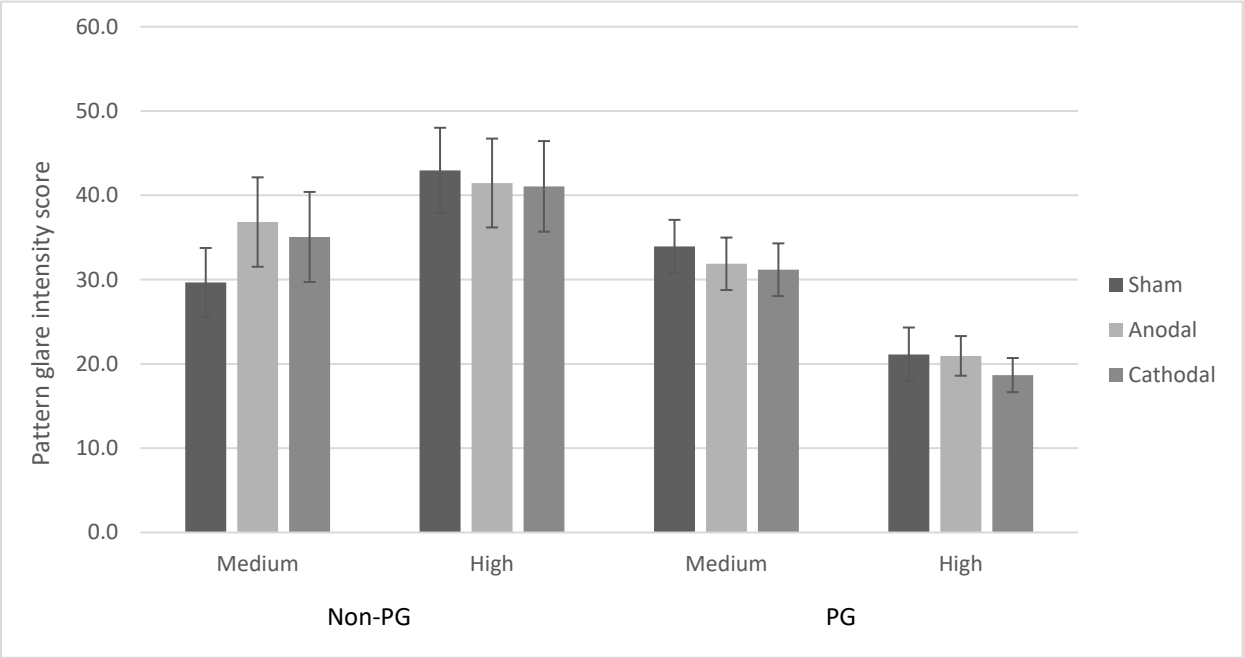

Figure 3.6 – Bar graph showing pattern glare intensity scores for each grating type (medium, high) for the non-PG and PG groups, in each tDCS condition (sham, anodal). Error bars = standard error of the mean.

3.2.2.2 Trait-based analysis

The relationship between questionnaire and PG intensity ratings across tDCS conditions were explored using Pearson's correlations. Analyses showed no significant correlations between any questionnaire scores and pattern glare M-HΔ AVD intensity ratings, under any stimulation condition ($p>0.05$ for all comparisons). Therefore, additional subgroup analyses were not conducted on this data.

3.3 Discussion

Building on Study 1, the present study investigated the effects of tDCS brain stimulation on anomalous visual experiences, which were measured by a state-based pattern glare task and trait-based questionnaires. Experiences of visual distortions were assessed under sham (no stimulation), anodal, and cathodal tDCS conditions. As in Study 1, there were no significant differences in the intensity of visual distortions between stimulation conditions when collapsed across the entire sample. However, significant differences in the tDCS responsiveness were again observed when data was split into “PG” and “non-PG” groupings based on sham (baseline) pattern glare ratings. This indicates that the tDCS stimulation conditions do not straightforwardly translate to the traditionally expected effects. For example, in the PG group, anodal stimulation did not act in the expected “excitatory” manner, and cathodal stimulation did not act in the expected “inhibitory” manner.

Further, a trend for opposite directions of tDCS effect was again observed for the different pattern glare groups. For the PG group, there were no significant differences in pattern glare ratings between stimulations conditions. Anodal and cathodal tDCS appeared to have a null effect on state-based visual distortions in this group, with neither condition significantly affecting pattern glare experiences as compared to sham. In the non-PG group, both anodal and cathodal stimulation significantly increased pattern glare intensity as compared to sham stimulation. There were no significant differences between pattern glare ratings in the anodal and cathodal conditions.

3.4 General Discussion

Study 1 explored the effects of 20 mins anodal tDCS over Pz (contrasted with a sham condition) on state-based pattern glare experiences. Study 2 explored the effects of 10 mins anodal and cathodal stimulation over POz (contrasted with sham) on state-based pattern glare experiences. These effects were compared with measures of trait-based predisposition to anomalous experiences (CHi and CAPS questionnaires) in both studies.

Study 1 demonstrated a positive correlation between the "*Positive Aberrations*" CHi factor and pattern glare intensity, for the PG group only. Both studies demonstrated differences in tDCS responsiveness and pattern glare intensity within groups that did not appear to follow the traditionally expected directions of effect for each tDCS condition. That is, anodal stimulation did not necessarily act in an "excitatory" manner for all groups and so increase pattern glare experiences (as initially expected). These and other key findings are explored further below.

Anomalous experience questionnaires

CHi score descriptives from the current studies closely resemble those from the CHi's debut paper (Braithwaite, Marchant, et al., 2015), and total CHi scores were also not significantly different between Studies 1 and 2. In contrast, CAPS

findings were less consistent between studies[11]. Notably, the Study 2 sample was much less predisposed to CAPS-type experiences than the Study 1 sample, and compared to previous work (Braithwaite, Mevorach, et al., 2015). The reasons for this are not entirely clear. One suggestion is that anomalous visual experiences associated with latent cortical hyperexcitability may be more common and consistent in the general population as compared to CAPS-type experiences. This makes sense given that the CHi measures relatively elementary visual experiences, whereas as the CAPS measures multi-modal, more complex anomalous perceptions. Further work is needed to establish the generalisability of these patterns.

These results demonstrate that a variety of anomalous perceptions can and do occur in the absence of any apparent neurological or psychological condition or disorder. Previous research into the prevalence of anomalous experiences in the healthy general population supports the idea that anomalous experiences (including hallucinations and aberrant perceptions) are distributed as a continuum in the general population (Allen et al., 2005; Baumeister et al., 2017; Braithwaite et al., 2011; Heriot-Maitland et al., 2012; Johns, 2005; Johns & van Os, 2001; Kao et al., 2013; Pearson et al., 2016; van Os & Reninghaus, 2016; Waters & Fernyhough, 2017).

PG ratings under tDCS

[11] Note, this effect occurred when questions that featured on both the CHi and CAPS were removed from the CHi so that they were not repeated across measures (to avoid artificial inflation of correlations).

Results from both Study 1 and 2 suggested no reliable effects of tDCS on endorsement of pattern glare experiences (relative to the sham) when the analysis was collapsed across the whole sample. However, grouping data into “pattern glare” (PG) and “non-pattern glare” (non-PG) groups suggested significant differences in PG experiences within these groups, and a trend of opposite directions of tDCS responsiveness between these groups. Although the results of Studies 1 and 2 are not directly comparable due to design differences, these patterns are nevertheless interesting.

For the PG group in Study 1, anodal stimulation *decreased* the intensity of pattern glare experiences (and hence, the underlying excitability giving rise to them) relative to baseline. In contrast, in Study 2, anodal and cathodal stimulation appeared to have a *null* influence on pattern glare experiences (as compared to baseline) for this group. For the non-PG group, in Studies 1 and 2, both anodal and cathodal stimulation significantly *increased* pattern glare experiences (pushed scores towards 0) as compared to baseline. Given previous work evidencing interactions between baseline states and tDCS efficacy (Hsu et al., 2016; Romei et al., 2016; Silvanto et al., 2018), we suggest that individual differences in state baseline excitability could explain some variation in the sample responses here. We expand on this in more detail below.

Baseline excitability mediates tDCS efficacy

As there were no significant differences in the intensity of visual distortions between stimulation conditions in either study when collapsed across the entire

sample, it is tempting to suggest that tDCS did not in fact alter cortical excitability. However, we suggest this is unlikely for several reasons. First and foremost, features of the current designs, such as stimulation intensity, duration, and montage, have successfully altered visual cortex activity or visual perception in a host of previous studies (Antal et al., 2003b; Antal et al., 2004; Antal et al., 2001; Braithwaite, Mevorach, et al., 2015), with significant effects (Braithwaite, Mevorach, et al., 2015; Ding et al., 2016; Sood, 2016). These factors were carefully considered during study design. Furthermore, in both studies we observed selective tDCS effects and significant within-group differences, with similar tDCS effects for the non-PG group between studies (despite a difference in montage). Although the differences in montages must be kept in mind when interpreting results, such that direct comparison between studies is not possible, it seems reasonable that the tDCS montages were successful in exciting/inhibiting extrastriate cortex here. We suggest that our findings illustrate the influence of baseline excitability on tDCS and task responsiveness.

A typical assumption in tDCS brain stimulation research is that anodal stimulation tends to “excite” neurons while cathodal stimulation tends to “inhibit” them (Bikson, 2016), yet present findings demonstrate that the reality is far more complex. While this relationship may be true for some participants, it does not hold across all individuals – especially when screening for certain factors (something missing from many previous tDCS studies). Current results indicate that, for extrastriate cortex, the excitation/inhibition effects are not so straightforward. Differential effects of tDCS over striate and extrastriate visual cortex may be due to differences in excitatory/inhibitory (E/I) balance across cortical regions/layers (Yang & Sun, 2018), function (Alekseichuk et al., 2016), and network dynamics

(D'Souza, Meier, Bista, Wang, & Burkhalter, 2016) between these areas. Recent research has also demonstrated that brain stimulation can have different effects depending on baseline cortical excitability (Alekseichuk et al., 2016; Boroojerdi, Bushara, et al., 2000; de Graaf, Duecker, Stankevich, Ten Oever, & Sack, 2017; Jacobson et al., 2012; Silvanto et al., 2018). Moreover, tDCS over higher extrastriate areas will interact with ongoing cortical activity in this region, and also affect recurrent feedforward/feedback processes between visual and other brain areas (Gilbert & Li, 2013). Therefore, stimulating at different processing "stages" (i.e. at striate and extrastriate cortex) may produce different effects, and further work is needed to explore this fully.

A key finding here for the PG group was that anodal stimulation had an inhibitory effect in Study 1, and a null effect in Study 2. This latter result may be due to the reduced stimulation time in Study 2 (10 mins) as compared to Study 1 (20 mins), or to an interaction between tDCS and viewing pattern glare stimuli during stimulation in Study 2. For example, because extrastriate cortex can become hyperexcitable in response to visually-aversive or pattern glare stimuli, and during visual hallucinations (Hadjikhani et al., 2001; Huang et al., 2011), simultaneous tDCS and viewing of pattern glare stimuli may have interacted to produce the observed effects here. These effects are unlikely to reflect basic ceiling effects (where pattern glare stimuli excite the cortex to the extent that tDCS cannot exert any effect), as it is unlikely that non-clinical samples would reach an "absolute" background ceiling state that renders tDCS ineffective (Braithwaite, Mevorach, et al., 2015). Further, Study 1 demonstrated a significant inhibitory effect of anodal tDCS for the PG group. It may be that, in Study 2, this effect was

masked or nullified in Study 2 by increased excitability from viewing pattern glare stimuli during tDCS, triggering “non-additive mechanisms” and so reversing or nullifying any inhibitory effects (Bortoletto, Pellicciari, Rodella, & Miniussi, 2015; Schabrun, Chipchase, Zipf, Thickbroom, & Hodges, 2013).

Alternatively, the concept of “neural noise” may explain Study 2 results (as this explanation is most relevant for explaining interactions between concurrent tDCS and tasks (Bortoletto et al., 2015)). Under this framework, tDCS effects will depend on the signal-to-noise ratio (SNR), where the signal is neural activity relevant to the task and the noise is random background neural activity (Bortoletto et al., 2015). As tDCS influences ongoing neural activity and targets large populations of neurons fairly indiscriminately, its efficacy can be understood as altering the signal-to-noise ratio across these neurons. Neurons that are highly excitable and close to “saturation” in response to the task (signal) will respond least to excitatory stimulation, whereas neurons that are less activated by the task will respond most to this stimulation and influence task performance/effects (Bortoletto et al., 2015). Combined with pre-existing imbalances in excitability between PG groups, this may provide an explanatory framework for some of the current findings. That is, those with “high” excitability (PG group) may be less influenced by anodal stimulation when viewing pattern glare stimuli (as the response is already close to saturation), and also by cathodal stimulation due to an “excitable” default system threshold and deficient inhibition (Braithwaite, Mevorach, et al., 2015). Under this view, the PG group cannot be influenced as readily by tDCS, and so there is little SNR change. In contrast, in those with low to moderate excitability (non-PG group), pattern glare stimuli would not cause initial hyper-activation of the relevant networks and so they may be more readily influenced by anodal tDCS. In

this group, cathodal stimulation may have excitatory effects by “priming” neurons by reducing thresholds for subsequent anodal stimulation, as seen in motor studies (Lang et al., 2004; Schabrun et al., 2013), so that excitability is increased once excitatory stimuli (such as pattern glare) are applied/presented (Christova, Rafolt, & Gallasch, 2015). Such an interaction may have increased the intensity of PG experiences in the non-PG group.

Despite this research, many previous tDCS studies have focused on whole samples without accounting for state factors (e.g. by stratifying participants into subgroups). This may explain why some meta-analyses have reported no significant tDCS effects (Horvath, Forte, & Carter, 2015; Medina & Cason, 2017). Not accounting for baseline excitability or other factors now known to influence tDCS responsivity (such as time of testing – see Methods) may mask tDCS effects or skew data interpretation. Pre-existing excitation/inhibition balances will determine the net effect of brain stimulation, and may be related to differences in brain states such as alertness (Krause & Kadosh, 2014). This pre-existing balance will also influence network flexibility and the functionality of specific brain areas (Krause & Kadosh, 2014). Several studies have now demonstrated that behavioural tDCS effects are dependent on individual baseline performance (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015; Hsu et al., 2016; Juan et al., 2017). By taking into account possible individual differences in baseline excitability in our analysis, we evidenced significant relationships between PG data and questionnaire scores in Study 1 for a specific group (suggested to have high background excitability), and within PG group data in Study 2. Under the concept of a “continuum” of cortical hyperexcitability as a factor in hallucination proneness (Braithwaite, Mevorach, et al., 2015), differences in latent cortical excitability

across individuals will create heterogeneity in both individual predisposition to anomalous experiences and responses to tDCS (with tasks also interacting with tDCS efficacy). Therefore, future research should consider the influence of participants' baseline excitability and possible tDCS response variations by cortical area. Future studies of brain stimulation may also benefit from individual-difference stratification, to determine more complex interactions between individual brains and fixed stimulatory montages.

Questionnaires and PG ratings under tDCS

First and foremost, a significant correlation between the CHi *"Positive Aberrations"* factor and pattern glare experiences was observed in Study 1, but for the PG group only. This suggests a relationship between trait predisposition to elementary visual anomalous experiences and state anomalous perception, specifically in those with latent levels of hyperexcitability. This finding is supported by previous work in non-clinical groups (Braithwaite, Mevorach, et al., 2015) and migrainers (Fong et al., 2019).

There were no significant relationships between pattern glare ratings and the "*Heightened Visual Sensitivity and Discomfort*" (HVSD) or "*Negative Aberrations*" factors of the CHi. Although caution should be expressed when interpreting null results (though the Bayes factors allow some speculation here), it might be the case that these types of experiences have their basis in more posterior brain regions to those stimulated here, with the possibility that at least some of the HVSD items may also be driven by pre-cortical (i.e. ocular) factors (as suggested

by Conlon & Lovegrove, 2001; Conlon, Lovegrove, Chekaluk, & Pattison, 1999; Evans & Stevenson, 2008; Harle & Evans, 2004; Wilkins et al., 1984). Therefore, brain stimulation directed towards extrastriate cortex may have been somewhat benign for these items. Furthermore, the *Negative Aberrations* factor received very little endorsement (the lowest of all the factors) in both studies, which may reflect how rare such experiences were in these samples and that they were simply not sufficiently present for possible associations to emerge.

It is also interesting to note that data from both studies did not support a relationship between CAPS questionnaire scores and pattern glare under any of the stimulation conditions. This contrasts with previous work that has observed a reliable correlation between TLE-type and pattern glare experiences under tDCS (Braithwaite, Mevorach, et al., 2015). However, in comparison the current studies used a different set of montages and a different method of analysing pattern glare ratings, via a medium-high grating comparison (M-HΔ) rather than focusing on medium-frequency gratings as compared to the summed baselines (low + high frequency). The lack of correlation between CAPS and PG scores here may also be due to items on the CAPS measure describing complex and generally non-visual hallucinations, whereas PG-type distortions are more directly linked to hyperexcitability associated with visual stress and simple visual distortions.

In contrast to Study 1, no correlations were observed in Study 2 between the CHi questionnaire measure and pattern glare experiences. Although this may be viewed as a possible point of contention, it should be noted that Study 2 used a very different stimulatory montage (different duration before starting the task, different electrode location) and so cannot be cast as a direct replication of Study

1. However, at the very least, this result suggests that predisposition to trait-based anomalous experience may not always be directly coupled to the occurrence of state-based anomalous experience. In line with this, it has been suggested that the actual “state” of hallucinating, and the “trait” of being an individual who is predisposed to hallucinations, may involve contributions from different brain networks and regions (Smith et al., 2013). A meta-analysis of state and trait aspects of auditory hallucinations in schizophrenia found a clear dissociation of brain regions involved in state- versus trait-hallucinatory experiences, with the state of experiencing hallucinations involving speech production areas such as Broca’s, area and the trait of hallucination proneness involving auditory cortex (Kühn & Gallinat, 2012). Cortical inhibition (as indicated by P50 evoked potentials) has also been shown to have differential relationships to state- and trait-anomalous experience in patients with schizophrenia, with this measure being related to trait, but not state, reports of hallucination severity (Smith et al., 2013).

It may be that a similar relationship is at play in the current studies, with relationships between questionnaire scores and pattern glare being mediated differently by activity in Brodmann’s areas 17-19 (targeted by electrode at site POz) as compared with Brodmann’s areas 5 and 7 (targeted by electrode at site Pz). Excitability changes in Brodmann’s areas 5 and 7, but not Brodmann’s areas 17-19, may moderate the relationship between state experiences of, and trait predisposition to, anomalous perceptions. In contrast, excitability changes within Brodmann’s areas 17-19 may moderate state anomalous experience (such as pattern glare), but this may share less of a relationship to trait predisposition. This makes sense given the lower-level, primary visual function of areas 17-19, as compared to the higher-level integrative function of areas 5 and 7 (Cavanna &

Trimble, 2006). The degree of hyperexcitability present in specific cortical regions may provide an indicator of or mediate the relationship between trait/state predisposition to anomalous experiences, even in non-clinical groups, but additional work is needed to corroborate this.

Therefore, current findings support the contention that at least some of the factors of the CHi measure are a useful proxy measure of cortical hyperexcitability in non-clinical individuals, and that the CHi is a useful co-variate that is sensitive to differences in visual cortical excitability (indicated here by PG-grouping). Results suggest that trait predisposition to anomalous experience can be related to online aberrant perception, with predisposition to simple hallucinations being associated with increased cortical hyperexcitability. Furthermore, differences in state aberrant visual experiences depending on tDCS condition were observed within groups. We suggest that these differences in tDCS efficacy depend on differences in participants' baseline excitability – though this relationship appears complex. For example, in those with low or typical baseline excitability, anodal stimulation has the "traditionally"-predicted excitatory effects. However, in those with high baseline excitability of extrastriate cortex and who are predisposed to trait-based anomalous experiences, anodal stimulation appears to either *reduce* excitability (appearing to act akin to cathodal stimulation), or have no effect. Therefore, our new findings here cannot be explained merely by the notion that a brain prone to anomalous perceptions is necessarily more 'reactive' to tDCS stimulation. The current studies extend previous work by providing evidence for the presence of a hyperexcitable cortex in those who are predisposed to anomalous experiences, but now extending beyond primary visual cortex into extrastriate cortex and in the non-clinical

population. The degree of hyperexcitability present in specific cortical areas may differentially mediate trait and state predispositions.

3.4.1 Limitations and future directions

Both studies presented here used random sampling methods of predominantly undergraduate populations. Predisposition to hallucinations was a random factor and was free to vary across our studies here – and may go some way to explaining the diverse effects found. One future direction might be to specifically target non-clinical hallucinators directly to ensure that a reasonably sized group of individuals reporting reasonably frequent and intense experiences are represented. Such approaches might facilitate a stronger coupling between trait based and state-based factors, as trait-based aspects would be represented more strongly for comparison.

As discussed above, strong inferences cannot be made when comparing PG and tDCS results between Studies 1 and 2 due to differences in the design parameters. Formal comparisons could also not be made between PG groups due to PG scores being used to split groups initially. Therefore any discussion that theoretically connects these results is speculative at this stage, and further work is needed to clarify these relationships.

Study 1 did not utilise a cathodal condition. This decision was based on the observation that previous work found no significant influence of cathodal stimulation on pattern-glare experiences, and cathodal stimulation is also

notoriously unreliable in cognitive studies (Jacobson et al., 2012; Nitsche et al., 2008). However, including a cathodal condition in Study 2 and contrasting pattern-glare experiences in the manner outlined here did provide additional data points, and allowed more detailed exploration of tDCS effects. To clarify the influence of baseline excitability on tDCS efficacy and anomalous experiences, additional tDCS research that systematically varies stimulation parameters (stimulation type, intensity, duration, etc.) with other objective co-variates is needed. Additionally, future work could employ multi-channel tDCS (MtDCS) in order to improve stimulation focality (Ruffini, Fox, Ripolles, Miranda, & Pascual-Leone, 2014; Ruffini, Ripolles, & Vall, 2015; Shin et al., 2015). For example, MtDCS devices that control current flow using multiple small electrodes can provide more focal stimulation and allow greater control over both the intensity and spatial distribution of the electric field over target regions, as compared with conventional bipolar montages (Miranda et al., 2018; Ruffini et al., 2014; Ruffini et al., 2015).

Current electrical field modelling studies of tDCS efficacy suggest that variables such as cerebrospinal fluid thickness, cortical gyri/sulci morphology, and skull thickness may influence inter-subject variability (Miranda et al., 2018). Recently, Huang et al. (2017) conducted the first study that validated current-flow models of electric fields induced via tDCS, using intracranial EEG recordings from implanted subdural electrodes in epilepsy patients. Current-flow model parameters were adjusted (such as skull and brain conductivity) to reflect actual electric field distributions, so that model predictions were highly accurate even across subjects (Huang et al., 2017). Therefore future iterations of this study may benefit from the

use of similar advanced modelling, to attempt to account for these sources of variability and more accurately predict tDCS effects.

A recent transdiagnostic review of the contribution of hyperexcitability to visual hallucinations concluded that variations in types or locations of brain hyperexcitability may account for the heterogeneity of hallucination content experienced by people across contexts (Carter & ffytche, 2015). To clarify the specific contribution of hyperexcitability to anomalous experiences, a key focus of future research must be exploring and quantifying the different types and mechanisms of hyperexcitability. For example, some potential contributors to hyperexcitability in epilepsy and migraine are glial dysregulation (Devinsky et al., 2013), the photoparoxysmal response (Ferlazzo et al., 2005), brain inflammation (Vezzani, Aronica, Mazarati, & Pittman, 2013), inhibition dysregulation (Aurora, Barrodale, Tipton, & Khodavirdi, 2007; Gunthorpe, Large, & Sankar, 2012), lack of habituation (Coppola & Schoenen, 2012), and cortical spreading depression (Cui et al., 2014). To move forward, the field requires detailed, systematic explorations of the mechanisms that alter brain activity within specific functional areas, and how these are related to specific types of anomalous experience in non-clinical populations.

One systematic review of the features of hallucinations across diagnoses suggested that further research is needed to determine the similarities and differences in phenomenological features of hallucinations across diagnostic and non-clinical groups (Waters & Fernyhough, 2017). Similarly, exploring the similarities and differences in hyperexcitability between clinical and non-clinical

populations, and trans-diagnostically, will provide valuable clues as to the biophysiological correlates of anomalous experience (Carter & ffytche, 2015).

3.5 Conclusions

The current studies provide evidence that individuals predisposed to elevated intensities of pattern-glare experiences also display signs of increased cortical hyperexcitability extending to extrastriate cortex. Study 1 revealed a relationship between a trait-based measure and state-based positive anomalous perceptions that were influenced by anodal tDCS brain stimulation, but only in those predisposed to pattern glare. Studies 1 and 2 evidenced relationships between state experiences of pattern glare and altered state excitability levels across all participants. These findings are consistent with an increased predisposition to anomalous experience being associated with cortical hyperexcitability. Importantly, tDCS responsivity appears to vary considerably depending on baseline excitability. Brain stimulation offers an established and practical way to explore the relationship between hyperexcitability and anomalous experience, but as with any constantly evolving field, future research should aim to systematically determine how baseline and task-induced excitability influence both tDCS responsivity and hallucinatory predisposition.

Foreword to Chapter 4

The previous two chapters explored the contribution of visual cortical excitability to anomalous experiences in visual and other modalities. This was investigated by manipulating state cortical excitability in extrastriate cortex, measuring state and trait anomalous experiences, and exploring the influence of baseline cortical excitability on these measures. Chapter 2 evidenced a relationship between trait-based "positive aberrations" factor of the CHi measure and state-based pattern glare scores under sham and anodal stimulation, but only for those with high PG scores (i.e. those with hyperexcitable visual cortices). Significant trait-state relationships were restricted to comparisons within the visual modality – comparing visual pattern glare scores with the multi-modal trait measure CAPS revealed no significant relationship. Chapters 2 and 3 also evidenced significant relationships between state-based pattern glare scores and tDCS type (anodal, cathodal) that were dependent on PG group, across two different stimulatory montages. Again, these relationships were restricted to comparisons within the visual modality. Overall, these results suggest that tDCS efficacy and pattern glare experiences are dependent on baseline excitability.

A question arising from these findings is how hyperexcitability in other cortical areas contributes to anomalous experiences in other modalities. For example, might hyperexcitability as measured in auditory cortex be associated with auditory anomalous experiences *only*? If so, this would suggest that hyperexcitability and its effects can be "restricted" to certain cortical areas and associated modalities. Alternatively, might hyperexcitability measured in one

modality (e.g. auditory) be associated with anomalous experiences in another (e.g. visual)? If so, this would suggest a relationship between hyperexcitability across cortical areas and modalities, and that hyperexcitability as measured in one modality may not be restricted there and can influence, or is at least related to, experience in other modalities. Very little such cross-modal research currently exists. In the previous chapters, comparing experiences in the visual modality with those in multiple modalities may have obscured specific cross-modality relationships.

Therefore, to explore whether the relationships observed in Chapters 2 and 3 could be extended to the auditory modality, Chapter 4 investigated whether a state measure of auditory cortex inhibition was related to trait and state measures of anomalous experience and cortical hyperexcitability in visual and other modalities. Here, auditory inhibition was measured using an EEG-based "repetition suppression" task. Repetition suppression is a process by which the nervous system attenuates its response to repetitions of the same stimulus, to prevent informational overload (Boutros, Belger, Campbell, D'Souza, & Krystal, 1999; Park et al., 2015; Patterson et al., 2008; Wan, Thomas, Pisipati, Jarvis, & Boutros, 2017), and can therefore be conceived as indicating cortical inhibition or reflecting the E/I balance (Dalecki, Johnstone, & Croft, 2015; Hirano et al., 2010). Repetition suppression has been linked by numerous EEG studies to anomalous experiences in clinical groups (Keil, Roa Romero, Balz, Henjes, & Senkowski, 2016; Smith et al., 2013; Thoma et al., 2017)(**see Appendix O**), but few have investigated this link in non-clinical samples. In Chapter 4, this state-based repetition suppression measure was correlated with trait questionnaire measures of anomalous

experience and a state measure of visual cortical hyperexcitability (pattern glare task), to investigate trait-state and state-state relationships cross-modally.

Chapters 2 and 3 of this thesis showed that trait-state relationships (between trait anomalous experience and state visual aberrations) seem to exist for comparisons within the visual modality only, and not when comparing visual and multi-modal measures. It may be that comparing experiences in a single modality with experiences in multi-modalities obscures specific relationships between individual modalities (and therefore, the networks that process this information). Furthermore, only some anomalous experiences have been specifically associated with cortical hyperexcitability in the literature, and so the most accurate comparisons will be between questionnaires that are based in the concept of cortical hyperexcitability and measures of cortical inhibition. Therefore, it was tentatively hypothesised that Chapter 4 would evidence a relationship between trait visual anomalous experiences specifically associated with cortical hyperexcitability, and state auditory inhibition. If no relationship between state visual and auditory measures of hyperexcitability is observed in Chapter 4, this would suggest that hyperexcitability may be restricted within modalities somehow and does not necessarily impact processing in other modalities, in a new non-clinical sample.

Further, previous research has suggested that repetition suppression deficits represent a functional correlate of schizophrenia neuropathology specifically (Bodatsch, Brockhaus-Dumke, Klosterkotter, & Ruhrmann, 2015; Park et al., 2015). However, repetition suppression has been related to anomalous

experiences in healthy groups as well (Anokhin, Vedeniapin, Heath, Korzyukov, & Boutros, 2007; Croft, Lee, Bertolot, & Gruzelier, 2001b; Kisley, Noecker, & Guinther, 2004; Park et al., 2015), and the amount of suppression overlaps considerably between clinical and non-clinical groups (Coffman, Haigh, Murphy, & Salisbury, 2017; Patterson et al., 2008). Under the continuum view, mechanisms for anomalous experience may be shared between clinical and non-clinical groups. Therefore if repetition suppression deficits are also apparent in a healthy sample, *and* are linked to anomalous experience predisposition, this would evidence mechanistic continuity across groups.

Materials relevant to this chapter (consent / screening forms and questionnaires) are presented in **Appendices I – L.**

4 Chapter 4

4.1 Introduction

4.1.1 Repetition suppression

The ability to quickly detect and adapt to novel, deviant, and repeated stimuli is fundamental to human auditory processing (Grimm & Escera, 2012). This can be achieved through “sensory gating”; the “ability of the brain to modulate its sensitivity to incoming stimuli” (Boutros et al., 1999). This allows important and redundant stimuli to be distinguished (Park et al., 2015; Patterson et al., 2008). The purpose of sensory gating is to prevent the flooding of higher cortical areas with unimportant sensory information (Möller et al., 2007).

One type of sensory gating is “repetition suppression”; a measure of the reduction in neural activity in response to repeated stimuli (Grill-Spector, Henson, & Martin, 2006). This is thought to reflect the “pre-attentional habituation of responses to repeated sensory input”, where a much-reduced neural response to repeated stimuli reflects strong recurrent inhibitory mechanisms (Patterson et al., 2008). Repetition suppression can therefore be conceived as a type of “gating-out” process. In healthy brains there is usually a 70% reduction in response to a repeated second stimulus relative to the first (Shaikh et al., 2015), and this gating is usually highly stable and reliable in healthy neurotypical controls (Thoma et al., 2017). When measured using auditory stimuli, repetition suppression can therefore be conceived as a measure of auditory cortex inhibition (Grill-Spector et al., 2006; Hirano et al., 2010).

The various neural mechanisms underlying repetition suppression are all thought to depend on changes to the excitation/inhibition balance at some stage: **firing-rate adaptation**, where temporarily reduced excitability leads to reduced probability of neural spiking; **synaptic depression**, where temporary reductions in pre-synaptic neurotransmitter release lead to reduced synaptic efficacy; and **long-term depression and potentiation**, long-term decreases and increases in synaptic efficacy due to multiple stages/mechanisms (e.g. reduced Ca2+ concentration, changes to gene expression and protein synthesis) (Grill-Spector et al., 2006).

As balanced excitation and inhibition is required for accurate perception (as outlined in the Introduction - seeAleman & Vercammen, 2013; Isaacson & Scanziani, 2011; Jardri et al., 2016; Stafstrom, 1998), it is no surprise that repetition suppression abnormalities have been linked to perceptual aberrations. Some individuals cannot appropriately “gate” (or filter) out signals from irrelevant or redundant sensory information, which may result in excessive information becoming salient and being attended (Keil et al., 2016; Patterson et al., 2008). This could lead to sensory overload, hallucinations, and cognitive deficits (Park et al., 2015; Keil et al., 2016). Because of this, sensory gating generally and repetition suppression specifically are key ideas used to explain deficits in attention and perception as part of schizophrenia. Numerous studies have investigated sensory gating and repetition suppression in schizophrenia (Coffman et al., 2017; Randeniya, Oestreich, & Garrido, 2018; Rentzsch, Shen, Jockers-Scherübl, Gallinat, & Neuhaus, 2015), however relatively few have examined the relationship between repetition suppression and predisposition to positive symptoms such as

hallucinations specifically (Keil et al., 2016). Despite this, some recent research has indeed observed relationships between deficient repetition suppression and trait hallucinatory disposition (questionnaire-based) in patients with schizophrenia (Micoulaud-Franchi et al., 2014; Smith et al., 2013). One study also found that poorer repetition suppression was associated with greater severity of active auditory hallucinations occurring during EEG recording (Thoma et al., 2017). Importantly, Hirano et al. (2010) suggested that deficits in repetition suppression in left hemisphere may contribute to a hyperexcitable response to voices, and so auditory hallucinations, in schizophrenia.

Although far fewer studies have examined the relationship between repetition suppression and anomalous experience in non-clinical groups predisposed to anomalous experiences, there is some evidence that repetition suppression can also be impaired in healthy individuals, and may similarly lead to perceptual abnormalities (Croft, Lee, Bertolot, & Gruzelier, 2001a; Kisley et al., 2004; Oestreich et al., 2016). Of the studies outlined in **Appendix O**, which gives an overview of previous work that has correlated repetition suppression and symptom measures, only two (Croft et al., 2001 and Park et al., 2015) analysed this relationship in healthy control or schizotypy groups. Therefore there is a data gap here that needs addressing.

Comparatively, there is little evidence that other forms of “gating-out”, such as prepulse inhibition (PPI), are associated with anomalous experiences. PPI is whereby “a weaker prestimulus (prepulse) inhibits the reaction to a subsequent strong stimulus (pulse)” (Wan et al., 2017). There is no consistent evidence that

PPI “deficits” are associated with clinical course or specific symptoms of schizophrenia (or schizotypy), including positive symptoms (Swerdlow, Weber, Qu, Light, & Braff, 2008; Wan et al., 2017).

For example, recently Mena et al. (2016) found no correlations between PPI and any positive or negative symptoms in schizophrenia patients. Similarly, in a healthy sample Abel et al. (2004) found no relationship between PPI deficits and schizotypy symptoms (including unusual experiences). Further, although Kumari et al. (2008) observed a correlation between PPI deficits and psychosis-proneness in healthy individuals, the latter was measured using the “Psychoticism” subscale of the Eysenck Personality Questionnaire, which focuses on personality traits and does not include any items on anomalous experiences.

Instead, PPI may be more related to psychosis-specific executive or cognitive dysfunction / disorganisation, or poor global functioning (Kohl, Heekeren, Klosterkötter, & Kuhn, 2013; Kumari, Peters, et al., 2008; Swerdlow et al., 2008; Wan et al., 2017). For example, Kumari et al. (2008) suggested that PPI deficits may be specifically related to the perceived controllability of hallucinations in schizophrenia, and did not find any relationships between PPI and any other aspect of auditory hallucinations or other symptom dimensions. Further, in this study pre-pulse latencies were significantly correlated with duration of illness, again suggesting a specific clinical relationship. Similarly in healthy individuals with high schizotypy, a recent review suggested that PPI deficits were related to cognitive (working memory, attention, and executive) dysfunction, but did not present any evidence of a link between PPI and positive or negative symptoms (Giakoumaki,

2012). However, other research has failed to find associations between PPI and cognitive deficits in schizophrenia when correcting for multiple comparisons (Hasenkamp et al., 2011). Therefore these relationships are still unclear.

Therefore, PPI deficits may be related to cognitive dysfunction specifically (regardless of clinical diagnosis) and are not related to positive symptoms or anomalous experiences, in either clinical or non-clinical groups. Unlike repetition suppression deficits, it appears that PPI deficits are not continuously distributed as a possible “risk factor” for anomalous experiences in clinical and normal populations. This thesis is concerned with exploring possible correlates of anomalous experiences specifically, that may be applicable across clinical and non-clinical groups, and so PPI is not a good candidate. Based on the above, repetition suppression was identified as the most suitable measure of auditory inhibition for correlating with anomalous experiences in a non-clinical sample.

