Understanding Charles Bonnet syndrome: mechanisms and intervention

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Abstract

Background: Charles Bonnet Syndrome (CBS) is defined by the occurrence of vivid, recurring visual hallucinations (VH) secondary to visual impairment in the absence of psychiatric illness or cognitive impairment. Previous research has proposed that deafferentation, due to loss of sensory input from the eyes, leads to spontaneous hyperexcitability in the visual cortex resulting in VH. Approximately one-third of people with CBS report distress and disruption to daily functioning as a consequence of VH, however there are currently no effective treatments and a lack of research into the aetiology of VH has hindered their development.

Aims: 1) To investigate the role of visual cortical activity in the production of VH in CBS, compared to non-hallucinating controls, to better understand why VH occur in some patients but not others. 2) To investigate whether inhibitory non-invasive transcranial direct current stimulation (tDCS) could be used to remediate VH by reducing cortical excitability in CBS.

Methods: Study 1: A comparison study consisting of people with CBS (n=19) and non-hallucinating sight-matched controls (n=18) was performed utilising transcranial magnetic stimulation, functional magnetic resonance imaging, and magnetic resonance spectroscopy to compare differences in visual cortical activity between groups. Study 2: Informed by a pilot study in continuous CBS hallucinators, sixteen members of the CBS group received 4-consecutive days of active and sham inhibitory tDCS over the primary visual cortex, comparing visual cortical activity and VH ratings before and after stimulation between active and sham weeks.

Results: Study 1: Comparable visual cortical excitability was observed in both groups, although greater excitability was associated with more severe VH in the CBS group. Functional activation of the visual cortex was observed to be lower in the CBS group than controls during an eye movement task, with greater functional activation associated with lower visual cortical excitability. Study 2: Active cathodal tDCS of the primary visual cortex resulted in a significant decrease to VH frequency and intrusiveness compared to sham stimulation. No significant changes to cortical activity were observed following stimulation.

Conclusions: This thesis constitutes the largest neurophysiological comparison and treatment study performed in CBS to date. These data support the role of changes to visual cortical activity in the production of VH following sight loss, providing a basis for further study.

Furthermore, tDCS was observed to present a potential effective new treatment option for CBS, however further study is needed to understand underlying mechanisms.

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List of Abbreviations

AD	Alzheimer's disease
AMD	Age-related Macular Degeneration
ANOVA	Analysis of Variance
BOLD	Blood oxygen level dependent
CBS	Charles Bonnet syndrome
Cr	Creatine
CSF	Cerebral spinal fluid
DLB	Dementia with Lewy bodies
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DTI	Diffusion tensor imaging
EEG	Electroencephalography
ERG	Electroretinogram
FDG-PET	Fluorodeoxyglucose positron emission tomography
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GDS	Geriatric depression scale
HPPD	Hallucinogen Persisting Perception Disorder
IADL	Instrumental activities of daily living
LBD	Lewy body dementia
LGN	Lateral geniculate nucleus
LSD	Lysergic acid diethylamide
MEG	Magnetoencephalography
MMSE	Mini mental state examination
MRS	Magnetic resonance spectroscopy
NEVHI	North East visual hallucination interview
NPI	Neuropsychiatric inventory
PAD	Perception and attention deficit model

PD	Parkinson's disease
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PT	Phosphene threshold
REM	Rapid eye movements
ROI	Region of interest
SD	Standard deviation
SHAPED	**S**tudy of **ha**llucinations in **P**arkinson's disease, **E**ye disease, and **D**ementia
SPECT	Single-positron emission computed tomography
SSVEP	Steady-state visual evoked potentials
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VEP	Visual evoked potential
VH	Visual hallucination(s)
VISMAC	Treating **vis**ual hallucinations in **mac**ular degeneration: a non-invasive stimulation study.

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Chapter 1 Introduction to Charles Bonnet syndrome

1.1 Charles Bonnet Syndrome: An Overview

First described by the renowned 18th century Genevan naturalist and philosopher, Charles Bonnet, in relation to the vivid hallucinatory experiences of his grandfather, Charles Bonnet syndrome (CBS) is typified by the presentation of recurring visual hallucinations (VH) secondary to a visual impairment (Teunisse et al., 1996). In his seminal essay, Bonnet described the accounts recorded by his grandfather, Charles Lullin: an 89-year-old former magistrate, of images he had seen following his vision loss due to severe bilateral cataracts (Menon et al., 2003). Lullin described, in great detail, entirely silent perceptions of people, animals, carriages and buildings which varied in size and shape; Bonnet further noted that his grandfather retained intact cognition and was fully cognisant of the unreality of his visions, describing them as 'fictions of his brain' (Fernandez et al., 1997).

The observations described by Bonnet have formed the basis of modern-day classifications of CBS, with visual hallucinations in CBS described as characteristically clear and well-defined, occurring in the presence of preserved cognition and insight, and in the absence of hallucinations in other modalities. It has therefore been argued that the phenomena differ from similar hallucinatory experiences in psychosis-related disorders such as schizophrenia, dementia and delirium where introspective insight into the unreality of the hallucinations is not so clear (Teunisse et al., 1996).

While the content of visual hallucinations in general can take many forms, including the presence of persistent after images (palinopsia), and scintillating scotoma (teichopsia; most commonly associated with migraine; Aurora et al., 1999), hallucinations experienced by people with CBS predominantly consist of imagery that can be separated into simple or complex phenomena. Simple hallucinatory phenomena are the most commonly reported phenomena in eye disease and typically consist of flashing or shimmering lights, dots, lines, and amorphous shapes (known as photopsia) which may remain static or move across the visual field (Collerton et al., 2005). In comparison, complex hallucinatory phenomena, which are often considered the hallmark of CBS, may consist of abstract, repetitive geometric patterns (tesselopsia), or vivid, formed, imagery of people, animals, objects, and topographic scenes, which may be familiar or unfamiliar to the patient (ffytche, 2007).

Typically, hallucinations can last between seconds to minutes before spontaneously disappearing or following eye-closure (Hughes, 2013; Khan et al., 2008; Menon et al., 2003), although some patients may report continuous VH throughout their waking hours. Onset of VH in the presence of visual impairment can occur gradually or spontaneously, and initial simple hallucinations, such as amorphous shapes, may progress to become more complex over time (Menon et al., 2003). Frequency of hallucinations can range from several times a day to once every few months and can continue for several years after onset, although some studies have suggested that hallucinations may reduce or even cease following complete loss of sight (Khan et al., 2008; Menon et al., 2003; Teunisse et al., 1996). While patients typically indicate that VH occur independent of external triggers, some report that the incidence of hallucinations can increase with fatigue, stress, and in low light environments (Menon et al., 2003).

Patient reactions to VH imagery can vary, and the presence of preserved insight can result in individuals reporting hallucinations as pleasant and intriguing (Cox & Ffytche, 2014; Menon et al., 2003). Despite this, as many as one third of people with CBS report hallucinations as unpleasant, distressing, and disruptive of day-to-day functioning (Cox & ffytche, 2014; Menon et al., 2003; Teunisse et al., 1996) with the greatest negative outcomes associated with hallucination episodes which are more frequent and longer in duration (Cox & ffytche, 2014). CBS patients have been observed to exhibit anxiety and mild paranoia in response to hallucinatory imagery (Santhouse et al., 2000) and depression can be a frequently observed co-existing condition (Schultz & Melzack, 1993). Moreover, the commonly believed association between hallucinations and psychiatric illness can prove distressing for patients and relatives, resulting in a frequent reluctance for individuals to disclose their hallucinatory experiences and seek medical advice (Khan et al., 2008; Lannon et al., 2006; Menon et al., 2003). Furthermore, many patients report being unaware that hallucinations can be a common symptom of visual loss, which is further compounded by a general ignorance of CBS amongst medical professionals, with up to one third of CBS patients indicating that medical professionals also seemed unaware or unsure of the diagnosis (Cox & ffytche., 2014).

1.2 Epidemiology

As CBS is often under-reported by patients and can go unrecognised by clinical personnel, it is difficult to know the exact prevalence within eye disease populations.

Furthermore, as VH are a common symptom in conditions such as schizophrenia, neurodegenerative dementia, delirium, and drug induced hallucinosis (Abraham & Duffy, 1996; Armstrong, 2012; Collerton et al., 2005; ffytche & Wible, 2014; Menon et al., 2003), determining the underlying pathology associated with the hallucinations can prove complex, and prevalence rates may reflect inaccurate diagnoses of CBS or associated hallucinatory conditions. Further complicating accurate diagnosis is the fact that neurodegenerative disorders associated with VH (e.g. dementia and delirium) occur later in life, coinciding with an increase in the prevalence of eye disease, meaning that some patients may experience concurrent conditions making it even harder to disentangle the aetiopathogenesis of the hallucinations. CBS is most commonly associated with the presence of age-related macular degeneration (AMD) in both its 'wet' and 'dry' forms (Khan et al., 2008; Manford & Andermann, 1998; Teunisse et al., 1996), but can occur in conjunction with a wide range of ocular pathologies including cataracts, glaucoma, retinitis pigmentosa, retinal detachment and diabetic retinopathy, as well as following vision loss as a result of ocular injury (Hughes, 2013; Menon et al., 2003; Teunisse et al., 1996). Due to the increased prevalence of visual impairment in later life, CBS is most commonly reported in the elderly population. However, CBS has also been observed in younger patients, including children, in the presence of sudden visual loss or deterioration (Menon et al., 2003; Teunisse et al., 1996). The incidence of visual hallucinations in patients with visual impairment has been estimated at 11-15% for complex hallucinations, and 41-59% for elementary, or simple, visual phenomena (Menon et al., 2003).

1.3 Diagnosis

The diagnosis of CBS in both clinical and research settings has, thus far, been inconsistent. Initial descriptions of CBS state that patients are required to present with formed and persistent visual hallucinations in the presence of full or partial insight, in the absence of primary or secondary delusions or hallucinations in other modalities (Gold & Rabins, 1989). Furthermore, most diagnostic criteria stipulate the presence of ocular disease or injury resulting in loss of vision and the absence of further psychiatric or neurological diagnoses including psychosis and dementia (Teunisse et al., 1994).

Despite this, there are currently no official criteria for the diagnosis of CBS by clinicians, and consensus on many features of the condition is still lacking (See **Table *1.1***). For example, the degree of vision loss required to be diagnosed with CBS, and whether this is

restricted to central acuity loss alone, is still a point of debate with some disputing that patients with global visual acuities above a certain threshold should not meet the criteria for CBS (Hamedani & Pelak, 2019). Further heterogeneity in the diagnosis of CBS includes the definition of 'formed' vs 'unformed' VH and the presence of mild cognitive impairment, particularly in older patients (Hamedani & Pelak, 2019). While many studies in CBS will specify that patients must have preserved cognition to fit the diagnosis (i.e. Podoll et al., 1989; Teunisse et al., 1996), many papers do not specify the means in which cognitive impairment was assessed or to what level.

Table 1.1 *Table of diagnostic criteria described in the literature for Charles Bonnet Syndrome.*

Reference	Content	Visual Impairment	Lack of Cognitive Impairment	Insight	Absence of Non-Visual hallucinations
Damas-Mora et al., (1982)	Not Specified	Yes[1]	Yes[1]	Full	Not Specified
Gold & Rabins (1989)	Formed; Complex	No	No	Full or Partial	Yes
Podoll et al (1989)	Not Specified	Yes[1]	Yes	Full or Partial	Not Specified
Holroyd et al., (1992)	Formed	No	No	Not Specified	Not Specified
Teunisse et al. (1996)	Formed; Complex	No	Yes	Full or Partial	Yes
Khan et al. (2008)	Unformed or formed	Yes	No	Full or Partial	Yes
Vukicevic & Fitzmaurice (2008)	Formed	Yes	Yes	Not Specified	Not Specified

[1] Recognised as a frequently occurring factor but not necessary for diagnosis.

VH occur in a number of pathologies which present predominantly in elderly populations, such as dementia with Lewy bodies (DLB), Parkinson's disease (PD) and delirium. As visual impairment due to eye disease, such as macular degeneration, also demonstrates increased prevalence in the elderly population, there is often an overlap between these conditions. In particular, Lewy body disease (LBD), which encompasses DLB, PD, and Parkinson's disease dementia (PDD), regularly exhibits visual dysfunction in addition to complex VH (Devos et al., 2005; Diederich et al., 2005; Onofrj et al., 2006). As such, it has been proposed that CBS in some elderly patients may be due to latent dementia or neurodegeneration (i.e. Lapid et al., 2012; Terao & Collinson, 2000) and as some patients with LBD retain full or partial insight into the unreality of their hallucinations (i.e. Collerton et al., 2005; Pagonabarraga et al., 2014), which is a key-criteria in CBS, this may cast further doubt upon the diagnosis of CBS

in some cases. Alternatively, CBS has been suggested to confer an increased risk of developing dementia later on. Indeed, a study by Pliskin et al., (1996) observed that patients with CBS had a higher frequency of mild cognitive impairment than age-matched controls. However, no large-scale systematic studies have been conducted which indicate a significant link between these conditions and, to date, reports remain predominantly anecdotal (Russell et al., 2018). Furthermore, it is worth considering that the incidence of CBS in young adults and children, while to date receiving less investigation than older cohorts, provides a counterargument for the association between CBS and dementia (Menon et al., 2003; Teunisse et al., 1996).

Despite similarities in symptomology, the pathogenesis of these conditions and subsequent treatments may differ substantially, meaning that it is important for clinicians to differentiate effectively between pathologies before reaching a diagnosis. For example, the neuroleptic clozapine, which is an antagonist at D4 receptors, is used in the treatment of VH in PD due to the implicated role of the dopaminergic system in their aetiopathogenesis (i.e. Devanand & Levy, 1995); certain neuroleptics, however, may also induce anticholinergic side effects, and drugs such as mianserin, an antidepressant and $5HT_s$ antagonist, which can have strong anticholinergic effects have also been reported to reduce VH in PD patients (Collerton et al, 2005). Despite this, anticholinergic effects have also been reported to exacerbate VH in DLB (Scheepmaker et al., 2003), and contribute to cognitive deficits in schizophrenia (Minzenberg et al., 2004), highlighting the importance of appropriate diagnosis of the pathology causing VH prior to treatment. Nevertheless, it is likely that effective research into CBS, and subsequently the development of successful interventions, has been impeded by the lack of robust and unified criteria required to reach an appropriate differential diagnosis of CBS.

1.4 Management

Currently, there are no established medical treatments for CBS, with practical strategies suggesting reassurance, illumination and eye-closure used to mitigate the occurrence and persistence of VH, with the suggestion that medications should only be used in cases where these strategies fail (Eperjesi & Akbarali, 2004; Menon et al., 2003). However, the use of pharmacological interventions including cholinesterase inhibitors, anticonvulsants, and anti-psychotics have been reviewed in the literature and found to offer little-to-no benefit or long-term improvement (Baldessarini, 2009; Hughes, 2013; Menon et al., 2003) although no

dedicated pharmacological intervention trials have yet been performed in CBS. Additionally, such medications are frequently associated with both significant and severe side effects and can require strict changes to a patient's daily routine to ensure adequate compliance, making the need for the development of alternative interventions distinctly important (Hughes, 2013; Collerton & Taylor, 2011).

A survey of CBS patients performed by the Macular Society (2012) suggested that effective treatment may not require the complete cessation of VH. Instead, patient feedback suggested that changing the nature of the hallucinations to a form which was less unpleasant, intrusive, or distressing may be sufficient to improve patient quality of life (Cox & ffytche, 2014). This could potentially be achieved by reducing the frequency, duration and intensity of hallucinations, factors which have been associated with increased negative outcomes (Cox & ffytche, 2014), helping to diminish their impact on day-to-day functioning. However, in order to achieve this, it is important to first understand the underlying mechanisms involved in the formation of visual hallucinations in CBS.

1.5 Visual hallucination aetiology: a question of increased excitability?

n.b. The following sections include content from the literature review: daSilva Morgan et al (2018) "The utility and application of electrophysiological methods in the study of visual hallucinations." Published in Clinical Neurophysiology.

1.5.1 Cortical activity in CBS

The aetiology of visual hallucinations in CBS is still a point of debate which has hindered the development of therapeutic interventions. Several models designed to elucidate the formation of VH have been proposed in the literature, with some positing spontaneous changes in visual cortical activity and bottom-up processing (i.e. ffytche et al., 1998; Jardri et al., 2013; Oertel et al., 2007; Santhouse et al., 2000), while others propose a more complex top-down interaction between visual, executive and attentional networks (i.e. Collerton et al., 2005; Diederich et al., 2005; Shine et al., 2011) (**Table *1.2***.). While evidence from both electrophysiology and neuroimaging have provided strong evidence for these models, it is likely that the pathological locus of VH may be highly dependent on disease group and thus no model can be considered 'one size fits all'.

Table 1.2 *Key models of visual hallucination aetiology and associated pathologies (daSilva Morgan et al, 2018).*

Model	Description	Associated VH-Pathologies
Deafferentation/Release Phenomena	Diminished visual input due to visual system or retinal dysfunction results in spontaneous, compensatory hyper-excitability and disinhibition of the visual cortex, producing both simple and complex VH.	CBS; Occipital stroke; Visual system lesion
Cortical irritation	Overactivity in brain regions containing specific imagery, memories and representations results in complex VH.	Occipital and temporal Epilepsy; CBS
Perception and Attention Deficit (PAD) (Collerton et al, 2005)	The combination of attentional and visual perceptual impairments interact with visual scene representations, resulting in incorrect perceptual proto-objects.	DLB; PDD; Schizophrenia
Integrative Model (Diederich et al, 2005)	The integrative contribution of poor vision, aberrant visual and associative cortex activation and disinhibition results in disturbance of gating and filtering of external perceptions and the production of internal images.	PD; LBD; CBS
Visual Misperception and Network Dysfunction (Shine et al, 2011)	Network dysfunction and impaired signalling between the default mode network (DMN) and ventral attentional network (VAN), in addition to lack of filtering from the dorsal attentional network (DAN), results in perceptual errors and the formation of VH.	PD; DLB

Abbreviations: CBS: Charles Bonnet Syndrome; VH: Visual hallucinations; DLB: Dementia with Lewy bodies; PDD: Parkinson's disease dementia; LBD: Lewy body dementia; PD: Parkinson's disease.

In the case of CBS, the deafferentation hypothesis provides one possible explanation for the formation and maintenance of VH. This theory proposes that the loss of visual input from the eye, as a consequence of visual impairment, results in spontaneous, compensatory hyper-excitability of the visual cortex, similar to the mechanism involved in 'phantom limb syndrome' in which a patient still experiences sensation in a limb following amputation (Menon et al, 2003)(**Figure 1.1**). In this sense, CBS may also be considered analogous to tinnitus, in which excessive spontaneous activity within the central auditory system gives rise to auditory hallucinations, as has been observed by both electrophysiologic and neuroimaging studies (Kaltenbach & Afman, 2000; Lockwood et al., 1999). The presence of spontaneous hyperexcitability in CBS may be further exacerbated by the absence of normal inhibitory

activity in the visual cortex, which would usually mediate excitability and prevent the perception of images in the absence of visual stimuli (Horowitz, 1964). The absence of this inhibitory activity may subsequently allow false perceptions to reach higher processing areas, allowing them to intrude on conscious perception (Horowitz, 1964; Menon et al, 2003).

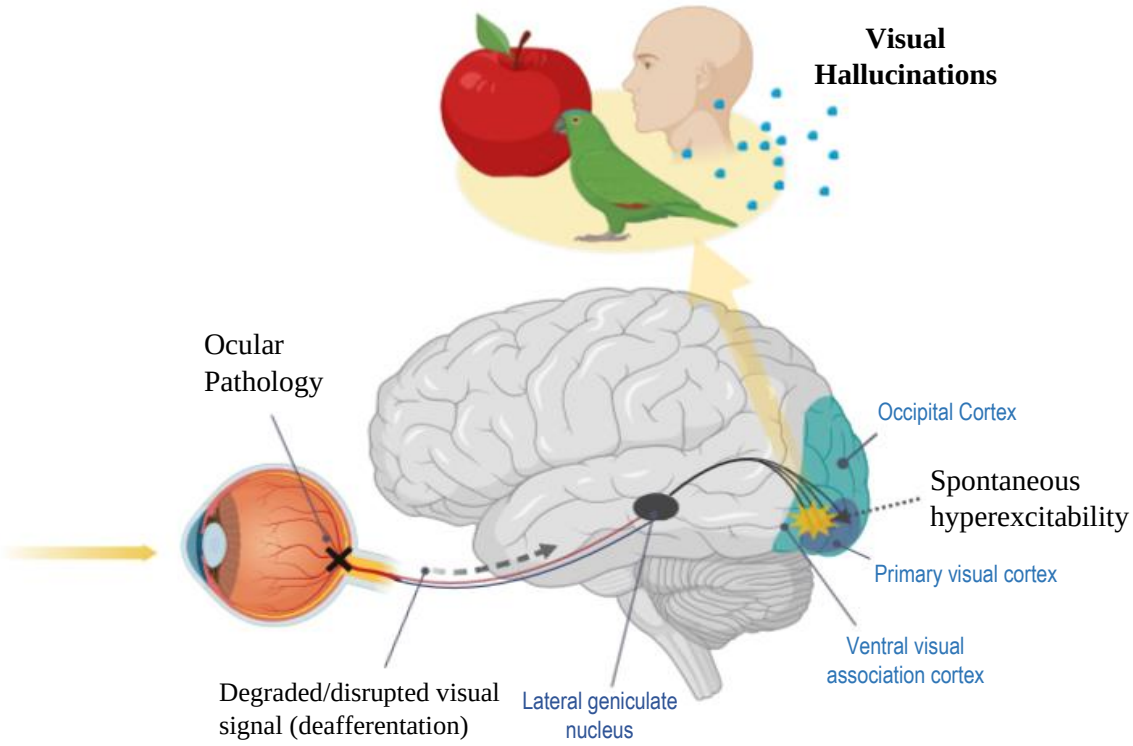

Figure 1.1. *Illustration demonstrating the deafferentation hypothesis of visual hallucination aetiology. Loss of visual input from the eyes results in compensatory spontaneous hyperexcitability in the visual cortex resulting in the production of vivid, formed visual hallucination imagery.*

In support of this theory, spontaneous hyperactivation of higher visual processing areas, specialised for different visual attributes, has been observed in CBS patients, with activation of specialised visual areas reflecting the specific content of hallucinations (i.e. the manifestation of a face hallucination corresponds with concurrent activation in the fusiform face area)(ffytche et al., 1998). Similarly, a rise in ventral occipital activity, detected using functional magnetic resonance imaging (fMRI), has been observed in CBS patients immediately before the onset of VH, which differs from the delayed response usually observed in healthy sighted controls when they are provided with visual stimuli (ffytche et al., 1998). Furthermore, increased ventral extra-striate activity has been observed in CBS patients which persists between hallucinations supporting the contribution of increased visual cortical excitability in CBS (ffytche et al., 1998; Santhouse et al., 2000).

With regards to electroencephalography (EEG), alpha-rhythm desynchronization has been posited as a measure of active cortical processing and cortical excitability (Barry et al., 2007; Pfurtscheller et al., 1996; Romei et al., 2008; Thut et al., 2006) and decreases in occipital alpha-power are associated with increased excitability and visual attention, while increased occipital alpha-power correlates with reduced occipital excitability (Thut et al., 2006). As such, generalised decreased alpha-power has been observed in CBS patients (Hanoglu et al., 2016) and is consistent with the argument for a bottom-up contribution to the formation of VH in CBS. Furthermore, macular degeneration patients with CBS have been observed to have significantly elevated visual-cortical responses to peripheral field stimulation, in the form of increased amplitudes of steady-state visual evoked potentials (SSVEPs), when compared to macular degeneration patients without VH and age-matched controls (Painter et al., 2018). While not performed in CBS specifically, studies of short-term visual deprivation have observed subsequent increases in excitability in the visual cortex, with false perceptions of light (known as 'phosphenes') being reported at lower thresholds following transcranial magnetic stimulation, supporting the role of visual impairment (even if temporary) in spontaneous visual cortical hyperexcitability (Boroojerdi, 2000).

While the above evidence appears consistent with the deafferentation hypothesis, further studies have observed alterations in aspects of cortical functioning present in CBS which may also contribute to the development of VH. Case reports in CBS have observed both slowing in posterior and occipital regions, and right-sided centro-parietal epileptiform discharges which were subsequently diminished by antiepileptic treatment in patients with CBS (Josephson & Kirsch, 2006; Lorberboym et al., 2002; Ossola et al., 2010). One case study observed increased posterior theta activity in CBS (Hanoglu et al., 2016), while another contradicted this finding, reporting diminished posterior theta-power during visual hallucinations in a patient with CBS (Kazui et al., 2009). While it is currently unclear how these changes in slow-wave and focal sharp-wave activity are directly linked to VH in CBS, it is possible that alterations of this nature may generate a physiological brain state permissive to the occurrence of VH. Such EEG abnormalities may also provide tentative evidence for functional changes in early visual cortex or association cortices in conjunction with the suppression of normal inhibitory input, which may be necessary for the VH to occur.

Building on this perspective, a study by Adachi et al (2000) observed asymmetrical hyperperfusion in the lateral temporal cortex, striatum and thalamus of five patients with CBS during complex VH, whilst the occipital lobes appeared unaffected. The inferior lateral

temporal cortex has been linked to the processing of featural information (LaBerge, 1995), while neural pathways between the thalamus, striatum and lateral temporal cortex are suggested to regulate aspects of visual attention suggesting that the over-excitation of these networks, indicated by asymmetrical blood flow, may give rise to VH (Middleton & Strick, 1996). Similarly, a case study of a patient with CBS showed increased functional connectivity between the precuneus and secondary visual cortex compared to blind controls, while blind controls demonstrated increased resting-state negative connectivity between the default mode network (DMN) and occipital fusiform gyrus not observed in the CBS patient or healthy controls (Martial et al., 2019).

While these findings again suggest that changes to cortical excitability may contribute to the development of VH in CBS, these data support the notion that alterations in excitability may occur in later regions of the visual association and attentional networks rather than the earlier visual regions located in the occipital lobe. While the deafferentation model proposes a bottom-up explanation for VH formation, particularly originating in the early visual cortex, these latter findings may suggest a greater involvement of higher visual perceptual and attentional processing areas as proposed by aetiological models such as the Perception and Attention Deficit (PAD; Collerton et al., 2005) and Attentional Control models (Shine et al., 2011).