Previous research has given support to the notion that repetition suppression deficits are related to anomalous experiences in both clinical (Thoma et al., 2017) and non-clinical (Croft et al., 2001a; Kisley et al., 2004; Oestreich et al., 2016) groups. However, comparatively there is much less non-clinical than clinical data. Further work is needed to determine whether repetition suppression could indeed represent a mechanistic correlate of anomalous experiences regardless of clinical status. This would extend the psychosis continuum model (Baumeister et al., 2017; Guloksuz & van Os, 2017; Stip & Letourneau, 2009) by evidencing a mechanistic continuum to complement the already well-evidenced phenomenological continuum. Some previous research has suggested that

repetition suppression deficits represent a functional correlate of schizophrenia spectrum neuropathology (Bodatsch et al., 2015; Brockhaus-Dumke et al., 2008; Park et al., 2015), however without sufficient complementary data from non-clinical groups who also experience anomalous perceptions, we cannot be certain that this is accurate. Therefore, this chapter sought to fill this gap by exploring possible relationships between repetition suppression and anomalous experiences, in a new, healthy sample.

The following sections outline the “paired-click” paradigm that is commonly used to measure repetition suppression across different ERP components and the neurophysiological mechanisms underlying repetition suppression as measured by this paradigm, and explore the current evidence for relationships between repetition suppression deficits and AEs in clinical and non-clinical groups.

4.1.2 Measuring repetition suppression using the “paired-click” paradigm

The onset of a sound stimulus evokes a stereotypical P50-N1-P2 component complex (Pratt, Starr, Michalewski, Bleich, & Mittelman, 2008). Therefore, repetition suppression specifically has been classically explored using the “paired-click” paradigm. This is an event-related measure of inhibition and repetition suppression in the auditory cortex (Möller et al., 2007; Patterson et al., 2008). The task involves presenting an identical pair of auditory “click” stimuli in close succession, usually 500ms apart. The polarities of the evoked potentials occurring in response to both the first (S1) and second (S2) clicks are measured and compared to estimate repetition suppression, i.e. the extent to which S2 is suppressed relative to S1.

S1 elicits an initial excitatory response and activates inhibitory pathways which will suppress the response to S2, and so S2 represents a test of the strength of recurrent cortical inhibitory mechanisms (Anokhin et al., 2007; Patterson et al., 2008). Two common methods for calculating repetition suppression responses are as a ratio (S2/S1), and as a difference (S2-S1), with research still debating which is the most reliable (Dalecki et al., 2011; Keil et al., 2016, suppl. material)). However, the S2-S1 difference is thought to reflect S1 amplitude more than S2 suppression (Dalecki et al., 2011), and the S2/S1 ratio is suggested to be a more reliable measure of repetition suppression specifically (Boutros, Gjini, Urbach, & Pflieger, 2011).

Traditionally, responses to auditory clicks are measured at approximately 50ms post-stimulus, known as the P50 wave (or auditory P1) (Keil et al., 2016; Light et al., 2010; Luck, 2014; Patterson et al., 2008), and so comparing the P50 response to these repeated clicks allows us to measure “P50 suppression”. However, repetition suppression can also be observed in other EEG components, most commonly the N1 and P2 components (Anokhin et al., 2007; Boutros et al., 2011; Grau, Fuentemilla, & Marco-Pallares, 2007; Grimm & Escera, 2012; Rosburg, 2018b). A brief overview of suppression responses for each of the key components is given below.

4.1.2.1 P50 component

A healthy, neurotypical brain suppresses the P50 wave evoked by the second click (as compared with the first click), particularly if the second click arrives

within 500ms of the first. This reflects adaptive repetition suppression of the irrelevant or redundant sensory information that is S2, resulting in a smaller P50 ratio (Keil et al., 2016; Park et al., 2015; Patterson et al., 2008). P50 suppression is thought to result from inhibitory signals suppressing activity of the primary generators of the P50 response (in the temporal lobes, with some later involvement from frontal lobes occurring approximately 10ms later), such that gating is observable in the resulting ERPs (Korzyukov et al., 2007).

In contrast, abnormal repetition suppression and a larger P50 ratio – reflecting a smaller response difference between S1 and S2 caused by lack of suppression of S2 – is observed in those with schizophrenia, suggesting that the brain is not “gating” redundant sensory information due to deficits in cortical inhibition (Keil et al., 2008; Light et al., 2010; Patterson et al., 2008). This can lead to sensory overload (Dalecki et al., 2011). In support of this, in those with schizophrenia, Popov et al. (2011) found that poor P50 suppression was restricted to S2 abnormalities, and that improvements to this suppression (achieved through cognitive training focused on improving auditory-verbal discrimination) were confined to S2 amplitudes specifically. This supports the “inhibitory return” theory of suppression, whereby S1 activates recurrent inhibitory mechanisms that result in an attenuated network response to S2 (Popov et al., 2011).

4.1.2.2 N1 and P2 components

Similar repetition suppression effects can be also observed for the N1 and P2 ERPs, using the same methodology (Anokhin et al., 2007; Boutros et al., 2011; Grau et al., 2007; Grimm & Escera, 2012; Rosburg, 2018b). The P50, N1, and P2

show the most prominent amplitude deflections in response to paired click stimuli, however the N1 and P2 suppression measures are thought to be more reliable due to much larger deflections than for the P50 (Rosburg, 2018). Additionally, the suppression ratios for P50, N1, and P2 components are not correlated, and so likely represent distinct features or phases of repetition suppression (Boutros et al., 2011). Anokhin et al. (2007) suggested that both N1 and P2 may be useful gating measures or endophenotypes for future studies exploring repetition suppression and psychopathology (Anokhin et al., 2007). As such, studies on repetition suppression in schizophrenia and related topics have recently begun to include N1 and P2 component measures (Boutros et al., 2011).

With regards to the N1 component, both early (~80-100ms; left and right temporal) and late (~130-140ms; frontal anterior and fronto-left temporal) activations are thought to contribute (although these activations overlap spatially and temporally, to a degree) (Grau et al., 2007). The N1 frontocentral subcomponents are thought to be generated by the supratemporal auditory cortex (Onitsuka, Oribe, Nakamura, & Kanba, 2013), a vertex subcomponent generated by an unknown site, and a laterally-distributed subcomponent generated by superior temporal gyrus (Luck, 2014). However, several additional areas have been identified as contributing to the N1, with the strongest N1 responses after temporal areas observed in parietal and cingulate cortices (Boutros et al., 2011).

Within the N1 component, the involvement of early areas is thought to facilitate the detection of basic stimulus features, whereas late involvement of frontal areas may suggest initiation of top-down mechanisms that modulate

stimulus salience (Grau et al., 2007) or novelty. Therefore early, pre-attentive processing may be reflected by both the P50 and N1 components. However, the N1 also reflects some later, frontal processing that is partly distinct from the P50 in mediating repetition suppression (Boutros et al., 1999; Pereira et al., 2014). Other work has suggested that N1 reflects match/mismatch categorisations, or an orienting response (Sur & Sinha, 2009). Interestingly, at S1 presentation both early and late areas are activated, however after S2 presentation only right and left temporal cortices remain active (and to a lesser degree), such that these “early” contributors adapt (decrease in activity) whereas “late” contributors are actively suppressed (Grau et al., 2007). Indeed, Boutros et al. (2011) found that frontal regions exhibited the strongest N1 repetition suppression (including left superior frontal gyrus, left orbitofrontal cortex, and inferior frontal gyrus).

Therefore, N1 repetition suppression is a measure of both suppressed frontal activation (reduced top-down modulation) and decreased (habituated) temporal activation (Boutros et al., 2011; Grau et al., 2007). Accordingly, N1 suppression is thought to rely on changes to the balance between excitation and inhibition in temporal cortex (Javitt, 2015).

As with the N1 wave, the auditory P2 wave is also involved in updating sensory contexts. For example, it is larger when target stimuli are infrequent; in oddball paradigms, oddballs elicit a larger P2 response (Luck, 2014). However, this effect for P2 only occurs when stimuli features are fairly simple (Luck, 2014). Although early work focused on a combined N1/P2 vertex potential, more recent work supports these components as functionally and temporally distinguishable

and independent (Crowley & Colrain, 2004; Ferreira-Santos et al., 2012; Pereira et al., 2014).

The P2 component peaks ~150-200ms post-stimulus and likely has several source generators, with these mainly residing in associative auditory temporal regions; however frontal and inferior parietal cortices may also contribute within the same time window (Ferreria-Santos et al., 2012). The P2 is thought to represent early stages of “forward processing”, where signals are passed to higher cortical areas for processing of meaning (Ranson, 2014). As such, the P2 likely reflects comparisons between predicted and actually-perceived states or events, and the match or mismatch between these (Ferreria-Santos et al., 2012). Accordingly, P2 suppression is usually observed in response to self-generated sounds that have short ISIs, aiding the identification of self-initiated stimuli (Sanmiguel, Todd, & Schroger, 2013). Despite this providing a potential link to auditory hallucinations caused by self-other misattributions, little research has explored the role of P2 in schizophrenia or hallucinations across groups (Ferreria-Santos et al., 2012).

A schematic of expected repetition suppression for the P50, N1, and P2 components in healthy and schizophrenia groups is shown in **Table 4.1**

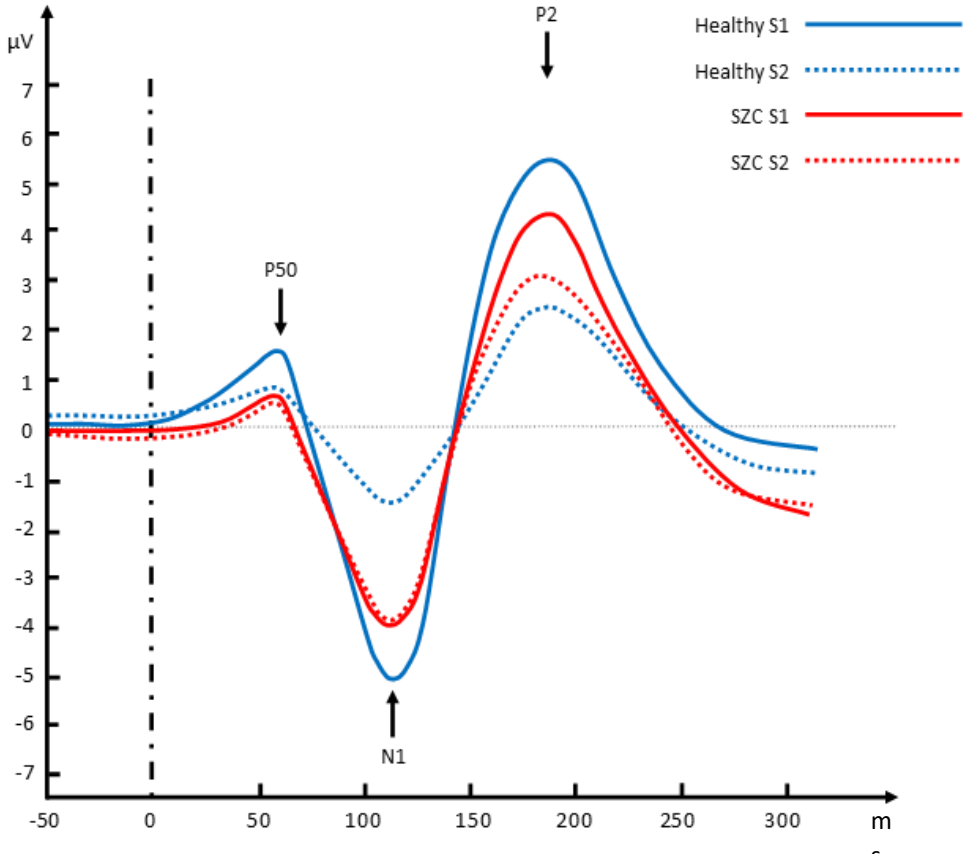

Figure 4.1 – Schematic of expected repetition suppression patterns in healthy controls and schizophrenia (SZC) groups, for first (S1) and second (S2) stimuli presentations. For healthy controls, S2 responses are suppressed as compared to S1 responses. For individuals with schizophrenia, S1 responses are decreased as compared to controls, and S2 responses resemble S1 data and are not suppressed to the same degree (based on Figure 3 from Gooding, Gjini, Burroughs, & Boutros, 2013; and data from van Tricht et al., 2015).

4.1.3 Repetition suppression and anomalous experiences in clinical and non-clinical groups

It is thought that repetition suppression deficits may be caused by cortical hyperexcitability resulting from defects in neuronal inhibition (Patterson et al., 2008; Rosburg, 2018). For example, functional deficits in repetition suppression may be mediated by a reduction of by inhibitory γ-aminobutyric acid (GABA) interneurons or GABAergic tone, which could reduce cortical inhibition so promote a general hyperexcitability across the cortex (Becker, 2004; Freedman, 2014; Hirano et al., 2010; Möller et al., 2007; Smucny et al., 2013; Vlcek, Bob, & Raboch, 2014).[12] Research has also implicated the dysregulation and hyperactivation of dopamine (acting on D2 receptors) and serotonin (acting on 5HT2 and 5HT3 receptors) systems (Becker, 2004; Uhlhaas & Singer, 2015; Vlcek et al., 2014).

Therefore, the roles of the excitation/inhibition (E/I) balance and GABAergic signalling are often highlighted in repetition suppression research. If the E/I balance is disturbed, this could lead to impairments in sensory processing, resulting in increased salience of abnormal and/or internal states, and so hallucinations (Jardri et al., 2016; Keil et al., 2016; Uhlhaas & Singer, 2015). This theory has also been supported outside of schizophrenia, to explain hallucinations in neurodegenerative diseases and delirium, for example (Burghaus, Eggers, Timmermann, Fink, & Diederich, 2012).

[12] This reduced GABAergic function may be caused by deficits in inhibitory nicotinic cholinergic activity in the hippocampus. Cholinergic stimulation of hippocampal CA3-4 GABAergic interneurons usually stimulates release of GABA, which acts on CA3 pyramidal neurons to block excitatory glutamate release, reduce cortical responses, and so “gate” redundant information (Vlcek et al., 2014).

4.1.3.1 P50

4.1.3.1.1 Non-clinical groups

Several studies have observed effective suppression in healthy participants (i.e. a much-reduced neural response to S2 as compared to S1), as would be expected in this group (Brockhaus-Dumke et al., 2008; Hazlett et al., 2015; Patterson et al., 2008). Usually, there is a 70% reduction in response to S2 as compared to S1 in heathy control groups (Shaikh et al., 2015).

Several studies have linked high schizotypy to reduced P50 suppression, however results have been mixed in relation to positive, negative, and cognitive disorganisation symptoms. Although Park et al. (2015) found that the greater the P50 deficit, the higher the overall schizotypy score, Croft et al. (2001a) found that poorer P50 suppression was associated with increased abnormal perceptual experiences only, and not other schizotypal symptoms. Park et al. (2015) did not find any association between P50 deficits and specific positive- or negative-type dimensions. Park and colleagues suggest that this may be due to using a different measure of schizotypy as compared to other studies (the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; (Mason & Claridge, 2006)), and the fact that different experiences will overlap across different dimensions between questionnaires.

However, these results may also be because the O-LIFE measure of schizotypy does not explore anomalous experiences in sufficient detail and in a way that is appropriate for non-clinical samples. O-LIFE questions on unusual

experiences are largely related to cognitive aberrations such as delusions and magical thinking, with any other anomalous experiences (such as sensory distortion) addressed rather superficially. Only a few questions explicitly address hallucinations in specific senses. This issue will be addressed in the current study by using questionnaires that explore a variety of anomalous experiences in detail, and using non-clinical language. This is important because clinical language could negatively bias honest self-report; for example, negative stigma around "symptoms" of mental health problems could lead to social desirability bias (see "Overview of current study" for further discussion).

Further, the O-LIFE questionnaire is a trait-based measure of anomalous experience, and as with many other investigations into anomalous experience in non-clinical groups, no state-based measure was used by Park et al. There is very little work exploring the relationships between state-based measures of anomalous experience and repetition suppression. Smith et al. (2013), for example, observed no relationship between P50 suppression and a state-based auditory hallucinations rating scale in those with schizophrenia, but did find that greater P50 suppression deficits were associated with greater severity of trait-based auditory hallucinations. This highlights a differential relationship for P50 suppression between trait predisposition to and state experience of auditory hallucinations. This is supported by work suggesting that state hallucinations tend to involve speech production areas, whereas trait predisposition is associated with earlier auditory processing in auditory temporal cortex – a central generator of the P50 (Kühn & Gallinat, 2012; Smith et al., 2013). Therefore including both state and trait measures in the current study will provide needed data to compare with these

clinical findings and inform our understanding of these relationships in non-clinical groups.

4.1.3.1.2 Clinical groups

Overall, research suggests that schizophrenia patients have much larger P50 ratios (i.e. similar responses to both S1 and S2) as compared to controls (Brockhaus-Dumke et al., 2008; Hazlett et al., 2015; Patterson et al., 2008). Generally, individuals with schizophrenia show only a 20-50% suppression in the response to S2 relative to S1 (Shaikh et al., 2015).

Some work has suggested that deficits in P50 repetition suppression may reflect early sensory dysfunctions in those with schizophrenia, caused by aberrant connectivity and communication between brain areas that process lower-level sensory information and its integration – which are mediated by inhibitory, excitatory, and cholinergic systems (Smucny et al., 2013; Vleck et al., 2014). Repetition suppression deficits may also reflect increased neural noise (unsynchronised, spontaneous background neural activity), which obscures relevant signals and so decreases the signal-to-noise ratio. Positive symptoms in particular are thought to be the result of attempts to cope with such aberrant neural activity, which could lead to an inability to filter out or inhibit redundant sensory information (such as repeated stimuli) (Smucny et al., 2013)(Bodatsch et al., 2015; Keil et al., 2016). This could in turn prevent accurate sensory processing and efficient top-down control, and lead to sensory overload and hallucinations (Powers, Mathys, & Corlett, 2017; Smucny et al., 2013; Thoma et al., 2017; Uhlhaas & Singer, 2015). In line with this, Keil et al. (2016) found that greater

sensory gating deficits and aberrant neural synchronisation were associated with more severe positive symptoms in schizophrenia. Further, the failure to label inner speech as being self-generated may be caused by pre-frontally-mediated executive control going “offline” and temporal lobe processing becoming predominant (Thoma et al., 2017).

4.1.3.1.3 Clinical/non-clinical group comparisons

Although many clinically-focused studies include control groups, few studies have compared P50 suppression between clinical and non-clinical groups in detail. In a unique meta-analysis, Patterson and colleagues (2008) compared results across 39 studies of P50 suppression ratios in schizophrenia and control groups, and found a mean difference in P50 suppression ratios of 46% between schizophrenia and control groups.

Accordingly, repetition suppression has been argued to reflect psychosis or schizophrenia stage and severity specifically (Bodatsch et al., 2015). However, as most of those who present with psychotic-like symptoms or are seen as “at-risk” for psychosis do not go on to develop psychosis, these types of experiences are argued to be a functional correlate of schizophrenia spectrum neuropathology, rather than a schizophrenia “prodrome” (Bodatsch et al., 2015; Park et al., 2015). This is supported by findings that P50 suppression is significantly impaired in, but not different between, those who are at-risk for psychosis, “truly prodromal”, and medication-free first-episode patients (Brockhaus-Dumke et al., 2008).

However, Patterson et al. (2008) also found that 40% of P50 suppression ratios for controls were within the same range as schizophrenia patients. Some studies have also reported abnormal suppression in controls, and normal suppression in schizophrenia patients on anti-psychotic medication (Patterson et al., 2008). Furthermore, Keil et al. (2016) did not observe significant differences in P50 suppression between their schizophrenia patients and control groups. Whilst Park et al. suggest that this finding raises questions about the specificity of the P50 measure, it could be argued that this observation supports an alternative viewpoint that is in line with the general proposal of this thesis; that this simply reflects natural variation along a spectrum of predisposition to anomalous experiences and cortical hyperexcitability. If suppression deficits are present in those with schizotypy (Chang, Arfken, Sangal, & Boutros, 2011; Croft et al., 2001a; Park et al., 2015), *and* those who experience anomalous perceptions but are otherwise healthy, then it does not follow that suppression deficits reflect specific neuropathologies *per se*. Accordingly, some research suggests that P50 deficits may indicate deficient repetition suppression and predisposition to psychotic-like symptoms across diagnoses (Sánchez-Morla et al., 2008). Therefore it may be hypothesised that healthy individuals who have anomalous experiences akin to (attenuated) positive symptoms would also exhibit slight suppression deficits in comparison to those who do not have these experiences (or have them less frequently). It may be that suppression deficits are common to all individuals experiencing perceptual aberrations, and not just those with schizotypy or schizophrenia.

Some work has suggested using evoked potentials to place individuals at-risk for psychosis into risk groups (Bodatsch et al., 2015). However, it may also be

possible (and in fact more accurate) to use evoked potentials to identify individuals who are predisposed to experiencing anomalous perceptions, outside of specific clinical diagnoses. If P50 repetition suppression deficits are observed in healthy individuals in the current study, and are related to anomalous experiences, this would suggest that repetition suppression should be conceptualised as a marker of predisposition to *anomalous experiences* rather than to clinical conditions or pathologies specifically.

4.1.3.2 N1 and P2

4.1.3.2.1 Non-clinical groups

There is very limited research on N1 and P2 repetition suppression as related to anomalous experience in non-clinical groups. Several studies have linked N1 suppression with perceived agency over actions and the ability to make self/other distinctions. Specifically, greater N1 suppression after speech onset, for example, may serve to label this speech as self-generated and reduce the likelihood that the agent's senses are overwhelmed or distracted by self-generated activity (Baess, Horváth, Jacobsen, & Schröger, 2011; Oestreich et al., 2016). For instance, one notable study from Oestreich et al. (2016) observed deficient N1 suppression in response to self-initiated (via button press) auditory tone stimuli in non-clinical participants with high schizotypy scores, suggesting that these action-binding deficits are not unique to schizophrenia and supporting the psychosis continuum hypothesis (Whitford et al., 2018). This connects with models suggesting that deficient action-outcome binding may result in inner speech being perceived as external (hallucinations) (Poonian, McFadyen, Ogden, & Cunnington, 2015).

In healthy samples, two studies have also evidenced a relationship between abnormal P50/N1 suppression and poor “perceptual modulation” (experiencing sensory information flooding)/increased awareness of background noises, respectively (Anokhin et al., 2007; Kisley et al., 2004).

To the best of the author’s knowledge, no studies exist that investigate the relationship between P2 suppression and anomalous (or similarly categorised) experiences in healthy groups alone, outside of those acting as controls in clinical studies (which are outlined below).

4.1.3.2.2 Clinical groups

Deficits in N1 suppression in clinical groups are thought to arise from changes to *N*-methyl-d-aspartate–type glutamate receptor (NMDAR) function, although there is far less research into this relationship than for mismatch negativity (Javitt, 2015) or the P50 component. NMDAR antagonists (which inhibit NMDAR function) and NMDAR deficits have been linked to early-stage N1 auditory and visual processing deficits in both monkey models of, and humans with, schizophrenia (Javitt, 2015). Such deficits in low-level processing may “generalise upwards” to disturb higher-level processing (Butler et al., 2005).

There is very little work on the neural mechanisms of the P2 component. One study in mice suggested that suppression of mouse P80 (equivalent to the human P2) in response to auditory tones was improved by administering olanzapine, an anti-psychotic with high affinity for dopamine and serotonin

receptors (Lajtha, 2009). However, olanzapine mediated its entire effect by increasing S1 response, rather than enabling adaptive suppression of S2 (Lajtha, 2009).

As with P50, several studies have evidenced a relationship between repetition suppression deficits as indexed by N1 and P2, and sensory processing abnormalities (Crowley & Colrain, 2004; Gjini, Arfken, & Boutros, 2010)(Anokhin et al., 2007). However, there is far less research on these components relative to the abundance of P50 research.

An early study by Boutros et al. (1999) showed that patients with schizophrenia exhibit suppression deficits across P50, N1, and P2 components, implying that repetition suppression is impaired across multiple stages of sensory processing. More recently, van Tricht et al. (2011) observed significantly reduced N1 responses to single tones in a high-risk group who transitioned to psychosis (versus non-transitioning and control groups). Several other studies have evidenced similar deficits in N1 suppression in those with schizophrenia (Gjini et al., 2010; Javitt, 2015; Laurent et al., 1999; Lepock et al., 2018; Roth, Pfefferbaum, Kelly, Berger, & Kopell, 1981; Whitford et al., 2018).

However, neither Boutros et al. (1999) nor van Tricht et al. (2011) correlated suppression deficits with specific symptom types for the clinical groups, and no symptom data was collected for the control group in van Tricht's study, precluding between-group comparisons. As such, N1 deficits may not be a marker of disease progression (as suggested by van Tricht and others; see Lepock et al., 2018), but

of specific symptoms. Additional data on these measures from non-clinical groups is needed to make conclusions here.

In those studies that have explored the relationships between N1 and P2 suppression deficits and perceptual aberrations specifically, there are mixed results. Some have failed to find an association (Brockhaus-Dumke et al., 2008), whereas others have (Rosburg, 2018b; Thoma et al., 2017). In a systematic review of the role of N1 in schizophrenia, Rosburg (2018b) concluded that there is some evidence of a relationship between lower N1 response amplitudes / deficient N1 suppression and acute auditory verbal hallucinations, but not other symptom types. Conversely, Thoma et al. (2017) found that significantly impaired suppression ratios for P50, N1, and P2 components during auditory verbal hallucinations were *not* associated with trait hallucination scores. Thoma et al. (2017) actually found that *improved* N1 gating predicted greater trait severity of auditory verbal hallucinations in patients with schizophrenia, but only when auditory hallucinations were not simultaneously present. Why might better suppression predict more severe hallucinations? Thoma et al. (2017) suggest this may be due to either over-compensation of corrective inhibitory mechanisms, or due to hallucination formation leading to reduced processing of external versus internal stimuli – or perhaps both. However, these suggestions are speculative and require further investigation, particularly as intact suppression supposedly represents normal functioning.

Also relating suppression to hallucinations, Grau et al. (2007) argued that auditory N1 suppression is a measure of both suppressed frontal activation

(reduced top-down modulation) and decreased (habituated) temporal activation. Accordingly, Chen et al. (2011) suggested that neural synchrony between speech production (Broca's) and processing (auditory cortex) areas acts as the "neural instantiation" of motor command efference copies, which allow self/other distinctions. These copies of action or motor signals (such as inner or prepared speech) are sent from planning to sensory brain areas, and allow the agent to distinguish between intended/self-generated and external/other-generated movement. For example, Chen et al. (2011) demonstrated that higher neural synchrony between speech production and processing areas *prior* to speech onset was correlated with greater N1 suppression *after* speech onset. Therefore, this enhanced synchrony may serve to label the prepared speech as self-generated, which in turn leads to greater suppression of the auditory cortex N1 response to the sound of the uttered speech or inner voice. This reduces the likelihood that the agent's senses are overwhelmed or distracted by self-generated activity. Under this explanation, efference copies sent from speech production systems act to control auditory cortex activity in a top-down manner (Chen et al., 2011). Linking the above concepts, Kort et al. (2017) demonstrated that, in both healthy controls and those with schizophrenia, NMDAR dysfunction (via blockade) reduced N1 suppression during predicted speech (talking).

Related to inhibition, Ambrosini et al. evidenced a lack of habituation in visual evoked potentials (VEPs) (N1-P1, P1-N2) recorded over Oz in migrainers with aura (but not healthy controls) when viewing repeated visually-irritating stimuli (Ambrosini, Coppola, Iezzi, Pierelli, & Schoenen, 2017; Schoenen, Wang, Albert, & Delwaide, 1995). Importantly, the amplitudes of these VEPs in migrainers with

aura actually *increased* with repetition (but decreased in controls) (Schoenen et al., 1995). This is suggestive of aberrations in the networks controlling repetition sensitivity in clinical groups, with reduced or no repetition suppression occurring – perhaps due to deficient inhibition (Schoenen et al., 1995) or top-down control of visual cortex (Demarquay & Mauguiere, 2016).

4.1.3.2.3 Clinical/non-clinical group comparisons

Notably, one recent study by Coffman et al. (2017) found no differences in P50, N1, or P2 repetition suppression between those with schizophrenia and healthy controls, with intact suppression evident in both groups. However, this result may be due to the paradigm used, which was not a paired-click task with 500ms ISI but instead a five-tone task with 750ms between blocks. Therefore the "S1" in this study was always slightly suppressed, and so direct comparisons with "true" repetition suppression results cannot be made (Coffman et al., 2017). Additionally, data on positive and negative symptoms were only gathered for the patient group in this study, and so again comparisons between these symptoms and suppression deficits could not be made.

Interestingly, one study comparing repetition suppression in cocaine-dependent patients and healthy controls found that poorer P2 suppression was associated with increased experiences of perceptual aberrations in patients, but with social anhedonia in controls (Gooding et al., 2013). This suggests that deficits in repetition suppression may be related to different processes in patient and control groups. This study also illustrates the value of directly comparing clinical and non-clinical groups to give new perspectives on these relationships.

4.1.3.3 Outstanding issues

As highlighted by the above literature, considerably little research has explored the relationship between repetition suppression across different ERP components and specific experiences, particularly in healthy groups. This means that conclusions cannot be made regarding which repetition suppression deficits, if any, are unique to specific clinical conditions or symptoms. A considerable number of studies suggest that certain suppression deficits may be used as neurobiological markers or endophenotypes of various clinical conditions (such as Earls, Curran, & Mittal, 2016; Johannesen et al., 2005; Park et al., 2015), but these hypotheses cannot be verified if comparisons are not made with non-clinical groups who exhibit similar symptoms in the absence of diagnoses and other confounding variables. Considerable interest in the psychosis spectrum has arisen in recent years, however additional research is needed to conclude whether the well-evidenced experiential continuum is supported by a *mechanistic* continuum.

For example, the use of medication is a significant confounder in clinical EEG research, influencing general EEG measurement (Ferreira-Santos et al., 2012; Hyun, Baik, & Kang, 2011; Oestreich et al., 2016), and possibly inducing the low-frequency EEG abnormalities often observed in schizophrenia patients (Ranlund et al., 2014). So, in medicated groups it can be difficult to conclude whether observed EEG data are specific to clinical groups or symptoms, or are in fact caused by the medication itself. Therefore, medication free non-clinical groups can offer valuable data that is not confounded by either acute or chronic effects of medication, or illness.

Repetition suppression is conventionally explored with a 500ms delay between S1 and S2. However, such paradigms are limited as they do not provide data on the extent and/or limits of the suppression effect. A mechanistic continuum theory may predict that, in those predisposed to anomalous experiences, repetition suppression would become more inefficient as severity of hallucinations increases, for example. By extension, it could also predict that repetition suppression deficits become less apparent as ISI increases – because tones that are very close together in time are more "difficult" to accurately gate (higher processing demand), whereas tone that are further apart in time are relatively "easier" to gate (lower processing demand). Therefore, in a healthy, well-functioning sample, suppression deficits may be more (or only) apparent for "difficult" (shorter) ISIs. Some previous work has explored ranges of repetition suppression values and their test re-test reliability in healthy participants (Fuerst, Gallinat, & Boutros, 2007), but very little work has explored how suppression patterns change with varying inter-stimulus intervals (ISIs) between S1 and S2. The majority of research has fixed the ISI at 500ms. Early work suggested that this ISI allows most accurate discrimination between participants with schizophrenia and non-clinical controls (Nagamoto, Adler, Waldo, & Freedman, 1989) – however this approaches the matter in a discrete way (clear clinical/non-clinical divide) rather than the continuous manner proposed here, and also does not account for the influence of anomalous experience on repetition suppression. This chapter will address this by using varied ISIs between S1 and S2, to increase our understanding of the impact that ISI may have on suppression effects in non-clinical individuals predisposed to anomalous experiences.

4.1.4 Overview of the current study

This study will build on previous research by exploring P50, N1, and P2 repetition suppression in a non-clinical group that is not necessarily schizotypal. Rather, this study is concerned with examining whether both state and trait anomalous experiences are associated with deficits in repetition suppression in the absence of any clinical diagnosis. These relationships will be tested in the current study using anomalous experience questionnaires (trait measure) and a pattern glare task (state measure; a correlate of visual cortical hyperexcitability), in addition to the paired-click task (state measure, deficits in which may indicate cortical hyperexcitability) (Hirano et al., 2010; Vlcek et al., 2014). No previous studies have explored the relationship between repetition suppression and pattern glare experiences in non-clinical participants. The current study also builds on Chapters 2 and 3 (Marchant, Mevorach, & Braithwaite, *under review*) to explore whether the theorised relationship between cortical hyperexcitability and predisposition to anomalous experience in non-clinical samples can be extended from visual to auditory cortex, and whether there are distinct relationships between trait and state, or specific types of, anomalous experiences and ERP measures.

If anomalous experiences across clinical and non-clinical groups have shared neurophysiological mechanisms, then healthy groups predisposed to such experiences may also exhibit repetition suppression deficits (albeit to an attenuated degree) (Oestreich et al., 2016; Whitford et al., 2018). The majority of previous (albeit clinical) work might suggest that that greater deficits in auditory suppression (and so inhibition) would be correlated with increased self-report of trait anomalous

experiences. However, Thoma et al. (2017) found the opposite; that *improved* N1 gating predicted greater trait severity of auditory verbal hallucinations in patients with schizophrenia. Therefore, a firm directional hypothesis for the relationship between repetition suppression and trait/state measures in a healthy group cannot be made here.

Both previous work, and Chapters 2 and 3, suggest that auditory/visual trait and state anomalous experiences are related to hyperexcitability in the corresponding modality's "early" sensory versus "late" cortical areas, respectively (i.e. in auditory/primary visual cortex, versus Broca's/extrastriate) (Kühn & Gallinat, 2012). As the central generators of auditory repetition suppression are in temporal lobe (an "early" area), we might therefore expect that suppression deficits would be associated with trait, but not state, anomalous experience (Korzyukov et al., 2007). Previous research has indeed shown this, with P50 suppression deficits being related to trait, but not state, anomalous experiences in those diagnosed with schizophrenia (Smith et al., 2013). This chapter will build on this, exploring cross-modal trait-state comparisons and in a healthy sample.

As there are mixed results in the literature concerning how positive- and negative-type experiences are related to repetition suppression (particularly P50) in non-clinical participants, the current study will use questionnaires that explore a wide variety of anomalous experiences, across modalities (and that are not necessarily derived from clinical diagnoses), and use non-clinical language appropriate for the current sample. Particularly, the "Cortical Hyperexcitability index II" (see Methods) explores experiences that are empirically evidenced as being

related to cortical hyperexcitability (Fong et al., 2019). Even though all CHi-II-type experiences are associated with the general concept of cortical hyperexcitability, different groups may experience specific clusters of anomalous experience (Fong et al., 2019), possibly due to variation in the type (and/or location) of cortical excitability (Carter & ffytche, 2015). Given the recency of Fong et al.'s work, exploring the CHi-II's correlation with EEG here will provide further insight into its utility (as in Fong et al., 2020).

The current study will employ a pattern glare task, as substantial evidence exists that the visual aberrations induced by the striped grating stimuli in this task (such as colour and motion) are mediated by cortical hyperexcitability (Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite, Mevorach, et al., 2015; Fong et al., 2019; Huang & Zhu, 2017; Huang et al., 2011; Wilkins, Tang, Irabor, Baningham, & Coutts, 2008; Wilkins, 1995; Wilkins et al., 1984; Wilkins & Evans, 2010).

Using a healthy, non-clinical group significantly reduces the confounding factor of medication. The current study also excludes regular users of recreational drugs, and tobacco or nicotine products (including cigarettes, gum, patches, and vaping). Early repetition suppression may be facilitated by nicotine intake (Wan, Crawford, & Boutros, 2007)(Park et al., 2015), and nicotine consumption and withdrawal alters both corticospinal and intra-cortical excitability levels in humans (Grundey et al., 2013). Nicotine also interacts with several other neurotransmission systems implicated in the regulation of cortical excitability, such as dopamine, serotonin, GABA, and glutamate (Grundey et al., 2013). Nicotine use has not been

controlled for in many past studies exploring P50 suppression, which may have compromised findings (Wan et al., 2017).

4.2 Methods

4.2.1 Participants

27 participants took part in the study. Of these, 24 (89%) were female and 24 (89%) were right-handed. Participant age ranged from 18 to 30 years ($\bar{x}$ = 21.4, σ = 3.2). All participants were undergraduate or postgraduate students from the University of Birmingham (UK). Participants received research credits or monetary compensation in return for participation.

Exclusion criteria included in study advertisements excluded any potential participant with: a neurological or psychiatric condition, personal or family history of seizure/epilepsy/recurrent fainting; compromised vision or physical state (including excessive caffeine/alcohol consumption the previous night; sleep disorder/s; regular users of recreational drugs; smokers (regularly smoking the equivalent of at least one cigarette every day (including vaping)), or users of nicotine patches/gum; metal or medical implants (cochlear implant, pacemaker, medication pump, surgical clips); taking any prescribed or unprescribed medication that may interfere with cognitive function; on-going anti-malarial treatment; very little sleep the previous night; and previous significant head injury, concussion, or eye-surgery. A screening questionnaire was administered at the start of each session to ensure that participants did not meet any of these exclusion criteria.

Informed consent was obtained from participants using a consent form that described the nature of the study, potential benefits and risks, and participant compensation. Participants were given the opportunity to have any questions answered to their satisfaction before signing the form in the presence of the researcher. The study was approved by the Ethics Committee of the University of Birmingham [ERN_15-0887].

4.2.2 Materials

4.2.2.1 Questionnaire measures

4.2.2.1.1 Cortical Hyperexcitability Index II

The Cortical Hyperexcitability Index II (CHi-II; Fong et al., 2019) is a parametrically- and empirically-validated proxy correlate of cortical hyperexcitability, consisting of 26 items. All CHi-II questions feature two response dimensions; “frequency” and “intensity”. For each item, participants give responses to two dimensions along a 7-point Likert scale (0-6; 0 = “Never”/”Not at all”, 6 = “All the time”/”Extremely intense”).

CHi-II questions relate to the presence, intensity, and frequency of experiences from three distinct but inter-correlated factors: “*Heightened Visual Sensitivity and Discomfort*” (*HVSD*; 11 items), “*Aura-Like Hallucinatory Experiences*” (*AHE*; 9 items), and “*Distorted Visual Perception*” (*DVP*; 6 items). The *HVSD* factor relates to sensory sensitivity in response to environmental sources of irritation, such as lights and certain patterns. These visual stress

symptoms, which can include somatic discomforts such as nausea, are directly related to cortical hyperexcitability (Fong et al., 2019). Items on the *AHE* factor relate to low-level, elementary positive hallucinations (such as phosphenes, flashes of light and colour) and negative-type hallucinatory experiences (loss of visual information, such as tunnel vision and blind spots). The *DVP* factor contains items related to “distortions” of visual perception (such as changes to the shape and colour of objects, people, and the environment) and complex hallucinations such as out-of-body experiences. (The full CHi-II questionnaire can be seen in **Appendix K**).

4.2.2.1.2 Cardiff Anomalous Perceptions Scale (CAPS)

The same version of the CAPS was used as in the previous two chapters.

4.2.2.1.3 Multi-modality unusual sensory experiences questionnaire (MUSEQ)

The MUSEQ is a recently developed self-report trait measure that assesses unusual sensory experiences across six modalities; auditory, visual, olfactory, gustatory, bodily sensations, and sensed presence experiences (Mitchell et al., 2017). This measure was developed to be useable by both clinical and non-clinical groups, and so uses non-clinical language. The MUSEQ has been validated using a large sample of 1300 participants. A small clinical group of 32 participants with schizophrenia spectrum disorder or bipolar disorder provided data showing that the MUSEQ could discriminate between the clinical and non-clinical groups tested, with the clinical groups scoring significantly higher on both the overall MUSEQ (mean = 79) and on each subscale as compared to controls. However, there was some overlap in the frequency distributions of clinical and non-clinical group

scores, supporting the notion of an anomalous experience continuum (Mitchell et al., 2017). Test re-test reliability, conducted with 96 participants, showed that the MUSEQ had stable internal consistency over time (tests 6 months apart).

The MUSEQ consists of 43 items, with each item rated on a 5-point Likert scale from 0 (“Never – Never happened”) to 4 (“Frequently – At least monthly”). MUSEQ items can also be split into six different modality-based factors: auditory (7 items), visual (8 items), olfactory (8 items), gustatory (8 items), bodily sensations (8 items), and sensed presence experiences (4 items). Items explore various anomalous experiences under each modality, for example: “Sounds were louder than they would normally be” (auditory); “I thought of a smell and I could almost smell it for real” (olfactory); “I have felt the presence of a relative or friend who has passed away” (sensed presence). The items under each modality were created to represent a wide range of experiences, from broad sub-clinical sensory experiences (such as “My eyes have played tricks on me”) to hallucinations (such as “I saw people, faces, or animals, and then found that nothing was there”). The original MUSEQ study found that all factors were positively inter-correlated, suggesting that greater endorsement of items in one modality was associated with greater endorsement of items in other modalities. (The full MUSEQ questionnaire can be seen in **Appendix L**).

4.2.2.2 Psychophysical task

4.2.2.2.1 Pattern Glare (PG) task

The same stimuli and procedure for the PG task were used as in the previous chapters.

4.2.2.3 EEG procedure and paired-click task

EEG was recorded using an ANT Neuro eegosports™ amplifier, 64-channel AgCl ANT Neuro Waveguard caps, and LE-200 eego software (v. 1.6.1, ANT Neuro). A custom montage was used to record from 8 of the available 64 electrode locations: FPz, M1, M2, Cz, Pz, FCz, C5, C6. EEG was recorded continuously at a 2048Hz sampling rate. Online recordings used a common reference CPz which was later re-referenced offline to the mastoid electrodes. All impedances were reduced to ≤20kΩ before recording began. Data was high-passed at 0.3Hz and low-passed at 30Hz.

The paired-click task involves participants listening to brief (10ms) auditory "clicks" (white noise, generated using Matlab) through headphones, presented in pairs (Stimulus 1 (S1) and Stimulus 2 (S2)). For the paired-click task, auditory stimuli were presented in one block using an auditory data file generated from a custom Matlab script. S2 was presented after a randomised delay of 400ms, 600ms, or 800ms after S1 presentation. A total of 300 click pairs were presented with 5s inter-stimulus interval (total task time = 28mins 30s, approximately 100 pairs with each delay type). Clicks were presented binaurally through headphones at 55dB.

EEG data was collected in a sound-proofed chamber to reduce noise interference as much as possible. The temperature of this chamber was maintained at a comfortable level via the in-built cooling system to prevent participants perspiring, which can cause problems with EEG recording (Light et al., 2010). During the paired-click task, lights in the booth were switched on to reduce participant fatigue or sleepiness. During EEG recording, participants were asked to stay awake, alert, and as still and relaxed as possible (to reduce electrical interference from muscle movements).

Participants sat in a comfortable chair in front of a computer monitor in the sound-proofed booth. Headphones were fitted and adjusted for participant comfort and to ensure the speakers were aligned directly over participant's ears for good sound transfer. The top band of the headphones was pulled away from the EEG cap as much as possible so that it did not rest on top of the cap and introduce noise into the EEG signal. Before beginning the main experiment, the sound stimuli were briefly played to participants to ensure they could hear the stimuli clearly. The task was explained to participants and they were given the opportunity to ask questions. Once participants were comfortable and ready to begin, the experimenter left the room and the door to the sound booth was closed to reduce external noise interference. The auditory stimuli file was then played whilst EEG data was recorded. Participants watched a film or television show of their choice, without sound but with subtitles, for the duration of the paired-click task (similar to previous experiments; see Graux, Bidet-Caulet, Bonnet-Brilhault, Camus, & Bruneau, 2014). This served to keep participants awake and alert for the duration of the

experiment, without directing their attention explicitly to or away from stimuli. Participants were told that they did not have to actively attend or ignore stimuli. This setup is in line with conventional repetition suppression paradigms that do not explicitly manipulate attention (Rosburg, 2018).

During recording, monitors placed within and without of the booth allowed the researcher and participant to communicate if needed, and for the researcher to observe participants within the booth to ensure accordance with task instructions (for example, that participants were alert and not moving excessively) and participant wellbeing. Signal quality was also monitored throughout data collection to ensure that any interference or issues were recognised and dealt with immediately.

4.2.2.4 Other

PG task stimuli were presented on a Dell P2210 20” monitor (30x47.5cm), 1680x1050 screen resolution, 59Hz refresh rate. The present study employed the same computerised version of the PG task used in previously published experiments (Braithwaite, Mevorach, et al., 2015). Both tasks were run using custom E-Prime 2.2 and Matlab programs in a sound-proofed room. For the PG task, the main source of illumination was the computer monitor, and participants used the keyboard and mouse to input task responses. For the repetition suppression task, participants were not required to make any responses to task stimuli.

4.2.3 Design and Procedure

All participants completed all study measures (questionnaires, tasks, and EEG recording).

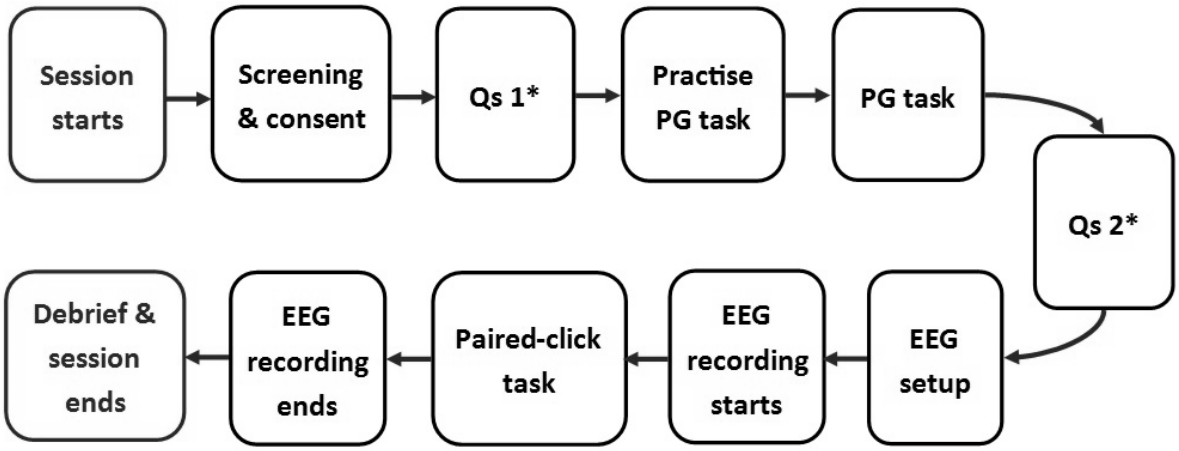

Figure 4.2 – Procedure of the current study. Participants were first screened, and eligible participants gave informed consent. Questionnaires were split into two blocks to reduce participant fatigue (*Qs 1 & 2 = blocks 1 and 2). The order and number of questionnaires (CHi-II, CAPS, MUSEQ) in each block was randomised for each participant. Before EEG, participants completed the PG task (practise and main). The EEG recording system was then set up. After a brief initial baseline recording period (of eye blinks, facial muscle movement, etc. for use in artifact removal), participants were moved to the sound-proofed booth and the paired-click task was explained. EEG was recorded continuously whilst participants completed the paired-click task. Finally, participants were debriefed.

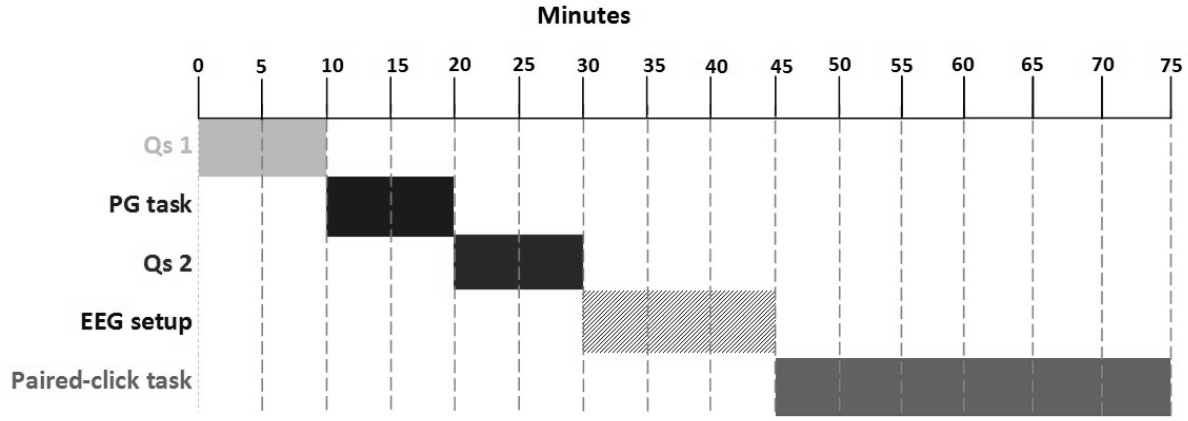

Figure 4.3 – Timings of the main components of the current study.

4.2.4 Data analysis

4.2.4.1 Questionnaires

The same procedure for scoring the CAPS was used as in the previous two chapters.

To score the CHi-II, frequency and intensity dimensions were pooled across questions for analysis. Mean CHi-II total and factor scores were calculated by dividing total scores by the number of questions (maximum score per question = 12, score range = 0 – 312).

To score the MUSEQ, scores were pooled across questions to give an overall score (maximum score per question = 4, score range = 0 – 172). Individual MUSEQ factors were not explored (due to small sample size and so limited power).

Corrected means were calculated for all questionnaire subscales by multiplying raw factor scores by the ratio of factor questions to total questions. This calculation prevents inaccurate score comparisons by accounting for the fact that there are differing numbers of questions per factor.

4.2.4.2 Pattern glare task

The same procedure for analysing PG task data was used as in the previous two chapters, with the exception of splitting the sample into “pattern glare” (positive M-HΔ ratings) and “no pattern glare” groups (zero or negative M-HΔ ratings) using M-HΔ ratings. The small number of participants in the current study precluded such a split. In the study design phase, comparisons in all chapters and studies were planned to be continuous, based on previous work finding continuous relationships between trait and state measures of anomalous experience in both non-clinical (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Broglia, Brincat, et al., 2013; Braithwaite, Mevorach, et al., 2015; Croft et al., 2001a; Gooding et al., 2013) and clinical samples (Gooding et al., 2013; Laurent et al., 1999; Rosburg, 2018b; Roth et al., 1981; Thoma et al., 2017). The PG split conducted in the previous two chapters was a later addition recommended by a manuscript reviewer, well after data collection for the current chapter was complete. Further, the number of participants recruited for the current chapter was based on previous work exploring relationships between repetition suppression measures and anomalous experience questionnaires. A PG-split in the current chapter would produce a “pattern glare” group of only five participants; far too small for meaningful analysis.

In place of a PG split, a median split based on PG scores was considered. This would allow consideration of the PG variable as categorical rather than continuous, similar to the PG-split method outlined above. However, splitting the sample based on the median M-HΔ score of -8 resulted in two groups of n=13 with mean M-HΔ scores of -7.1 (σ = 21.6) and -8.3 (σ = 25.3). An independent samples, two-tailed t-test suggested that these group scores were not significantly different from each other (t(24) = .133, p=0.895) – and so such a split would also not produce any meaningful results. This general issue is further considered in the Discussion.

4.2.4.3 EEG data

Data were processed using the EEG Lab (Delorme & Makeig, 2004) and FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) Matlab toolboxes. The EEG data was first segmented into epochs of 1100ms, starting 100ms before the S1 stimulus onset and ending 1000ms post-stimulus onset. Next, movement, eye-blink, and other artifacts were removed by screening channels for extreme values (-75 to +75μV threshold) and manual visual inspection of data, leaving 93% of data to be included in waveform averaging. The EEG data was then segmented again to 400ms epochs taken around S1 and S2 onsets, starting 50ms before stimulus onset and ending 350ms post-stimulus onset. The P50, N1, and P2 components were taken from the FCz electrode using average mastoid reference. P50, N1, and P2 amplitudes were defined as the largest peak amplitude with an interval of 40-60ms, 90-110ms, and 150-210ms after the first (S1) and second (S2) stimulus in each paired click respectively. The latency interval for calculating the mean

amplitude of these components was based on visual inspection of the data, independent of condition (i.e delay between S1 and S2) and stimulus type (S1 and S2). Average amplitudes at S1 and S2, per participant and condition (delay type), were extracted based on the intervals defined above.

For all repetition suppression analyses, S2/S1 ratios were used, as these give a more reliable indication of the relationship between the S1 and S2 data as compared to considering S1 or S2 alone (Chang et al., 2011; Park et al., 2015), or S2-S1 differences (Chang et al., 2011; Gooding et al., 2013). This is because S2/S1 ratios should reflect attenuated S2 responses regardless of S1 amplitudes (Boutros et al., 2011; Gooding et al., 2013), whereas S2-S1 differences are not proportional and may be more representative of or skewed by S1 responses (Boutros et al., 2011).

Suppression for P50, N1, and P2 was calculated as a ratio (S2/S1). For all ERPs, a larger ratio (further away from 0, positive or negative) indicates weaker suppression, whereas a smaller ratio (closer to 0) indicates greater suppression. Repetition suppression ratios are represented as percentages by calculating 100 x (1-(S2/S1)).

4.2.4.4 Comparisons between questionnaire and EEG data

Based on available data, it is possible to make the clear hypothesis that CHi-II scores would be correlated with repetition suppression in the current chapter. The CHi-II and repetition suppression measures are both strongly connected to the

concept of cortical hyperexcitability. Repetition suppression is a stable and well-evidenced measure of auditory cortical inhibition that depends on the E/I balance (Grill-Spector et al., 2006; Hirano et al., 2010; Javitt, 2015; Light et al., 2010; Patterson et al., 2008; Rosburg, 2018b; Thoma et al., 2017). The CHi and CHi-II questionnaires were constructed with the specific aim of bringing together visual experiences whose relationships with cortical hyperexcitability are well evidenced in the literature (see Braithwaite, Marchant, et al., 2015; Fong et al., 2019). In support of this, Chapter 2 evidenced a significant positive correlation between pattern glare and CHi scores. Other work has also provided similar evidence (Fong et al., 2019) and supported the relationship between elevated pattern glare scores and other anomalous experiences (Braithwaite, Broglia, Bagshaw, et al., 2013; Braithwaite, Mevorach, et al., 2015). Fong et al. (2019) suggested that the individual factors of the CHi-II may represent unique but related aspects of the general concept of cortical hyperexcitability. For example, both healthy and migrainer groups with high pattern glare scores tend to have high *AHE* factors scores, suggesting that pattern glare-type visual cortical hyperexcitability is associated with elementary visual hallucinations and somatic sensations such as nausea (Fong et al., 2019). However, the *HSVD* factor and pattern glare scores were only associated in a migrainer group (which may be related to hyperexcitability of trigeminovascular pain networks). The *DVP* factor was not associated with pattern glare at all – and these experiences may be driven by a "wider range of abnormal neural activities" than the *AHE* and *HSVD* factors (Fong et al., 2019). Therefore, it is possible that distinct relationships may also be apparent between the CHi-II factors and auditory excitability, as measured via repetition suppression.

However, a similarly clear hypothesis could not be made for the relationships between the CAPS / MUSEQ and repetition suppression measures. In contrast to the CHi-II, there is insufficient evidence in the literature to suggest that state auditory cortical hyperexcitability is as strongly related to CAPS- and MUSEQ-type experiences as to CHi-II-type experiences. Indeed, Chapters 2 and 3 of this thesis evidenced no relationships between a visual state measure of anomalous experience (pattern glare) and trait CAPS questionnaire scores. No previous studies have compared CAPS or MUSEQ scores with auditory repetition suppression measures. Further, both the CAPS and MUSEQ are also multi-modal questionnaires, which introduces a considerable degree of variability into comparisons – particularly with a uni-modal repetition suppression measure. Although the CAPS can be subdivided into “TLE” and “non-TLE” factors, both include experiences in several modalities. The MUSEQ has been fractionated into six uni-modal subscales (Mitchell et al., 2017), however the small sample size here does not provide the statistical power needed to make many multiple comparisons based on subscale splits. Therefore, in the current chapter, comparisons between repetition suppression and CAPS / MUSEQ total scores were exploratory only. Current results will be useful preliminary data to inform the direction of future work.

Effect sizes are indicated for relevant comparisons (as correlation coefficients, and Cohen’s *d* for pairwise t-tests due to equal sample sizes (Lakens, 2013)).

4.3 Results

As before, outliers for the PG task were defined as any total PG ratings for the low-frequency gratings in the sham (baseline) condition greater than $\bar{x} \pm 2SD$ for the total sample (two-standard deviation band method) (Bloom et al., 2009). No data needed to be excluded on this basis. Data from 1 participant was excluded due to an EEG data file error, so that the final sample included data from 26 participants; 23 (88%) female; 23 (88%) right-handed; $\bar{x}$ age = 21.5 years (σ = 3.2, range = 18-30).

4.3.1 Questionnaires

4.3.1.1 CHi-II

Descriptive statistics for CHi-II questionnaire scores are shown in **Table 4.1**. The current sample produced an overall mean CHi-II score of 59.5, with endorsement of items on all three factors.

	Overall	Heightened sensitivity & discomfort	Aura-like hallucinatory experiences	Distorted visual perception
Mean	59.5	13.5	2.6	1.3
SEM	8.2	1.8	0.5	0.3
σ	42.0	9.4	2.6	1.4
Range	144	33.7	8.4	5.2

Table 4.1 – Descriptive statistics for CHi-II questionnaire total and factor scores. Each factor mean is corrected for the number of questions per factor.

	N	Overall	Heightened sensitivity & discomfort	Aura-like hallucinatory experiences	Distorted visual perception
25th	7	28.0	5.8	1.0	0.0
50th	6	46.5	10.5	2.0	1.0
75th	12	83.7	20.0	4.0	2.0
95th	1	149.5	33.3	7.7	5.0

Table 4.2 – CHi-II total and factor mean scores split by percentiles of CHi-II total score. Factor means are corrected for the number of questions per factor.

CAPS

Descriptive statistics for CAPS questionnaire scores are shown in **Table 4.3**. A mean total TLE score of 1.6 indicates a relatively low degree of this type of anomalous perceptual experience in the current sample.

	Mean total score	
	TLE	**Non-TLE**
Mean	1.6	2.1
SEM	0.3	0.5
σ	1.6	2.7
Range	5.8	8.1

Table 4.3 – Descriptive statistics for CAPS questionnaire scores. Each factor mean is corrected for the number of questions per factor. TLE = Temporal Lobe Experience factor; non-TLE = remaining questions.

Differences in CAPS factor scores were explored using a paired t-test. This suggested a significant difference between CAPS TLE and non-TLE scores ($t(25)= -3.56$, $p=0.002$, Cohen's $d=0.23$, $BF_{10}=23.7$), showing that participants endorsed significantly more non-TLE-type than TLE-type experiences.

4.3.1.2 MUSEQ

Descriptive statistics for MUSEQ questionnaire scores are shown in **Table 4.4**. The current sample produced an overall mean MUSEQ score of 36.6, with endorsement of items on all factors. Sensed presence was the rarest experience, with only two participants endorsing questions on this factor.

	Sum	Auditory	Visual	Olfactory	Gustatory	Bodily sensations	Sensed presence
Mean	36.6	1.5	1.4	1.0	1.1	1.3	0.2
SEM	5.6	0.2	0.2	0.2	0.2	0.2	0
σ	28.6	0.9	1.1	1.2	1.2	1.2	0.2
Range	101.1	3.3	3.9	3.7	4.7	4.7	0.6

Table 4.4 – Descriptive statistics for MUSEQ questionnaire total and factor scores. Each factor mean is corrected for the number of questions per factor.

4.3.1.3 Pattern glare

Descriptive statistics for pattern glare scores are shown in **Table 4.5.** To explore PG scores further, delta values were calculated between the scores for the medium frequency minus the high frequency gratings (**M-HΔ**). Only five participants had a M-HΔ score ≥ 1, indicating a fairly low incidence of pattern glare in the current sample.

	Mean AVD intensity		
	Medium	**High**	**M-HΔ**
Mean	34.0	41.7	-7.7
SEM	8.0	8.3	4.5
σ	40.8	42.4	23.1
Range	200	168	107

Table 4.5 – Descriptive statistics for mean total AVD intensity scores.

4.3.1.4 Questionnaires and pattern glare

Spearman's correlations suggested no significant relationships between questionnaire and pattern glare scores (see **Table 4.6**).

	Pattern Glare M-HΔ
CHi-II mean total	-0.20
CAPS mean total	0.04
MUSEQ mean total	-0.02

Table 4.6 – Spearman's correlations between questionnaire total scores and pattern glare M-HΔ scores. None of the relationships were statistically significant.

4.3.2 Repetition suppression

ERPs were grand averaged across all participants and trials, for each condition.

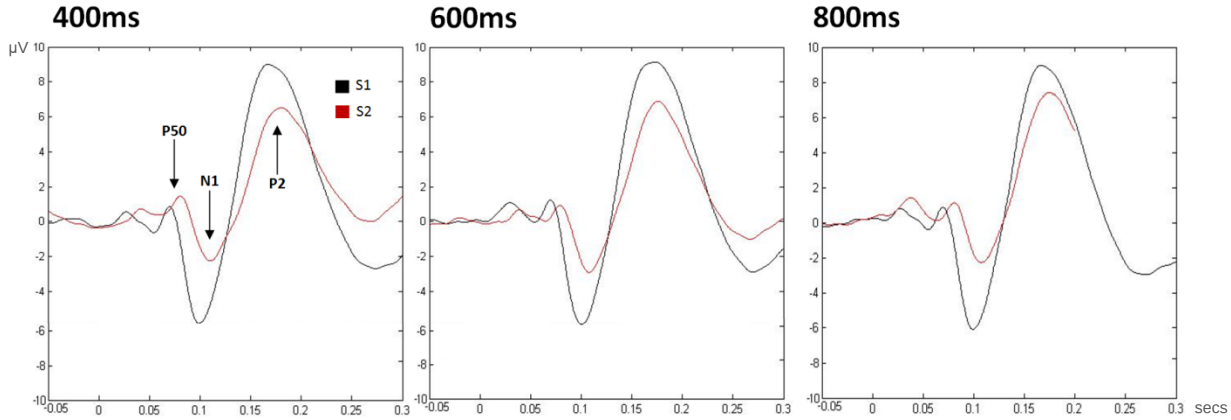

Figure 4.4 – Grand mean averaged ERPs in each condition (400ms, or 600ms, 800ms delay between S1 and S2), showing P50, N1, and P2 components.

Cook's distances were calculated for all ratio data in all components. Two outlier values were identified in the P50 data (Cook's distances ≥ 1) from two participants; one with a ratio of 704.7 in the 400ms condition, and one with a ratio of -76.0 in the 600ms condition. These outliers were removed from further P50 analysis. No outliers were identified in the N1 and P2 data (all Cook's distances < 1). **Table 4.7** shows descriptives for P50, N1, and P2 ratio data (with outliers removed). P50 standard deviations and ranges demonstrate this data was highly noisy as compared to N1 and P2 data.

	P50			**N1**			**P2**		
	400	**600**	**800**	**400**	**600**	**800**	**400**	**600**	**800**
Mean	0.2	0.9	1.1	0.2	0.9	0.4	0.8	0.8	0.9
SEM	0.4	0.7	0.5	0.1	0.5	0.1	0.1	0.1	0.0
σ	2.2	3.3	2.4	0.5	2.4	0.4	0.5	0.3	0.2
Range	9.9	18.6	10.2	2.5	13.2	1.8	2.5	1.8	0.9

Table 4.7 – Descriptive statistics for P50, N1, and P2 ratio data.

Three separate repeated measures ANOVAs were performed for each of the P50, N1, and P2 components (in line with previous work: Rentzsch et al., 2015) to explore the relationships between condition (400ms, 600ms, or 800s ISI / delay between stimulus pairs) and stimulus (S1, S2) EEG amplitude data.

4.3.2.1 P50

The assumption of sphericity was met for both condition (χ^2 (2) = 3.405, p=0.182) and the condition x stimulus interaction (χ^2 (2) = 4.604, p=0.100).

ANOVA results suggested no significant main effect of condition (ISI) (F(2,50) = .573, p=0.567, BF_{10} = 0.01), but a significant main effect of stimulus (S1 or S2) (F(1,25) = 8.078, p=0.009, Cohen's d=-0.56, BF_{10} = 17.07). This suggests no difference in amplitudes as a function of condition, but a significant difference in amplitudes as a function of stimulus (i.e. first and second presentations). There was no significant interaction between condition and stimulus (F(2,50) = 1.338, p=0.272, BF_{10} = 0.33), suggesting no differences in S1 and S2 amplitudes as a function of time between their onset.

Figure 4.5 shows the mean and spread of suppression ratios in the 400ms, 600ms, and 800ms delay conditions for the P50 ERP.

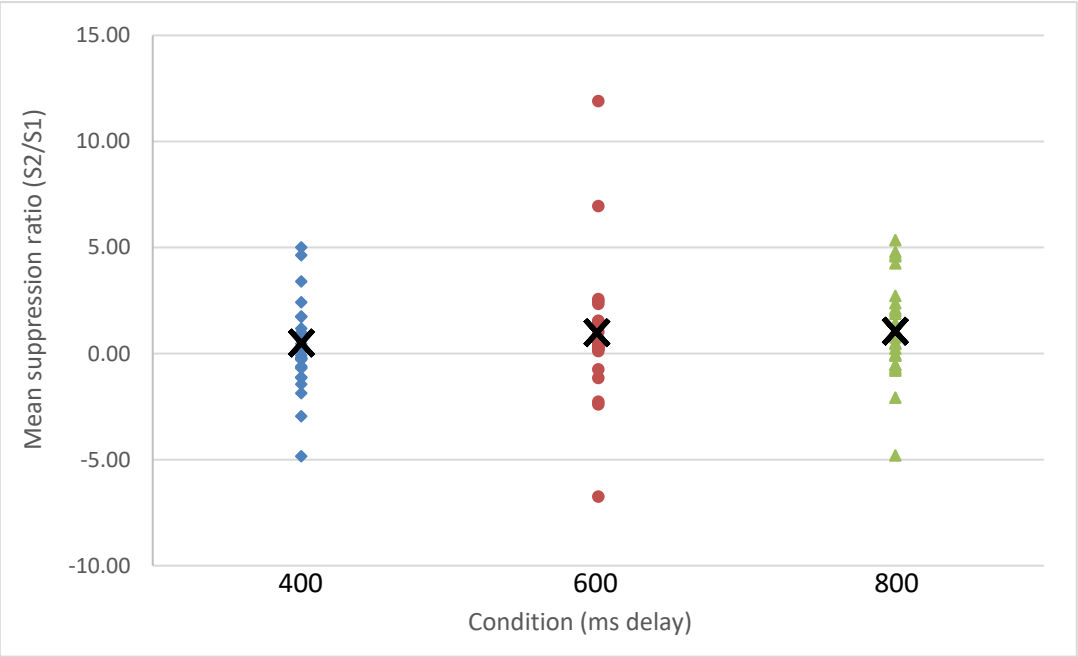

Figure 4.5 – Mean suppression ratios (S2/S1) for all participants in the 400ms, 600ms, and 800ms delay conditions for the P50 ERP. X = condition mean. A larger ratio (further away from 0, positive or negative) indicates weaker suppression, whereas a smaller ratio (closer to 0) indicates greater suppression. The two outlier P50 ratios (as indicated by Cook's distances ≥ 1) are not shown in this figure to improve readability (as these extreme values significantly altered the scales and display).

4.3.2.2 N1

The assumption of sphericity was met for both condition (χ^2 (2) = 3.157, p=0.207) and the condition x stimulus interaction (χ^2 (2) = 0.866, p=0.649).

ANOVA results suggested no significant main effect of condition (i.e. ISI between tones) (F(2) = 1.402, p=0.256, BF_{10} = 0.08), but a significant main effect

of stimulus ($F(1) = 76.88$, $p<0.001$, Cohen's d=-1.72, BF_{10} >1000). Again this suggests no difference in amplitudes as a function of condition, but a significant difference in amplitudes as a function of stimulus (i.e. first and second presentations). There was no significant interaction between condition and stimulus ($F(2) = 1.033$, $p=0.363$, BF_{10} =0.19), suggesting that there was no difference in the amplitude of the S1 and S2 as a function of time between their onset.

Figure 4.6 shows mean and spread of suppression ratios in the 400ms, 600ms, and 800ms delay conditions for the N1 ERP. On average, S2 responses were suppressed by 77% at 400ms delay, 63% at 600ms delay, and 73% at 800ms delay.

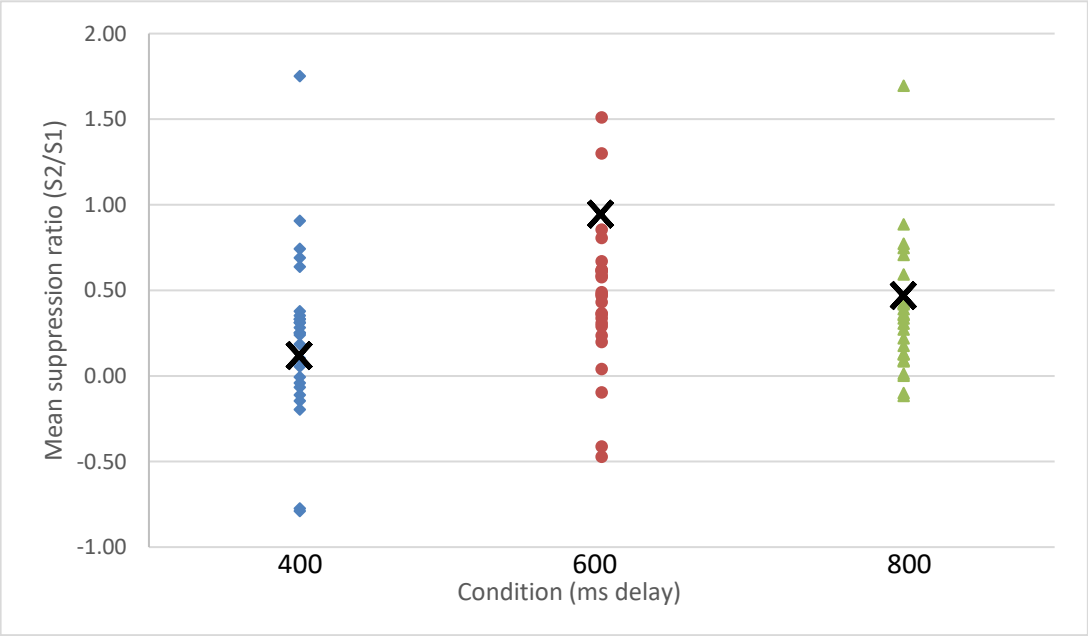

Figure 4.6 – Mean suppression ratios (S2/S1) for all participants in the 400ms, 600ms, and 800ms delay conditions for the N1 ERP. X = condition mean. A larger ratio (further away from 0, positive or negative) indicates weaker suppression, whereas a smaller ratio (closer to 0) indicates greater suppression. No outliers were identified in N1 data (all Cook's distances < 1).

4.3.2.3 P2

No outliers were identified in the data by Cook's distances (all Cook's distances < 1). The assumption of sphericity was met for both condition (χ^2 (2) = 0.325, p=0.850) and the condition x stimulus interaction (χ^2 (2) = 1.330, p=0.514).

ANOVA results suggested no significant main effect of condition (F(2) = 2.235, p=0.118, BF_{10} =0.12), but a significant main effect of stimulus (F(1) = 33.99, p<0.001, Cohen's d=1.14, BF_{10} >1000). Again this suggests no difference in amplitudes as a function of condition, but a significant difference in amplitudes as a function of stimulus (i.e. first and second presentations). Interestingly, here we did find a significant interaction between condition and stimulus (F(2) = 3.880, p=0.027, BF_{10} =2.17). This suggests significant differences in S1 and S2 amplitudes as a function of the time between their onsets.

Post-hoc paired t-tests suggested significant differences between S1 and S2 mean amplitudes in all conditions (400: t(25) = 4.516, p<0.001, Cohen's d=0.89, BF_{10} = 210.05; 600: t(25) = 4.401, p<0.001, Cohen's d=0.86, BF_{10} = 160.65; 800: t(25) = 3.644, p=0.001, Cohen's d=0.72, BF_{10} = 28.70, Bonferroni corrected p value ≤0.017). There were no significant differences in S1 amplitudes between conditions, however S2 amplitudes were significantly different between the 400ms and 600ms versus 800ms conditions only (400/800: t(25) = -2.870, p=0.008, Cohen's d=0.56, BF_{10} = 5.56; 600/800: t(25) = -2.893, p=0.008, Cohen's d=0.57, BF_{10} = 5.83; Bonferroni corrected p value ≤0.008).

Figure 4.7 shows mean and spread of suppression ratios in the 400ms, 600ms, and 800ms delay conditions for the P2 ERP. On average, S2 responses were suppressed by 29% at 400ms delay, 30% at 600ms delay, and 13% at 800ms delay.