Such alterations in cortical activity linked to the occurrence of VH in CBS may have important implications for the development of subsequent treatments. While treatment investigations are currently lacking, the role of hyperexcitability and deafferentation previously observed in CBS may indicate the potential utility of techniques designed to target and modulate regions demonstrating aberrant activity, such as non-invasive brain stimulation. One such technique, transcranial direct current stimulation (tDCS), can be used to modulate cortical activity using a weak electrical current applied through the scalp, with anodal stimulation producing an excitatory response, while cathodal stimulation produces an inhibitory effect (Stagg & Nitsche, 2011). Previous studies using tDCS to modulate activity in different patient groups have found that this technique may be used to target specific dysfunctional regions, either by increasing or decreasing activity, producing a subsequent effect on an associated symptom (i.e. Boggio et al., 2009; Brunelin et al., 2012; Doruk et al., 2014; Shiozawa et al., 2013), and may therefore present a novel therapeutic option for the treatment of CBS. The neurological basis of tDCS, its therapeutic applications, and potential for use in CBS are discussed in detail in the introduction to **Chapter 5.**

1.5.2 Limitations of Current CBS Research

Research into the mechanisms involved in CBS is still lacking, with only a handful of dedicated studies investigating the mechanisms underlying the condition in isolation from other pathologies (i.e. Pliskin et al, 1996; ffytche et al, 1998; Painter et al, 2018). In addition, many studies investigating CBS consist of single patient case studies or report extremely small sample sizes (i.e. Adachi et al., 2000; Hanoglu et al., 2016; Josephson & Kirsch, 2006; Kazui et al., 2009; Lorberboym et al., 2002; Ossola et al., 2010) (see **Table *1.3***) with many only reporting incidental clinical findings following patient assessment, or lacking comparison to suitable control groups, which limits the extent that conclusions can be drawn regarding the underlying pathogenesis of CBS.

While case studies and small sample sizes provide valid information, particularly on the presentation of CBS and its prevalence within eye disease populations, over-reliance on such studies in the literature can lead to generalisations that may hinder not only the understanding of its aetiology, but also the diagnosis and management of the condition in patients (Carpenter et al., 2019). For example, the understanding that VH abate following complete vision loss has been perpetuated in the literature for many years, but can be traced back to a case report of a single patient by Olbrich et al., (1987), despite studies since reporting the presence of CBS in patients with total blindness (i.e. Alfaro et al., 2006).

Further evidence of the sparsity of data-driven literature in CBS is the relatively high volume of review articles (i.e. Carpenter et al., 2019; Hamedani & Pelak, 2019; Hughes, 2013; Menon et al., 2003; O'Farrell et al., 2010) in comparison to original data papers, and in which the incidence of newly published studies unreported by other reviews is often low. In addition, prevalence papers make up a similarly large proportion of the CBS literature (i.e. Cox & ffytche, 2014; Khan et al., 2008; Singh & Sørensen, 2012; Tatlipinar et al., 2001; Teunisse et al., 1996; Vukicevic & Fitzmaurice, 2008). While these articles are important for understanding the clinical presentation and occurrence of CBS in different populations, the extent to which they can provide further insight into the aetiology of the condition is limited. Subsequently, while such research could ultimately be useful in improving the diagnosis of CBS in a clinical setting based on symptom presentation, the lack of mechanistic studies means that the development of effective treatments for patients with CBS has been hindered.

As such, the need for further dedicated interrogation of the neurophysiology of CBS is distinct.

In addition, heterogeneity in the diagnosis and identification of CBS also means that it is difficult to assess the purity of the sample in many studies, and so differences observed between studies may be due to additional unreported or unknown neuropathology. Furthermore, studies investigating cortical changes during an active hallucination ('state' changes i.e. ffytche et al., 1998; Adachi et al., 2000) do not necessarily explain why VH arise in the first place; therefore, it can be difficult to determine whether these alterations are the cause or consequence of the hallucination. Similarly, studies investigating long term factors such as resting-state excitability and slow-wave activity ('trait' changes, i.e. Hanoglu et al., 2016; Painter et al., 2018; Lorberboym et al., 2002) cannot adequately account for the episodic nature of VH in most patients with CBS although they may represent factors related to VH susceptibility, with these changes creating a brain environment necessary for the manifestation of visual hallucinations.

Table 1.3. *Overview of key studies investigating underlying neurophysiological mechanisms and changes observed in Charles Bonnet Syndrome*

Study Reference	CBS Sample size (n=)	Main Approaches	Principle findings	CBS Study only	Comparison with non-hallucinators
Pliskin (1996)	*n=15*	EEG; Neuropsychological assessment	6 of 8 patients demonstrated abnormal VEPs not attributable to age; CBS patients demonstrated greater neuropsychological impairment than controls.	Yes	Yes[1]
ffytche et al. (1998)	*n = 4*	fMRI during VH	CBS patients demonstrate increased ventral extrastriate activity during VH in regions corresponding to specific VH content.	Yes	No
Adachi et al. (2001)	*n = 5*	SPECT	Excessive cortical hyperperfusion in the lateral temporal cortex, striatum and thalamus during VH.	Yes	No
Lorberboym et al. (2002)	*n = 1*	SPECT; EEG	Diffuse slowing of brain waves without focal abnormalities; Increased parieto-occipital activity during acute VH.	No	No
Josephson and Kirsch (2006)	*n = 1*	EEG; MRI	Slowing in the right occipital region during complex VH; Increased T2 signal in right occipital cortex without restricted perfusion.	No	No
Kazui et al. (2009)	*n = 2*	SPECT; MEG	Hypoperfusion in the ventral portion of primary and secondary visual cortices. Suppression of 4-8Hz band activity in bilateral visual association cortices.	Yes	No
Ossola et al. (2010)	*n = 1*	EEG	Right-sided periodic lateralised epileptiform discharges and focal seizures associated with VH.	Yes	No
Hanoglu et al. (2016)	*n = 2*	EEG	Increased theta power in right occipital and left temporo-parietal regions, reduced alpha power across all regions in CBS patients compared to controls.	Yes	Yes

Painter et al. (2018)	*n = 8*	Peripheral visual field stimulation; EEG	CBS patients demonstrated elevated visual cortical responses to peripheral field stimulation when compared to patients without VH & healthy controls.	Yes	Yes
Hanoglu et al., (2019)	*n = 3*	FDG-PET	Eye disease patients with CBS demonstrated underactivity of the left Broca, left inferior primary visual cortex, and anterior and posterior cingulate cortex compared to healthy controls. Eye disease patients without VH demonstrated underactivity of the pons and overactivity in primary visual and parietal cortex.	Yes	Yes
Martial et al. (2019)	*n=1*	fMRI; Functional connectivity analysis	Reduced grey matter volume and cortical thickness of occipital cortex; greater functional connectivity in secondary visual cortex in CBS patient compared to controls.	Yes	Yes

Abbreviations: EEG: electroencephalography; VEP: visual evoked potential; CBS: Charles Bonnet syndrome; fMRI: functional magnetic resonance imaging; VH: visual hallucinations; SPECT: single photon emission computerised tomography; MRI: magnetic resonance imaging; MEG: Magnetoencephalography; FDG-PET: Fluorodeoxyglucose positron emission tomography.
[1]Healthy controls without visual impairment compared in neuropsychological assessments only.

1.5.3 Cortical excitability in other pathologies with visual hallucinations

As research into the underlying mechanisms involved in the production of VH in CBS is currently limited, investigation into the aetiology of VH in other patient groups may provide further insight. This is summarised below in sections **1.5.3.1-1.5.3.2** describing evidence from electrophysiology and neuroimaging. Particular focus has been given to approaches utilised later in this thesis including transcranial magnetic stimulation, fMRI, and magnetic resonance spectroscopy (MRS).

1.5.3.1 Evidence from Electrophysiology

Evidence from studies utilising resting-state EEG and Magnetoencephalography (MEG) has demonstrated a link between alpha-rhythm desynchronization, indicative of changes to cortical excitability (Pfurtscheller et al., 1996; Thut et al., 2006), and VH. In the case of pharmacologically-induced VH in healthy participants by means of potent serotonergic hallucinogens, significant posterior alpha-power changes have been observed including decreases in parieto-occipital alpha-power following administration of psilocybin (Kometer et al., 2013) and decreased peak alpha-amplitudes in the posterior cingulate cortex and precuneus induced by lysergic acid diethylamide (LSD), both of which subsequently strongly correlated with ratings of VH (Carhart-Harris et al., 2016). A further study of individuals experiencing recurrent VH as a long term consequence of LSD usage (Hallucinogen Persisting Perception Disorder, or HPPD), observed accelerated alpha frequencies compared to non-HPPD controls, albeit with an absence of alpha-amplitude differences (Abraham & Duffy, 1996). Accelerated alpha rhythms observed in LSD animal studies (i.e. Brawley & Duffield, 1972) have been postulated to be an observable effect of disrupted inhibitory function of $5HT_2$ receptors by LSD; consequently, such acceleration in HPPD may similarly indicate chronic disinhibition of the visual system contributing to the occurrence of VH.

In addition, VH-prone pathologies including DLB and PDD also demonstrate decreased resting state posterior/occipital alpha-power indicative of increased cortical excitability (Bonanni et al., 2008; Bosboom et al., 2009; Ponsen et al., 2013), although these studies did not directly investigate the relationship between this phenomena and the occurrence of VH in these cohorts, or make comparisons with non-hallucinating counterparts. It is therefore difficult to assess whether these differences are inherently related to the disease state itself or play a role in VH susceptibility.

While not directly assessing visual cortical excitability, electroretinogram (ERG) can be used to detect visual processing abnormalities by recording the electrical response of the retina to light stimulus as a biphasic wave form, consisting of an a-wave and b-wave. In DLB, cone a-waves, b-waves and rod b-waves demonstrate significant latency increases, while rod b-waves display decreases in amplitude compared to PD patients without VH and healthy controls, indicating the influence of photoreceptor layer dysfunction and degraded sensory input on the formation of VH in this patient group (Devos et al., 2005). Similar abnormalities have been observed in PD, which in turn have been linked to dysfunction of the dopaminergic retinal system, decreases in surround inhibition in the eye, and have further been associated with the formation of VH (Diederich et al., 2005; Onofrj et al., 2006; Weil et al., 2016). Such findings in VH-prone conditions such as PD and DLB may support the contribution of retinal dysfunction in the formation of VH, a necessary element of CBS due to the presence of vision loss, further supporting bottom-up explanations associated with this condition.

Similarly, event related potentials collected from EEG recordings of the visual cortex during visual stimulation enable the investigation of visual pathways leading from the retina to the visual cortex. The subsequent visual evoked potentials (VEPs) can, in turn, be used to examine distinct visual processes, including pattern recognition and target detection, using measures of VEP waveform latency and amplitude. VEP latency provides information about the integrity of visual pathways and transmission between cortical areas, while the amplitude reflects the synchronicity of the site being recorded. Elongated VEP components in various stages of visual processing have been associated with the occurrence of VH and in VH-prone pathologies. The P100 component, which is a marker of early visual processing, has been observed to be delayed in PD patients with VH but not in non-hallucinating counterparts (Matsui et al., 2005), supporting, albeit indirectly, the role of bottom-up components such as deafferentation in VH formation. Conversely, delays to visual processing components associated with visual perception, such as the P200 VEP, have been observed in PD and DLB hallucinators (Kurita et al., 2010), while shorter peak P200 latencies were observed in HPPD patients compared to controls (Abraham & Duffy, 1996). Furthermore, increased P300 latencies, a VEP component associated with higher-order visual and attentional processing, have been noted in PD, PDD and DLB patients with VH compared to non-hallucinating AD patients (Kurita et al., 2005, 2010) and controls (Chang et al., 2016). Although limited, evidence of such alterations may indicate a role of attentional and perceptual dysfunction in

the formation of VH in these pathologies, supporting perceptual and attentional VH models (i.e. Collerton et al., 2005; Shine et al., 2011).

Transcranial Magnetic Stimulation

Another means of assessing excitability in the visual cortex is transcranial magnetic stimulation (TMS). Applied by means of a magnetic coil placed against the participant's scalp, TMS uses a single or double magnetic pulse to briefly stimulate underlying cortical structures. TMS of the occipital cortex can be used to elicit spontaneous perceptions of spots of light in the visual field, known as phosphenes. The percentage of stimulation intensity at which these phosphenes are produced provides an indication of excitability in the visual cortex, with a more excitable cortex producing phosphenes at lower TMS intensities (Kammer, 1998; Meister et al., 2003). Subsequently, a more excitable visual cortex is described as possessing a lower 'phosphene threshold' (PT).

The use of TMS as a measure of visual cortical excitability has been widely reported throughout the literature, including some limited findings in pathologies susceptible to VH. In DLB, lower PTs denoting increased cortical excitability have been found to negatively correlate with the severity of VH, indicating that greater visual cortical excitability is associated with more severe VH (Taylor et al., 2011). While comparisons have found that PTs do not significantly differ between DLB and healthy controls, a negative correlation has been observed between PTs and the magnitude of blood oxygen dependent (BOLD) response in the primary visual cortex in response to checkerboard stimuli, indicating an association between increased BOLD activation and increased hyperexcitability, compared to the positive correlations observed in healthy controls (Taylor et al., 2016). This BOLD response may indicate activity in both excitatory and inhibitory neuronal populations, whereas phosphene thresholds are likely to be dependent on the relative balance between excitatory and inhibitory activity within the region being stimulated, therefore a positive relationship suggests that inhibition outweighs excitation. Conversely, the negative relationship observed in DLB may indicate the opposite, with increased cortical excitability acting as a marker for VH severity (Taylor et al., 2016). Similarly, migraine patients susceptible to visual disturbances and aberrant visual perceptions known as 'aura' also demonstrate significantly lower PTs than migraine patients without aura and healthy controls, indicating that aura may arise as a result of aberrant hyperexcitability in migraine (Aurora et al., 2003; Brighina et al., 2009; Khedr et al., 2006).