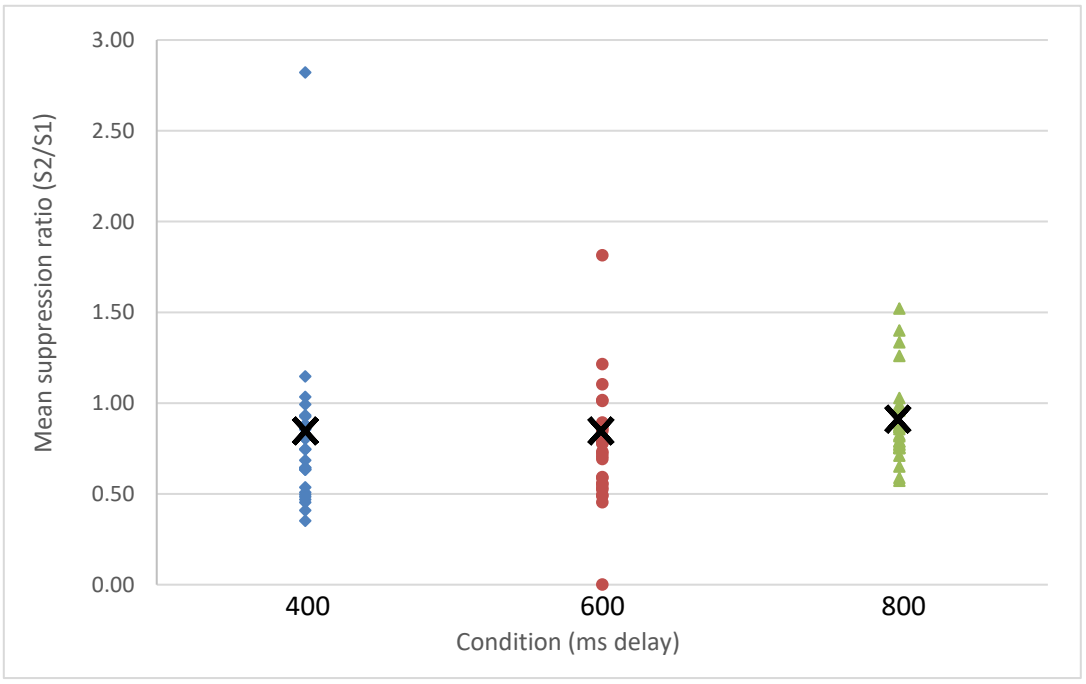

Figure 4.7 – Mean suppression ratios (S2/S1) for all participants in the 400ms, 600ms, and 800ms delay conditions for the P2 ERP. X = condition mean. A larger ratio (further away from 0, positive or negative) indicates weaker suppression, whereas a smaller ratio (closer to 0) indicates greater suppression. No outliers were identified in P2 data (all Cook's distances < 1).

4.3.3 Correlational analysis

As the above P50 data was noisy and did not follow the expected suppression pattern, this data was not analysed further. For the N1, as no significant differences were observed for condition or stimulus, ERP data was

collapsed across all conditions for further analysis. For the P2, as significant differences were observed between the 400/600ms and 800ms conditions but not between the 400 and 600ms conditions, ERP data was collapsed across the 400ms and 600 conditions (P2_a), with 800ms condition data (P2_b) analysed separately.

4.3.3.1 Repetition suppression and CHi-II

Cook's distances suggested two outliers (Cook's distance >1) for linear correlations between CHi-II factor scores and S2/S1 ratios in one participant's data. This participant's data was subsequently removed from all further analysis.

Spearman's correlations between total CHi-II factor scores and S2/S1 ratios suggested two significant relationships (see **Table 4.8**), between the *HVSD* factor and P2_b S2/S1 ratio ($r(26) = -0.446$, $p = 0.026$, $BF_{10}=1.61$), and between the *DVP* factor and P2_a S2/S1 ratio ($r(26) = -0.601$, $p = 0.001$, $BF_{10}= 7.16$) (see **Figure 4.8**). Only the latter survived Bonferroni correction for 12 tests to $p<0.006$.

		HVSD	AHE	DVP
N1	Coefficient	-.066	.174	.183
	Sig. (2-tailed)	.759	.405	.381
P2_a	Coefficient	-.326	-.349	**-.601****
	Sig. (2-tailed)	.112	.087	**.001**
P2_b	Coefficient	-.446*	-.081	-.072
	Sig. (2-tailed)	.026*	.933	.731

Table 4.8 – Table of Spearman's correlation coefficients and p values for comparisons between CHi-II factor scores and EEG S2/S1 ratio scores N1 (pooled across all delay conditions), P2_a (pooled 400ms and 600ms delays), and P2_b (800ms delay) components. *p<0.05, **p<0.001. Bolded statistics survived Bonferroni correction for 12 tests to p<0.006.

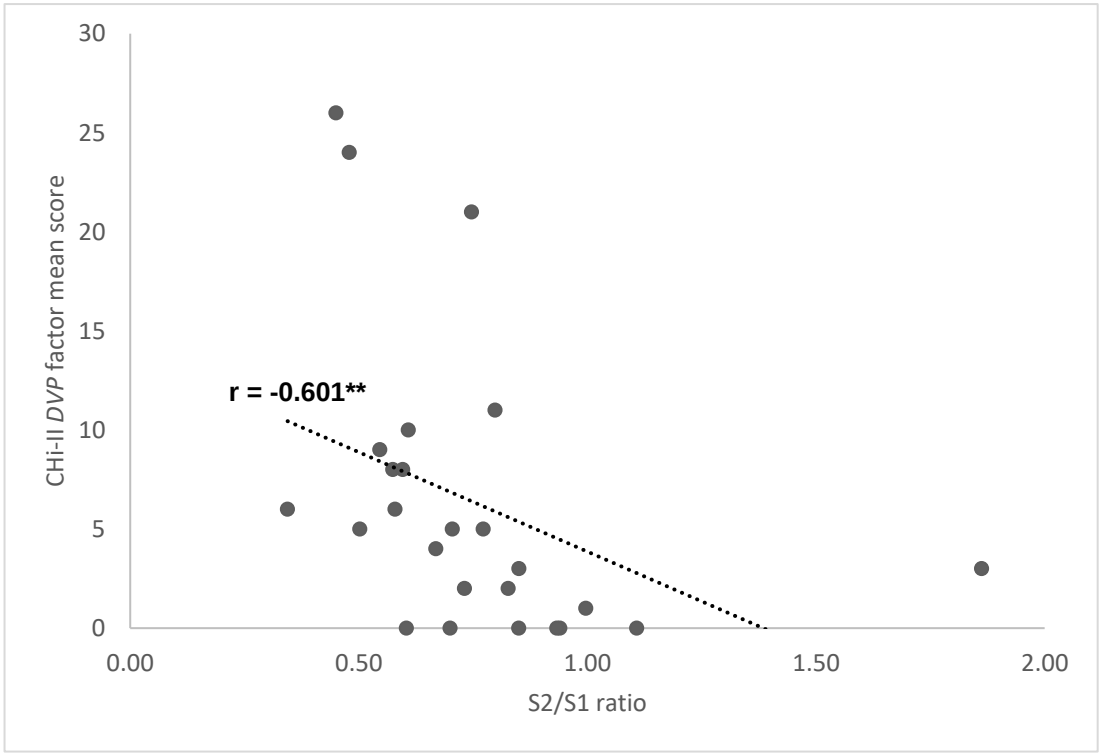

Figure 4.8 – Scatter plot of relationship between CHi-II *DVP* factor total score and S2/S1 ratio for the EEG P2_a component (pooled 400ms and 600ms delay condition data). As CHi-II *DVP* factor score increases, S2/S1 ratio tends towards 0 – i.e., higher scores on the *DVP* factor are associated with greater S2 suppression (relative to S1). ** p<0.001. The two identified outliers (Cook's distance >1) were not included in this analysis.

4.3.3.2 Repetition suppression and CAPS / MUSEQ

As outlined above, the relationships between repetition suppression and CAPS / MUSEQ measures were investigated with exploratory analysis only. Scatterplots did not indicate any relationships, with trend lines flat for all comparisons (see **Suppl. Figures 1-2 in Appendix N**).

4.3.3.3 Repetition suppression and pattern glare

Spearman's correlations between pattern glare M-HΔ scores and S2/S1 ratios for N1, P2_a, and P2_b components suggested no significant relationships between these variables ($p>0.05$ for all comparisons) (see **Suppl. Figure 3 in Appendix N**).

4.4 Discussion

This chapter aimed to explore whether hyperexcitability may be "supra-modal"; that is, whether the trait-state and state-state relationships observed within the visual modality in Chapters 2 and 3 could be extended to cross-modal comparisons (visual-auditory). This question was addressed by comparing an auditory, state "paired-click" measure (which indicates the degree of inhibition in auditory cortex) with visual trait and state measures of anomalous experience (questionnaires and a pattern glare task). These comparisons suggested a relationship between repetition suppression and distorted perceptual experiences, however this is to be taken with caution due to the sample size. Findings are discussed in more detail below.

4.4.1 Questionnaire measures

Overall, questionnaire data supports the notion that healthy individuals can experience anomalous perceptions traditionally be associated with clinical, neurological, or other medical diagnoses – an observation made by several studies in recent years (Heriot-Maitland et al., 2012; Pechey & Halligan, 2012; Preti et al., 2014). This study extends previous work by utilising two new measures (the CHi-II

and MUSEQ) and providing evidence of anomalous experiences from these measures in a healthy sample. These results lend further credence to the concept of an experiential psychosis continuum (Baumeister et al., 2017; Johns & van Os, 2001; van Os & Reninghaus, 2016).

The mean CHi-II score of 59.5 (17%) observed here suggests that the current sample are moderately predisposed to anomalous experiences associated with cortical hyperexcitability, supporting previous work conducted using an earlier version of the CHi (Braithwaite, Marchant, et al., 2015). This value was only very slightly lower than that reported by the original CHi-II paper (64.6; 18%) (Fong et al., 2019), despite differences in sample sizes (26 here versus 300+ in Fong et al.). This tentatively supports the notion of a fairly consistent overall level of these experiences in non-clinical undergraduate student populations. However, as the CHi-II has only at present been employed by Fong et al. (2019) and this thesis, further research is needed to clarify the frequency and phenomenology of these experiences in non-clinical groups. In the general population, the lifetime prevalence of anomalous experiences varies widely at 5-40% (Maijer et al., 2018; McGrath et al., 2016; Mitchell et al., 2017; Ohayon, 2000), but although several studies have explored the prevalence of hallucinations in very large samples (see Larøi et al., 2019; McGrath et al., 2016; Maijer et al., 2018; Ohayon et al., 2000), these have not focused on experiences that have been empirically linked to cortical hyperexcitability in the literature. A widescale survey of general population samples using the CHi-II would provide valuable data for comparison with previous work, and much-needed information about the frequency and mechanisms of this

phenomenon in non-clinical groups, particularly if paired with more objective co-correlates such as fMRI.

The current sample experienced a rate of CAPS-type anomalous experiences comparable with some previous work (Lien et al., 2015). The CAPS aims to specifically measure experiences associated with temporal lobe disturbance, which “has been linked to almost every “stage” on the psychosis continuum” (Bell et al., 2006), and TLE-type were present in the current sample (albeit to a relatively low degree, as is expected in non-clinical groups), thus evidencing the presence of “psychotic-like symptoms” in a healthy sample and supporting previous work (Lien et al., 2015; Parra & Argibay, 2016).

An overall mean MUSEQ score of 36.6 was again slightly lower than that observed in the original MUSEQ study (50.5; Mitchell et al., 2017). In the current study, as expected, auditory and visual experiences were the most common, which contrasts with Mitchell et al. (2017) finding that auditory and bodily sensation experiences were the most frequent, followed closely by visual experiences. These findings support other research showing that anomalous experiences in the auditory, visual, and bodily modalities are most common in the general population (McGrath et al., 2016; Ohayon et al., 2000).

Interestingly, three participants here had MUSEQ scores above the mean score of the clinical group (79) from Mitchell et al. (2017). Similarly, Mitchell et al. also found a degree of overlap in the frequency distributions of their clinical and non-clinical groups, and this has been observed for other measures, such as the

CAPS, as well (Bell et al., 2011). Therefore, the MUSEQ and CAPS' ability to reliably discriminate clinical from non-clinical participants is not guaranteed, and current results further evidence an overlap in the frequency of anomalous experiences between these groups. To the best of the author's knowledge, this study is the first to use the MUSEQ in a new, non-clinical population since the original publication.

Due to the relative novelty of the CHi-II and MUSEQ measures, further work is needed to explore the relative frequency of different types of experiences in the general non-clinical population, and further comparisons with different clinical populations are needed. These measures also have slightly different aims. The CHi-II was developed with the specific aim of quantifying latent cortical hyperexcitability by exploring related visual experiences, building on the original CHi measure (Braithwaite, Marchant, et al., 2015). The MUSEQ was developed to provide a comprehensive measure of anomalous experiences across modalities, and give needed attention to modalities that are under-researched (such as olfactory, gustatory, and bodily sensation experiences) (Mitchell et al., 2017). Therefore variation in scores between these measures in expected, but requires further investigation. It is important that future work focuses on dissociating possible mechanisms and identifying how these may contribute differently to different anomalous experiences.

4.4.2 Pattern glare

The pattern glare task is argued to reflect latent cortical hyperexcitability of visual cortex (Fong et al., 2019), with positive and zero/negative M-HΔ differences

suggesting high and moderate/low visual irritability respectively (Evans & Stevenson, 2008). For the pattern glare task, an overall M-HΔ score of -7.7 suggests a relatively low degree of pattern glare and inferred visual cortical excitability in the current sample on average – which is to be expected in a non-clinical sample. Although there was also a wide range of M-HΔ scores (from -62 to +45) in the current sample, evidencing large variability in individual pattern glare experiences), most participants scored close to or below zero which suggests low pattern glare in the majority of this sample (see **Table 4.5**). Similar patterns have been seen in previous work. For example, Fong et al. (2019) used the same PG task and method of score calculation as in the current study, and found a similar mean M-HΔ score of -8 in the "low" pattern glare group of a non-clinical sample (whereas the "high" group score was 3.9). The bias in the current sample towards low pattern glare scores could be rectified in future by focusing on obtaining a sample that more equally represents low and high pattern glare scores, to enable more accurate comparisons with other measures.

4.4.3 Questionnaires and pattern glare

Current results suggested no significant correlations between any questionnaire measure and pattern glare M-HΔ scores, which contrasts with previous work (Braithwaite, Broglia, Brincat, et al., 2013; Fong et al., 2019). However, the lack of relationship observed here may be due to the relatively low levels of hyperexcitability in the current sample (as discussed above). Although Chapter 2 and previous work have found significant relationships between trait and state aberrant experience when considering these variables continuously (Braithwaite, Broglia, Bagshaw, et al., 2013; Brockhaus-Dumke et al., 2008; Croft

et al., 2001a; Park et al., 2015; Smith et al., 2013; Thoma et al., 2017), these used larger sample sizes and/or patient groups with very frequent or intense experiences. Therefore, collapsing pattern glare scores across the sample as a whole may have obscured possible relationships. Both Chapters 2 and 3, and Fong et al. (Fong et al., 2019), stratified samples into high and low pattern glare groups (indicating baseline excitability) to reveal nuances in trait-state relationships. However additional data is needed to clarify these relationships (see **Future research directions**).

4.4.4 Repetition suppression

4.4.4.1 P50

We did not observe a P50 suppression effect in our data set. In contrast to expectations, there was no suppression of S2 relative to S1 for any of the delay conditions when considering the sample as a whole. This is surprising, given that repetition suppression is a core feature of normal brain functioning (Gotts, Chow, & Martin, 2012; Grotheer & Kovacs, 2016).

Although experimental confounds such as use of medication and nicotine may have obscured the P50 signal (Patterson et al., 2008) by interfering with brain function and cognition (particularly the E/I balance (Bauernfeind et al., 2011; Grundey et al., 2013; Grundey et al., 2012; Thirugnanasambandam et al., 2011)), these factors were controlled for as far as possible in the current study. Any reports of recreational drug use, use of prescribed or unprescribed medication known to influence perception, or nicotine (in any form), precluded participation (although these were self-reported).

Failure to observe P50 suppression here may be accounted for by large variability in P50 responses in the current sample, particularly for the 600ms delay condition (see **Table 4.7**). Significant variability has also been observed in other studies examining P50 responses in both clinical and non-clinical groups (Patterson et al., 2008). This variability contributes to “noisy” data, which may be why the P50 has notoriously low test-retest reliability (Fuerst et al., 2007; Rosburg, 2018b). This, combined with small amplitude deflections for the P50 component (Rosburg, 2018), likely led to no clear suppression being observed here.

So are previous P50 findings reliable, and what does this imply for future research; should the P50 be used, or not? Might a different measure be more appropriate? It is likely that P50 deficits are more pronounced in clinical groups, and that these are due to factors such as drug or medication use, or illness chronicity (Ferreira-Santos et al., 2012; Hyun et al., 2011; Ranlund et al., 2014). Research does suggest that the P50 is not as reliable a measure as other components, such as the N1 and P2 (Rosburg, 2018a). However, it may be that these components simply have different relationships with anomalous experiences or other symptoms in different groups, such that P50 may be relevant in clinical but not non-clinical groups. However the current sample size is small, and so further work is needed to determine which components are the most reliable and which correlate with anomalous experiences specifically, in both clinical and non-clinical groups.

4.4.4.2 N1

In contrast to the P50, current results evidence clear suppression of N1 responses to S2 as compared to S1 for all delay conditions. However, there were no significant differences in suppression between conditions; S2 was suppressed to a similar degree across all conditions.

These results suggest intact and functioning repetition suppression in the current sample as a whole, which is expected given that the current sample consists of healthy individuals. Accordingly, a large meta-analysis suggested that N1 repetition suppression (as measured by S2/S1 ratios) is significantly impaired in patients with schizophrenia as compared to healthy controls (Rosburg, 2018). However, as other studies have shown a significant decrease in S1 but not S2 N1 response amplitudes in patients (as compared to controls), it is likely that the difference between these groups for the S2/S1 ratio is skewed by S1 differences. Therefore, it is not repetition suppression *per se* that is deficient in those with schizophrenia, but rather the initial response of the auditory cortex to S1 (Rosburg, 2018).

This deficit may be due to deficient or prolonged refractory periods (Rosburg, 2018), where incomplete recovery of the generators of the N1 component means that subsequent responses are weaker (Pereira et al., 2014). Interestingly, Rosburg (2018) suggests that these deficits and prolonged refractory periods may be associated with predisposition to hallucinations. Research suggests that auditory verbal hallucination symptoms are exclusively linked to N1 suppression, with no other symptoms (negative, cognitive, emotional, or degree of

hostility) being significantly associated (Rosburg, 2018). Usually, the N1 auditory cortex response is suppressed during talking, which may help to distinguish self- from other-generated sounds during speech (Wang et al., 2014). Further, it is possible that these phenomena may be linked by cortical hyperexcitability. If N1 response deficits are a result of prolonged refractory periods, then a general, persistently heightened level of excitability in the cortex would prevent complete neuronal recovery and result in weaker responses to stimuli. However, this is purely speculative, as these relationships have not yet been investigated in either clinical or non-clinical aberrant experience.

Data also suggest that the N1 response is not sensitive to the time delay between repeated stimuli, within the time windows investigated here. This is in line with expectations; the auditory N1 is known to display strong repetition suppression, and this is proposed to reflect the refractory periods of responding neurons in auditory cortex (Hsu, Hamalainen, & Waszak, 2014). Repetition suppression paradigms usually use an inter-stimulus interval (ISIs) of around 500ms (Boutros et al., 2011). Recently, Pereira et al. (2014) observed decreasing N1 response amplitudes with decreasing ISIs (6000, 3000, 1000, and 600ms) in a repeated single-tone paradigm (suggesting greater suppression with shorter ISIs). However, Pereira et al. did not specifically investigate the degree of N1 suppression at S2 for these ISIs, or any ISI below 600ms; indeed, little work has explored changes in repetition suppression with varying ISIs. Here, we evidence N1 suppression at three different but short ISIs (400, 600, and 800ms). It would therefore be interesting to further explore the limits of this effect by using additional ISIs (of, for example, from the earliest N1 subcomponent at 100ms post-stimulus

(Luck, 2014) up to 6000ms (as in Pereira et al., 2014)) or even 10s (at which point the initial N1 response strength is restored (Javitt, 2015)), to map the onset and decay of N1 suppression.

Furthermore, current results suggest that direct or focused attention to stimuli is not required in order to see this N1 suppression effect, as in the current study participants did not pay direct attention to the stimuli but instead listened passively. This supports previous work; Hsu et al. (2014), for example, found that the suppression of N1 in response to repeated stimuli was independent of attention, suggesting that N1 suppression reflects the spontaneous filtering-out of redundant sensory input (Grimm & Escera, 2012).

4.4.4.3 P2

There was also clear evidence of suppression of the P2 response to S2 relative to S1, across all conditions. Interestingly, for this ERP there were also differences in the degree of suppression between conditions. S2 was suppressed to a similar degree (relative to S1) in both the 400ms and 600ms delay conditions, however S2 was suppressed to a lesser degree in the 800ms delay condition. These results are again in line with expectations for a healthy sample with “effective” repetition suppression, with increasing “recovery” or “re-sensitising” of neuronal responses at 800ms. As above, this could be explained by refractory periods, where responses to closely repeated stimuli are suppressed or reduced due to incomplete recovery of the generators that underlie these ERP components, such that subsequent responses are weaker (Pereira et al., 2014).

A recent meta-analysis concluded that P2 amplitude reductions in response to single tones appear to be dependent on ISI, such that patients exhibit reduced P2 responses for shorter ISIs (relative to controls) but there is no difference in responses between patients and controls for larger ISIs (Ferreira-Santos et al., 2012) – perhaps as gating is “easier” for larger ISIs (as outlined above). It would therefore be interesting to investigate this ISI-dependent effect on P2 suppression in non-clinical groups with high and low predisposition to anomalous experiences, which has not yet been explored. This would build on work from Ranson (2014), who found that both increased schizotypy and experiences of non-clinical auditory hallucinations were associated with increased P2 amplitudes (in response to single tones), to determine if these relationships could be extended to experiences in other modalities and using measures other than schizotypy. Interestingly, Ranson (2014) observed that increased schizotypy and hallucination scores were related to greater P2 amplitudes in “listen-self” versus “listen-other” conditions, suggesting a bias towards internal signals at the expense of external ones.

With regards to attention, current results are broadly in line with previous work. Hsu et al. (2014) suggested that repetition suppression for P2 is observable when attention is moderate, abolished when attention is explicitly directed away from stimuli, and “masked” by the effects of attention when attention is intensely focused towards stimuli. As there was clear P2 suppression at 400 and 600ms ISIs in the current study, attention here was likely at the “moderate” level; participants were not explicitly instructed to either attend or ignore stimuli, but rather passively listen.

4.4.5 Repetition suppression and questionnaires

The current study found a significant negative correlation between S2/S1 ratio and CHi-II factor 3 (*DVP*), for the P2_a ERP component only (where P2 amplitudes in response to clicks in the 400ms and 600ms delay condition were pooled). This suggests that as CHi-II *DVP* score increases, S2/S1 ratio trends towards 0, implying that greater predisposition to perceptual distortions is associated with greater suppression of S2 relative to S1, for this component. (A BF_{10} statistic of 22 lends moderate support to this relationship, over the null hypothesis.) The DVP factor of the CHi-II specifically measures perceptual distortions, both visual and bodily (as it includes a question on out-of-body experiences). As such the DVP factor has been conceptualised as a measure of both interoceptive and exteroceptive perceptual distortion (Fong et al., 2019). Although the direction of this correlation contradicts the expectation that anomalous experiences are associated with *deficits* in repetition suppression, some previous work can elucidate these findings.

First and foremost, research has evidenced a relationship between anomalous experience and forward processing as indexed by the P2 component. As outlined above, the P2 component is thought to reflect the match or mismatch between predicted and actually-perceived states or events (Ferreria-Santos et al., 2012). A match may be indicated by suppressed P2, which helps to identify a stimulus as self-generated, whereas a mismatch may be indicated by enhanced P2, identifying a stimulus as other-generated (Timm, Schönwiesner, Schröger, &

SanMiguel, 2016). Errors in this processing (at the prediction or perception stages, or both) may lead to inaccurate self/other labelling.

These mechanisms may underlie current findings, with greater suppression of S2 indicating increased suppression of external signals in favour of processing internal ones. Accordingly, Sanmiguel et al. (2013) concluded that P2 suppression is a more direct measure of sensory predictions than N1 suppression, and aids the identification of self-initiated stimuli. As such, increased P2 suppression may bias processing away from external information towards internal stimuli, leading to decreased reality monitoring or "control" of perception by external stimuli. This may contribute to distortions of interoception, multi-sensory integration, and conscious experience; such as out-of-body experiences (which feature on the DVP factor). The role of P2 in such higher-level experiences makes sense given that generators of the auditory P2 likely reside in secondary (association) auditory cortices (Sanmiguel et al., 2013).

However, as the current study explored P2 repetition suppression as opposed to single tone responses, and for external sounds only, further work would be needed to clarify these relationships. Previous findings regarding the relationship between P2 responses and self/other-generated sounds are inconsistent (Knolle, Schröger, & Kotz, 2013; Wang et al., 2014). Also, some models of auditory hallucinations suggest that elevated resting state activity and hyperexcitability in the auditory cortex could interfere with forward processing, and lead to similar neural responses to self- and other-generated sounds, such that internally-generated sounds are interpreted as externally-generated (Northoff &

Qin, 2011; Ranson, 2014). Therefore, studies exploring ERPs in response to both internally- and externally- generated stimuli, and considering baseline excitability, are needed. This could be achieved by including a resting-state condition in future ERP studies, for example.

In contrast to the current findings, Gooding et al. (2013) found a positive correlation between auditory P2 repetition suppression and anomalous experiences; deficient P2 repetition suppression was associated with increased body-based perceptual aberrations, in a group of abstinent but cocaine-dependent patients (Gooding et al., 2013). However, this result is complicated by this "abstinent" status. In the short term, cocaine use increases cortical excitability and so promotes seizures and hallucinations (Boutros et al., 2005; Corominas-Roso et al., 2013). However, chronic, long term cocaine use (as seen in addiction) is known to decrease baseline cortical excitability by disrupting the balance between excitatory (Glu) and inhibitory (GABA) neurotransmitters – and this effect persists into abstinence (Boutros et al., 2005; Gjini, Ziemann, Napier, & Boutros, 2012; Hanlon et al., 2015). This suppression effect is thought to be a compensatory mechanism that protects against persistently enhanced excitability (mediated by increased intracortical GABA) (Boutros et al., 2005; Flavel, White, & Todd, 2012). Therefore, long-term use of and then abstinence from cocaine in Gooding et al. (2013) would have significantly influenced patients' baseline cortical excitability – which may explain the contrast between Gooding's study and the current findings. The link between *deficient* suppression and perceptual distortions in abstinent cocaine users may be moderated by a generalised *decrease* in cortical excitability. Reciprocally, the link between *intact* suppression and perceptual distortions in the

current healthy sample may be moderated by a generalised *increase* in cortical excitability. However, no firm conclusions can be made, as Gooding et al. did not control for baseline excitability or nicotine use (which has significant effects on cortical excitability: Brunelin, Hasan, Haesebaert, Nitsche, & Poulet, 2015; Grundey et al., 2013; Grundey et al., 2012).

Another possible explanation for this result is that the lack of S2 suppression in fact represents high “neural fatigue” in the responding neurons. That is, persistently heightened excitability in auditory cortex (expected in those predisposed to anomalous experience) leads to an extreme response to S1, followed by neural fatigue (reduced synaptic efficiency) and so an inability to respond to S2. This inefficient synaptic response would manifest as a decreased or suppressed response. This is known as the “neural fatigue” model of repetition suppression, where repeated stimulations exhaust the responsive capabilities of task- or stimulus-relevant neurons (Grill-Spector et al., 2006). Therefore here, P2 “suppression” may not represent active repetition suppression or suppression *per se,* but rather the degree of neural fatigue present. Under this explanation, persistently heightened excitability would be associated with both increased neural fatigue and predisposition to anomalous experience.

In line with this, Thoma et al. (2017) found that greater suppression of the N1 S2 was associated with more severe hallucinations, in patients with schizophrenia. The authors suggest two possible explanations. Intact or increased S2 suppression may occur as (i) a compensatory inhibition mechanism that attempts to reduce processing of stimuli that could trigger hallucinations, and/or (ii)

be a consequence of predisposition to anomalous experience, where processing of external stimuli is suppressed in favour of increased processing of internal stimuli (which could decrease reality-monitoring and self-other distinctions) (Thoma et al., 2017). In a similar vein, current results could be the consequence of both: (i) increased auditory inhibition, compensating for a heightened sensitivity to external stimuli that could contribute to anomalous experience, and/or (ii) increased suppression of processing of external stimuli in favour of internal events. Here, it would follow that greater predisposition to these experiences would result in greater compensatory inhibition.

With the exception of P2_a suppression and CHi-II *DVP* factor, none of the other comparisons between CHi-II factor scores and repetition suppression were significant. Therefore although previous work supports the logical possibility that individuals experiencing anomalous perceptions similar to the “positive” symptoms experienced by clinical groups may experience slight deficits across measures of repetition suppression (P50, N1, P2), albeit to a lesser degree than clinical groups, current results do not evidence this for all components – at least when considering these variables continuously.

The cross-modality comparisons made here between state and trait measures also have important implications. Here, trait *visual* perceptual distortions were correlated with state inhibition or neural fatigue in *auditory* cortex (which may reflect self/other predictions and/or perceptions). Therefore, it appears that relationships between trait anomalous experience and state excitability may be supra-modal; i.e. changes to the E/I balance in one sensory modality may influence

changes in other modalities. Previous work has suggested trait-state relationships within single modalities, such as between trait visual anomalous experiences and state hyperexcitability of visual cortex in non-clinical samples (Braithwaite, Mevorach, et al., 2015; Fong et al., 2019), and between trait auditory anomalous experience and state disinhibition of auditory cortex in patients with schizophrenia (as indexed by P50) (Smith et al., 2013). However, the current chapter provides tentative evidence of a cross-modal relationship between anomalous experience and changes to the E/I balance.

4.4.5.1 Repetition suppression and pattern glare

Similarly, there were no significant relationships between repetition suppression and pattern glare measures, suggesting that state auditory inhibition is not associated with state experiences of aberrant visual perception, in the current non-clinical sample. If hyperexcitability occurs as a general, brain-wide state, it may be expected that increased excitability in one modality would indicate increased excitability in another (discussed further in **Chapter 5, Future research directions**). However current results suggest this is not necessarily the case.

However, Smith et al. (2013) also found no relationship between state P50 deficits and state-based experiences of auditory hallucinations (as reported using a state-dependent hallucinations rating scale), in people with schizophrenia. The current study evidences a similar lack of relationship, now between modalities. Further, Smith et al. (2013) suggested that auditory repetition suppression may better indicate trait predisposition to, rather than state experience of, auditory

anomalous experience – which is supported by current results, but now cross-modally.

In contrast to this, Thoma et al. (2017) did observe state-state relationships in those with treatment resistant hallucinations; significant repetition suppression deficits across P50, N1, and P2 components were apparent during active auditory verbal hallucinations. However the contrast between Thoma and Smith et al.s' findings may be due to the type of state measure used, with Smith et al. using a questionnaire-based measure of state auditory hallucinations (and the current studying using a task-based measure of state visual anomalous experience). Therefore future research should seek to determine why there may be differences in state-state relationships depending on the methodology used. It may be that state-state relationships between measures of excitability and anomalous experience are only observable if these variables are measured simultaneously (such as in Thoma et al.'s study). This would somewhat control for the influence of other brain states and/or baseline activity (which vary widely from moment to moment) on conscious experience (as discussed in Chapters 2 and 3). Methodologically, the validity and applicability of different state measures needs to be assessed, for example by comparing data for questionnaire-, task-, and evoked potential-based measures.

Additionally, "state" indicators of abnormal perception (such as temporary activity changes in speech perception networks) are thought to be less stable than "trait" indicators of abnormal perception (as modulated by early rather than late areas), as these trait indicators can better discriminate between hallucinators and

non-hallucinators (Kühn & Gallinat, 2012). However so far this has only been evidenced for clinical hallucinators, and so it is vital that additional data on these indicators in non-clinical hallucinators is obtained for comparison.

4.4.5.2 Limitations

As little previous work has explored the relationship between anomalous experience and P2 *suppression* specifically, the possibilities outlined here are tentative. Intact repetition suppression is traditionally viewed as indicating an efficiently functioning brain, and so additional studies are needed to clarify how such suppression could instead be linked to dysfunctional processing and anomalous perception. These experiences are likely the result of several concurrent processes and/or deficits, and this study addresses just one of these.

One limitation of this chapter is the small sample size, which led to some comparisons being underpowered. Future experiments should recruit larger samples with a wide range of scores on anomalous experience measures, to explore whether trait-state relationships are truly continuous or are only apparent at “extremes” of these measures. The current sample size was determined through review of previous studies correlating EEG-based repetition suppression with questionnaire measures in both clinical and non-clinical groups. Healthy control groups had a mean sample size of 27 (see **Appendix O**). However, the trends identified here remain useful and will inform future work. Depending on the planned analyses in future work, power calculations should be used to determine an appropriate sample size. Larger samples could be stratified into subgroups (such

as low and high questionnaire or task scorers, using subscales where needed), or fractionated to make single-modality comparisons (such as comparing trait auditory or visual anomalous experience with auditory or visual ERPs). As cortical hyperexcitability and anomalous experiences are, by definition, rare in non-clinical as compared to clinical populations, future studies could also focus on recruiting non-clinical individuals with very frequent or intense anomalous experiences (which should be feasible, as surprisingly high percentages of non-clinical groups report such experiences (Waters & Fernyhough, 2017)).

4.5 Conclusions

As in the previous two chapters, this study provided evidence of healthy individuals experiencing anomalous perceptions in the absence of traditionally-predisposing factors (such as psychopathological, neurological, or other medical conditions). This supports a large body of emerging research on the psychosis continuum, where “psychotic-like” experiences such as hallucinations occur throughout the general population without necessarily being associated with psychosis or other psychopathologies.

With regards to ERPs, in contrast to other work, this study did not observe P50 suppression. This was likely due to large variability in P50 ratios across participants, which has also been observed in previous reviews of P50 suppression. However, repetition suppression was clear for the N1 and P2 ERP components across 400, 600, and 800ms delay conditions, indicating intact repetition suppression in this sample within the studied time window.

This chapter provided new evidence of differential relationships between trait and state measures of anomalous experience in a healthy sample. Results give tentative evidence that greater predisposition to anomalous experiences is associated with greater P2 suppression. Previous work has suggested that P2 suppression is associated with labelling stimuli as self-generated. Therefore here, increased P2 suppression may bias processing away from external stimuli and towards internal ones, which could lead to errors in source labelling or multi-sensory integration and so perceptual distortions (Thoma et al., 2017). These errors may be made more likely by baseline cortical hyperexcitability, which has been hypothesised to interfere with forward processing. The literature suggests multiple possible mechanisms for how increased P2 suppression could be associated with increased predisposition to anomalous experience. For example, neural fatigue may be responsible; where pre-existing heightened excitability leads to an extreme response to S1 followed by fatigue (reduced synaptic efficacy) and so an inability to respond to S2. It is also possible that increased inhibition may act as a compensatory mechanism for increased excitability and/or processing of stimuli that could potentially trigger hallucinations (Thoma et al., 2017). These results are, however, preliminary.

Results did not evidence a relationship between two state measures of visual anomalous experience and auditory cortex inhibition. This is broadly in line with previous work, which failed to observe state-state relationships within single modalities. However, further work is needed to explore these relationships more fully for within- and between-modality comparisons, which have not been

sufficiently studied in non-clinical groups predisposed to anomalous experiences for firm conclusions to be made here.

5 General Discussion

In this chapter, an overview of the thesis and the key findings from each chapter are given. Contributions to the literature and implications are then outlined, followed by limitations and strengths of the thesis. Future research directions are suggested, and the chapter is concluded with final remarks.

5.1 Thesis overview and key findings

There is currently limited knowledge about the neural mechanisms of anomalous experiences in non-clinical populations. This knowledge is particularly sparse for the visual modality, and possible relationships between modalities (such as visual-auditory) have also not been explored. The overall aim of this thesis was to address this significant gap by exploring whether cortical hyperexcitability of visual (Chapters 2 and 3) and auditory (Chapter 4) cortices was related to anomalous experiences across modalities, in three separate non-clinical samples. This section gives an overview of the empirical studies in each of these chapters, and summarises key findings.

5.1.1 Chapter 2

5.1.1.1 Overview

The aim of this chapter was to explore the contribution of visual cortical excitability to anomalous experiences in visual and other modalities, by

investigating the relationship between trait (questionnaire) and state (pattern glare) anomalous experiences under tDCS of extrastriate cortex (targeted by stimulating electrode site Pz). Trait questionnaires covered visual (CHi) and mixed modality (CAPS) anomalous experiences. A pattern glare task was used as a correlate of excitability; this task measures state anomalous experiences thought to be caused by hyperexcitability of visual cortex. This study explored whether those who are more predisposed to anomalous experiences during pattern glare (indicating higher baseline cortical hyperexcitability) would respond differently to tDCS. In this study, a sample of 86 non-clinical participants underwent 20 mins of single-blind anodal and sham tDCS of extrastriate cortex (anode at Pz and cathode at Cz). Twenty minutes after tDCS onset, participants completed a computerised pattern glare task. For analysis, the sample was split into non-PG (low/moderate excitability) and PG (high excitability) groups based on pattern glare scores.

5.1.1.2 Key findings

Chapter 2 suggested that state-based pattern glare scores were dependent on PG group, with significant differences in tDCS effects between groups. In the PG group, anodal stimulation *decreased* PG scores relative to sham. In the non-PG group, anodal stimulation *increased* PG scores relative to sham. This suggests that tDCS affected participants differently based on their state-based baseline excitability (indicated by PG scores).

Results also revealed significant correlations between state-based pattern glare scores and the trait-based “positive aberrations” factor of the CHi measure under sham and anodal stimulation, but only for those with high PG scores.

Therefore, higher state PG scores – indicating heightened baseline excitability – predict greater trait experiences of anomalous perceptions to some degree.

Together, these results suggest that trait screening and state measures may be useful for identifying individual differences that may impact tDCS efficacy. Considering even non-clinical samples as a whole may ignore potentially important differences in baseline excitability, which will influence tDCS efficacy and impact variable comparisons if not controlled for.

5.1.2 Chapter 3

5.1.2.1 Overview

Building on Chapter 2, the aim of Chapter 3 was to explore whether the relationship observed between visual cortical excitability and anomalous experiences in Chapter 2 could be extended to a different area of extrastriate cortex, BA 17-19 (stimulatory site POz). In this chapter, the relationship between trait (questionnaire) and state (pattern glare) anomalous experiences during tDCS over site POz was investigated. The same measures of trait (questionnaires) anomalous experience were used as in Chapter 2, to allow direct comparison between the results for these variables. However, it should be noted that as several tDCS parameters were changed from Chapter 2 to 3, tDCS results are not directly comparable between these chapters. In this chapter, a completely new sample of 79 non-clinical participants underwent single-blind anodal, cathodal, and sham tDCS brain-stimulation of a different extrastriate cortex location (anodal and sham

stimulation = anode at POz, cathode at Cz; cathodal stimulation = anode at Cz, cathode at POz). Given that results differed by stimulation condition and group in Chapter 2, a cathodal condition was included here to generate additional data points. To explore "online" effects of tDCS, as recommended by newer tDCS literature, participants completed the PG task five minutes after tDCS onset. This new sample was again split into non-PG (low/moderate excitability) and PG (high excitability) groups based on pattern glare scores, to explore whether those predisposed to anomalous experiences during pattern glare (indicating higher baseline cortical hyperexcitability) would respond differently to tDCS over a different cortical location.[13]

5.1.2.2 Key findings

As in Chapter 2, differential relationships between tDCS condition and PG groups were observed in Chapter 3 – this time using a completely different stimulatory montage. In contrast to Chapter 2, in the PG group, both anodal and cathodal tDCS appeared to have a *null* effect on PG experiences. In the non-PG group, both anodal and cathodal tDCS appeared to have an excitatory effect, increasing PG intensity. This again suggests that tDCS affected participants' PG experiences differently based on their baseline excitability (as indicated by PG scores).

[13] As other aspects of the stimulatory design were also changed to accord with newer tDCS literature and recommendations, it is important to note here that Chapter 3 was not intended as a direct replication of Chapter 2 over a different cortical area. These differences in design mean that the results of Chapters 2 and 3 cannot be directly compared, and any theoretical integration of these results as discussed here is currently speculative.

In contrast to the first study, however, results from this study did not suggest any relationship between state-based pattern glare scores and trait questionnaire measures of anomalous experience. Therefore, state pattern glare experiences, as manipulated by stimulation of site POz, cannot be used to predict trait anomalous experiences. This is in line with research showing that the mechanisms sub-serving state-trait relationships are mediated differently (Smith et al., 2013; Kuhn & Gallinat, 2012). It may be that "lower" or earlier areas in the visual hierarchy (BA 17-19; targeted by electrode at site POz) moderate state experience only, whereas "higher" areas such as BA 5 and 7 (site Pz) moderate the relationship between state and trait experience. Overall, these results again support using state measures as screening tools to identify individual differences that may impact tDCS efficacy at the time of testing. However, as noted in the Chapter 3 discussion, because Chapter 2 and 3 used different stimulatory montages and so cannot be directly compared, this integrated theoretical explanation of results is speculative at present.

Chapters 2 and 3 both evidenced a relationship between state experiences of pattern glare and altered state excitability (indicated by PG scores) across all participants, with two different tDCS montages both affecting participants differently depending on this state excitability. These findings support the notion that a hyperexcitable brain predisposes even non-clinical individuals to anomalous visual experiences, now extending beyond primary visual cortex into extrastriate cortex. These findings also highlight complex interactions between baseline

excitability and anodal versus cathodal tDCS effects, which require further clarification.

5.1.3 Chapter 4

5.1.3.1 Overview

Building on Chapters 2 and 3, the aim of Chapter 4 was to explore whether the trait-state relationships observed within the visual modality in the previous chapters could be extended to auditory cortex; that is, whether trait-state relationships exist between measures of visual and multi-modal anomalous experience, and auditory inhibition. This would suggest cross-modal interactions between these variables. As in previous chapters, trait and state anomalous experiences were measured using questionnaires and pattern glare respectively. To index state auditory cortex inhibition, an EEG-based “paired-click” paradigm was used to measure a form of sensory gating: repetition suppression. Deficits in repetition suppression are associated with cortical hyperexcitability (Grill-Spector et al., 2006; Hirano et al., 2010; Vlcek et al., 2014).

In this study, a new sample of 27 healthy participants underwent EEG recording to collect data on repetition suppression. Participants listened to 300 pairs of brief 10ms clicks, with click 2 randomly presented at a 400ms, 600ms, or 800ms delay after click 1 (such that there were 100 pairs of clicks per delay type). P50, N1, and P2 component peak amplitudes were analysed. Participants also completed the pattern glare task and questionnaire measures on trait anomalous experience. Alongside the CAPS measure, to build on previous chapters, an improved version of the CHi measure was used (the Cortical Hyperexcitability

index II (CHi-II; Fong et al., 2019)), and an additional measure of multi-modal experience was added; the Multi-modal Unusual Sensory Experiences Questionnaire (MUSEQ; Mitchell et al., 2017).

5.1.3.2 Key findings

In line with previous chapters, questionnaire scores evidenced experience of anomalous perceptions in a healthy sample. In agreement with previous work, data from the MUSEQ questionnaire suggested that auditory and visual experiences are most common in non-clinical samples.

Results did not evidence P50 repetition suppression in this sample, which is likely due to large variability in P50 amplitudes across participants. For the N1 and P2 components, significant suppression of S2 was observed across all delay conditions, indicating intact repetition suppression.

Correlational analyses comparing repetition suppression and pattern glare / questionnaire scores suggested only one significant relationship; a negative correlation between CHi-II *DVP* score and P2 component at 400ms and 600ms delays. This result suggests that greater state suppression of P2 is associated with increased trait predisposition to perceptual distortions (including OBEs), and provides a cross-modal link between changes to the E/I balance and anomalous experience. As P2 suppression is associated with distinguishing self-generated events and may bias processing towards internal stimuli, greater P2 suppression may lead to decreased reality monitoring and increased perceptual distortions. Cortical hyperexcitability may contribute to these experiences by interfering with

these processes (Ranson, 2014; Sanmiguel et al., 2017; Thoma et al., 2017). This extends previous work that has observed similar trait-state relationships within modalities only (Fong et al., 2019; Smith et al., 2013).

No state-state relationships between auditory inhibition and visual pattern glare were found. This accords with previous work which did not observe state-state relationships between auditory measures (Smith et al., 2013). Interestingly, Smith et al. suggest that auditory repetition suppression may better indicate trait predisposition to, rather than state experience of, anomalous perceptions – which is supported by the current findings. However a key determinant of whether state-state relationships are observed may be the method by which state experience is measured – and so this requires further research.

5.2 Contributions to the literature and implications

The contributions made by this thesis to the current literature are outlined below, including methodological and theoretical implications.

5.2.1 Evidence of anomalous experience in healthy populations (All chapters)

Chapters 2 to 4 provided substantial additional evidence for the occurrence of a range of visual (CHi, CHi-II, and pattern glare) and multi-modal (CAPS and MUSEQ) anomalous experiences in three new non-clinical samples. In Chapter 4, data was gathered on two recently developed measures of anomalous experience – the CHi-II (Fong et al., 2019) and the MUSEQ (Mitchell et al., 2017). At the time

of writing, this is only the second time that these scales have been used in empirical work after their initial publication. Chapter 4 provided exploratory comparisons between these scales and other correlates of anomalous experience and cortical inhibition, to explore their utility in this area of research.

These chapters also evidence anomalous experiences in non-clinical samples after screening for several potentially confounding factors that have likely influenced the results of previous studies on anomalous experience in both clinical and non-clinical groups. These include use of medication, nicotine, and other recreational drugs (which can contribute to anomalous experiences and interfere with cortical excitability) (Bauernfeind et al., 2011; Cowan et al., 2015; Grundey et al., 2013), cognitive dysfunction (which is common in those with long-term psychopathology / neurodegenerative disease), and extraneous effects of illness presence and chronicity. Previous findings on the neural correlates of anomalous experiences, particularly hallucinations in clinical groups, may be confounded by one or several of these variables. For example, abnormal dopamine synthesis has been observed in several studies on clinical hallucinations, however Howes et al. (2013) found that dopamine synthesis was not altered in healthy voice hearers as compared to controls. Therefore, changes to dopamine synthesis may not be directly involved in hallucination generation (Howes et al., 2013). This illustrates how restricting exploration of anomalous experience to clinical groups may confound our conclusions about their substrates.

5.2.2 Effects of tDCS stimulation over extrastriate cortex (Chapters 2 and 3)

The research outlined in this thesis contributes to knowledge on the effects of tDCS over extrastriate cortex, providing evidence that this method can manipulate cortical excitability and experiences of pattern glare in non-clinical samples. This extends previous work that has evidenced similar effects in non-clinical primary visual cortex (Braithwaite et al., 2015). Previous studies using fMRI have also evidenced hyperexcitability of extrastriate areas in migraine with aura (Huang et al., 2003, 2011). Together with the current work, this implies that manipulations of excitability in extrastriate cortex may be linked with anomalous experiences in both clinical and non-clinical groups.

Furthermore, methodologically, this thesis shows that tDCS is an effective and practical way of manipulating excitability in extrastriate visual cortex, with Chapters 2 and 3 tentatively evidencing specific effects of this stimulation for conscious experience dependant on the area stimulated. One implication of this is that tDCS is a useful method for exploring excitability changes in non-clinical participants, and that comparing responses to tasks during tDCS can reveal interesting individual differences in tDCS responses, which may be linked to baseline excitability.

5.2.3 Importance of baseline excitability (Chapters 2 and 3)

Chapters 2 and 3 provide evidence that baseline excitability interacts with tDCS and visual stimuli to produce differential effects. That is, state PG experience is affected differently by tDCS type (anodal, cathodal) depending on baseline PG

score; “high” and “low/moderate” PG groups appeared to respond very differently to tDCS (although these relationships could not be formally tested). These patterns of group differences, and the significant differences within groups, are here attributed to differences in baseline cortical excitability. Numerous studies have demonstrated that PG effects are cortically-mediated and indicate increased visual cortex excitability (Braithwaite, Mevorach, et al., 2015; Huang & Zhu, 2017; Huang et al., 2011). Therefore, the current results provide an important contribution to the literature on interactions between baseline excitability and tDCS efficacy, as well as expanding our limited knowledge of how these factors interact with hallucination proneness in non-clinical groups.

An important implication of these results is that brain stimulation experiments must give consideration to baseline excitability. Chapters 2 and 3 suggest that the PG task may prove a useful method for screening participants when conducting brain stimulation experiments on visual processing. The computerised PG task only takes ~7 minutes to run, with basic analysis being relatively straightforward, and so offers a quick and practical way to estimate and/or control for baseline excitability of visual and visual association cortex. Accounting for this will reduce the confounding influence of baseline excitability on experimental results, and enable more precise conclusions to be made about the brain mechanisms responsible for changes to conscious perception. As seen here, anodal stimulation is not necessarily “excitatory”, and cathodal stimulation is not necessarily “inhibitory” – as has been assumed in the tDCS literature until recent years (Bikson, Rahman, & Datta, 2012). Therefore accounting for baseline excitability will provide further insight into the mechanisms underlying tDCS and

task responsivity in different stimulation paradigms. It would be interesting to explore, for example, whether baseline excitability as indicated by the PG task could predict differential effects of tDCS for other types of task, such as working memory which has been shown to be influenced by baseline excitability (Hsu et al., 2016).

5.2.4 New perspectives on trait- and state- anomalous experience and cortical hyperexcitability (All chapters)

A further contribution of this thesis is new insight into trait-state relationships. In Chapters 2 and 4, a continuous relationship between trait and state measures of anomalous perceptions and cortical excitability was evidenced. This suggests that changes to the E/I balance (increased activity in extrastriate cortex and increased inhibition in auditory cortex) are associated with increased predisposition to anomalous experience. Furthermore, Chapter 2 suggested that trait and state anomalous experience were significantly related only for a group with high baseline excitability (indicated by pattern glare scores). However, such a relationship was not apparent in Chapter 3 – although excitability of a different area of extrastriate cortex was manipulated here and using a very different stimulatory design. Overall, these results suggest that trait-state relationships may vary depending on the sensory modality and/or associated networks being studied.

In line with and extending previous work (Smith et al., 2013), Chapters 2 and 3 together suggest the interesting possibility that relationships between trait and state anomalous experience within the visual modality may be mediated differently by activity in different extrastriate areas. Specifically, “earlier” visual

areas may moderate state anomalous experience, whereas “later” areas may moderate trait predisposition. Therefore, the degree of brain hyperexcitability present in specific cortical regions may differentially affect trait and state predispositions, even in healthy groups. Although this interpretation must be taken with caution due to the different stimulatory montages used in Chapters 2 and 3, this is a novel finding that requires further investigation.

Chapter 4 further contributes to our knowledge of trait-state relationships between modalities in non-clinical participants, with the novel finding that that auditory repetition suppression is related to trait predisposition to perceptual distortions specifically, in a non-clinical sample. Specifically, increased auditory inhibition as measured by the P2 component is associated with increased perceptual distortions. This extends findings from Chapters 2 and 3, and evidences some degree of supra-modal interaction between the networks involved in trait and state anomalous experience. Although these findings are tentative, it is particularly interesting that they evidence a link between two phenomena associated with self/other processing – the P2 component, and OBEs. It is possible that greater suppression of the auditory P2 component could bias processing towards internal stimuli, and lead to decreased reality monitoring and increased perceptual distortions. Background cortical hyperexcitability may contribute to these experiences by interfering with stimuli processing. Together with the other chapters of this thesis, these results suggest the interesting possibility that “extremes” of *either* excitation and/or inhibition could alter processing and contribute to perceptual distortions – but this hypothesis requires further research.

5.2.5 Utility of the CHi/CHi-II for predicting state anomalous experience (Chapters 2 and 4)

The significant trait-state relationships observed between pattern glare and CHi scores in Chapter 2, and between repetition suppression and CHi-II scores in Chapter 4, provide evidence of a relationship between cortical hyperexcitability and trait predisposition to anomalous experiences in non-clinical groups. This improves our ability to determine the types of experiences a healthy individual may be predisposed to, when their baseline excitability is high. Methodologically, this suggests that the CHi-II is likely to prove a useful correlate in studies of anomalous experiences, and offers a quick and practical way of gauging excitability in any group of participants. However, this thesis is among the first research to evidence these relationships, and so additional work is needed to verify the consistency of this effect and whether it can be extended to other cortical areas (within and between other modalities).

5.2.6 Continuity of experience, continuity of mechanism?

Overall, all three experimental chapters contribute support for the notion of a “fully dimensional” psychosis continuum of experience, where anomalous experiences are spread throughout the population and are not necessarily related to clinical or medical conditions (as supported by Nelson et al., 2013). This is an important contribution to this literature, as it further evidences the occurrence of these experiences in non-clinical samples across a range of modalities. These results also demonstrate that non-clinical samples can shed light on anomalous experience mechanisms, whilst avoiding many confounds expected when working

with clinical groups (such as hospitalisation, medication, and cognitive deficits) (Nelson et al., 2013).

Although additional evidence is needed to make firm conclusions, continuous trait-state relationships were observed in Chapters 2 and 4. Therefore, results lend some support the notion of a mechanistic continuum to match this "experiential" continuum. That is, a continuum of trait hyperexcitability may underlie a continuum of state anomalous experience (although this hyperexcitability may be localised or attenuated as compared to clinical groups).

However, Chapters 2 and 3 also showed that state-state relationships were observable only when considered discontinuously, as baseline excitability (indicated by pattern glare) predicted differing experiences of anomalous perceptions that were dependent on tDCS condition. It may be that the general relationship is continuous, but that specific types of anomalous experiences are more strongly associated with specific types or locations of cortical excitability. Considering state-state relationships continuously may therefore obscure subtle differences. Indeed, no state-state relationship between pattern glare and auditory repetition suppression was observed in Chapter 4 when considering these relationships continuously. To clarify this, further work should examine both anomalous experiences and changes to cortical excitability in more detail.

Previous work has suggested that increased spontaneous cortical activation in the sensory cortex corresponding to the modality of the hallucination is a unique candidate for a continuous mechanism between clinical and non-clinical groups

(Waters & Fernyhough, 2019). However, further work is needed to tease out subtle relationships and differences in these patterns when considering trait and state measures of anomalous experience, particularly cross-modally. This thesis suggests that there may be different mechanisms underlying trait versus state experiences.

5.3 Future research directions

5.3.1 Further explore relationships between "trait" and "state" anomalous experience

This thesis provides evidence for a trait-state relationship between predisposition to perceptual distortions and measures of cortical excitability (PG and repetition suppression). Studies exploring relationships between trait and state anomalous experience in healthy samples do not often analyse modality specific relationships and their implications. Studies relating repetition suppression to a wide range of anomalous experiences in non-clinical samples also remain scarce (e.g. Croft et al., 2001; Park et al., 2015). Pattern glare has received greater attention in non-clinical studies, however the exact mechanisms of these experiences have still not been explored in detail in non-clinical groups, which limits the conclusions that can be made about trait-state relationships. Several studies have investigated how repetition suppression is related to the general schizotypy syndrome (e.g. Wan, Crawford, & Boutros, 2006; Wan et al., 2007), but very few focus on "positive" symptoms such as hallucinations. Further, this thesis did not provide evidence for a state-state relationship between visual and auditory

measures of cortical excitability and anomalous experience. This accords with previous work that has not observed state-state relationships within the auditory modality (Smith et al., 2013). However, similar studies are few and far between.

To further clarify state-state relationships, it would be interesting to correlate state hallucinations and state *visual* repetition suppression. This could be achieved using fMRI, for example, with which previous work has observed both repetition suppression and enhancement in extrastriate visual cortex in response to repeated facial stimuli, in healthy volunteers (de Gardelle, Waszczuk, Egner, & Summerfield, 2013). Interestingly, De Gardelle found that signal suppression and facilitation were associated with “lower” and “higher visual regions, and bottom-up (prediction) versus top-down (prediction error) processes, respectively (de Gardelle et al., 2013). These findings highlight the need to explore cortical inhibition and excitation at different stages in processing hierarchies. Combining this with the research outlined above, future work could explore how state measures such as repetition suppression and enhancement are related to interpretation of external and internal signals, and whether these correlate with anomalous experience.

Future studies should seek to characterise relationships between a wider range of trait and state anomalous experience measures. Some research has explored the neural networks underlying both trait and state anomalous experiences (Kühn & Gallinat, 2012), however this work is focused on auditory verbal hallucinations in patients with schizophrenia. Additional work in other clinical groups and non-clinical samples (which allow for better control of the many confounding factors in patient research) will allow us to determine what networks

underlie trait predisposition and state experiences of different types of anomalous perceptions, how these networks interact, and potential trans- and extra-diagnostic similarities and differences. Possible methods for addressing this are explored below.

5.3.2 Systematically explore tDCS effects in non-clinical groups

This thesis evidences considerable complexity in the responses of non-clinical groups to tDCS and concurrent psychophysical tasks. Therefore, future research should systematically explore the effects of tDCS on conscious experience, such as through tasks indexing cortical excitability and/or anomalous experience (such as pattern glare or the simple flickering ring paradigm from Pearson et al., 2016). Stimulation parameters (such as site, duration, types), and whether stimulation is concurrent with the task or not (online vs offline), should be varied systematically to compare effects. Intensity could also be varied, however stimulation at 2mA tends to produce significantly more unwanted side effects (such as burning, tingling, itching) which impacts study blinding and participant comfort (O'Connell et al., 2012) – and so intensity should be varied cautiously. However, new computational methods for modelling current flow should also be used where possible to inform montage design (such as with *Spheres,* available at https://www.parralab.org/spheres/ (Dmochowski, Bikson, & Parra, 2012), or *Roast,* available at https://www.parralab.org/roast/ (Huang, Datta, et al., 2019) – see **Appendix H**), for example to account for how individual differences in brain architecture can influence current flow. For example, gyri and sulci morphology has considerable inter-individual variability and likely influences tDCS efficacy due to the differing orientations of the stimulated cells (Datta et al., 2009; Datta et al.,

2012). Therefore, computational modelling of current flow using anatomical scans will be useful for this future work (as in Huang et al., 2013).

5.3.3 Determine utility of methods for indexing state baseline excitability

Very few studies have explored the relationships between the E/I balance and non-clinical anomalous experience, and so this will be a key area of development for the future. To achieve this, we must establish methods for accurately determining E/I balances in human cortex, and for correlating these with psychological measures.

Based on the results of this thesis, PG task scores can be used to group participants and indicate likely variation in tDCS responsiveness – likely due to variation in baseline excitability between groups. However, additional research that compares group responses to additional tDCS stimulation paradigms and other tasks could inform us of the possible applications and limits of these for indicating state baseline excitability. As the PG task is visually-focused, it will be important to identify additional state measures applicable to other senses – such as the auditory repetition suppression paradigm used here. Visual repetition suppression paradigms are rare and inconsistent across the literature, however Jones (2016) developed a basic visual paradigm comparable to the auditory paired-click procedure that should prove useful for future work. Each trial of this task involves a white circle flashed twice on a black background, 50ms apart – similar to its auditory counterpart. Based on previous work and this thesis, accounting for baseline excitability would allow increased precision for detecting and

understanding relationships between brain activity and anomalous perceptions in non-clinical groups.

Further research on other methods of assessing excitation/inhibition levels in different parts of the cortex in non-clinical individuals would also be useful. Recommended standardised protocols would enable direct comparisons between studies. Although light deprivation has previously been employed to decrease phosphene thresholds by increasing baseline excitability (Boroojerdi, Bushara, et al., 2000), there is considerable inter-individual variation in changes to phosphene levels at different time points using this paradigm. One participant's threshold reduced by 10% and plateaued after 45 mins deprivation, but another's was reduced by 25% with no evidence of plateau even after 180 mins deprivation (Boroojerdi et al., 2000). Therefore this method does not increase excitability to the same degree across participants. Furthermore, it is not an indicator, but a manipulation, of excitability.

Spectroscopy also presents an intriguing possible method of modelling neurotransmitters related to the E/I balance (such as glutamate and GABA) in specific cortical areas. This has only been explored in clinical groups so far (Bridge et al., 2015; Zielman et al., 2017), and similar data on non-clinical groups who are predisposed to anomalous experience is needed for comparison.

Deep brain electrodes are useful for determining neural activity in clinical groups (such as where they have been implanted to control epileptic seizures or Parkinsonian temors), but this invasive approach is not possible in non-clinical

groups. One promising complementary method is measuring alpha-band power over occipital sites using EEG, as decreases in alpha power here correlate with decreased phosphene thresholds induced via TMS and so indicates increased excitability in healthy participants (Romei et al., 2008).

5.3.4 Further explore network activity and dynamics underlying hyperexcitability in healthy brains

Further to the above, it would be interesting to extend the current work through additional modality specific and cross-modal comparisons, which would require large samples that can be split into subgroups and still retain statistical power. In this thesis, visual-visual (as in Chapters 2 and 3) and visual-auditory (Chapter 4) comparisons revealed some significant associations, whereas visual-multimodal (Chapters 2 and 3) and auditory-multimodal comparisons (Chapter 4) did not. However, current data cannot determine whether this hyperexcitability is localised to visual cortex or generalised to other cortical areas. Therefore, there is a need to further explore excitability beyond single modality comparisons, and associated network dynamics in different areas of the human cortex, to understand possible reciprocal relationships and why cortical hyperexcitability in one modality may not necessarily extend or be related to hyperexcitability in another modality. This may be a consequence of the brain's homeostatic mechanisms, which likely maintain E/I balances within a workable range in different modalities / relevant sensory cortices, particularly in "healthy" brains (Adesnik, 2018; Yang & Sun, 2018). It may be that, in some cases, baseline or trait hyperexcitability is localised to one cortical region and is prevented from spreading by cortical homeostasis or architecture, and so may be restricted to affecting the corresponding modality. This

may be comparable to those who experience partial (localised) seizures, which tend to be associated with hallucinations in the corresponding modality only (Stafstrom, 1998). Alternatively, in other cases a spreading hyperexcitability may explain the presence of multi-modal, complex hallucinations – such as in the generalised hyperexcitability combined with cortical spreading depression seen in migraine (Mastria et al., 2018), or spreading seizures as part of TLE (Persinger & Makarec, 1987; Stafstrom, 1998). Further work is needed to determine how changes to network activity and dynamics influence uni- or multi-modal hallucinations in non-clinical groups. Additional research is also needed to determine how E/I imbalances are regulated and limited in healthy brains (such as through homeostasis, cortical architecture, and other "control" systems).

5.3.5 Compare non-clinical and clinical groups using consistent methods

After determining which methods are most appropriate and practical for assessing baseline excitability levels, future work should aim to recruit both non-clinical and clinical samples within the same studies to allow for direct comparison of mechanisms and variable outcomes. Large variation in the methods previously used to explore anomalous experiences and the associated neural mechanisms between different groups makes comparisons challenging. With mounting evidence for anomalous experiences in non-clinical individuals, future studies should make a point of including hallucination-prone healthy groups and non-hallucinating clinical groups as controls. This will give greater insight into any potential similarities and differences in the mechanisms of anomalous experience between these groups.

Further, studies need to move beyond exploring schizotypy and give needed attention to a wider variety of anomalous experiences. Many studies in non-clinical groups tend to employ questionnaire measures focused on schizotypal positive, negative, and depressive “symptoms”, with mixed results. No consistent relationship has been evidenced between positive symptoms (such as hallucinations) and P50 deficits in schizotypy specifically (Park et al., 2015). Interestingly, Fong et al. (2019) found no relationship between the “Community Assessment of Psychic Experiences” (CAPE) measure of schizotypy and pattern glare task scores, whereas *AHE* CHi-II factor scores were significantly and positively related to pattern glare scores. This suggests that visual, pattern-glare-type cortical hyperexcitability is associated with increased “aura-type” anomalous experiences (i.e. phosphenes, scotomas, flashes of colour, etc.), but not with broader schizotypal experiences.

With regards to trait excitability, using established measurement paradigms such as resting state EEG or default mode network (DMN) activity via fMRI could be helpful. The DMN refers to a network of resting-state activity, and increased or decreased DMN activity directly influences the brain’s responsiveness (Mayhew, Ostwald, Porcaro, & Bagshaw, 2013). There has also recently been keen interest in how the DMN is related to schizophrenia, with associated symptoms thought to be the result of DMN hyperconnectivity (Hu et al., 2017). Simultaneous EEG-fMRI recording may offer a valuable tool for investigating interactions between baseline and state/task-induced excitability, across groups. For example, baseline E/I balance in auditory-visual networks can be reflected in interactions between increases/decreases in alpha power and positive/negative BOLD responses

(associated with visual or auditory stimulation) (Mayhew et al., 2013). Mayhew at al. found that, when pre-stimulus alpha power was low (indicating high cortical excitability), a checkerboard visual stimulus elicited a greater, positive V1 BOLD response. By comparison, high pre-stimulus alpha power (indicating increased inhibition) was associated with a negligible V1 response. Similarly, decreased alpha-band power over occipital sites has been shown to correlate with decreased thresholds for inducing phosphenes via TMS (Romei, Rihs, Brodbeck, & Thut, 2008).

5.3.6 Record phenomenology and appraisals of anomalous experience longitudinally in non-clinical groups

Exploring these characteristics of hallucinations more fully in non-clinical groups will enable us to understand why hallucinations are sometimes benign and sometimes require intervention and treatment. What exactly causes these benign experiences to (sometimes) become “clinically relevant” is not yet fully understood. Research has suggested that individual interpretations of and emotional reactions to anomalous experiences may have substantial impacts on coping and outcomes, with significant differences in distress between clinical and non-clinical groups (Badcock et al., 2017; Bell et al., 2011; Howes et al., 2013; Iudici et al., 2019; Upthegrove et al., 2016). Other work has shown that clinical groups are more likely to endorse delusional or threatening explanations for their experiences, whereas non-clinical groups endorse rationalising explanations (Johns & van Os, 2001; Underwood, Kumari, & Peters, 2016). This, combined with previous working demonstrating that anomalous experience phenomenology (and perhaps mechanisms) are not significantly different between clinical and non-clinical

groups, could suggest that it is not the actual experience of hallucinating that is problematic, but the *interpretation* of this experience (Underwood et al., 2016). Therefore a question to answer is, do clinical populations more often have experiences that are likely to cause distress (i.e. very negative or vivid hallucinations), or are clinical populations simply more predisposed to negatively interpreting hallucinations regardless of their content, or a combination of both, as compared to non-clinical populations?

The direction of these relationships is not clear, and they may in fact be reciprocal. Therefore, future research should focus on tracking anomalous experience phenomenology and emotional/causative appraisals in non-clinical groups longitudinally, combined with repeated measures of stress and anxiety. This would also enable identification of any individuals who do go on to develop psychopathologies. Research should also consistently record ratings of anomalous experiences along several sub-spectra, such as frequency, intensity, duration, arousal, emotional valence, perceived externality and control, etcetera. This will allow us to compare these experiences more directly with those from clinical groups, and determine what possible courses of action can be taken to prevent hallucinations from becoming a source of stress or anxiety and intruding on people's daily lives.

5.4 Thesis limitations and strengths

5.4.1 Limitations

One limitation of this thesis is that the study samples were taken from the student population at an affluent university. Therefore, these results cannot be generalised to populations that are dissimilar to these samples, e.g. groups that are not university educated. However, limiting samples to students constrained the age of participants to within a fairly narrow range (18-31, $\bar{x}$ = 20 years across all studies) and so somewhat limited the influence of variation in results due to age. Additionally, Bell et al. (2011) broadly replicated the range of CAPS scores previously seen in a student sample (Bell et al., 2006) in a much more varied sample, including participants from various socioeconomic brackets. In Bell et al. (2011), the percentage of non-clinical participants scoring above the mean of a group with psychosis was 11.9%, closely matching the 11.3% reported in Bell et al. (2006). This suggests that although there may be some limitations to using student samples, in the case of anomalous experience these samples appear to give a fair estimation that may be applicable to other groups. It is important to note, however, that this may be truer for hallucination-type experiences than for other experiences related to cortical hyperexcitability in the literature, such as visual stress. Results from student samples are likely to be skewed for questions on Factor 1 of the CHi and CHi-II questionnaires, which relate to visual stress, as this can be induced by screens (e.g. computers, smart phones) and by indoor environments with fluorescent or bright lights. Modern students spend a considerable amount of time using technology and in these environments. That being said, Fong et al. (2019) did not find a relationship between high pattern glare task scores and the CHi-II “heightened visual sensitivity and discomfort” factor

scores. This factor addresses anomalous experiences induced by irritating environments such as indoor and fluorescent lights, and from working on computers. Therefore, it is unlikely that this factor influenced the results observed in the current studies, despite it likely being higher in students as compared to the general population, as it appears to be less directly related to cortical hyperexcitability-induced anomalous experience. However again, future work should ensure to measure any environmentally-induced visual discomfort (such as by using the CHi-II), perhaps also taking into account screen-usage.

An additional limitation was the small sample recruited for Chapter 4, such that conclusions are tentative. The sample size was determined from conventions in EEG repetition suppression studies (see Patterson et al., 2008). However, Chapter 4 still revealed interesting relationships between anomalous experience and auditory cortical inhibition. To build on this, future studies could, for example, screen participants using the pattern glare task or a specified questionnaire measure, so that a large number of “extreme” low and high scorers can be recruited to the main study, for increased precision. This should prove practically achievable, as Chapters 2 and 3 included 47 and 40 participants in the “high” PG group respectively.

An additional aspect of this thesis which may be considered a limitation is the complexity of the relationships studied. Despite this, this thesis has revealed some interesting findings that can be logically explained within current theoretical frameworks. These findings also significantly extend the current literature, as outlined above. However, there is still uncertainty and limited literature available in

several key areas related to this thesis, such as: baseline excitability and E/I balance in different cortical areas and networks in healthy individuals; the exact biophysical mechanisms by which tDCS exerts its effects, and its interaction with baseline excitability and ongoing activity in neural networks; mechanisms responsible for possible cortical hyperexcitability in healthy individuals; consensus on the types and mechanisms of cortical hyperexcitability underlying anomalous experience in clinical groups; neural mechanisms underlying pattern glare in healthy individuals (as much of the research base focuses on migraine); and relationship between trait and state predisposition to anomalous experience, in both clinical and non-clinical groups. This thesis cannot definitively determine the full story of these relationships – however it does move our understanding forward and provide a foundation for exploring these in more detail. Future studies may wish to approach the outstanding questions identified by this thesis at a more basic and fundamental level – such as systematically varying tDCS parameters to explore its effects on conscious experience and brain activity (using fMRI, for example) in clinical and non-clinical groups.

5.4.2 Strengths

The central strength of this thesis is that it extends the knowledge and theory underpinning state-trait and state-state relationships between a range of anomalous experiences and cortical excitability, in non-clinical groups. Very little research has explored these relationships in healthy participants outside of schizotypy. As a construct, schizotypy does not allow accurate study of the broad range of anomalous experiences known to occur in healthy individuals, due to

focusing on those associated with schizophrenia specifically (and sometimes including other domains such as delusions, which can muddy relationships). In this thesis, a wide range of anomalous experiences were explored across several modalities by using trait questionnaires designed for non-clinical groups. Additionally, state excitability was approached from different angles, being measured or manipulated using pattern glare, tDCS, and EEG-based repetition suppression. This thesis therefore has important implications for future work in this area; it can inform and guide selection of the most appropriate measures or manipulators of excitability, whilst also highlighting their potential limitations.

A further strength of this thesis is that it takes into account, and builds on, recent advances in the brain stimulation literature that highlight the importance of baseline excitability in participant responsivity (Silvanto et al., 2018; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008). This thesis not only adds to the evidence for the role of baseline excitability in mediating tDCS efficacy, but also extends previous work that has found relationships between tDCS of primary visual cortex and anomalous experience predisposition (Braithwaite et al., 2015). A persisting assumption in brain stimulation research is that anodal stimulation is "excitatory" and cathodal stimulation is "inhibitory". However, recent work (Romei et al., 2016; Silvanto et al., 2018) and this thesis provide evidence to the contrary. Given our ever-advancing ability to model stimulation flow in the brain computationally, future work will no doubt continue to reveal the complexity of tDCS-brain interactions and how baseline excitability can influence hallucinatory predisposition (e.g. Corlett et al., 2019).

Despite some possible limitations, the current sample also has several strengths. The samples are sizeable in Chapters 2 and 3, providing good variation of responses and power for the analyses conducted. The samples in all empirical chapters are free from many of the confounding factors from patient groups that may have impacted comparisons with non-clinical or control groups in other studies on anomalous experience, such as psychopathological illness chronicity and low socioeconomic status (Martins et al., 2012; Ranlund et al., 2014), and medication, nicotine, and other recreational drug use (which can interfere with cortical excitability: Bauernfeind et al., 2011; Cowan et al., 2015; Hanlon et al., 2015; Thirugnanasambandam et al., 2011). Cognitive dysfunction or impairment is a common feature of psychopathology and other medical conditions in which hallucinations also occur (Aarsland, 2016; Green, 2016; Lenka, Hegde, Jhunjhunwala, & Pal, 2016; Russell, Harper, Allen, Baldwin, & Burns, 2018), however as anomalous experiences can also occur in healthy individuals, these factors represent confounds when exploring the mechanisms underlying hallucination. The impact of these factors is much reduced by using healthy samples, and so this is a key strength of this thesis.

Sample age is also a strength here, given that adolescence and early adulthood are known to be a critical period for the development of many mental health conditions, such as psychosis (Marin, 2016; Paus, Keshavan, & Giedd, 2008). This thesis addressed the need to explore anomalous experiences in healthy individuals of this age, adding valuable data on these experiences to the literature. The fact that a considerable degree of AEs was observed in this age group here contributes to the need to determine whether there are any unique

characteristics of anomalous experience in clinical groups, and the factors that potentially contribute to mental health decline.

5.5 Concluding remarks

This thesis explored whether anomalous experiences are associated with cortical hyperexcitability in non-clinical samples, and whether there are differences in this relationship depending on how these factors are measured and manipulated. The influence of trait- and state-based, and uni- versus multi-modal, comparisons were investigated. The empirical chapters built on previous work by using multiple measures of trait anomalous experiences that explored a wider variety of experiences than are usually considered in similar research, across multiple modalities. State cortical excitability was also approached from different angles – using a psychophysical task, tDCS, and EEG-based repetition suppression – and in different modalities. Overall, this thesis demonstrates that relationships between anomalous experience and cortical excitability differ depending on the trait / state and modality comparisons made.