Examples of increased cortical excitability associated with VH have also been demonstrated using TMS in non-clinical populations. Users of the drug 'ecstasy' who experience VH have been noted to exhibit significantly lower PTs than users who do not (Oliveri & Calvo, 2003). With relevance to visual impairment and sight loss, decreased PTs have also been observed following short-term visual deprivation, suggesting a correlation between a lack of visual input and higher cortical excitability, and may be indicative of a similar response in CBS (Boroojerdi, 2000; Fierro et al., 2005).

The use of TMS to assess visual cortical excitability in CBS has not yet been performed and may provide important insight into the propensity of the occipital cortex to respond to spontaneous hyperactivity that may lead to the occurrence of VH.

1.5.3.2 Evidence from Neuroimaging

Functional Imaging

Functional magnetic resonance imaging (fMRI) has been used to demonstrate differences in the cortical activation of patients with VH, which may help to elucidate the aetiology of the symptom. Differential 'trait' cortical activity, referring to activation outside of VH occurrence, has been observed in LBD patients with VH compared to non-hallucinators, providing evidence for visuo-cortical dysfunction and perceptual deficits which may contribute to the formation of VH (Goetz et al., 2014; Meppelink et al., 2009; Stebbins et al., 2004; Taylor et al., 2012). In support of bottom-up models of VH, increased activation of the visual association and sensory cortices has also been observed using fMRI in patients with PD and first episode psychosis experiencing VH (Holroyd & Wooten, 2006; Jardri et al., 2013).

Studies of trait differences in VH populations are the most commonly reported investigations within the VH literature and may provide insight into which cortical alterations are associated with VH susceptibility (Taylor et al., 2020). Nevertheless, these studies can also be challenged when drawing conclusions about precisely how these alterations influence or result in VH, therefore necessitating interrogation of changes associated with the occurrence of VH themselves (VH-state).

In non-clinical populations, VH induced by flickering-light stimulation have been found to produce unexpected decreases in lateral geniculate nucleus (LGN) activity during VH, and differences between the onset and maintenance of long- and short-range coherence

related to the occurrence of VH has supported the role of connectivity dysfunction in their formation (ffytche, 2008). Phasic increases in cerebral blood flow in the visual cortex during VH have also been found to correlate strongly with VH ratings in people under the influence of LSD (Carhart-Harris et al., 2016). While fMRI has also noted decreases in posterior brain activity and increased activation in anterior cortical regions (associated with attentional and perceptual processing) in hallucinating PD patients compared to non-hallucinators (Stebbins et al., 2004), with decreased activation of the primary visual system in conjunction with increased frontal activity during complex visual hallucinations observed in a patient with PD (Goetz et al, 2014). Such differences between state and trait cortical alterations could therefore indicate that phasic changes in cortical activity may be necessary for the formation of VH in these patients.

Spectroscopy

Magnetic Resonance Spectroscopy (MRS) can be used to quantifiably measure the balance of both excitatory and inhibitory neurotransmitters such as glutamate and GABA which are involved in bottom-up processing and are therefore relevant to models of deafferentation. Within the spectrum produced by MRS, peaks at separate frequencies are used to measure the different chemicals included in the sample region, with the height of these peaks providing a measure of their chemical concentration (Brown et al., 2016)(**Figure 1.2**).Current research suggests that GABA, specifically, is involved in the homeostatic balance of excitatory and inhibitory modulatory pathways, which is used to mediate cortical plasticity throughout the life-span (Hensch & Fagiolini, 2005).

To this end, reduction in GABAergic inhibition has been observed to modulate visual cortical function and plasticity and, relevant to eye disease and visual impairment, monocular deprivation has been demonstrated to result in reductions to resting-state GABA in the primary visual cortex, resulting in ocular dominance plasticity (Lunghi et al., 2015).

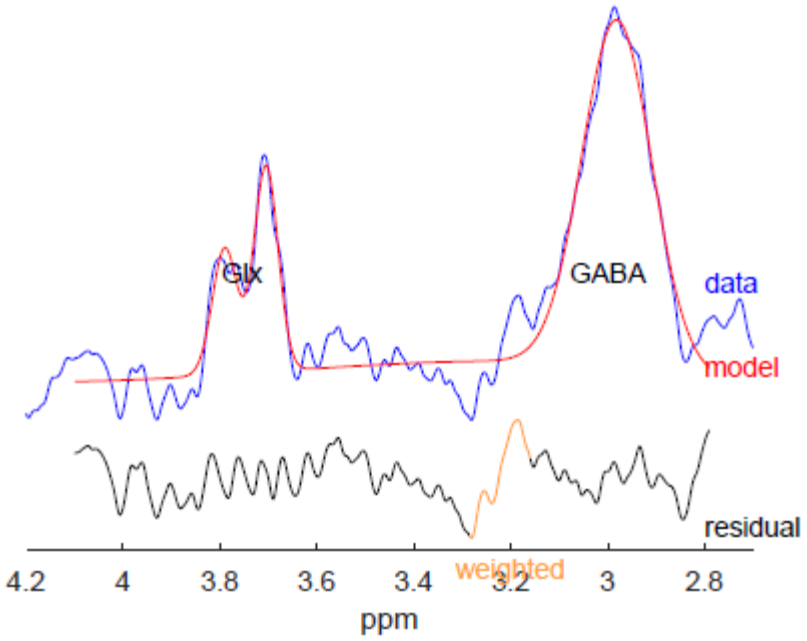

Figure 1.2 *GABA- and Glutamate (Glx)-edited spectra produced using a MEGA-PRESS sequence using the GANNET tool for MatLab. GABA- and Glx-edited data are represented by the blue line, with a model of best fit represented in red. The black line represents the residual between this model and the data. Chemical shift is represented on the x-axis in parts per molecule (ppm).*

With regards to VH, altered GABAergic transmission has been observed in DLB hallucinators, and has thus been postulated as an underlying metabolic factor in cortical excitability and the development of hallucinations (Firbank et al., 2018; Khundakar et al., 2016; Su et al., 2016). More recently, lower GABA+/creatine ratios were observed in PD patients with VH than those without hallucinations and healthy controls, supporting the association of visual cortical GABA concentrations with VH in this patient group (Firbank et al., 2018). Despite this, the association between visual cortical GABA and VH in CBS has yet to be investigated.

1.6 Summary

While the deafferentation hypothesis provides a plausible explanation for the development of visual hallucinations following sight loss, existing studies remain either small or provide only a fragmented understanding of their aetiology. Although the study of VH aetiology in other pathologies is more extensive and may provide a reference point for the investigation of Charles Bonnet hallucinations, it is unclear how applicable these findings

may be to visually impaired cohorts. The current lack of robust categorisation of CBS or enquiry into its aetiology in the literature has subsequently hindered the development of effective treatments, while it is still not understood why some patients with sight loss experience CBS while others do not. As such, there is a distinct need for further investigation. This thesis aims to use neuroimaging techniques, including fMRI and MRS, to further investigate the extent to which bottom-up processing is involved in the formation and maintenance of VH in CBS and how this is related to measures of visual cortical hyperexcitability, such as those observed using TMS. Furthermore, this thesis aims to investigate the utility of non-invasive brain stimulation in CBS, including the effect of perturbation of cortical systems related to VH and its potential therapeutic benefits. The following studies will investigate differences in visual cortical activity between patients who experience CBS compared to people with sight loss who do not and, consequently, whether targeting regions demonstrating altered activity, such as by using transcranial brain stimulation, may help to remediate VH symptoms.

Chapter 2 Aims and Hypotheses

2.1 Aims

The following thesis has two primary aims with regards to visual hallucinations in people with eye disease:

1) To investigate visual-cortical activity in people with Charles Bonnet syndrome (CBS) in comparison to patients with eye disease with no VH (Controls), using neuroimaging and electrophysiological approaches, with a view to better understanding the aetiology of VH in this patient group and thus inform the development of therapeutic interventions.
2) To investigate the therapeutic potential of non-invasive brain stimulation as a means of remediating visual hallucinations in people with eye disease.

2.2 Hypotheses

Based on these aims, this thesis has two central hypotheses:

2.2.1 Comparing visual-cortical activity between people with CBS and eye disease controls

Hypothesis:

There will be a significant difference in the visual cortical activity of people with CBS when compared to people with eye disease who do not experience visual hallucinations (Controls).

The deafferentation hypothesis states that VH in CBS may be the consequence of increased spontaneous, compensatory hyper-excitability of the visual cortex caused by the loss of sensory input from the eyes (Menon et al., 2003). Evidence for this has previously been shown using fMRI during CBS hallucinations, demonstrating increases in visual-cortical excitability in regions associated with hallucinatory content (ffytche et al., 1998; see **Chapter 1**). However, no comparison between hallucinators and non-hallucinators has yet been performed in eye disease patients.

Predictions:

1) Phosphene thresholds, as measured by occipital transcranial magnetic stimulation (TMS) will be lower in CBS than controls, indicating increased visual cortical excitability.
2) fMRI BOLD activation will be greater in the visual cortex of people with CBS than controls, indicating greater visual cortical excitability.
3) Concentrations of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) will be lower in the primary visual cortex of people with CBS when compared to controls, indicating reduced inhibition in the visual cortex.

2.2.2 The utility of non-invasive brain stimulation as a treatment for visual hallucinations in CBS

Hypothesis:

Active inhibitory cathodal transcranial direct current stimulation will produce a significant change to aspects of visual hallucinations in patients with CBS when compared to placebo (sham) stimulation.

Non-invasive brain stimulation, such as transcranial direct current stimulation (tDCS) can be used to modulate cortical activity, with anodal stimulation producing an excitatory response, while cathodal stimulation produces an inhibitory effect (Stagg & Nitsche, 2011). As the deafferentation hypothesis suggests that CBS may be the result of hyperexcitability of the visual cortex (Menon et al., 2003), the use of inhibitory tDCS may be used to decrease this activity, potentially providing a beneficial effect on VH and providing an alternative therapeutic intervention for CBS (see **Chapters 5 & 6 for more details**).

Predictions

1) CBS patients will report significant improvements to aspects of VH such as the frequency, duration, and emotional impact of VH as measured by the Neuropsychiatric Inventory Hallucination subscale (NPI^{hall}) and North East Visual Hallucination Interview (NEVHI) following active stimulation compared to sham.
2) Active inhibitory tDCS will result in a subsequent change to visual cortical activity when compared to sham in the following domains:

i. Changes to occipital fMRI BOLD activity indicating a decrease in overall visual cortical excitability.
ii. Changes to occipital GABA concentrations indicating an increase in inhibitory GABAergic transmission in the visual cortex.

Chapter 3 General Methods

3.1 Subjects and Recruitment

A total of 43 participants were recruited to this study from three participant populations:

1) Individuals with CBS experiencing continuous hallucinations (n=6)
2) People with CBS experiencing multiple VH per week (CBS group; n=19)
3) People with eye disease without VH (Control group; n=18).

Ethical approval was granted by the Tyne and Wear South Research Ethics Committee and Newcastle NHS Research and Development Committees (REC reference: 17/NE/0131). Screening and recruitment of participants occurred under the following NHS Foundation Trusts: Cumbria, Northumberland, Tyne and Wear (CNTW), Newcastle upon Tyne Hospitals (NuTH), City Hospitals Sunderland (CHSFT), and South London and Maudsley (SLaM).

Participants from both groups were identified via contact with consultants in ophthalmology at each of the participating NHS Trusts, and from the Macular Society database of members interested in research participation. Suitable participants were, in the first instance, contacted by the clinical care team or by a representative of the Macular Society in order to assess interest in research participation. Patients interested in participating in research were then contacted by a member of the research team (KdM) and screened for eligibility (see ***Table 3.1*** & ***Table 3.2*** for inclusion and exclusion criteria). In addition, an advert for the study was printed by the Macular Society in their bi-annual newsletter, providing details for members interested in participation to contact the researchers directly and undergo screening. Control participants were matched as closely as possible to the CBS group by age and visual acuity. Following assessment of eligibility, participants were invited to join the study as part of one of the three study groups (see **Figure 3.1**). All study participants had full mental capacity and gave written informed consent. The diagnosis of CBS was confirmed by experienced clinicians (JPT, Df).

Table 3.1. *Study inclusion criteria for both the CBS and Control groups.*

All Participants	
1. Age >18, either sex 2. Provision of written informed consent 3. MMSE-blind >24 4. Absence of any concurrent major psychiatric or neurological illness, including but not limited to major depression, dementia, schizophrenia, or patients with a brain lesion 5. Absence of severe physical illness or comorbidity that may limit ability to fully participate in study procedures 6. Sufficient English to allow assessment scales and cognitive testing	
CBS	**Controls (Eye disease no VH)**
1. Meet the diagnostic criteria of CBS (Podoll et al, 1989; Teunisse et al, 1996): Cognitively intact, having visual hallucinations (with no hallucinations in other modalities or delusions, as assessed by the NPI^{hall}), full insight into the unreality of these, and presence of eye disease sufficient to cause visual impairment. 2. Evidence of persistent and recurrent episodes of complex or simple visual hallucinations determined to be of stable frequency with the expectation of at least one hallucination per day.	1. Presence of eye disease sufficient to cause moderate to severe visual impairment 2. No prior history of hallucinations in any modality.