This thesis therefore raises some interesting questions around the interactions between different types of anomalous experiences and cortical excitability, with trait and state experiences / relationships possibly being subserved by different mechanisms or networks. This highlights the need for clarification of the neural processing underpinning specific trait and state measures and experiences, so that their interactions can be more fully understood. Future studies should further consider how these interactions may differ by modality and

the type or location of cortical hyperexcitability. To answer these questions, and interrogate the relationships observed here, additional studies on non-clinical groups are needed, using simultaneous neuro-imaging or -recording and psychophysical tasks. These approaches will enhance our understanding of the similarities and differences in neurocognitive mechanisms underlying anomalous experience across clinical and non-clinical groups.

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7 Appendices

Appendix A

CONSENT TO PARTICIPATE IN RESEARCH ON CORTICAL HYPEREXCITABILITY AND VISUAL DISTORTIONS

School of Psychology, University of Birmingham

What is the purpose of this study?
The purpose of the study is to examine biases of latent cortical hyper-excitability between individuals who report visual distortions or hallucinations and those that do not, using a form of brain stimulation called transcranial direct current stimulation (tDCS).

What does this study involve?
This study will take place over two sessions. Participants will first be screened for their suitability to take part. In each session, the researcher will use tDCS to pass a weak electrical current through an area of the brain (parietal cortex) for 20 minutes whilst participants complete some questionnaires for measuring proneness to visual irritability, distortions, and other anomalous perceptions. Participants will then complete a computerised task involving the presentation of patterned discs, known as the "pattern-glare" task. This task requires participants to view some stimuli and then provide a series of ratings for each stimulus (via the computer).

Will you be paid to participate in this study?
In exchange for your participation in both sessions of this study, you will earn 2.5 credits toward your RPS participation requirements. Credits will be awarded after completion of both sessions.

Other important information you should know:

- **Benefits from participation:** You will not benefit directly from participating in this study, but your participation may provide you with the indirect benefit of learning more about this research project and experimental psychology in general.

- **Risks associated with participation:**
    - **tDCS** – tDCS involves the application of weak electric currents (generated by a 9-volt battery) to alter the likelihood that neurons in the brain will fire. The actual current entering the brain during tDCS is very small. tDCS has been used safely in hundreds of experimental studies, and is completely safe to use within the parameters established by previous investigations. Please be aware, however, that tDCS may cause some slight and temporary discomfort. You may notice some mild tingling or itching where the electrode is placed on the scalp. It is also possible that you may feel tired after stimulation and experience itching where the electrode was. It is possible you may also experience some slight nausea or headache. These effects are temporary and tDCS has not been known to cause any permanent negative effects. It is not known absolutely that these are the only known risks associated with tDCS, and therefore there may be some unknown risks associated with application of tDCS. Please make sure to report any adverse effects you experience during the experiment to the researcher.

- **Pattern-glare task** – you will view some briefly-presented stimuli which you may find irritating

- **Withdrawal from the study:** You may choose to stop your participation in this study at any time. Your decision to stop your participation will have no effect on your academic standing. Should you decide to withdraw from the study, your compensation will be prorated to reflect the portion of the study that you have completed. Your data will be destroyed immediately on withdrawal. Participants can decide to have their data withdrawn up to one week after the end of the experiment.

- **Data collection:** The data collected in this study will include (i) the responses that you make on the questionnaires and the task described above, (ii) basic performance in terms of ratings, (iii) basic demographic information about you (e.g., sex, age, schooling). The data collected in this study will be used only for the purpose described in this form, and will be available only to the researcher and principal investigator listed in this consent form. Raw data gathered from this study will be maintained for 10 years as required by regulations, following the publication of empirical articles or communications describing the results of the study.

- **Confidentiality:** Every effort will be taken to protect the names of the participants in this study. Your identity will not be recorded as part of your data, and will not be revealed in any publication that may result from this study; your consent form will not be stored with your data, to ensure that your identity cannot be linked in any way to your data. All information you provide will be kept confidential, except as governed by law.

Who should you call with questions about this study?
Questions or concerns about this study may be directed to the staff member in charge of this research project:
Dr Jason Braithwaite (email: J.J.braithwaite@bham.ac.uk – telephone:).

CONSENT (please tick)					
I have read the above information and have been given an opportunity to ask questions	I agree to participate in this study	Participant Name	Participant Signature	Researcher Name	Researcher Signature

Appendix B

The Selective Attention and Awareness Laboratory
School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT

Screening & Safety Questionnaire

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

	YES	NO
Have you ever suffered from any neurological or psychiatric conditions?		
If YES please give details (nature of condition, duration, current medication (if any):		
Have you ever had a significant head/brain injury or surgery, or concussion?		
Do you have photosensitive epilepsy?		
Have you ever suffered from any other form of epilepsy, febrile convulsions in infancy, or had recurrent fainting spells?		
If YES please give details:		
Does anyone in your immediate or distant family suffer from epilepsy?		
If YES please state your relationship to the affected family member:		
Do you suffer from migraines?		
Have you ever undergone a neurosurgical procedure (including eye surgery)?		
If YES please give details:		
Do you currently have any of the following fitted to your body (please circle)? Cochlear implant Heart pacemaker Medication pump Surgical clips Other		
Is there any chance you may be pregnant?		
Are you currently taking any unprescribed or prescribed medication?		
If YES please give details:		
Are you currently undergoing anti-malarial treatment?		
Have you had any alcohol in the last 12 hours?		
If YES please estimate how many units and how long ago:		
Have you had any tea, coffee, energy drinks, or other sources of caffeine, in the last 12 hours?		

If YES please estimate how many cups/cans of each and how long ago:		
Have you used recreational drugs in the last 24 hours?		
Did you have very little sleep last night?		
Do you have any skin problems or conditions?		
If YES please give details:		
Have you ever participated in a tDCS/TMS study before?		
If YES please indicate the last time you participated in a tDCS/TMS study:		

Handedness: Left / Right Date of Birth ____/____ /____ Age: ____ Sex: F/M

Degree course: Undergraduate / Postgraduate / Other
Subject/Area: _____

I confirm that the above information is accurate to the best of my knowledge.

PARTICIPANT

Name (in block capitals):
.....

Signed: ..... Date:
.....

RESEARCHER

Signed: ..... Date:
.....

Screening & Safety Questionnaire – Session 2

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

	YES	NO
Are you currently taking any unprescribed or prescribed medication?		
If YES please give details:		
Are you currently undergoing anti-malarial treatment?		
Have you had any alcohol in the last 12 hours?		
If YES please estimate how many units and how long ago:		
Have you had any tea, coffee, energy drinks, or other sources of caffeine, in the last 12 hours?		

If YES please estimate how many cups/cans of each and how long ago:		
Have you used recreational drugs in the last 24 hours?		
Did you have very little sleep last night?		
Do you have any skin problems or conditions?		
If YES please give details:		
Have you ever participated in a tDCS/TMS study before?		
If YES please indicate the last time you participated in a tDCS/TMS study:		

I confirm that the above information is accurate to the best of my knowledge.

PARTICIPANT

Name (in block capitals): .....

Signed: ..... Date:.....

RESEARCHER

Signed: ..... Date: .....

Appendix C

CONSENT TO PARTICIPATE IN RESEARCH ON CORTICAL HYPEREXCITABILITY AND VISUAL DISTORTIONS

School of Psychology, University of Birmingham

What is the purpose of this study?
The purpose of the study is to examine biases of latent cortical hyper-excitability between individuals who report visual distortions or hallucinations and those that do not, using a form of brain stimulation called transcranial direct current stimulation (tDCS).

What does this study involve?
This study will take place over **three** sessions. Participants will first be screened for their suitability to take part and complete some questionnaires for measuring proneness to visual irritability, distortions, and other anomalous perceptions. In each session, the researcher will use tDCS to pass a weak electrical current through an area of the brain (parietal cortex) for 15 minutes. Participants will then complete two computerised tasks involving; (1) the presentation of a visual illusion, and (2) the presentation of patterned discs, known as the "pattern-glare" task. This second task requires participants to view some stimuli and then provide a series of ratings for each stimulus (via the computer).

Will you be paid to participate in this study?
In exchange for your participation in both sessions of this study, you will earn 3.5 credits toward your RPS participation requirements, **or** £20. Credits / cash will be awarded after completion of **all** sessions.

Other important information you should know:

- **Benefits from participation:** You will not benefit directly from participating in this study, but your participation may provide you with the indirect benefit of learning more about this research project and experimental psychology in general.

- **Risks associated with participation:**
    - **tDCS** – tDCS involves the application of weak electric currents (generated by a 9-volt battery) to alter the likelihood that neurons in the brain will fire. The actual current entering the brain during tDCS is very small. tDCS has been used safely in hundreds of experimental studies, and is completely safe to use within the parameters established by previous investigations. Please be aware, however, that tDCS may cause some slight and temporary discomfort. You may notice some mild tingling or itching where the electrode is placed on the scalp. It is also possible that you may feel tired after stimulation and experience itching where the electrode was. It is possible you may also experience some slight nausea or headache. These effects are temporary and tDCS has not been known to cause any permanent negative effects. It is not known absolutely that these are the only known risks associated with tDCS, and therefore there may be some unknown risks associated with application of tDCS. Please make sure to report any adverse effects you experience during the experiment to the researcher.
    - **Pattern-glare task** – you will view some briefly-presented stimuli which you may find irritating.

- **Withdrawal from the study:** You may choose to stop your participation in this study at any time. Your decision to stop your participation will have no effect on your academic standing. Your data will be destroyed immediately on withdrawal. Participants can also decide to have their data withdrawn up to one week after the end of the experiment.

- **Data collection:** The data collected in this study will include (i) the responses that you make on the questionnaires and the task described above, (ii) basic performance in terms of ratings, (iii) basic demographic information about you (e.g., sex, age). The data collected in this study will be used only for the purpose described in this form, and will be available only to the researcher and principal investigator listed in this consent form. Raw data gathered from this study will be maintained for 10 years as required by regulations, following the publication of empirical articles or communications describing the results of the study.

- **Confidentiality:** Every effort will be taken to protect the names of the participants in this study. Your identity will not be recorded as part of your data, and will not be revealed in any publication that may result from this study; your consent form will not be stored with your data, to ensure that your identity cannot be linked in any way to your data. All information you provide will be kept confidential, except as governed by law.

Who should you call with questions about this study?
Questions or concerns about this study may be directed to the staff member in charge of this research project:
Dr Jason Braithwaite (email: J.J.braithwaite@bham.ac.uk – telephone:).

By signing below, you confirm that you have: completed the screening questionnaire; received enough information about the study; had the opportunity to ask questions; received satisfactory answers to any questions asked; and also understand that you are free to leave the study at any time without having to give a reason. By signing you also confirm that the nature, purpose, and possible consequences of the outlined procedures have been explained and that you are happy to participate.

	CONSENT			
Ppt. ID	**I agree to participate in this study**	**Participant Name**	**Participant Signature**	**Researcher Signature**

Appendix D

Selective Attention and Awareness Laboratory
School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT

Screening & Safety Questionnaire

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

	YES	NO
Have you ever suffered from any neurological or psychiatric conditions?		
If YES please give details (nature of condition, duration, current medication (if any):		
Have you ever had a significant head/brain injury or surgery, or concussion?		
Do you have photosensitive epilepsy?		
Have you ever suffered from any other form of epilepsy, febrile convulsions in infancy, or had recurrent fainting spells?		
If YES please give details:		
Does anyone in your immediate or distant family suffer from epilepsy?		
If YES please state your relationship to the affected family member:		
Do you suffer from migraines?		
Have you ever undergone a neurosurgical procedure (including eye surgery)?		
If YES please give details:		
Do you currently have any of the following fitted to your body (please circle)? Cochlear implant Heart pacemaker Medication pump Surgical clips Other		
Is there any chance you may be pregnant?		
Are you currently taking any un-prescribed or prescribed medication?		
If YES please give details:		
Are you currently undergoing anti-malarial treatment?		
Have you had any alcohol in the last 12 hours?		
If YES please estimate how many units and how long ago:		
Have you had any tea, coffee, energy drinks, or other sources of caffeine, in the last 12 hours?		
If YES please estimate how many cups/cans of each and how long ago:		
Do you regularly use any recreational drugs? If YES please specify:		
Have you used recreational drugs in the last 24 hours?		
Are you a smoker (do you regularly smoke at least 1 cigarette a day, every day), or do you use nicotine patches / gum?		
Did you have very little sleep last night?		
Has your regular sleep pattern been disturbed during the past week?		

If YES please give details:		
Do you have any skin problems or conditions?		
If YES please give details:		
Have you ever participated in a tDCS/TMS study before?		
If YES please indicate the last time you participated in a tDCS/TMS study:		

Handedness: Left / Right **Date of Birth**: ____/____/____ **Age**: ____ **Sex**: F/M

Ethnicity: Please circle your ethnicity (people's ethnicity describes their feeling of belonging, and attachment to, a distinct group of a larger population that shares e.g. their ancestry, language, religion, etc.):

Caucasian	Latino/Hispanic	Middle Eastern
African	Caribbean	South Asian
East Asian	Mixed (please indicate)	Other (please indicate)

Longest lifetime country of residence: _____
Please estimate duration (e.g. years): _____

Degree course (e.g. BA, MSc, PhD): _____
Subject/Area: _____

I confirm that the above information is accurate to the best of my knowledge.

Session 1	**Name**	**Signature**	**Date**
Participant			
Researcher			

Screening & Safety Questionnaire – Sessions 2 & 3

	Session 2		**Session 3**	
	YES	**NO**	**YES**	**NO**
Are you currently taking any un-prescribed or prescribed medication?				
If YES please give details:				
Are you currently undergoing anti-malarial treatment?				
Have you had any alcohol in the last 12 hours?				
If YES please estimate how many units and how long ago:				
Have you had any tea, coffee, energy drinks, or other sources of caffeine, in the last 12 hours?				

If YES please estimate how many cups/cans of each and how long ago:				
Have you used recreational drugs in the last 24 hours?				
Did you have very little sleep last night?				
Do you have any skin problems or conditions?				
If YES please give details:				
Have you ever participated in a tDCS/TMS study before?				
If YES please indicate the last time you participated in a tDCS/TMS study:				

I confirm that the above information is accurate to the best of my knowledge.

Session 2	**Signature**	**Date**
Participant		
Researcher		

Session 3	**Signature**	**Date**
Participant		
Researcher		

Appendix E

Information sheet for participants in TDCS or TACS experiments

Dear Research Participant,

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involves. Please take time to read the following information carefully. Your participation at this research will help benefit understanding in the areas of knowledge about the cognitive and perceptual function of our brains. This information sheet broadly describes the behavioral experimental procedures and should be read as part of the information sheet regarding the stimulation procedure. If you have any further questions, please do not hesitate to ask. The research procedure described below has been approved by the University of Birmingham ethics committee.

What is Transcranial Current Stimulation (TDCS or TACS)?

TDCS is a method of stimulating the brain of conscious human subjects through the scalp. It was discovered more then a 100 years ago and has been used by scientists and clinicians ever since.

We would apply TDCS to safely and reversibly influence brain activity. Two electrodes are attached to your head, held in place with an elastic strap. They are connected to the device that passes a very small current though the brain. The TDCS device is battery operated, completely isolated from the mains electricity supply. There is no risk of electrocution. The current is very small (1-2mA) and is barely noticeable.

TACS is very similar but instead of the constant, direct, current used in TDCS, an alternating current is used. There are no additional risks associated with TACS and most people cannot tell which form of stimulation they are receiving.

The effects of stimulation on your behavior and cognition are imperceptible; they can only be detected by detailed analysis of the data and wear off within 45-60 minutes after the end of stimulation.

However, you may feel a tingling sensation under one or both electrode. This is a little like the tingle you get if you put your tongue onto a battery.

For your safety you will be asked to fill out a TDCS/TACS Safety Screening Questionnaire, prior to being exposed to any stimulation.

Can the experiment be interrupted?

Yes. You are free to leave the experiment at any stage. Even if you withdraw you will be paid the time you have spent on the study.

Please be aware that any information you provide on the TDCS/TACS checklist and throughout the experiment will remain confidential. The behavioural data obtained during the

experiment will be coded using random number (i.e. your anonymity will be kept). You have the right to ask for your data to be removed from the study at any time.

Are there potential risks of TDCS or TACS?

Transcranial current stimulation (TDCS or TACS) is a safe technique. But there are some small risks, which are described below. These risks are based on recent reviews [1,2] of over 209 studies of TDCS sessions with over 3800 participants. There are no published reviews of the risks of TACS; however, the high frequency of stimulation does not add any additional risk to that of the TDCS protocol, as the stimulation does not cause the neurons to fire. The only published paper assessing safety has reported no issues [3].

1. Itching or tingling: The most common report – by 62% of participants [2] – is that of a tingling sensation under the electrodes. This is present during and shortly after the period of stimulation, and has no adverse effects or risks. A small proportion of participants report this sensation as burning (9%) or discomfort (11%), although they scored the burning or painful sensation as quite mild (under 2 on a 5-point scale from none too intense) [1].
2. Fatigue: The next common report – by 35% of participants – was of tiredness during the stimulation, and 25% reported this continued afterwards. The authors of the study suggest this may be due to the prolonged and uninteresting tasks the participants were doing [1].
3. Headache: 10-15% of participants reported a headache after the stimulation [1,2]. Such headaches are usually mild and can be treated with normal over-the-counter painkillers, if required. There is no evidence that TDCS leads to any change in frequency or severity of headaches. Overall, less than 20% of the participants rated the stimulation procedure as mildly unpleasant and 80% reported that it was not unpleasant [1].
4. Irritation of the skin: Because of contact between the skin and the electrodes, there is a risk of electrochemical irritation. Our use of saline-soaked sponge pockets that surround conductive rubber electrodes minimizes any chemical irritation of the skin. We expect less than 1 in 20 participants to have slight irritation to the skin (with redness under the electrode) that will resolve naturally within minutes or up to 1 hour.
5. Skin burns: Electrical stimulation has the potential to burn the skin. We use stimulation currents that are 1/200th (half of 1%) of the level that might cause direct tissue damage. We have never experienced skin burns in several hundred applications of TDCS. However, daily repeated TDCS has been reported to cause significant skin irritation under the electrodes in a small number of cases. In addition, skin irritation and scalp burns have been reported when TDCS is applied after vigorous skin abrasion to reduce its impedance (a technique that we do not use). We will visually inspect the skin before applying the electrodes, to avoid stimulation of damaged or scratched skin. **The risk of skin burns is very low – we have had no incidences from the hundreds of stimulation sessions that we have performed (less than 1% risk).**

6. Seizures: TDCS/TACS has the potential to excite the brain and induce brief seizures, although this has never yet occurred, to our knowledge. These seizures are related to epileptic seizures but are short-lasting localised fits rather than grand mal epileptic seizures. They can be confused with syncope – a temporary faint or swoon – induced by anxiety.

The risk of a seizure is very low – there have been no reported incidences that we know of from the thousands of stimulation sessions that have taken place in many research laboratories or clinical units (0% risk).

We use published safety guidelines and expect the risk to be very low. Stimulation-induced seizures would be expected to last between tens of seconds to several minutes. There is no evidence to suggest that a stimulus-induced fit would be followed by any spontaneous fits – hence there is no evidence of any long term effect. Moreover, a seizure would occur at the time of experimental stimulation, if at all. So there is no risk of a delayed seizure outside of the care of the experimenter.

Are there any reasons why I should not take part in this study?

Some people, especially those with a history of epilepsy, may be prone to have a seizure related to an epileptic fit. It is therefore important that you do not volunteer for these experiments if you have a psychiatric or neurological disease, or if you or anyone in your immediate family has ever had a seizure.

As TDCS/TACS uses an electric current it is very important that you do not volunteer if you have any metal devices such as cochlea implants or cardiac pacemakers. Metal implants in the head (excluding standard orthodontic braces, fillings, etc.) would also exclude you from the study.

Localised skin damage under the stimulation electrodes may increase the risk of irritation of the skin, and this may mean that we will exclude you from the study. We will ask you if you currently have any skin diseases, and we will inspect the condition of the skin under the electrodes.

<u>As a safety precaution you should not volunteer if you have previously participated in two or more previous TMS or TDCS/TACS experiments in the last 6 months.</u>

You should also not volunteer if you are pregnant.

If you are uncertain about any of these points, please ask the researcher.

What does the procedure involve?

In a typical TDCS/TACS study we will measure your responses while (or immediately after) we stimulate your brain using very mild electrical stimulation (see above for more details). Therefore it is very important to keep focused and alert through out the study. The study may span across multiple sessions, carried out in different days each lasting ½ - 1 hour.

In some cases we may include a sham stimulation session. In this session we will start stimulating but immediately switch the stimulator off. As TDCS or TACS stimulation is very mild it

is unlikely that you would be able to differentiate between sham and real stimulation sessions. We use the sham condition as a control, to insure that any effects we observed are due to the real stimulation and not to other non-specific experimental effects.

At the end of the final session you will be debriefed and the aims of the research will be explained to you in details. We will also inform whether you experienced a sham session and in which session it was.

We request that 24 hours before each session you avoid alcohol consumption or the use of any recreational drugs and avoid drinking caffeinated coffee 2 hours before the sessions. This is required for your safety as both alcohol and caffeine may interact with the brain stimulation you will be exposed to. At the end of each session you will be asked to refrain from driving for at least 2 hours after the stimulation ended.

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. In other words, you are free to decide not to take part in this study, and you would be free to leave it at any stage. If the latter, you will be asked to decide on the future use of your data that was already collected. You will be assigned course credit/compensation money based on the number of sessions you participated in.

Your behavioral performance would be analyzed as part of a group of anonymous volunteers. For our internal record, information you provide in the safety questionnaire and the consent form will kept in a lock cupboard and will be destroyed after 10 years.

The results of the study you took part in are published in international and national research journals and a summary of them is available on the Internet. Please refer to the researcher web page for further details.

REFERENCES

[1] Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*(4-6), 208–214.

[2] Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *The International Journal of Neuropsychopharmacology, 14(08)*, 1133–1145.

[3] Chaieb, L., Antal, A., Pisoni, A., Saiote, C., Opitz, A., Ambrus, G. G., et al. (2014). Safety of 5kHz tACS. Brain Stimulation, 7(1), 92–96.

Appendix F

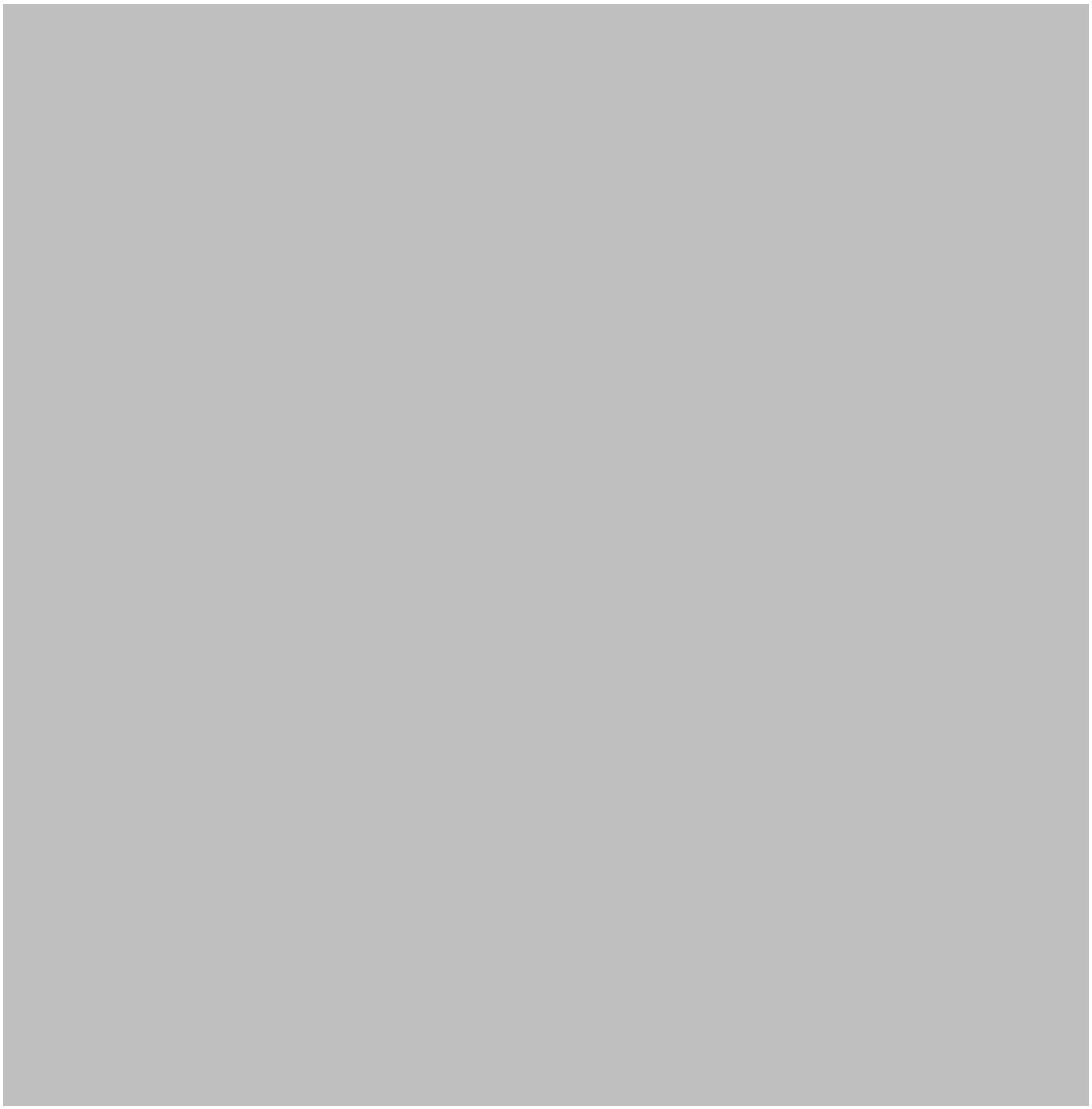
Birmingham Cortical Hyperexcitability Index (BCHi)

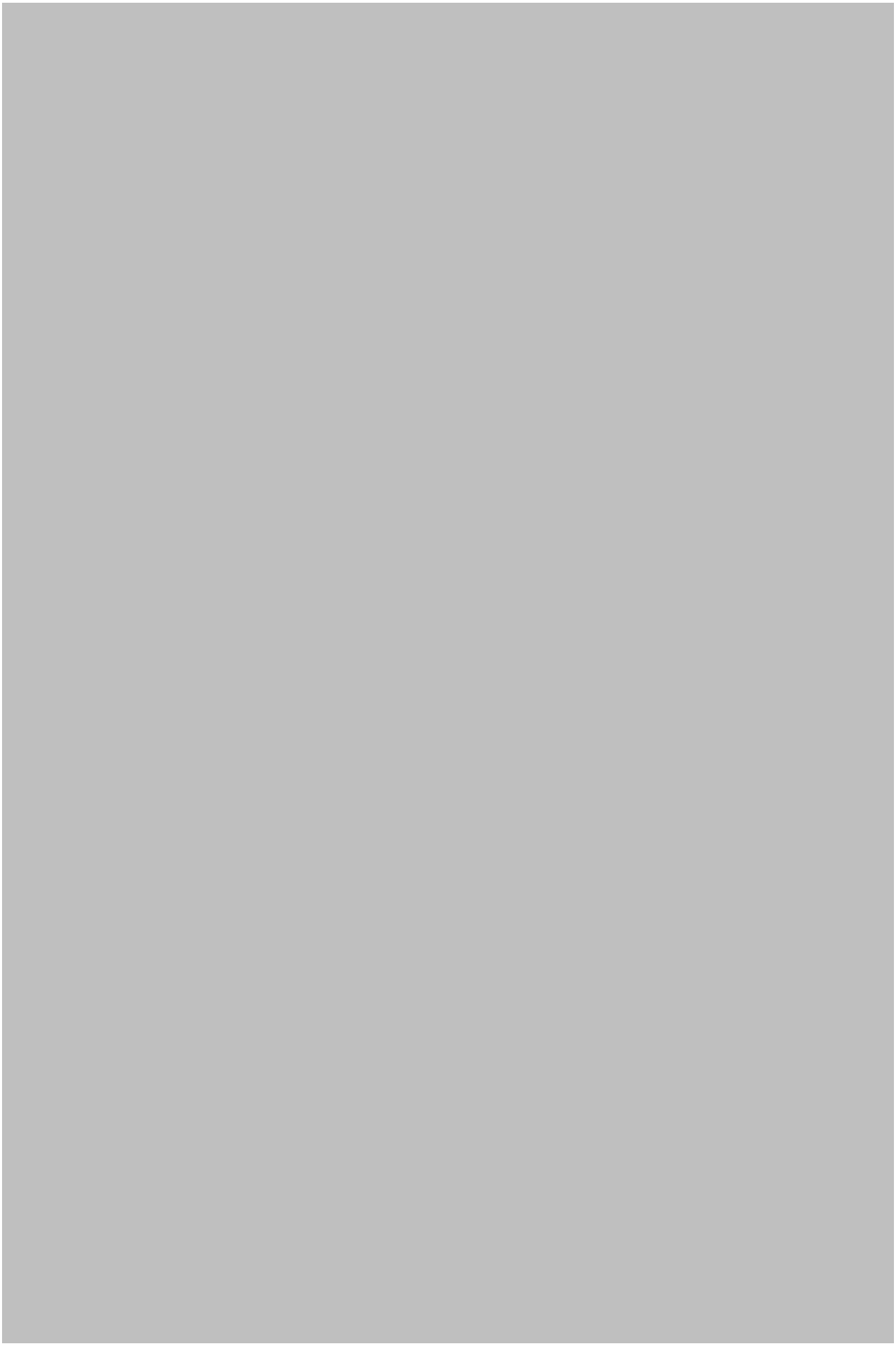
Jason J Braithwaite

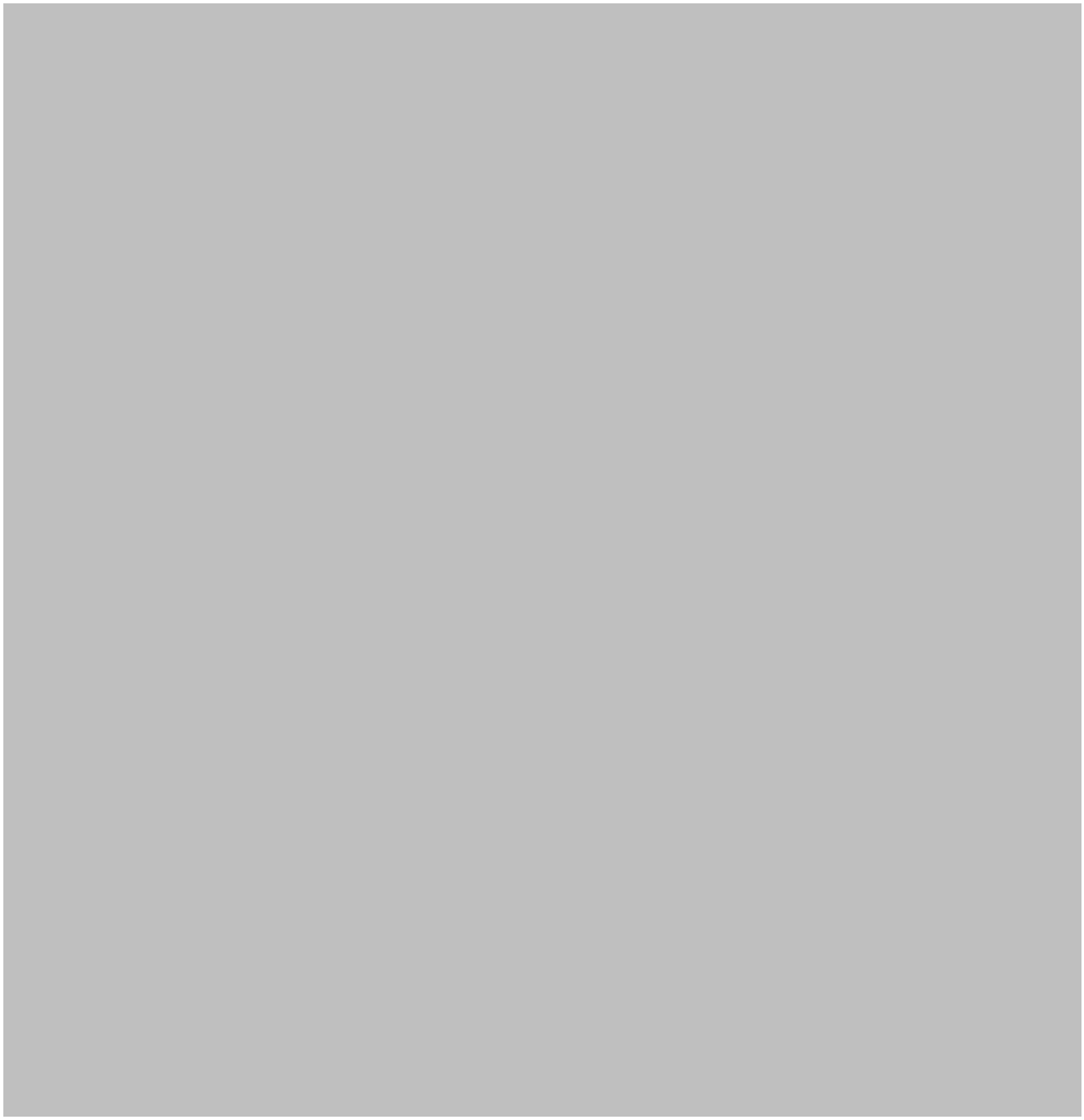
Rachel Marchant

Hayley Dewe

Chie Takahashi







Appendix G

Introduction

This questionnaire asks questions about sensations and perceptions you may have experienced. Some of the experiences are unusual, some of them are more everyday.

We realise circling answers may not always represent your experience as accurately as you might like. However, we would ask you to circle the answers that most closely match your experience and avoid missing any questions out.

We would appreciate it if you could be as honest as possible when giving your answers.

The only experiences we are not interested in are those that may have occurred whilst under the influence of drugs.

Instructions

Each item has a question on the left hand side. Please read the question and circle either YES or NO

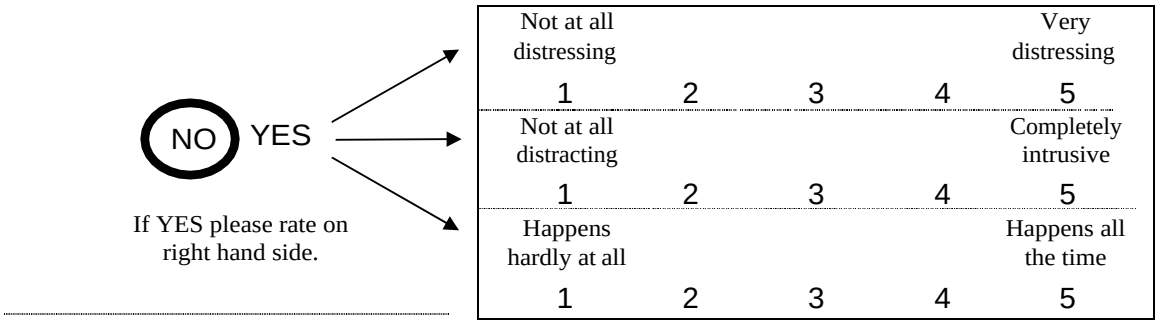
- If you circle **NO** please move straight on to the next question.
- If you circle **YES** please rate the experience *in all of the three boxes* on the right hand side of the item by circling a number between 1 and 5.

These ask about how distressing you found the experience, how distracting you found it, and how often the experience occurs.

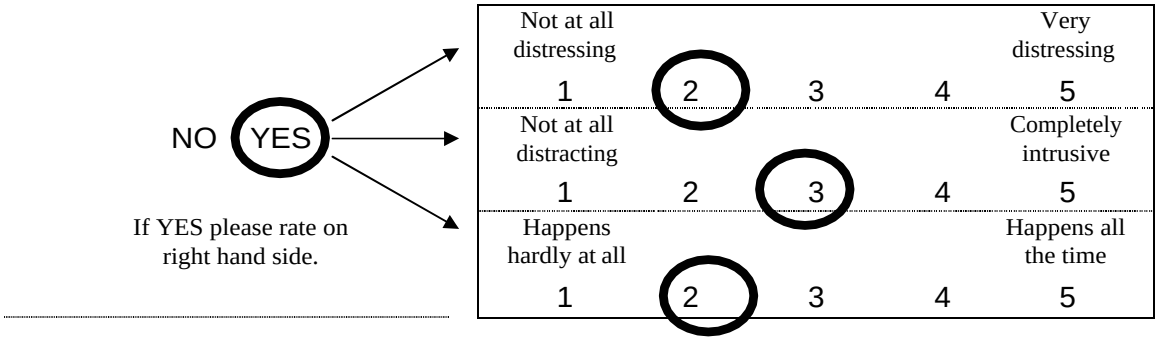
Example questions

You do not need to answer these questions, they are just examples to illustrate the instructions.

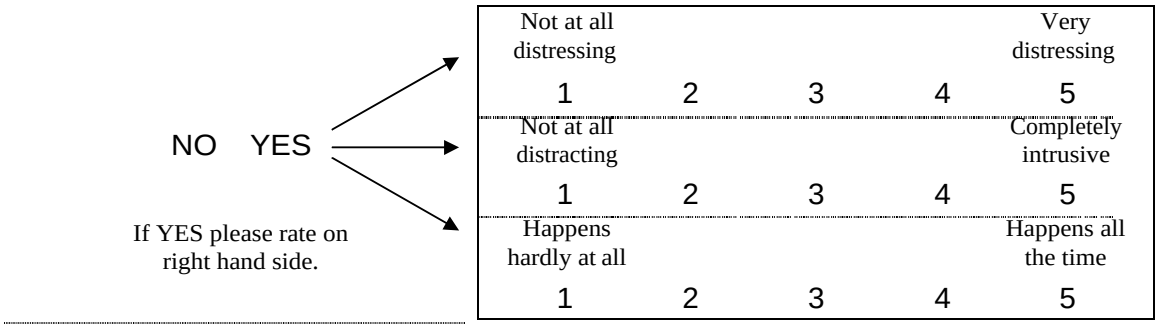
Do you ever notice that lights seem to flicker on and off for no reason ?



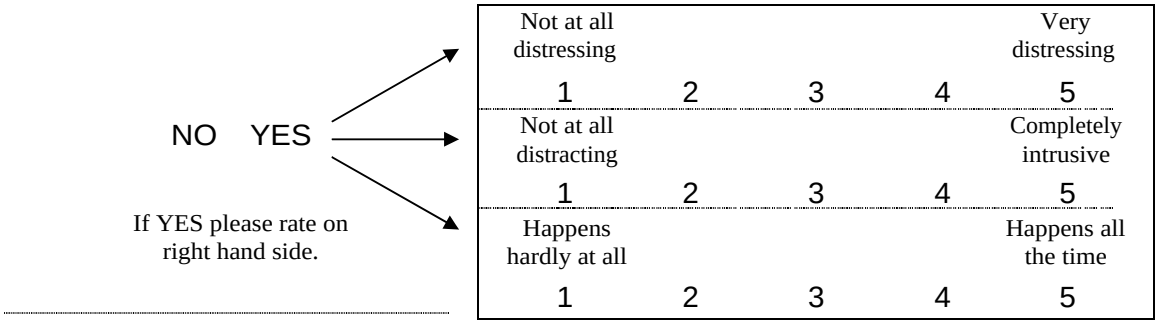
Do you ever feel that the sound on the TV or radio seems unusually quiet ?



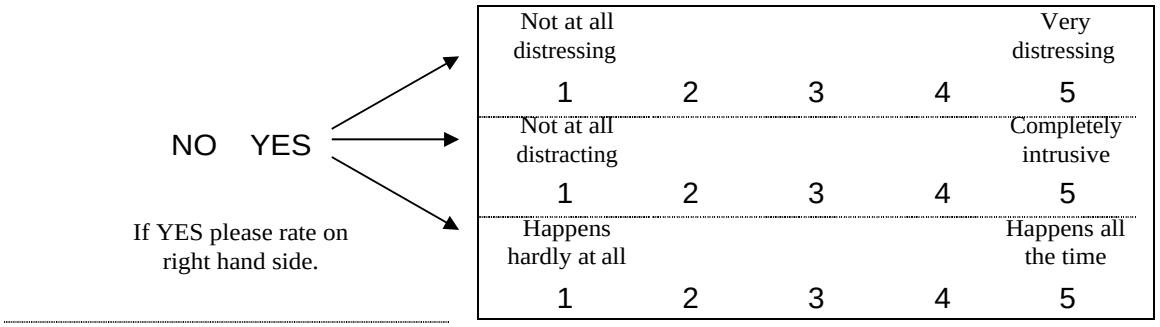
1) Do you ever notice that sounds are much louder than they normally would be ?



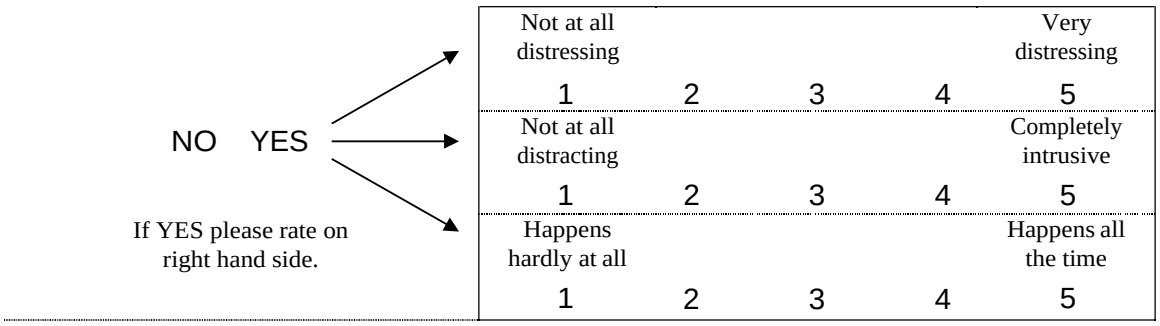
2) Do you ever sense the presence of another being, despite being unable to see any evidence ?



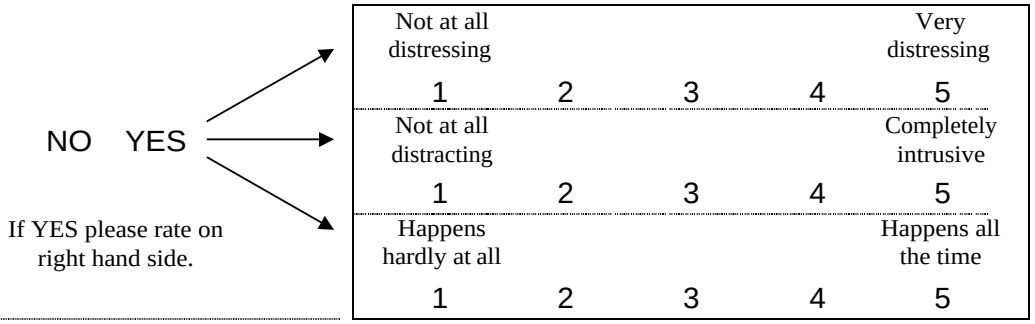
3) Do you ever hear your own thoughts repeated or echoed ?



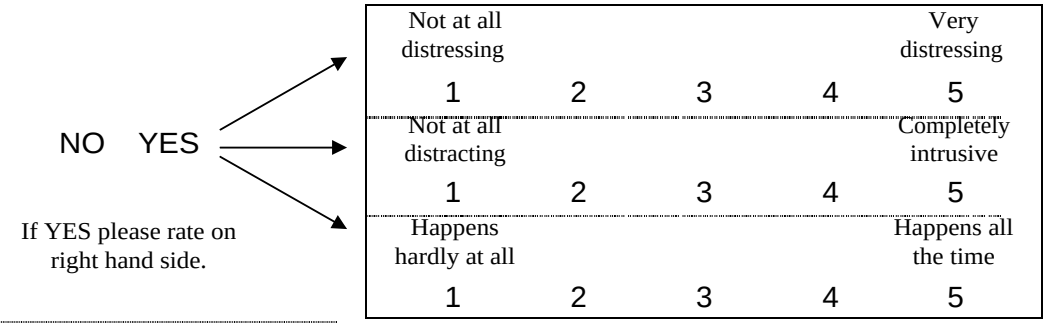
4) Do you ever see shapes, lights or colours even though there is nothing really there ?



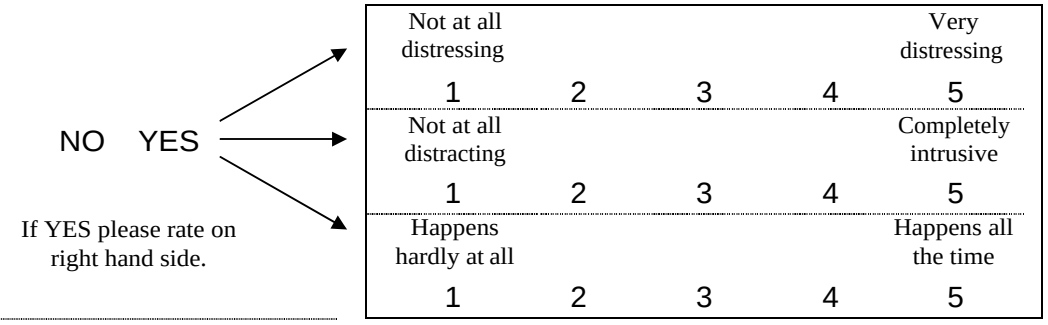
5) Do you ever experience unusual burning sensations or other strange feelings in or on your body ?



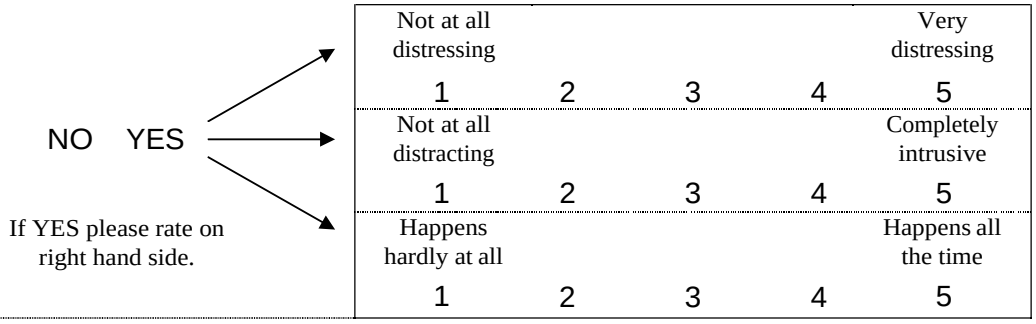
6) Do you ever hear noises or sounds when there is nothing about to explain them ?



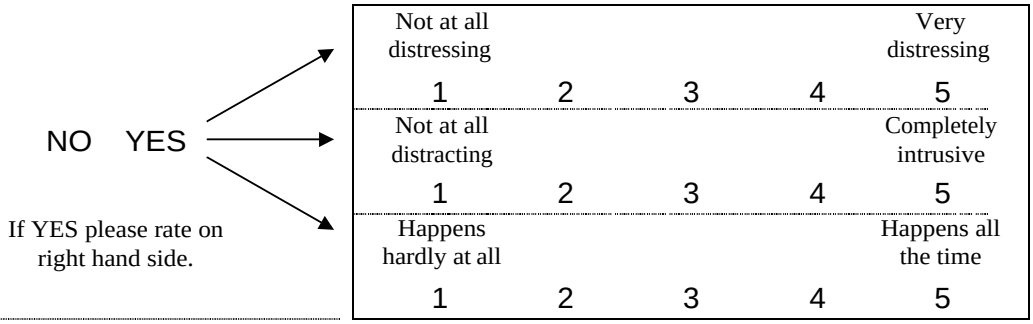
7) Do you ever hear your own thoughts spoken aloud in your head, so that someone near might be able to hear them ?



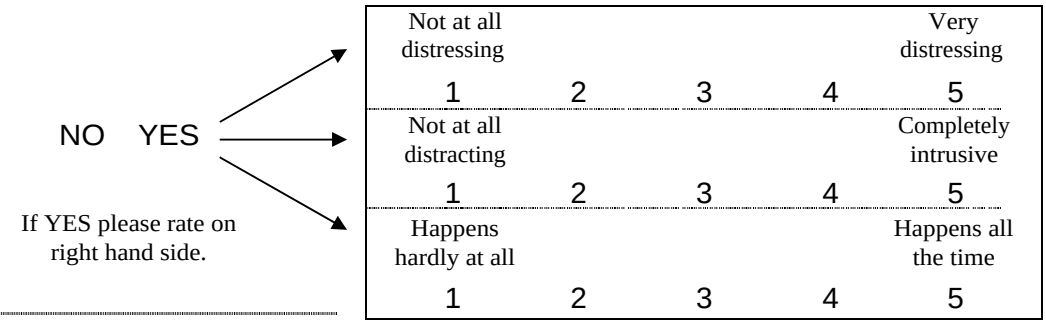
8) Do you ever detect smells which don't seem to come from your surroundings ?



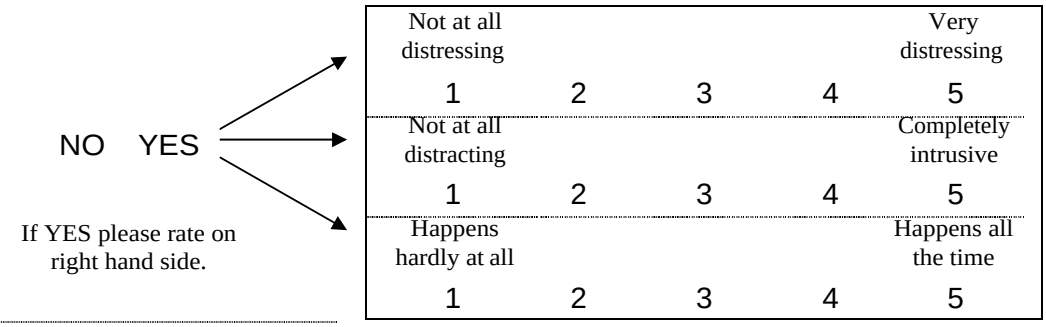
9) Do you ever have the sensation that your body, or a part of it, is changing or has changed shape ?



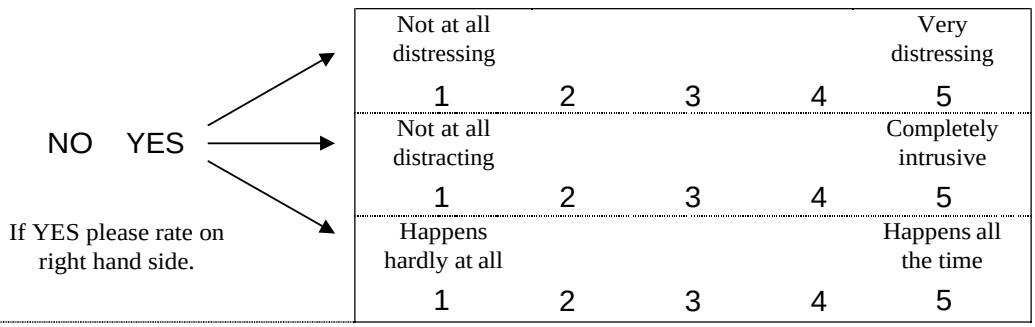
10) Do you ever have the sensation that your limbs might not be your own or might not be properly connected to your body?



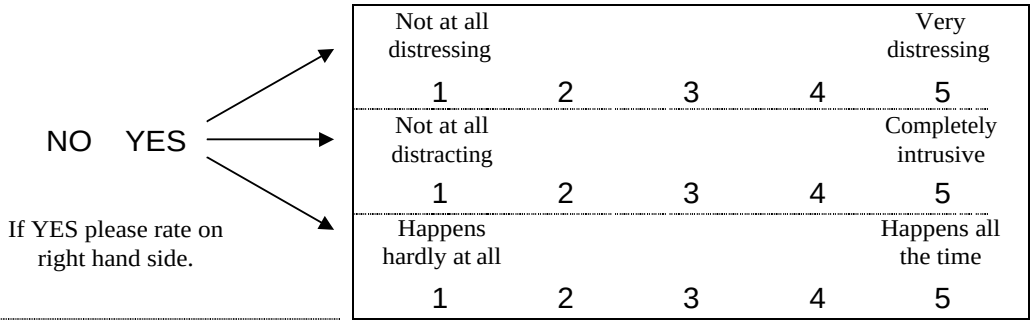
11) Do you ever hear voices commenting on what you are thinking or doing ?



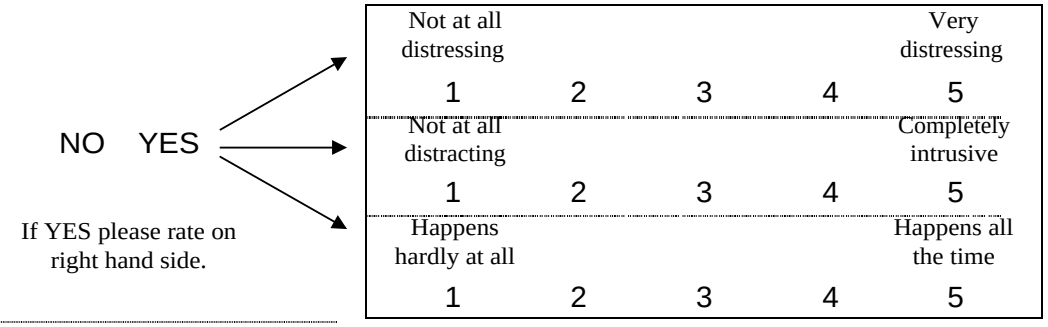
12) Do you ever feel that someone is touching you, but when you look nobody is there ?



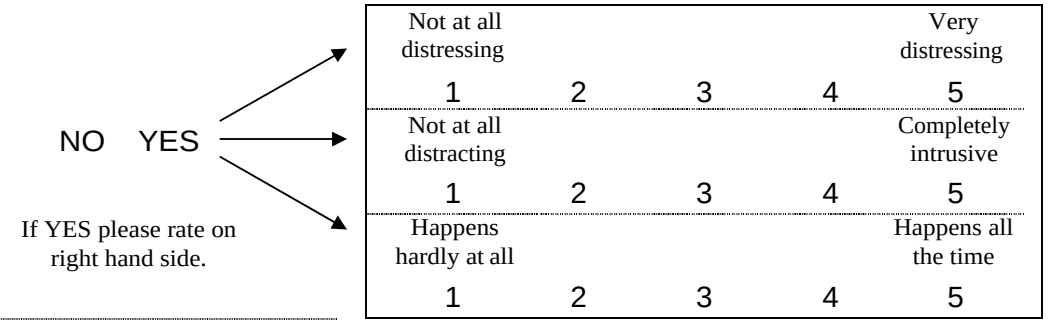
13) Do you ever hear voices saying words or sentences when there is no-one around that might account for it ?



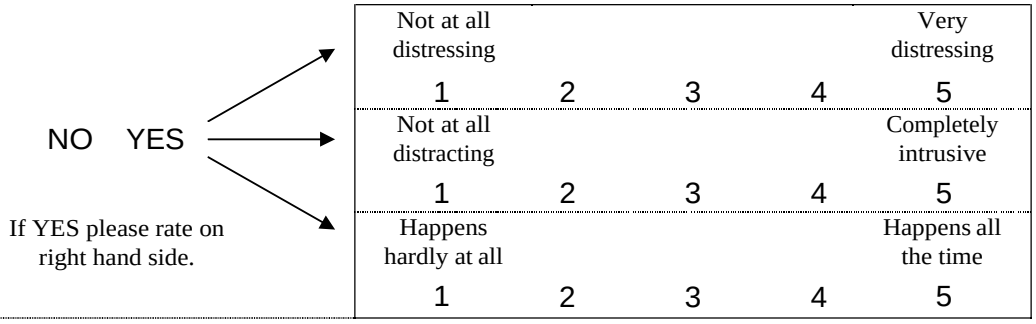
14) Do you ever experience unexplained tastes in your mouth ?



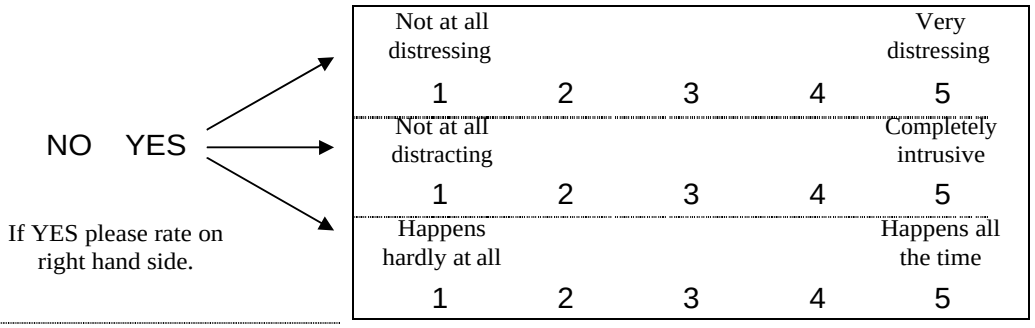
15) Do you ever find that sensations happen all at once and flood you with information ?



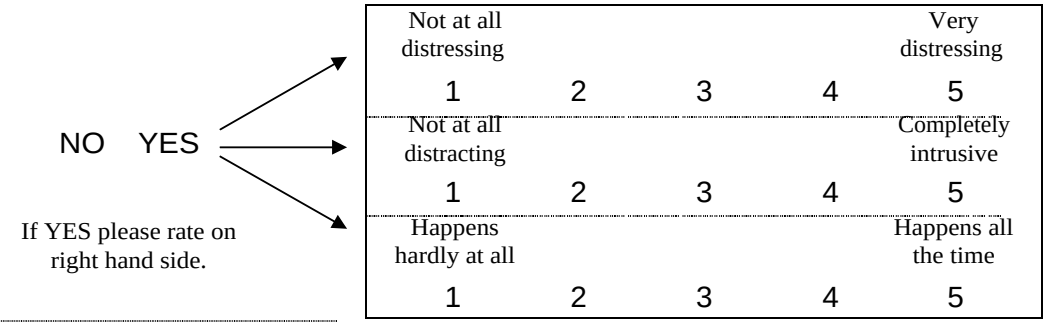
16) Do you ever find that sounds are distorted in strange or unusual ways ?



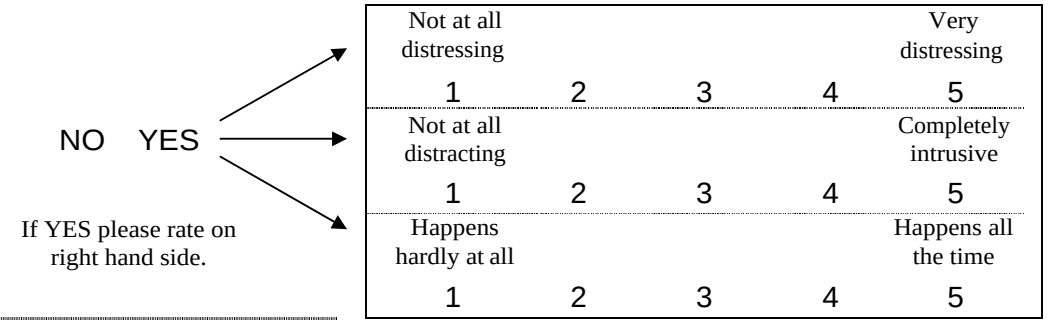
17) Do you ever have difficulty distinguishing one sensation from another ?



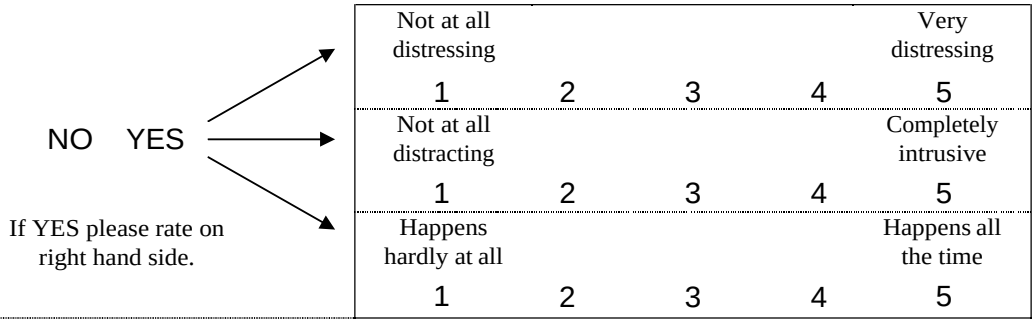
18) Do you ever smell everyday odours and think that they are unusually strong ?



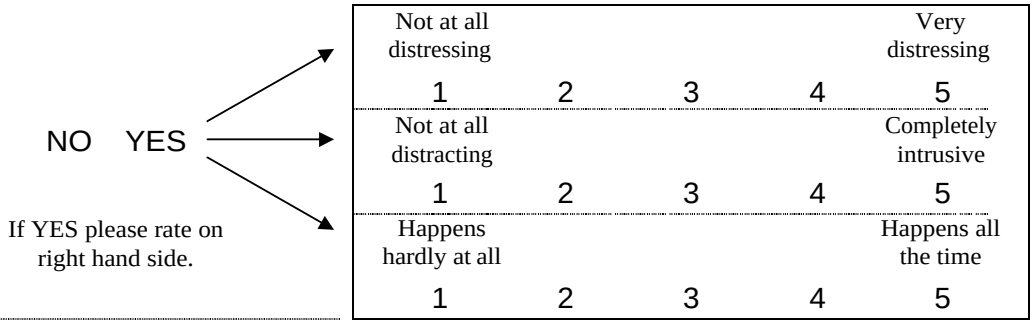
19) Do you ever find the appearance of things or people seems to change in a puzzling way, e.g. distorted shapes or sizes or colour ?



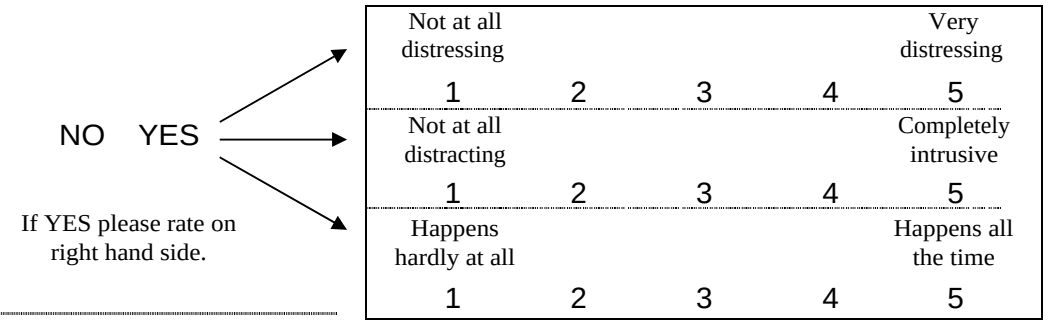
20) Do you ever find that your skin is more sensitive to touch, heat or cold than usual ?



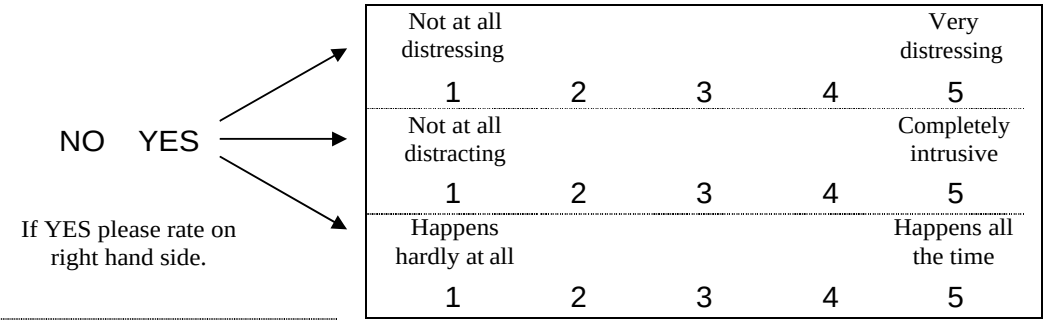
21) Do you ever think that food or drink tastes much stronger than it normally would ?



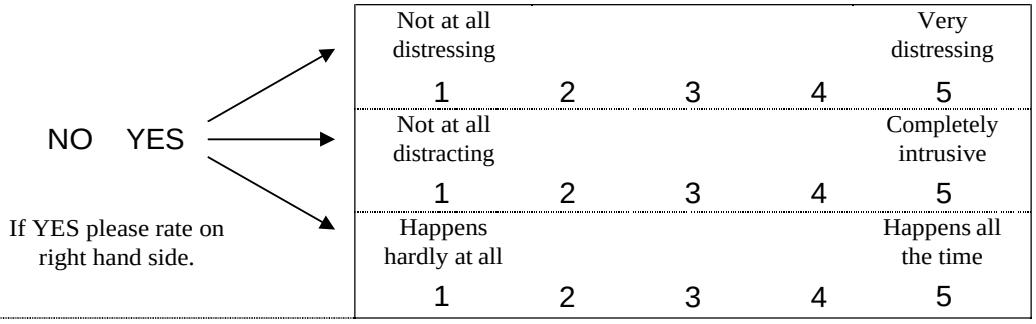
22) Do you ever look in the mirror and think that your face seems different from usual ?



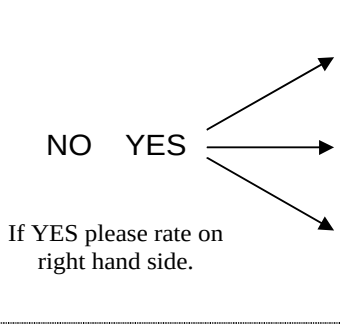
23) Do you ever have days where lights or colours seem brighter or more intense than usual ?



24) Do you ever have the feeling that of being uplifted, as if driving or rolling over a road while sitting quietly ?

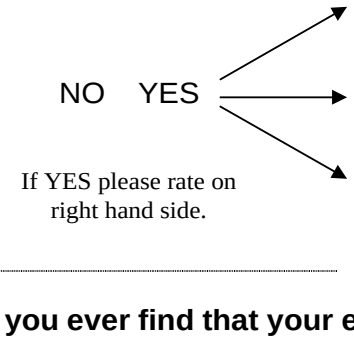


25) Do you ever find that common smells sometimes seem unusually different ?



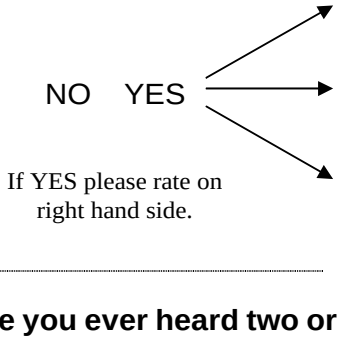
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

26) Do you ever think that everyday things look abnormal to you ?



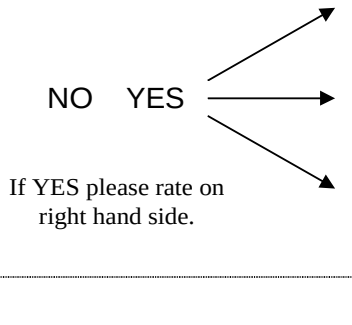
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

27) Do you ever find that your experience of time changes dramatically ?



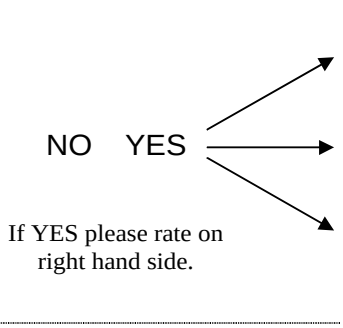
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

28) Have you ever heard two or more unexplained voices talking with each other ?



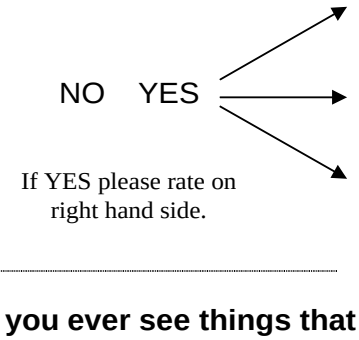
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

29) Do you ever notice smells or odours that people next to you seem unaware of ?



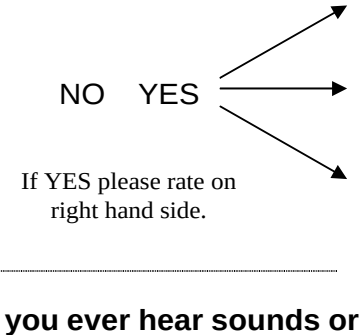
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

30) Do you ever notice that food or drink seems to have an unusual taste ?



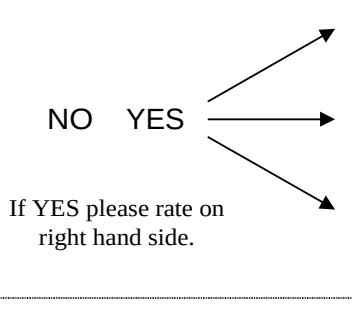
Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

31) Do you ever see things that other people cannot ?



Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

32) Do you ever hear sounds or music that people near you don't hear ?



Not at all distressing				Very distressing
1	2	3	4	5
Not at all distracting				Completely intrusive
1	2	3	4	5
Happens hardly at all				Happens all the time
1	2	3	4	5

Appendix H

Computational current flow models of tDCS, for Chapters 2 and 3. Current flow models were computed using *Spheres* (Dmochowski et al., 2012), a free software package for simulating tDCS current flow in the brain. Applied scalp current is expressed as brain current flow through a linear combination of spherical harmonics (see Dmochowski et al., 2012).

Chapter 2

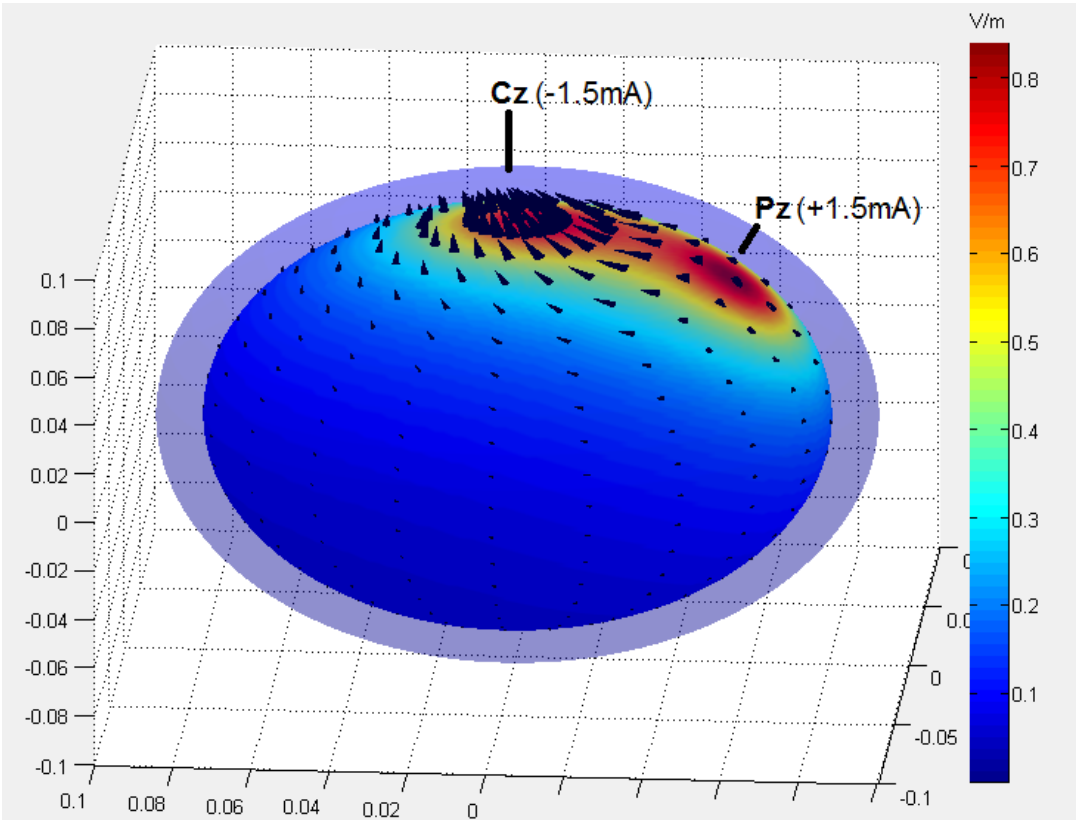


Figure H.i – Current flow model for the stimulatory montage used in Chapter 2. Setup for both anodal and sham stimulation: Anode at Pz, Cathode at Cz, 1.5mA, current density = 0.06mA/cm^2. Anodal stimulation = 20 minutes, 30s fade in/out; Sham stimulation = 30s, 10s fade in/out. V/m = electric field magnitude.