Abbreviations: MMSE: Mini mental state examination; CBS: Charles Bonnet syndrome; VH: Visual hallucinations; NPI^{hall}: Neuropsychiatric Inventory hallucination subscale.

Table 3.2. *Study exclusion criteria for both the CBS and Control groups.*

All Participants	
1. Skin allergies or sensitivities to electrode gels or any significant dermatological/scalp disease 2. Past history of excess alcohol intake 3. Past history of other neurological illness including, but not limited to, stroke, intracerebral pathology, epilepsy, or neurodegenerative disease. 4. Metal or electronic implants (including pacemakers) which might be affected by strong magnetic fields (occurring in TMS or magnetic resonance imaging component of the study) or electrical currents (tDCS component)	
CBS	**Controls (Eye disease no VH)**
1. Psychotropic and other medications which may significantly interfere with cognitive testing and tDCS efficacy (including high dose antipsychotics, dopamine agonists, sedative antidepressants, benzodiazepines except when in low dose and used as hypnotics, and/or centrally acting anticholinergic drugs). 2. Evidence of Lewy body symptoms and signs which may cast doubt on a CBS diagnosis (i.e. REM sleep disorder)	1. Past history of visual hallucinations or hallucinations in any other modality

Abbreviations: TMS: Transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; CBS: Charles Bonnet Syndrome; VH: visual hallucinations; REM: rapid eye movement.

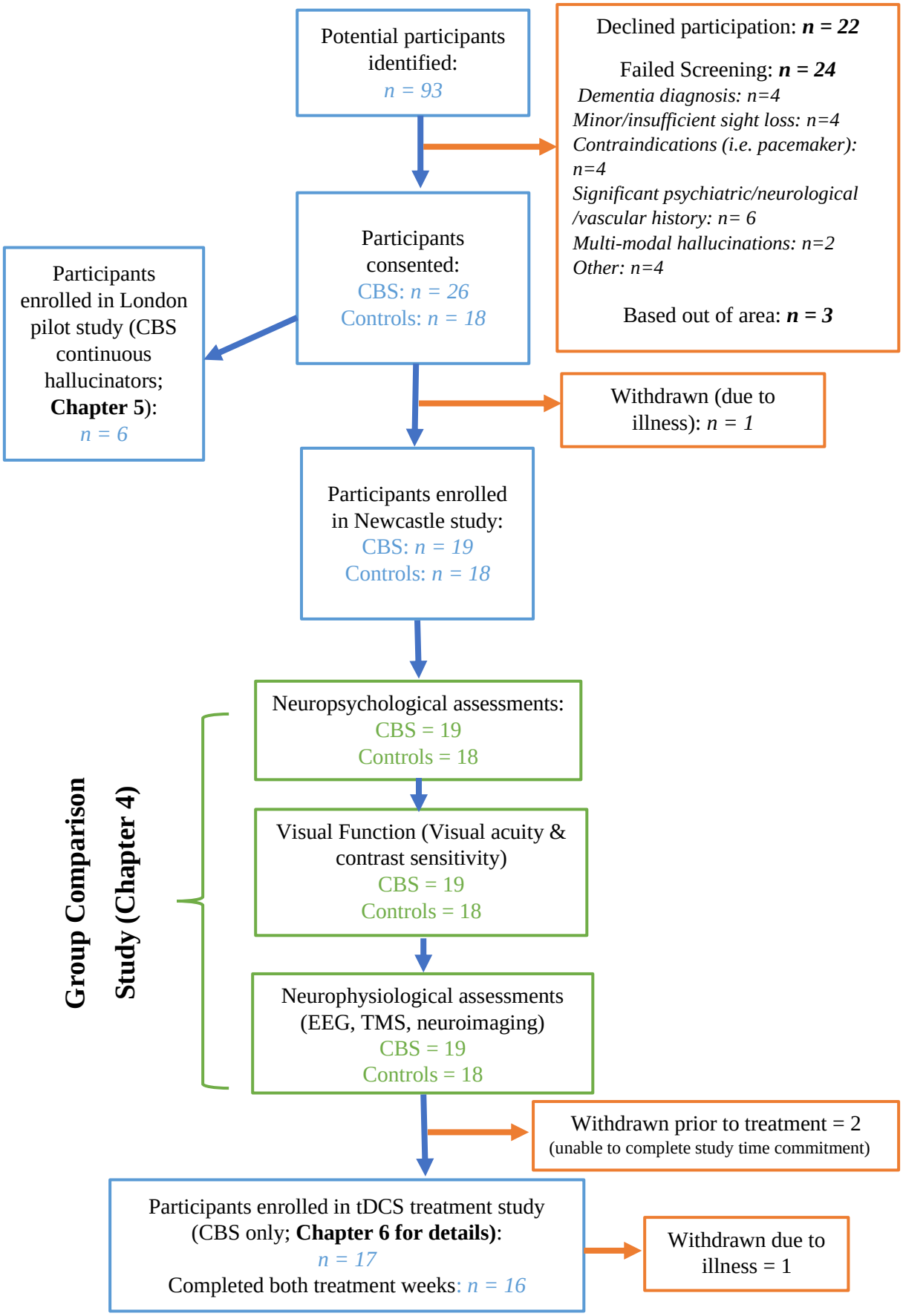

Figure 3.1. *Flowchart depicting number of participants included at each stage of the study.*

3.2 Neuropsychological Assessments

*Note: Sections 3.2 and 3.3 detail procedures completed by all participants with the exception of the continuously hallucinating CBS participants (n=6), see **Chapter 5** for details on assessments in this group. Details of tDCS intervention procedures conducted with CBS participants enrolled in the treatment study are found in **Chapter 6.***

On the first visit all participants underwent baseline neuropsychological assessments either in their home or at the Clinical Aging Research Unit (CARU) at the Campus for Ageing and Vitality (CAV). During this visit additional demographic information about the participant's medical history, eye disease, and medication were collected.

Global Cognitive Function

Primarily used as a screening tool for study inclusion, participant global cognitive performance was assessed using the mini mental state exam adapted for and validated in blind participants (MMSE-blind; Reischies & Geiselmann, 1997; maximum score = 27, cut off for participation in this study ≥24)(Appendix A) incorporating measures of memory recall, language, attention, and orientation (awareness of time and location). Visual elements of the MMSE including reading comprehension, writing and copying present in the full MMSE are excluded in the MMSE-blind, due to the variable levels of moderate to severe visual impairment in all eye disease participants.

Mood

The 15-item Geriatric Depression Scale (GDS; Yesavage et al., 1982; maximum score = 15)(Appendix B) was used predominantly as a screening tool assessing the mood of the participant over the previous week. Higher scores (>5) may indicate depressive symptoms in the participant, which may in turn influence ratings of distress towards VH in the CBS group so was considered for investigation. Participants reporting significant scores on the GDS (>10) were excluded from this study, as this may be an indication of major depressive illness which has been associated with psychotic symptoms such as hallucinations (Coryell, 1996).

Day-to-day functioning

The Instrumental Activities of Daily Living scale (IADL; Lawton & Brody, 1969; maximum score = 8)(Appendix C) was used to assess the ability of participants to complete a range of basic daily tasks, including household chores and travel, and their level of independence in doing so. This scale was included in order to assess any impact that sight loss and VH may have on daily functioning in eye disease patients.

3.2.1 Visual Hallucinations

The presence or lack of visual hallucinations in each group was determined using two established hallucinatory scales:

Neuropsychiatric Inventory

The Neuropsychiatric Inventory hallucinations subscale (NPI^{hall}; Cummings et al., 1994; maximum score = 12)(Appendix D) is designed to screen patients for the presence of hallucinations in any of five sensory modalities: visual, auditory, olfactory, gustatory, and tactile. Patients who report hallucinations in one or more of these domains are given a score to quantify the frequency (0-4) and severity (0-3) of the hallucinations (with higher scores denoting greater frequency/severity), which are subsequently multiplied to achieve the overall NPI^{hall} score. The scale also includes a caregiver distress scale (rated 0-5). However due to the preserved insight of the groups participating in this study, this rating scale was instead used by participants to indicate level of emotional distress experienced as a consequence of the hallucinations specified by the participant. As CBS presents with visual hallucinations in isolation (Menon et al., 2003; Teunisse et al., 1996) participants reporting hallucinations in modalities other than the visual domain (including auditory, somatosensory, olfactory or gustatory) were excluded from this study to best ensure that participants with concurrent or unknown neurological diagnoses that may be responsible for the hallucinations were not included in the analysis.

North East Visual Hallucinations Interview

For participants who confirmed the presence of visual hallucinations in the NPI^{hall}, a version of the North East Visual Hallucinations Interview (NEVHI; Mosimann et al., 2008)(Appendix E) originally adapted for use in the NIHR SHAPED study was used (Renouf et al., 2018). The adapted version of the NEVHI differs from the original in that it has been expanded to serve as a semi-structured interview designed to investigate the phenomenology of VH experienced, their occurrence, and overall impact on the person's life with as much detail as possible. The interview classifies participant VH phenomena into five distinct categories: illusion, presence, passage, simple, and complex. Participant accounts of their VH phenomena in each category were recorded in as much detail as possible including, but not limited to, the size, colour, location in the visual field, and whether the images were static or in motion; categories not endorsed by the participant were left blank. Quantitative scores were then assigned for each hallucination type with respect to their frequency (1-8; ranging

from ‘less than every few months’ to ‘Continuously – present throughout the day’) and duration (1-4; ranging from ‘seconds’ to ‘continuous while awake’). In the final section, participants were asked to indicate which hallucinatory phenomena they found the most distressing and provide a separate numerical rating for the distress (0-10; defined as how frightening or upsetting the hallucination was) and irritation (0-10; how annoying/irritating) caused by this hallucination. For the purpose of this study, and as many people with CBS do not class their VH as distressing (Cox & ffytche, 2014), participants were advised to provide these ratings for their most prominent hallucination that had the most impact on their daily lives.

3.3 Visual Function

All participants underwent basic assessments of baseline visual function.

Visual acuity

Global visual acuity (utilising both eyes) was assessed using a computerised Freiburg visual acuity test (Bach, 1996), which is a standardised and reliable method for assessing visual function in visually impaired groups (Bach, 2007). Participants were required to view a computer screen calibrated at 1 metre distance. In the centre of the screen a ‘Tumbling E’ optotype would appear at one of four different orientations (**Figure *3.2***) for 30 seconds or until a response was made. Participants were required to indicate to the researcher in which direction they perceived the letter to be oriented. The test contained a total of 24 trials and used an optimised strategy, with the target letter increasing or decreasing in size dependent on previous trial performance.

A final result was calculated based on the subject viewing distance and was presented following the completion of all trials in Snellen format and as decimal acuity (Snellen’s fraction). Normal visual acuity is deemed as 6/6 (1.0) but can range from 6/7.5 (0.8) to 6/4 (1.5), with partial and severe sight impairment defined as ranging between 6/18 (0.33) to 3/60 (0.05), dependent on overall visual field loss. Participants who lacked enough remaining vision to complete the visual acuity assessments were assigned an arbitrary decimal acuity of 0.0125 (6/480) in line with the SHAPED study (Renouf et al., 2018), as this was the highest score that could be produced in a patient unable to read the largest Snellen letter at a distance of 0.75m.

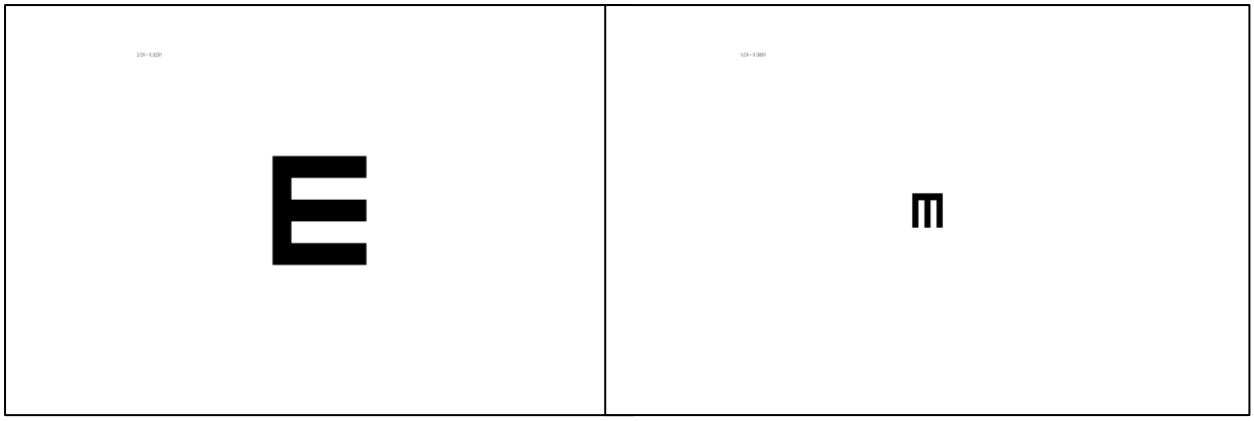

Figure 3.2. *Example trials from the Freiburg visual acuity display demonstrating different letter orientations and difficulty (letter size).*

Contrast sensitivity

Contrast sensitivity was assessed using a computerised Freiburg contrast test (Bach, 1996). Participants were required to view a computer screen at one metre distance. A Landolt-C optotype (***Figure 3.3***) was presented in one of eight different orientations in the centre of a grey screen for 30 seconds or until a response was entered. Participants were required to indicate the orientation of the gap in the Landolt-C in each trial. The test contained a total of 18 trials and used an optimised strategy, with the target letter increasing or decreasing in contrast dependent on previous trial performance. A final result was calculated and presented following all trials as a Weber value of contrast threshold based on the formula:

$$\text{Contrastw} = 100\% \frac{lmax - lmin}{lmax}$$

Where *lmax* and *lmin* are the luminance of the brightest and darkest parts of the screen respectively. Higher percentage contrast scores indicate poorer visual contrast sensitivity and are independent of visual acuity.

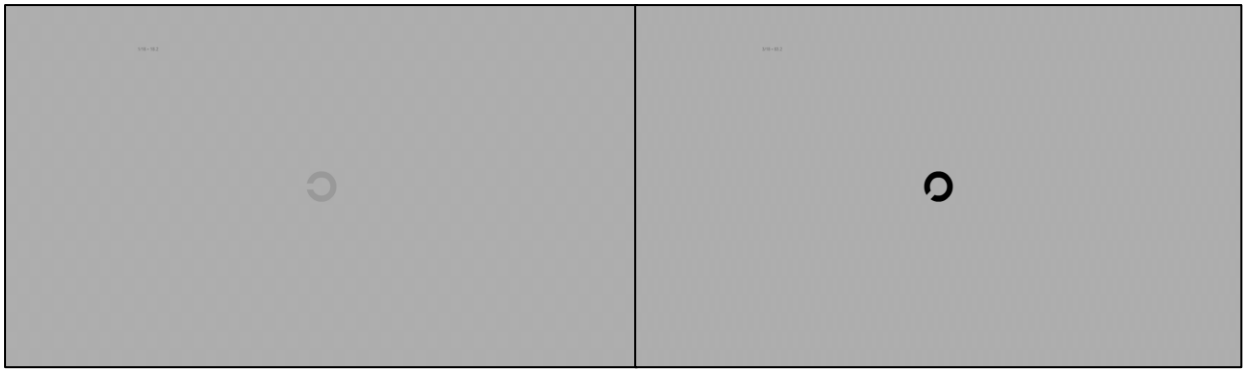

Figure 3.3. *Example trials from the Freiburg contrast sensitivity test demonstrating different Landolt-C orientations and contrasts.*

Visual Field and Distortion

Participant visual field and visual distortion were assessed using an Amsler grid (Marmor, 2000) consisting of horizontal and vertical lines. Each eye was tested individually, with the non-tested eye occluded. Participants were instructed to first look at the fixation point at the centre of the Amsler grid at a distance of approximately 15cm and report any areas of distortion, including areas of blurred or missing lines, or areas in which the lines appeared missing or obscured.

3.4 Neurophysiological tests

Following baseline neuropsychological and visual assessments, all participants underwent a battery of baseline neurophysiological assessments aimed at investigating features of resting-state cortical activity, structure and metabolism.

3.4.1 Transcranial Magnetic Stimulation

Equipment

Transcranial magnetic stimulation (TMS) was delivered using a handheld MagStim 70mm figure-of-eight coil connected to two monophasic MagStim 2002 stimulators via an integrated Bistim2 unit (MagStim Co, Dyfed, Wales) and pulse delivery was controlled via a coil mounted switch.

Protocol

Stimulation was performed in a semi-darkened room; participants wore an eye mask and were asked to keep their eyes closed during stimulations. Navigation of the TMS coil to occipital regions was facilitated by a surface latex grid taped to the participant's occiput. The grid had 8x8 1cm spaced points and was centred over the Oz point (10% of nasion-inion distance above the inion) (Taylor et al., 2011). The coil centre was placed on intersections of the grid with the handle held in the midline allowing current flow in the coil to be craniocaudal. Up to nine different grid intersection sites were assessed for phosphenes in 2cm steps (**Figure *3.4***) in a pseudo-random order to avoid serial effects using paired pulse stimulation. Paired pulse occipital stimulation has been found to elicit phosphenes with greater consistency than single pulse stimulation (Sparing et al., 2005). As such, a paired-pulse paradigm with an interstimulus interval (ISI) of 3ms and the conditioning stimulus intensity set at 90% of test stimulus was used to maximise phosphene response rate.

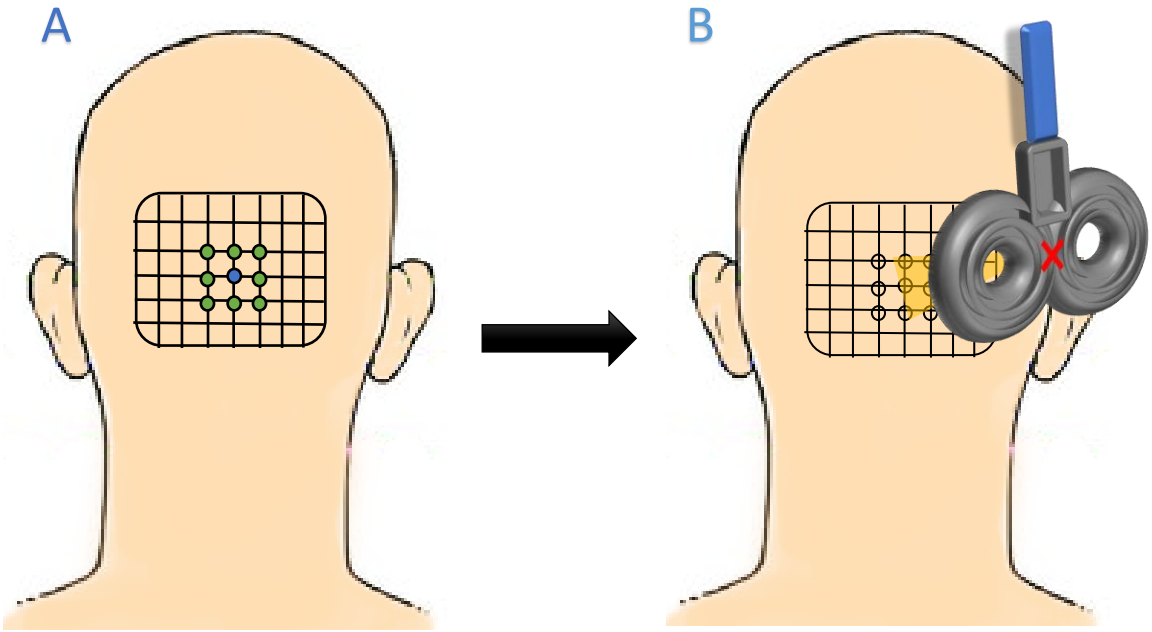

Figure 3.4. *Diagram illustrating the placement of the surface latex grid used to locate the nine grid intersections for eliciting phosphenes (A) centred over Oz (Blue point), and TMS coil orientation (B); The centre of the coil (X) is aligned with each individual point marked on the grid during assessment.*

Participants were first given time to become accustomed to the stimulation and familiar with phosphene reporting. At each grid site tested, the phosphene threshold was determined by increasing stimulation intensity from 60% in 10% increments up to 100% of stimulator output and decreasing stimulation intensity in 1% steps if phosphenes were elicited. In cases where phosphenes were elicited at 60%, stimulation intensity was reduced

to 30% and followed the same stepwise procedure. Four stimulations were given at each intensity, with the lowest stimulus intensity required to elicit at least one phosphene defined as the phosphene threshold (PT). The lower threshold (P = .25 opposed to P=.50) was used to minimise the number of participants who failed to respond to TMS (Taylor et al., 2011). To ensure the accurate reporting of phosphenes, sham stimulation was randomly interspersed amongst active stimulation at a ratio of approximately 1:10. Sham trials were performed by positioning the coil tilted against the head so that the centre surface which provides the stimulation was no longer in contact with the scalp but the patient could still feel the coil. During TMS, participants were asked to report any visual or subjective phenomena after each stimulation, including their colour, phenomenology, and location in their visual field (Appendix F). The number of locations at which phosphenes were elicited in each patient was also recorded as a percentage of total locations tested.

3.4.2 Magnetic Resonance Imaging

Equipment

Participants were scanned on a 3T whole body MRI scanner (Achieva scanner; Philips Medical System, the Netherlands) at the Newcastle Magnetic Resonance Centre at the Campus for Ageing and Vitality, Newcastle University. Participants were positioned supine on the MR scanner couch into the scanner bore and provided with ear plugs and sound attenuating headphones, including a patient communication system through which recorded study instructions could be played and MR radiographers could keep in contact with the participant throughout the study. The scanner head-coil was positioned around the participant's head, with a mirror system adjusted to ensure that they could clearly see out of the scanner to the presentation screen on which stimuli was presented during the fMRI scan.

Structural Imaging

A standard, high resolution structural T1 weighted 3D scan was performed at the start of the MR protocol, along with diffusion tensor imaging (DTI) sequence scans, prior to fMRI and magnetic resonance spectroscopy (MRS) acquisition.

Magnetic Resonance Spectroscopy

Following structural scans, participants received a resting-state MRS scan lasting approximately eight minutes. The MRS protocol used in this study followed the same protocol detailed in Firbank et al. (2018), which observed a significant difference in occipital

γ-aminobutyric acid (GABA+, acquired without micromolar suppression) /creatine concentrations between PD patients with VH and those without (Edden et al., 2012). The GABA signal collected from MRS is believed to reflect concentrations of metabolic GABA and ambient extracellular GABA levels, which contribute to tonic GABAergic activity (Dyke et al., 2017). MRS data acquisition used a MEGA-PRESS technique (Mescher et al., 1998) which uses a sinc Gaussian editing pulse applied alternately at 1.9 ppm (Edit-ON) and 7.5ppm (Edit-OFF). Subtraction of Edit-OFF from Edit-ON spectra allowed the separation of the 3-ppm GABA signal from the overlying creatine peak. MEGA-PRESS spectra were acquired from a 3x3x3cm region of interest located on the anatomical region of the occipital lobe aligned with the primary visual cortex (V1). A further MRS scan included a PRESS sequence with multiple echo time (TE) which was used to measure tissue water content within the selected volume, used as a concentration reference in GABA quantification. Overall sequence parameters included repetition time (TR) = 2000 milliseconds (ms), echo time (TE; 68ms), 320 averages, acquisition bandwidth (1000 Hz), and VAPOR (variable power radiofrequency pulses with optimized relaxation delays) water suppression.

Functional Magnetic Resonance imaging

The use of simple eye movement tasks has been observed to produce a response in the occipital cortex during fMRI (i.e. Bodis-Wollner et al., 1997), and can therefore be used as a means of measuring general activation of the visual cortex compared to resting state. The current study collected fMRI using the following parameters: FOV=192; 64x64 matrix; 27 slices, 3mm thick with a 1mm gap; TR=1920ms; TE=35ms; 156 volumes. An additional two spin-echo epi sequences using the same geometry as fMRI were collected with opposing phase encoding directions used to remove geometric distortion. A simple eye movement task was performed consisting of two conditions controlled by the psychophysics toolbox (http://psychtoolbox.org/; extension for MatLab (MathWorks, Natick, Massachusetts, USA). In Condition 1, participants were prompted by a verbal recording to move their eyes from left to right every second while viewing a high contrast checkerboard; in Condition 2, participants were asked to look straight ahead while viewing a grey screen (with a verbal prompt repeated every three seconds). Each condition lasted 15 seconds and was repeated alternately with the entire fMRI task lasting a total of five minutes. Participants with VH were given an additional squeeze ball during the fMRI acquisition and instructed to squeeze it at the start of any VH and again once the VH disappeared if they occurred during the scan.

In total, the imaging protocol used in this study, including all described scans, took approximately 45 minutes.

3.4.3 Electroencephalography

Equipment

Focal occipital electroencephalography (EEG) was recorded using a Starstim 8-Channel EEG/tCS data acquisition system (Neuroelectrics, Barcelona, Spain). Eight Ag/AgCl Pi-electrodes were placed according to the international 10-20 system within a neoprene cap over occipital and occipital-temporal regions, with a single electrode over the left dorsolateral prefrontal cortex (DLPFC). In order to ensure that recordings were accurately measuring electrical activity from the same source locations, three different cap sizes were used to account for differing cranial circumference (small: 49cm; Medium: 54cm; Large: 57cm). Reference and ground were taken from the left earlobe and all impedances were kept below 5 kOhms. Data was sampled at 500Hz from DC to 250Hz.

Protocol

Resting-state EEG activity was recorded during eyes open and eyes closed conditions over a five-minute period in order to compare posterior spectral patterns responding to eye closure. During EEG recording participants were asked to open or close their eyes in 30 second blocks. During eyes open conditions the participant was asked to remain looking straight ahead in order to reduce movement related artefacts and orienting of attention to objects in the environment. Note: EEG data was collected for a separate study and is therefore not analysed and reported as part of this thesis but has been described here for completeness.

3.5 Data Analysis

The pre-processing and analysis of neuroimaging data was performed using MatLab (Version R2016a, MathWorks, 2016).

3.5.1 Magnetic resonance spectroscopy

GABA quantification was performed using the GANNET toolbox for MatLab which consisted of alignment of each pair of spectra (Edit-ON, Edit-OFF), the subtraction of these aligned spectra to produce GABA spectra followed by averaging across acquisitions, and the

fitting of a Gaussian distribution to the 3-ppm GABA peak to quantify GABA based on the area beneath the curve. Creatine, N-acetylaspartate (NAA) and choline amplitudes were also quantified using non-edited spectra only, using the Advanced Method for Accurate, Robust, and Efficient Spectral fitting of MRS data with use of prior knowledge (AMARES) algorithm from jMRUI (java-based magnetic resonance user interface; Naressi et al., 2001). GABA and NAA were then expressed as ratios which were normalised to creatine. Macro molecular correction was performed on GABA quantification using tissue fractions taken from T1-weighted scans for white matter, grey matter and cerebral spinal fluid (CSF) fractions in the region of interest along with total water concentration, providing a corrected GABA+ concentration used for analysis. The fit quality of the MRS data was assessed by an experienced physicist (JDP) and data displaying unacceptable fit errors (>10%) were excluded from statistical analysis.