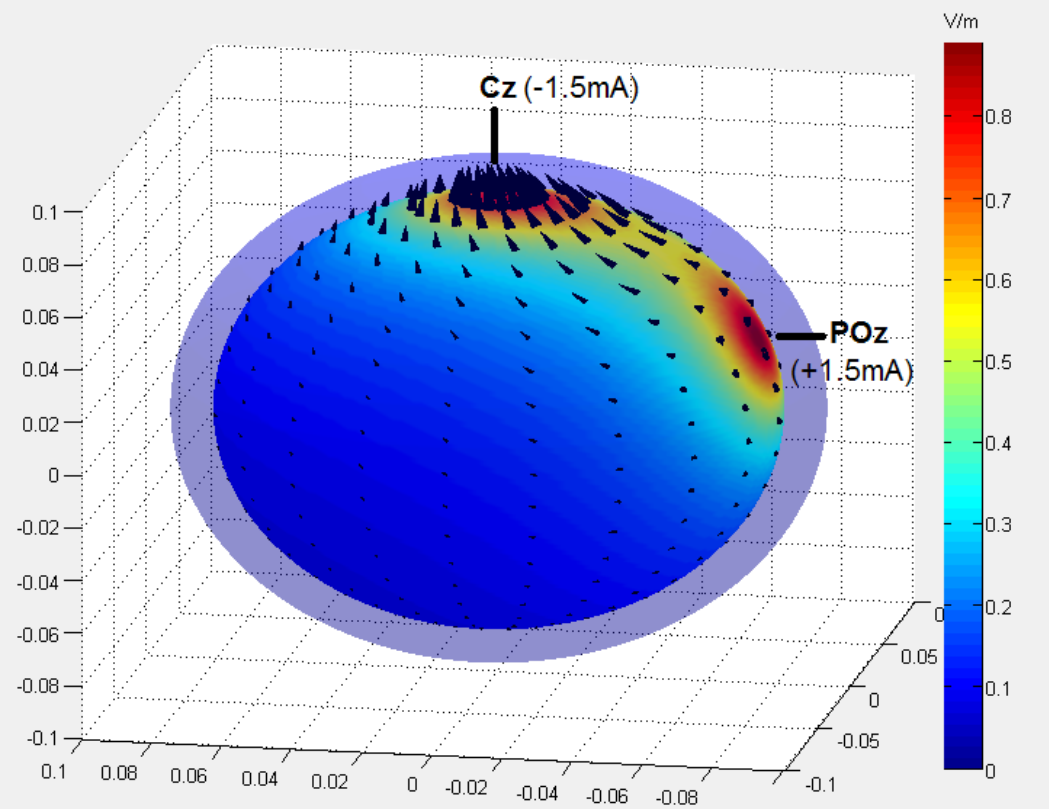


Figure H.ii – Current flow model for the stimulatory montage used in Chapter 3, for both anodal and sham stimulation: Anode at POz, Cathode at Cz, 1.5mA, current density = 0.06mA/cm^2. Anodal stimulation = 10 minutes, 30s fade in/out; Sham stimulation = 30s, 10s fade in/out. Cathodal stimulation model not shown. V/m = electric field magnitude.

Appendix I

CONSENT TO PARTICIPATE IN RESEARCH ON CORTICAL HYPEREXCITABILITY AND VISUAL DISTORTIONS

School of Psychology, University of Birmingham

What is the purpose of this study?

The purpose of the study is to examine biases of latent cortical hyper-excitability between individuals who report hallucinations as compared to those that do not, using a form of brain recording called electroencephalography (EEG). The experiment will last approximately 1 hour 30 minutes (up to 2 hours).

What is EEG?

Electroencephalography (EEG) is a technique widely used in neurology, with no known risks. The electrical activity generated by your brain is recorded by small electrodes which are placed on your scalp. Gel will be added to your scalp. You should not wear any hair products (gel, spray, etc.) on the day of the experiment.

What does this study involve?

During this session, you will first be screened for your suitability to take part and complete some questionnaires for measuring proneness to anomalous perceptions. You will complete a computerised task called the "pattern glare" task, which involves viewing some striped patterns. This task will take less than 10 minutes. The researcher will then set up the EEG equipment to record your brain activity. While your brain activity is being recorded, you will complete a computerised task that involves listening to some "click" sounds through headphones. This task will last for around 30 minutes. During the task you will be able to watch the TV show or movie of your choice (from a selection, with subtitles & no sound). After the task, the EEG electrodes will be removed and the study will be finished. The experimenter will then debrief you.

Will you be paid to participate in this study?

In exchange for your participation in this study, you will earn 1 credit per hour toward your RPS participation requirements, OR £8 per hour.

Other important information you should know:

- **Benefits from participation:** You will not benefit directly from participating in this study, but your participation may provide you with the indirect benefit of learning more about this research project and experimental psychology in general.
- **Risks associated with participation:**
  You will encounter no greater risks of discomfort than those incurred in routine daily activities. **EEG** – There are no known risks associated with EEG recording. You may experience some very mild irritation on the skin under the electrodes, but this will dissipate once the electrodes and gel are removed. **Pattern-glare task** – you will view some briefly-presented stimuli which you may find irritating.
- **Withdrawal from the study:** You may choose to stop your participation in this study at any time. Your decision to stop your participation will have no effect on your academic standing. Your data will be destroyed immediately on withdrawal. If you withdraw you will be compensated for the portion of the study you have completed. Participants can also decide to have their data withdrawn up to one week after the end of the experiment.

- **Data collection:** The data collected in this study will include (i) the responses that you make on the questionnaires and the task described above, (ii) basic performance in terms of ratings, (iii) basic demographic information about you (e.g., sex, age). The data collected in this study will be used only for the purpose described in this form, and will be available only to the researcher and principal investigator listed in this consent form. Raw data gathered from this study will be maintained for 10 years as required by regulations, following the publication of empirical articles or communications describing the results of the study.
- **Confidentiality:** Every effort will be taken to protect the names of the participants in this study. Your identity will not be recorded as part of your data, and will not be revealed in any publication that may result from this study; your consent form will not be stored with your data, to ensure that your identity cannot be linked in any way to your data. All information you provide will be kept confidential, except as governed by law.

Who should you call with questions about this study?
Questions or concerns about this study may be directed to the researcher (Rachel Marchant, email: rem393@bham.ac.uk) or the staff member in charge of this research project: Dr Ali Mazaheri (email: MazaherA@adf.bham.ac.uk – telephone:).

CONSENT

☐ I have read and understood the above information.

☐ I have been given an opportunity to ask questions and received satisfactory answers.

☐ I understand that I am free to leave this study at any time without having to give a reason.

☐ I understand that data collected during the study will be looked at by researchers from the University of Birmingham. I give permission for these individuals to have access to my data. I understand that my data will be stored anonymously.

☐ I agree to participate in this study.

_____

_____

Participant Name Participant Signature and Date

Rachel Marchant

_____

Researcher Name Researcher Signature and Date

Appendix J

Selective Attention and Awareness Laboratory
School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT

Screening & Safety Questionnaire

If you agree to take part in this study, please answer the following questions. The information you provide is for screening purposes only and will be kept completely confidential.

	YES	NO
Do you currently suffer from any neurological or psychiatric conditions?		
If YES please give details (nature of condition, duration, current medication (if any)):		
Have you ever had a significant head/brain injury or surgery, or concussion?		
Do you have photosensitive epilepsy?		
Have you ever suffered from any other form of epilepsy, febrile convulsions in infancy, or had recurrent fainting spells?		
If YES please give details:		
Does anyone in your immediate or distant family suffer from epilepsy?		
If YES please state your relationship to the affected family member:		
Do you suffer from migraines?		
Have you ever undergone a neurosurgical procedure (including eye surgery)?		
If YES please give details:		
Do you have any ocular (eye) conditions (e.g. astigmatism, colour blindness, optic neurosis)?		
Are you currently taking any un-prescribed or prescribed medication?		
If YES please give details:		
Are you currently undergoing anti-malarial treatment?		
Have you had any alcohol in the last 12 hours?		
If YES please estimate how many units and how long ago:		
Have you had any tea, coffee, energy drinks, or other sources of caffeine, in the last 12 hours?		
If YES please estimate how many cups/cans of each and how long ago:		
Do you regularly use any recreational drugs? If YES please specify:		
Have you used recreational drugs in the last 24 hours?		
Are you a smoker (do you regularly smoke at least 1 cigarette a day, every day), or do you use nicotine patches / gum?		
Did you have very little sleep last night?		
Has your regular sleep pattern been disturbed during the past week?		
If YES please give details:		
Do you have any skin problems or conditions?		
If YES please give details:		

Handedness: Left / Right **Date of Birth**: ____/____/____ **Age**: ____ **Sex**: F/M

Ethnicity: Please circle your ethnicity (people's ethnicity describes their feeling of belonging, and attachment to, a distinct group of a larger population that shares e.g. their ancestry, language, religion, etc.):

White/Caucasian	Latino/Hispanic	Middle Eastern
African	Caribbean	South Asian
East Asian	Mixed (please indicate)	Other (please indicate)

Do you consider yourself to be fluent in English? Yes / No

Longest lifetime country of residence: _____
Please estimate duration (e.g. years): _____

Degree course (e.g. BA, MSc, PhD): _____
Subject/Area: _____

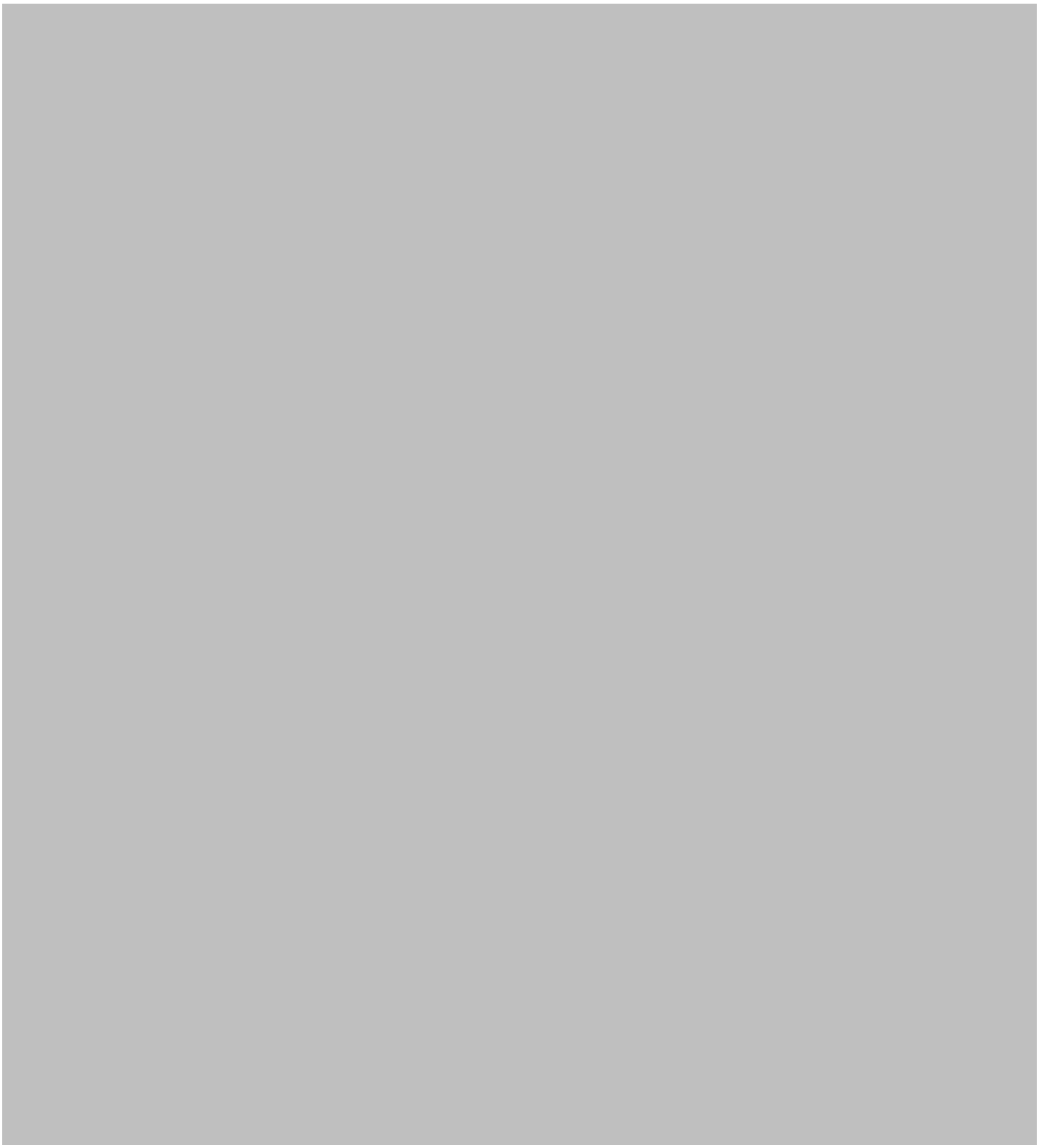
I confirm that the above information is accurate to the best of my knowledge.

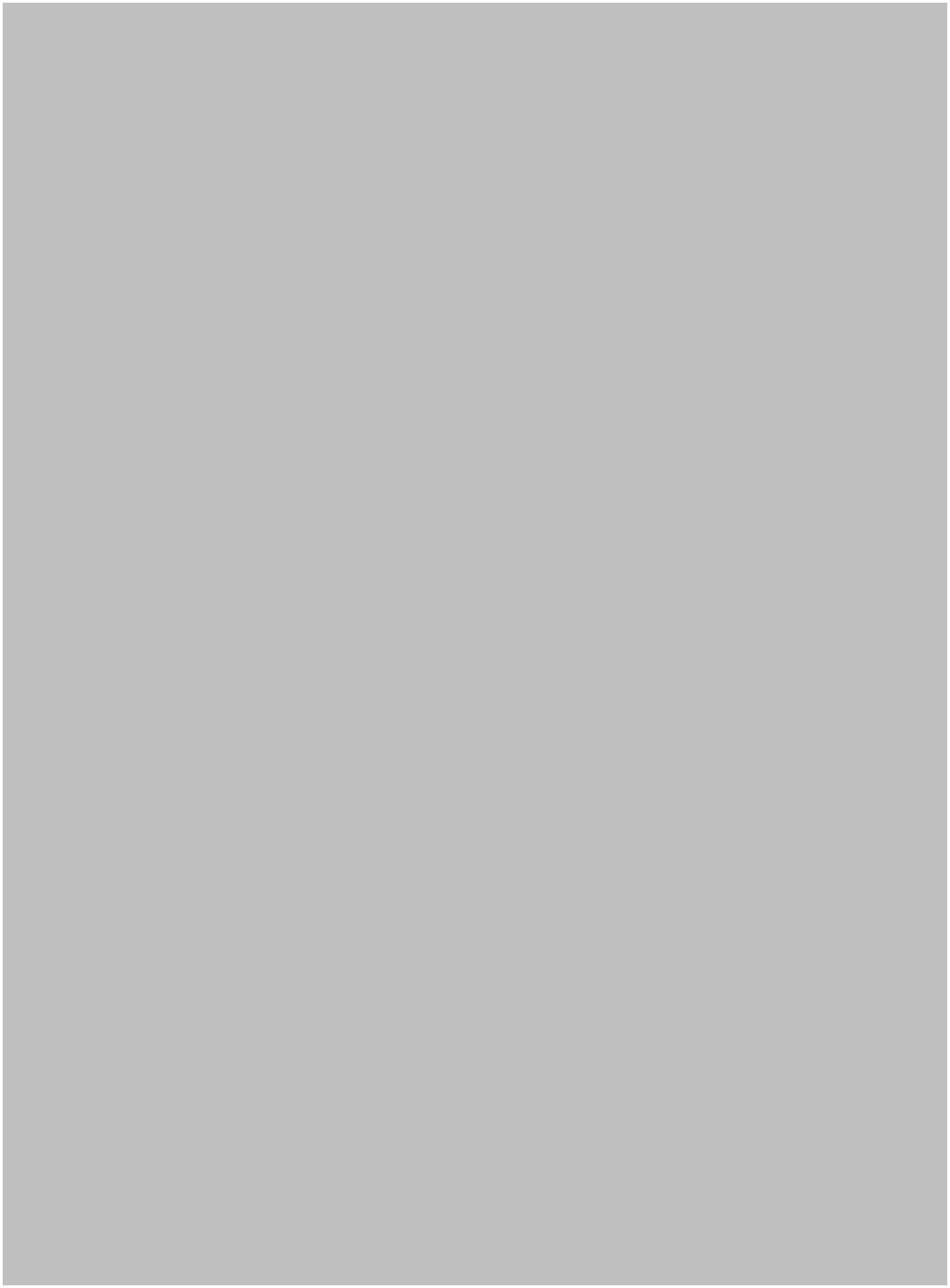
Session 1	**Name**	**Signature**	**Date**
Participant			
Researcher	Rachel Marchant		

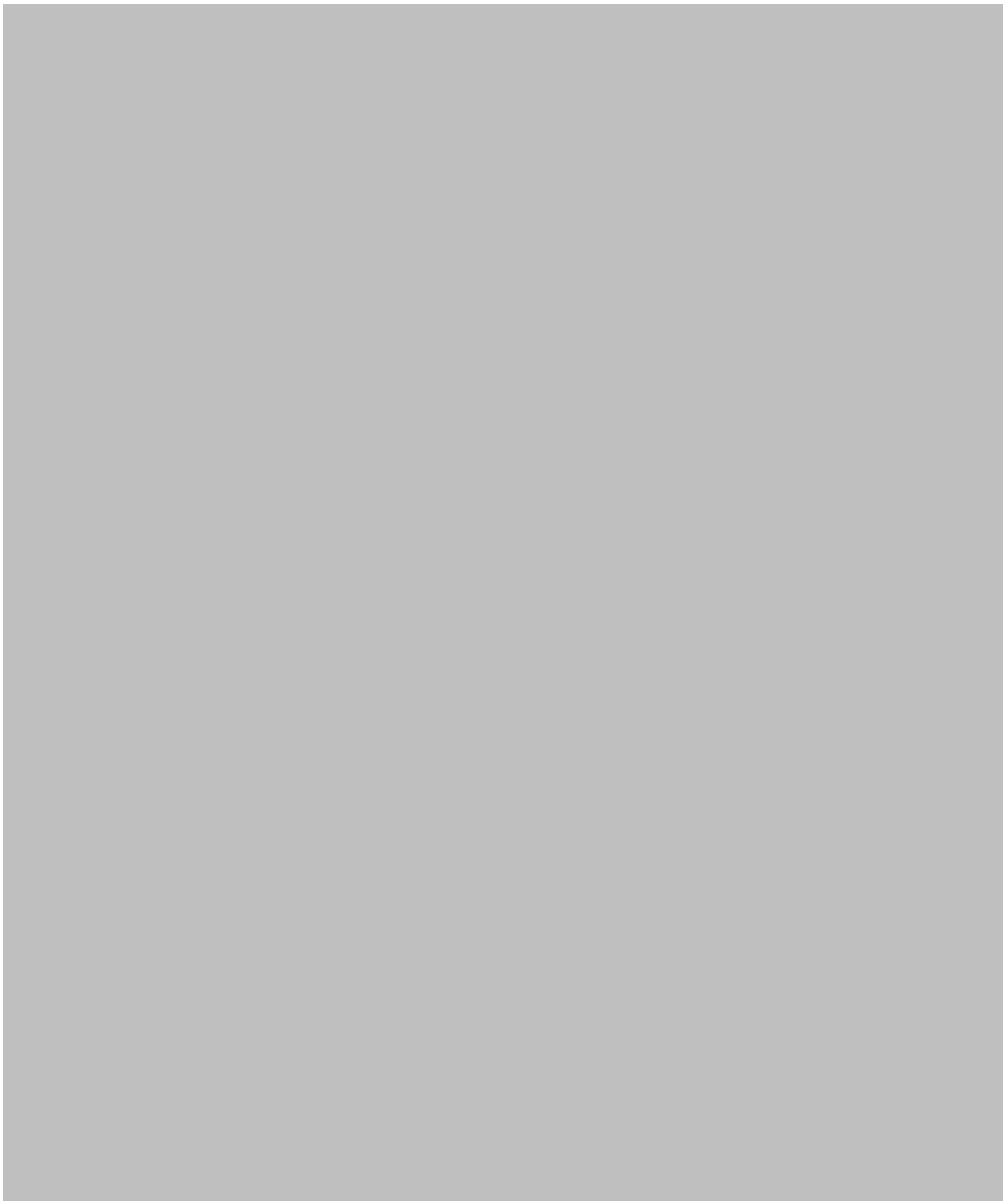
Appendix K

The Cortical Hyperexcitability index-II (CHi_II)

Chun Yuen Fong, Chie Takahashi, Jason J Braithwaite







Appendix L

Multi-Modality Unusual Sensory Experiences Questionnaire (MUSEQ)

We now know that both healthy people and people with medical or psychological conditions report having strange or unusual experiences. These experiences range from being very subtle to quite obvious. We want to find out more. Please answer **all** questions by **placing a tick or cross (✓ or X)** in the most appropriate response box. There are no right/wrong answers and your responses are kept confidential.

AUDITORY					
There have been times when…	***Never* (0)** (Never happened)	***Hardly Ever* (1)** (Once or twice in my life)	***Rarely* (2)** (Once or twice a year)	***Occasionally* (3)** (A few times a year)	***Frequently* (4)** (At least monthly)
1. My ears have played tricks on me					
2. Sounds were louder than they normally would be					
3. I thought of a song and could almost hear it with distinct clarity					
4. I was in a crowd or with other people and heard my name being called, only to find that I was mistaken					
5. I have heard my phone ring then found that it wasn't ringing at all					
6. I could hear sounds, music, or noises that other people could not hear					
7. I have heard a person's voice and then found that no-one was there					
VISUAL					
8. My eyes have played tricks on me					
9. I found that lights or colours seem brighter or more intense than they normally would be					

10. I thought of people, objects, or landscapes, and could almost see their image in front of my eyes					
11. I have looked at a patterned object (e.g., wallpaper, curtains, tiled floor) and a figure or face has emerged					
12. I have seen lights, flashes, or other shapes that other people could not see					
13. I looked at an object and it transformed itself before my eyes into something else					
14. I saw a brief image of an object, animal, or person pass me by in my peripheral vision, but when I looked there was nothing there					
15. I saw people, faces, or animals, and then found that nothing was there					
OLFACTORY					
There have been times when…	***Never* (0)** (Never happened)	***Hardly Ever* (1)** (Once or twice in my life)	***Rarely* (2)** (Once or twice a year)	***Occasionally* (3)** (A few times a year)	***Frequently* (4)** (At least monthly)
16. My nose (sense of smell) has played tricks on me					
17. I thought that everyday smells were unusually strong					
18. I thought of a smell and I could almost smell it for real					
19. Common smells seemed unusually different					
20. I noticed the smell of smoke, burning, or gas when there was nothing there					
21. I have suddenly been struck by an unpleasant or disgusting smell that no-one else could smell					

22. I have suddenly been struck by a very pleasant smell that no-one else could smell					
23. I have been struck with the smell of odd things which I interpreted as death, colours, or ghosts					
GUSTATORY					
24. My sense of taste has played tricks on me					
25. I thought that food or drink tasted stronger than it normally would					
26. I thought of a taste and found that I could taste it in my mouth as if it was real					
27. I ate the same food as another person and thought it tasted off, but the other person did not seem to think so					
28. I have consumed food or drink and it tasted like something completely different					
29. I had nothing in my mouth but I suddenly tasted something very confusing which faded very quickly					
30. I had nothing in my mouth but I suddenly tasted something unpleasant which was really persistent					
31. I had nothing in my mouth but I suddenly tasted something very pleasant which was really persistent					

BODILY SENSATIONS					
There have been times when…	***Never* (0)** (Never happened)	***Hardly Ever* (1)** (Once or twice in my life)	***Rarely* (2)** (Once or twice a year)	***Occasionally* (3)** (A few times a year)	***Frequently* (4)** (At least monthly)
32. My body senses have played tricks on me					

33. I found my skin to be more sensitive to cold, heat, or touch than usual					
34. I thought of a touch or other sensations on my skin and almost felt it on my skin					
35. I have experienced the sensation that my body (or part of my body) was different in shape or size					
36. I could feel burning, tingling, scraping, or heat on my skin, although there was nothing causing it					
37. I have felt things moving or crawling on or under my skin					
38. I have experienced the sensation that something was pressing on my skin, or that I was holding an object in my hand, but then found there was nothing there					
39. I have felt someone or something touching me, but when I turned to look there was nothing there					
SENSED PRESENCE					
40. I felt the presence of someone, even though I could not see them (e.g., behind me, or in another room)					
41. I have felt an unseen evil presence around me					
42. I have felt an unseen angelic presence around me					
43. I have felt the presence of a relative or friend who has passed away					

Appendix M

Pattern glare low frequency grating descriptive statistics for Chapters 2 and 3.

Chapter 2

	Non-PG		PG	
	Sham	**Anodal**	**Sham**	**Anodal**
Mean	6.0	5.2	9.1	7.9
SEM	1.3	1.0	1.3	1.1
σ	6.6	5.1	8.9	7.3
Range	39.0	30.0	39.0	30.0

Supplementary Table 1 – Descriptive statistics for pattern glare intensity ratings for low frequency gratings, split by pattern glare group (non-PG = M-HΔ PG ratings ≤ 0, PG = M-HΔ PG ratings ≥ 1) and tDCS condition (sham, anodal).

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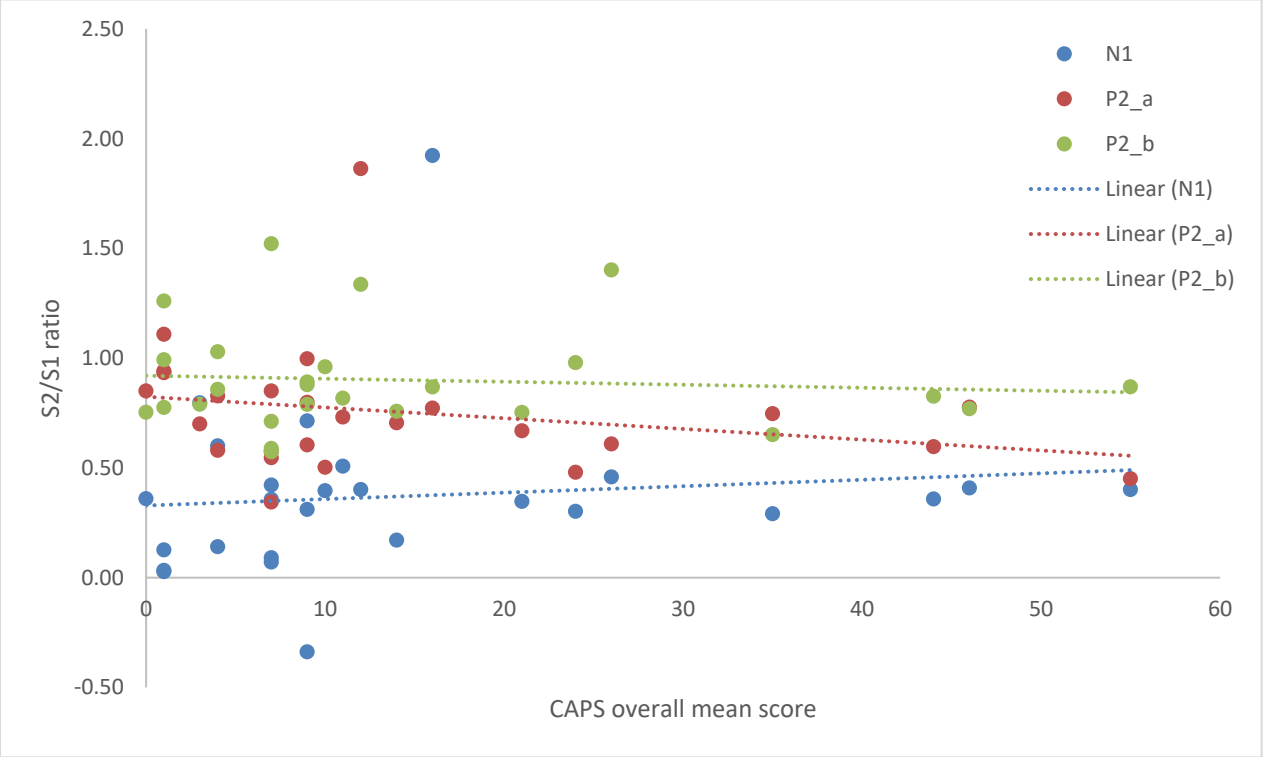
	Non-PG			PG		
	Sham	**Anodal**	**Cathodal**	**Sham**	**Anodal**	**Cathodal**
Mean	8.3	9.8	9.3	7.2	9.6	9.7
SEM	1.4	2.0	2.1	1.2	1.9	1.5
σ	8.3	11.6	12.3	7.6	11.8	9.7
Range	28.0	44.0	47.0	28.0	59.0	39.0

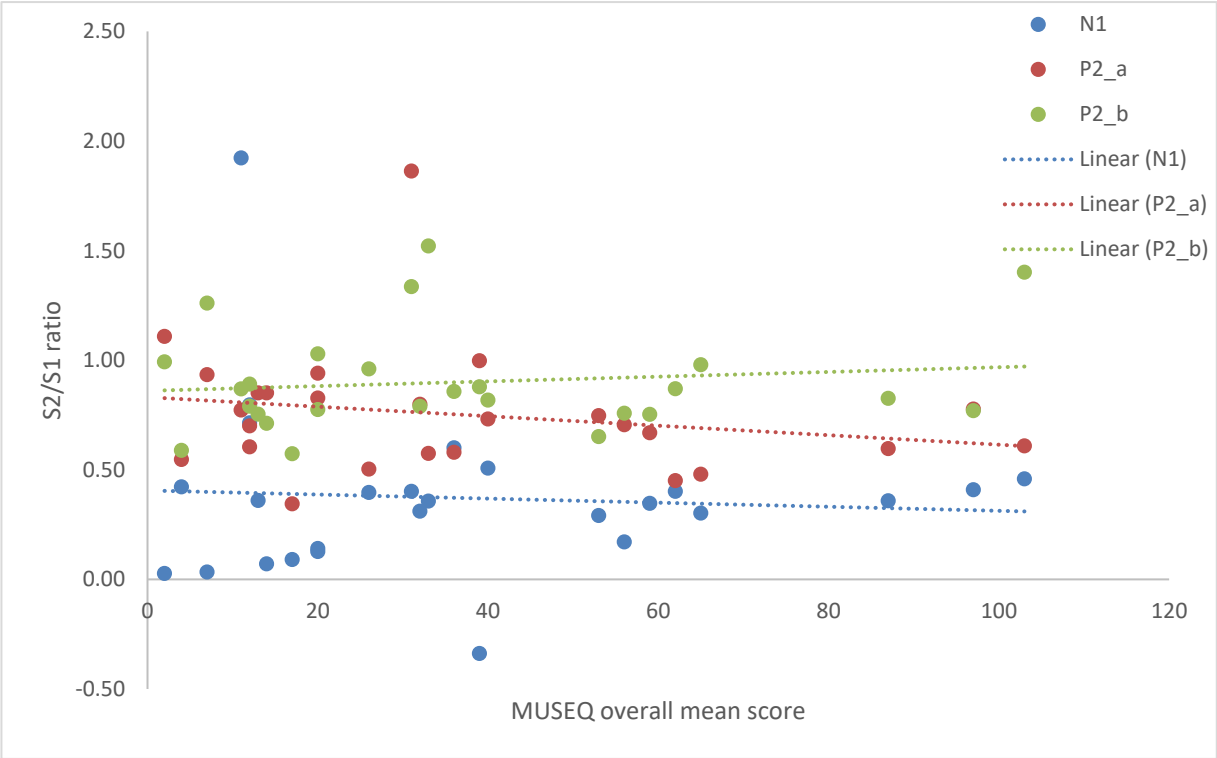
Supplementary Table 2 – Descriptive statistics for pattern glare intensity ratings for low frequency gratings, split by pattern glare group (non-PG = M-HΔ PG ratings ≤ 0, PG = M-HΔ PG ratings ≥ 1) and tDCS condition (sham, anodal, cathodal).

Appendix N

Sensory gating and CAPS / MUSEQ measures as investigated with exploratory analysis. Scatterplots did not indicate any relationships (**Suppl. Figures 1-2**).

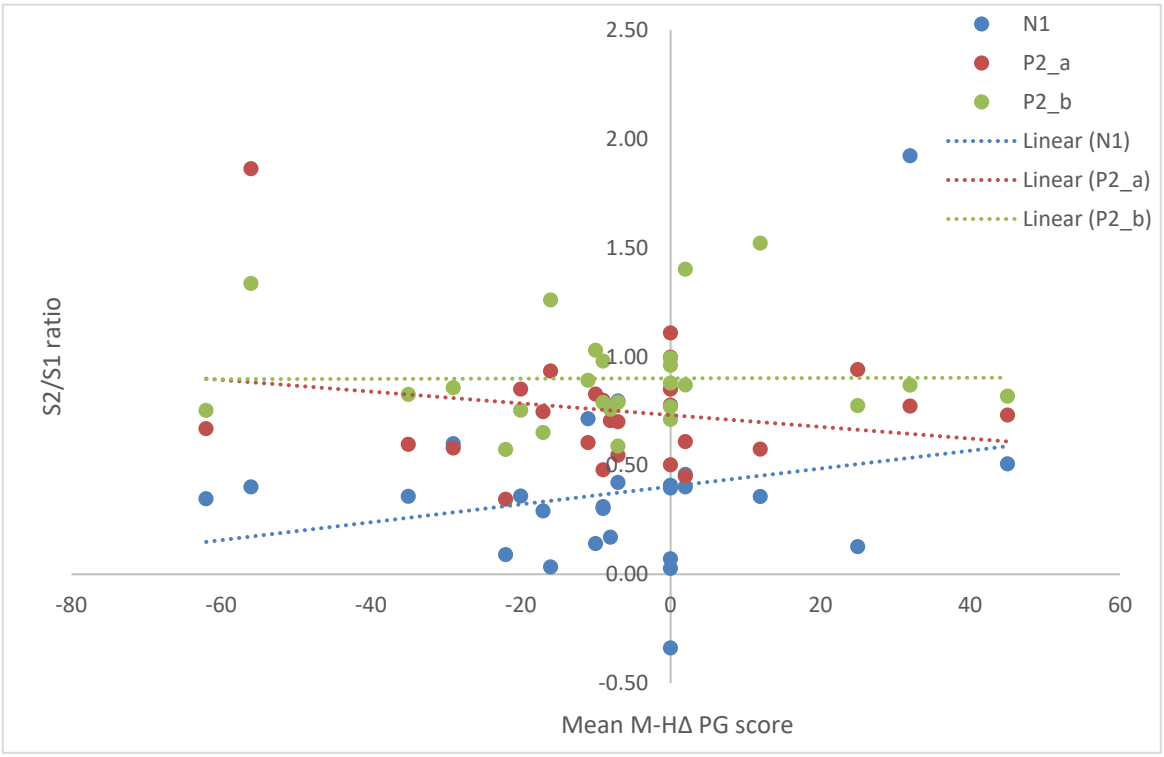


Suppl. Figure 1 – Scatterplot showing relationships between CAPS overall scores and S2/S1 ratios for the N1, P2_a, and P2_b components. Dotted lines = linear trend lines.



Suppl. Figure 2 – Scatterplot showing relationships between MUSEQ overall scores and S2/S1 ratios for the N1, P2_a, and P2_b components. Dotted lines = linear trend lines.

Sensory gating and pattern glare M-HΔ scores as investigated with exploratory analysis. Scatterplot indicates no relationships (**Suppl. Figure 3**).



Suppl. Figure 3 – Correlations between pattern glare M-HΔ scores and S2/S1 ratios for the N1, P2_a, and P2_b components. Dotted lines = linear trend lines. All correlations were non-significant (p>0.05).

Appendix O

Table of original empirical studies correlating EEG-based sensory gating with questionnaire measures. Studies with a healthy control (HC) group are bolded.

Author/s & Year	**Patients/Healthy Controls (HCs)**	**EEG measure/s**	**Questionnaire measure/s**	**Sample size/s**
Laurent et al., 1999	Patients (SZP)	P2 latency	PANSS	20
Adler et al., 1990	Patients (SZP)	P50 amplitude	PANSS	20
Brockhaus-Dumke et al., 2008	Patients (SZP) & **HCs**	P50, N1 amplitudes	PANSS	~100
Boutros et al., 2009	Patients (SZP) & **HCs**	P50, N1 amplitudes	PANSS	~**50** per group
Thoma et al., 2017	Patients (SZP)	P50, N1, P2 amplitudes	PSYRATS	12
Croft et al., 2001	**HCs**	P50 amplitude	Schizotypy (PSQ)	**35**
Park et al., 2015	**HCs**	P50 amplitude	Schizotypy (O-LIFE)	**48**
Smith et al., 2013	Patients (SZP) & **HCs**	P50 amplitude	PSYRATS	16 & **21**
Erwin et al., 1998	Patients (SZP)	P50 amplitude	SAPS/SANS	31
Arnfred & Chen, 2004	Patients (SZP) & **HCs**	P50 amplitude	Revised Social Anhedonia Scale	12 & **14**
Ringel et al., 2004	Patients (SZP) & **HCs**	P50 amplitude	PANSS	34 & **12**
Yee et al., 1998	Patients (SZP) & **HCs**	P50 amplitude	BPRS (anxiety, depression, thought disturbance, etc) & SANS	22 & **11**
Thoma et al., 2005	Patients (SZP)	P50 amplitude	SANS, PANSS, depression	20
Keil et al., 2016	Patients (SZP) & **HCs**	Oscillatory power & synchrony	PANSS	**22** per group
				Overall mean = 28 **HCmean = 27**