3.5.2 Structural Imaging

Data was pre-processed using Statistical Parametric Mapping (SPM)12 (https://www.fil.ion.ucl.ac.uk/spm/) in line with previous studies performed by this research group (Taylor et al., 2012). Anatomical TI images collected in each participant were first segmented and spatially normalised in SPM within default parameters. Total intracranial volume (TIV) was calculated as the sum of grey matter, white matter and cerebrospinal fluid (CSF) volumes and used as a covariate along with age and sex in a voxel-based morphometry (VBM) analysis looking at group differences across the whole brain and in specific regions of interest in the occipital lobe (see section **3.5.3** for details). The spin echo images with opposing phase encoding were processed using the top-up program in FMRIB Software Library (FSL) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/topup) to generate a field map.

3.5.3 Functional Magnetic Resonance Imaging

Following structural pre-processing, fMRI data for each of the two stimulus conditions (eye-movements vs rest) were slice timing corrected, motion corrected by aligning all functional images together, unwarped using the field map, and co-registered with the T1 anatomical image. Data was transformed into standard space with a voxel size of 3x3x3mm, using spatial normalisation parameters from the T1 segmentation, and smoothed with a 6x6x6mm full-width at maximum Gaussian kernel. A high-pass filter of 128 seconds was used and serial correlations removed using SPM's AR(1) model.

Whole brain analysis of the data was conducted using a general linear model (GLM) in SPM. A design matrix comparing the two conditions (eye-movements vs rest) was created by convolving the time course of the conditions with the canonical haemodynamic response function and its first derivative, including motion parameters as covariates. Contrast images were generated from β estimates of this comparison for each participant.

Region of interest (ROI) analysis was also performed with a focus on visual areas. Six ROIs in MNI (Montreal Neurological Institute) space were defined averaging across left and right hemispheres: 1) V1 and V2 combined for an overview of the primary visual cortex, 2) ventral extrastriate cortex (Areas hOC3v and hOC4v)(Rottschy et al., 2007), 3) fusiform area, 4) thalamus, (these anatomical locations were taken from the SPM Anatomy toolbox (fz-heulich.de/inm/inm-1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html)(Eickhoff et al., 2005), 5) precuneus, and 6) bilateral inferior, midline and superior occipital cortex (providing an overview of the occipital areas) defined using the automated anatomical labelling (AAL) template (Tzourio-Mazoyer et al., 2002) as part of Marseille ROI toolbox (MarsBar) for MatLab.

3.6 Statistical Analysis

Group level statistical analysis of demographic, neurophysiological and neuropsychological data was performed using the Statistical Package for the Social Sciences (SPSS, version 26, IBM corp, Armonk, NY) and second-level analysis of fMRI data, including both whole brain and ROI analysis, was performed in SPM12. The following details in this section are an overview of the general statistical analyses undertaken across most of the studies described in this thesis; for analyses specific to each study, please refer to the appropriate chapter.

Normality of the data was assessed using the Shapiro-Wilk test, as this has greater sensitivity to small sample sizes than other tests of normality (i.e. Kolmogorov-Smirnov test; Shapiro et al, 1968). Due to the neurophysiological data and many of the rating scales used in this study including negative scores and scores of absolute zero, much of the data violating assumptions of normality were not amenable to transformation to a normal distribution, necessitating the use of appropriate non-parametric tests. Analysis of normally distributed data used appropriate parametric tests.

Differences in groups were examined using one-way analysis of variance (ANOVA) or Mann-Whitney U tests to establish the statistical significance of these differences ($p<.05$). Where appropriate, an analysis of covariance (ANCOVA) was performed to investigate differences between groups and conditions while controlling for the effects of covariates known to impact the dependent variables (e.g. age, visual acuity). Second-level analysis of fMRI data was performed by comparing contrast images from the two conditions (eye movements – rest) for all participants. Results are shown with a voxelwise threshold of $p<.001$ (uncorrected) followed by a clusterwise threshold of $p<.05$ family-wise error (FWE)-corrected for multiple comparisons.

Spearman's correlations were performed between dependent variables and any variable that had previously been shown to impact their measurement. Where appropriate, variables showing a significant correlation ($p<.05$) were subsequently entered into a backwards regression analysis in order to test their overall ability to predict the dependent variable. Partial correlations (using Pearson's for parametric or Spearman's for non-parametric data) were used to control for potential covariates (e.g. age, visual acuity) when investigating associations between variables.

Chapter 4 Investigating the role of visual cortical excitability in CBS: comparing eye disease patients with and without visual hallucinations.

4.1 Introduction

Current research into CBS has indicated the role of deafferentation and increased spontaneous visual cortical excitability in the formation of visual hallucinations following sight loss (e.g. Adachi et al., 2000; ffytche et al., 1998; Painter et al., 2018). Nevertheless, as discussed in **Chapter 1**, the investigation of the neurophysiological mechanisms underpinning VH in eye disease are currently limited, with most previous studies consisting of case reports or small samples without appropriate comparison groups. This lack of aetiological investigation has consequently hindered the development of effective treatments for people with CBS, and the over reliance on single case reports may have perpetuated beliefs about the condition which have subsequently affected its diagnosis and management.

The following chapter aims to investigate differences in people with CBS compared to people with eye disease without VH, in an attempt to better understand why VH occur in some but not others. In order to provide context for the study population, participant demographics, neuropsychological measures, and visual functioning are compared between groups, and visual symptoms in the CBS group are described. Objective neurophysiological measures of cortical activity are compared with the aim of investigating biomarkers associated with CBS which may contribute to the manifestation of VH in these patients.

As outlined in **Chapter 2**, it is hypothesised that there will be a significant difference in visual cortical activity between the CBS group and control group (eye disease without VH) as assessed using neuroimaging techniques and TMS. In line with previous research and the deafferentation hypothesis, it is predicted that biomarkers of visual cortical excitability will be most apparent in the CBS group, in the form of lower phosphene thresholds, and differing fMRI BOLD activation and GABA concentrations in the primary visual cortex.

4.2 Methods

4.2.1 Study Flow – Participants and Assessments

Detailed descriptions of all neuropsychological and neurophysiological assessments performed in all participants can be found in **Chapter 3** (sections **3.2 – 3.4**). A diagram showing study activities can be found in ***Figure 4.1***.

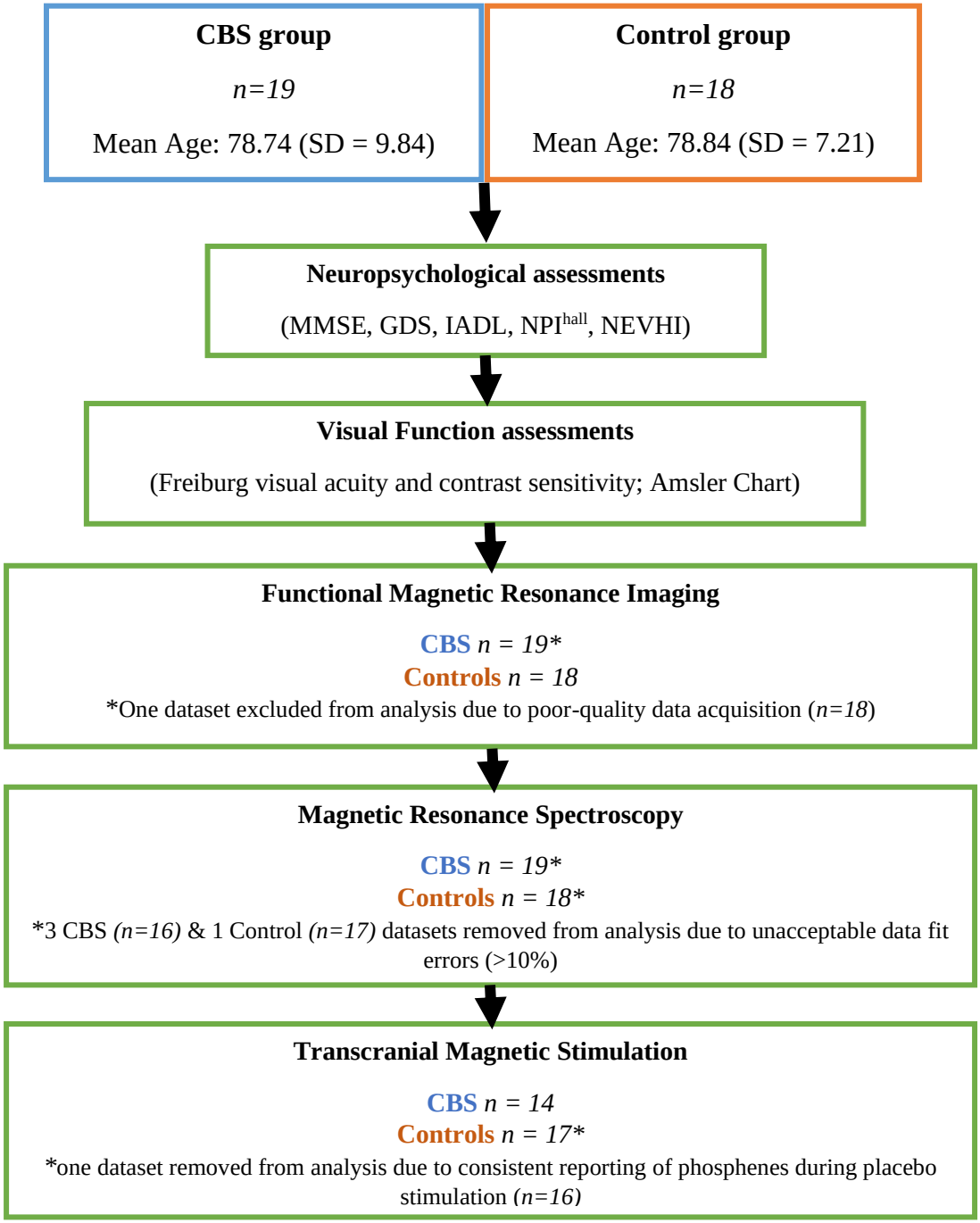

Figure 4.1. *Study flow diagram depicting assessments completed by all participants including n for each group and number of cases excluded from analysis.*

4.2.2 Data and Statistical Analysis

Complete descriptions of data analysis performed on imaging data and general statistical analyses (i.e. normality assessments) performed on the data are detailed in **Chapter 3**.

Group analysis

For the purpose of this study, two separate group comparisons were performed. Primary comparisons were performed between the CBS group and controls in order to assess elements specific to CBS and allowing for the investigation of mechanisms contributing to the formation of VH. A secondary analysis was also performed within the CBS group, in which participants were grouped depending on whether the phenomenology of their most prominent VH were complex (i.e. animals, people, faces, objects), or simple (i.e. lights, amorphous shapes and colours), in order to assess potential cortical differences related to the formation of specific phenomenology.

Demographic and neuropsychological data

Descriptive statistics for demographic and neuropsychological data collected from both groups were calculated as a summary of both samples. Differences in these data were then assessed using one-way analysis of variance (ANOVA), Chi-square tests, or non-parametric Mann-Whitney U tests at the 5% level ($p<.05$) where appropriate. Normality tests performed on neuropsychological measures determined a non-normal distribution inherent in key scales (i.e. GDS, MMSE, IADL, NPI^{hall}, NEVHI); some of this was driven by the selection processes for the groups which excluded people with cognitive impairment (low MMSE) or depression (high GDS), and to ensure hallucinators met the criteria for the treatment study (NPI^{hall}, NEVHI), therefore Spearman's correlations were performed between the dependent variables in order to assess associations between them ($p<.05$) and to inform potential covariates for further analyses.

In the CBS group, VH scores on the NPI^{hall} and NEVHI were taken at three separate time points across their study participation, unrelated to treatment (see **Chapter 6**). During data collection, it was observed that aspects of VH (in particular, the emotional impact and severity) had the propensity to fluctuate across time within participants. As it was expected that measures of cortical activity were likely to be more stable, an average score for each VH domain was calculated, as this provided a more accurate and reliable overview of the VH experience in each participant. While more objective measures of VH frequency and duration remained reasonably static across all participants, these scores were similarly averaged in order to remain comparable. Furthermore, as the interval between baseline questionnaire and neurophysiological assessments was variable across participants, this provided the most comparable measure across the group.

Neurophysiological data

Phosphene thresholds were expressed as the lowest percentage of stimulator output required to elicit phosphenes during one out of four stimulations performed at each location, designed to minimise the number of participants who fail to respond to TMS (see **Chapter 3**). The number of locations at which phosphenes were elicited (Phosphene Locations) were expressed as percentages of the total number of locations tested (i.e. 5/9 locations = 55.5%). Inspection of the data noted that these data were not normally distributed and not amenable to transformation, therefore group differences were analysed using Mann-Whitney U tests of significance ($p<.05$), in order to determine whether there was a significant difference in visual cortical excitability between CBS participants and Controls, or between CBS participants with simple vs complex hallucinations. Categorical reports by participants of the nature of the phosphenes (coloured/colourless; simple/complex) were analysed by group using chi-square analysis of independence and independent t-tests.

Whole brain and ROI analysis of fMRI BOLD data was performed between groups using two sample t-tests, in order to compare cortical activity in CBS with Controls across the brain and in specific visual cortical regions. Results were shown with a voxelwise threshold of $p<.001$ (uncorrected), followed by a clusterwise threshold of $p<.05$ Family-Wise Error (FWE)-corrected for multiple comparisons. Specific regions assessed included key areas of the visual system which have been shown to be involved in VH in both CBS and other VH conditions: 1) Primary visual cortex (V1 & V2) (e.g. Carhart-Harris et al., 2016; Meppelink et al., 2009; Taylor et al., 2012), 2) ventral extrastriate cortex (hOC3v & hOC4v) (e.g. ffytche et al., 1998; Meppelink et al., 2009; Shine et al., 2011), 3) fusiform area (e.g. ffytche et al., 1998; Goetz et al., 2014), 4) thalamus (e.g. Goetz et al., 2014; Shine et al, 2011), and 5) Precuneus (e.g. Martial et al., 2019; Oertel et al., 2007)(**Figure *4.2***). One further ROI was included in order to provide a larger representation of the whole visual cortex, combining anatomical regions for the bilateral inferior, midline and superior occipital cortex. A basic analysis of volumetric differences between groups was conducted using voxel-based morphometry (VBM) analysis assessing grey matter volumes across the whole brain and in the ROIs mentioned above. A two-sample t-test was performed in SPM to assess significant differences between groups with total intercranial volume (the sum of CSF, grey and white matter tissue volumes), age, and sex added as covariates.

GABA and GABA/Creatine (GABA+/Cr) concentrations collected using MRS were compared between CBS participants and Controls, in order to assess any differences in inhibitory GABAergic transmission in the primary visual cortex which may be related to the presence of VH. Inspection of the data revealed a non-normal distribution; therefore, concentrations were analysed using a non-parametric Mann-Whitney U test ($p<.05$).

As the dependent variables investigated here were predominantly observed to have non-normal distributions (i.e. TMS, MRS and neuropsychological assessments) associations between dependent variables were assessed using non-parametric Spearman's Rho correlations ($p<.05$). Correlations were performed between neurophysiological measures, including phosphene thresholds, GABA concentration and fMRI BOLD activity to examine potential correlations between different measures of visual cortical activity. In the CBS group only, associations between neurophysiological measures of cortical activity and ratings of VH on the NPI^{hall} and NEVHI were assessed using Spearman's correlations. Partial correlations (recoded to use Spearman's rather than Pearson's correlations for non-parametric data) were used to control for potential covariates (e.g. Age) when looking at the associations between visual cortical activity measures and VH.

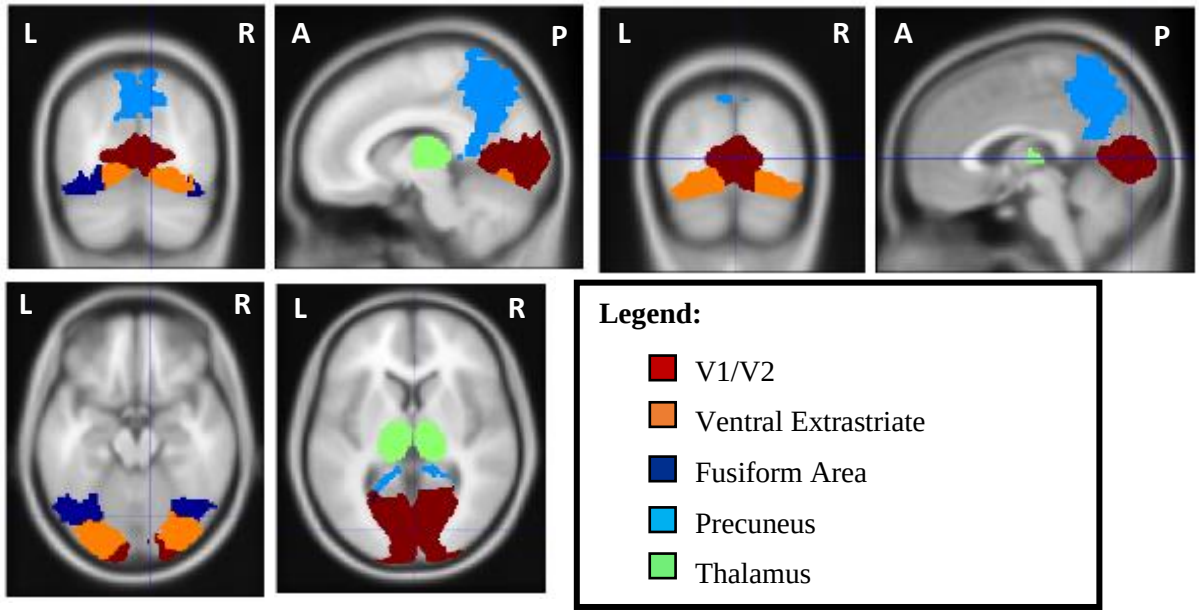

Figure 4.2. *Regions of Interest within visual cortical and visual association areas investigated during the imaging portion of this study. Left (L) Right (R) Anterior (A) Posterior (P).*

4.3 Results

4.3.1 Demographics

A summary of demographic and neuropsychological assessments is shown in ***Table 4.1***. During recruitment, groups were matched for both age and visual function, consequently no significant differences in age ($F(1,35) = .005$, $p = .942$), visual acuity ($F(1,35) = 1.01$, $p = .323$) and visual contrast sensitivity ($F(1,32) = 1.19$, $p = .283$) were observed. No difference in scores on the MMSE-blind were observed between the two groups ($F(1,35) = 417$, $p=.522$) and no participants in either group fell below the threshold of 24/27, indicating that neither group displayed signs of significant cognitive impairment; no clinical record of dementia or mild cognitive impairment was noted for any participant in either group. While the time since initial eye disease diagnosis in CBS participants was overall greater (11.00 ±13.95) than Controls (5.22 ±7.65), this was not found to be statistically significant ($F(1,34) = 2.37$, $p= .133$).

Table 4.1 *Demographic, neuropsychological and visual function information for CBS and Control groups.*

	CBS	**Controls**	**Statistical significance (*p* value)**
N	19	18	
Age	78.74 (±9.85)	78.94(±7.21)	.942
Sex **(M:F)**	7:12	7:11	1.0*
Years since eye disease diagnosis	11.00 (±13.95)†	5.22 (±7.65)	.133
MMSE-Blind **(0-27)**	25.74(±1.33)	26.00 (1.14)	.522
GDS **(0-15)**	2.79 (±1.27)	2.67 (±2.54)	.853
IADL **(0-8)**	6.74 (±1.10)	7.44 (±0.78)	**.031**
Visual Acuity	.274 (±.279)	.357 (±.226)	.323
Visual Contrast **(%)**	50.03 (±38.85)‡	35.66 (±37.82)	.283

Data displayed as mean (**± standard deviation).** Significance was assessed using one-way ANOVA. † n = 18 as one participant did not know when they were diagnosed; ‡ n=16 as 3 participants did not have enough vision to complete the task. *Fisher's Exact Test. *Abbreviations:* CBS: Charles Bonnet Syndrome; MMSE: Mini Mental State Examination; GDS: Geriatric Depression Scale; IADL: Instrumental Daily Activities of Living scale.

Both groups were well matched in terms of education, with 52.6% of the CBS group reporting 9-11 years (55.6% in controls), 26.3% reporting 12-13 years (22.2% in controls), and 21.1% reporting 14+ years in formal education (22.2% in controls).

Ocular pathology resulting in visual impairment in each group is displayed in **Table *4.2***. The most commonly reported eye disease in both groups was age-related macular degeneration (AMD) in both its wet and dry forms, with 68.4% of the CBS group and 72.2% of Controls reporting this as their primary eye disease resulting in their main source of sight loss. In addition, 36.9% of CBS participants reported a secondary, concurrent eye disease contributing to sight loss, compared to 22.3% of Controls. The 'Other' category included rarer causes of sight loss, such as toxoplasmosis and chloroquine retinopathy. All participants in both groups reported some degree of pathology and vision loss in both eyes.

Table 4.2. *Frequency of specific ocular pathologies reported in the CBS group and Controls.*

		CBS	Controls	Statistical sig. (p)
Primary Eye Disease	Macular Degeneration	13 (68.4%)	13 (72.2%)	.529
	Glaucoma	3 (15.8%)	1 (5.6%)	
	Retinitis Pigmentosa	1 (5.3%)	0	
	Other	2 (10.5%)	4 (22.2%)	
Secondary Eye Disease	Macular Degeneration	0	2 (11.1%)	.177
	Glaucoma	3 (15.8%)	1 (5.6%)	
	Cataracts	4 (21.1%)	1 (5.6%)	
	None	12 (63.2%)	14 (77.8%)	

Data displayed as frequency (percentage of total). Statistical significance calculated using Chi-square test to p≤.05. *Abbreviations:* CBS: Charles Bonnet Syndrome.

While no significant difference was observed in depressive symptoms reported by either group on the GDS ($F(1,35) = .035$, $p=.853$), the CBS group reported significantly lower IADL scores than Controls ($F(1,35) = 5.042$, $p= .031$), indicating poorer independence and ability to complete day-to-day tasks in the hallucinating group.

Spearman's correlations between demographic variables found a weak negative association between visual acuity and scores on the GDS (r_s=-.328, p = .048), a moderate

positive relationship between visual acuity and scores on the IADL (r_s= .510, p = .001) and a moderate negative relationship between visual contrast sensitivity and IADL scores (r_s=-.589, p<.001) indicating that poorer vision across both groups was associated with more depressive symptoms and more restricted independence. When entering visual acuity and contrast as covariates, no group differences in IADL scores were observed (F(1,37)=2.28, p=.141).

4.3.2 Visual Hallucinatory Symptoms

Onset of the first instance of VH in the CBS group was found to occur anywhere between 0-19 years following eye disease diagnosis and initial vision loss (median: 2.5 years, mean: 7.7 years, SD: 12.3). When looking at the most common eye disease group (Macular Degeneration) the average length of time from eye disease diagnosis to first VH was 5.58 years (SD: 6.42).

A summary of the types of visual hallucination phenomenology reported by the CBS group in this study can be found in ***Table 4.3***. Primary phenomenology was determined using participant reports of the most common/prominent VH at the time of assessment. The most commonly reported phenomenology was of complex imagery (52.63%, n=10) in contrast to 47.37% ($n=9$) of CBS participants who reported that their most prominent hallucination consisted of simple phenomenology, such as coloured lights, dots, lines and amorphous shapes. Nevertheless, 55.56% ($n=5$) of these latter participants reported having some form of complex VH, albeit less frequently, meaning that a total of 63.16% of participants experienced complex phenomenology at some point during the course of their CBS.

Table 4.3. *Visual hallucinatory phenomenology endorsed by the CBS group, displayed as frequency (percentage of participants).*

Primary Phenomenology		**No. of patients (%)**
Simple	Simple Only	4 (21.05%)
	Simple + occasional complex	5 (26.32%)
Complex	Complex Only	3 (15.79%)
	Complex + occasional simple	7 (36.84%)
	Patterns	*12 (80%)*
	Faces	*5 (33.33%)*
	Objects	*7 (46.67%)*
	People/Figures	*8 (53.33%)*
	Animals	*5 (33.33%)*
	Scenes	*3 (20%)*

Of the complex phenomenology reported by the CBS group (15/19), the most common was imagery of complex patterns, with 80% of participants endorsing them at some point during the course of their CBS. The least common complex phenomenology reported was that of scenes/landscapes (3/15 patients), in which participants described seeing detailed imagery of towns and countryside, usually made up of buildings, roads and fields. Most participants endorsing complex phenomenology reported multiple forms of complex content (i.e. faces and patterns) and this is reflected in **Table *4.3***.

The frequency, duration, severity and emotional impact of VH reported by CBS patients, as assessed by the NPI^{hall} and NEVHI, can be seen in **Table 4.4**. Overall, the CBS group did not differ in their ratings of VH frequency, severity, duration or irritation on either the NPI^{hall} or NEVHI, regardless of what they reported as their most prominent VH phenomenology (Mann-Whitney U test, $p>.05$). Ratings of distress on the NEVHI (0-10) were higher in participants who endorsed simple VH as their most prominent phenomenology ($p=.035$). However, this difference, whilst trending, was not seen in ratings of distress on the NPI (0-5; $p = .108$).

Table 4.4. *Visual Hallucination scores on the NPI^{hall} and NEVHI, and years since CBS diagnosis for the overall CBS group and split by most prominent hallucination phenomenology.*

	Overall	**Simple**	**Complex**	**Statistical sig. (p)**
N	19	9	10	
Years of CBS	3.32(±3.15)	2.89(±2.6)	3.70(±3.56)	.452
NPI^{hall} *(frequency x severity)*	6.29(±2.72)	6.37(±3.00)	6.40(±2.60)	.901
Frequency	3.63(±.63)	3.67(±.64)	3.60(±.64)	.753
Severity	1.74(±.61)	1.70(±.68)	1.77(±.59)	.864
Distress	1.40(±1.19)	1.89(±1.27)	.97(±.97)	.108
NEVHI				
Frequency	5.05(±1.34)	5.37(±1.48)	4.77(±1.22)	.301
Duration	2.32(±1.03)	2.22(±1.09)	2.40(±1.03)	.559
Distress	3.16(±3.03)	4.70(±3.03)	1.77(±2.38)	**.035**
Irritation	5.95(±3.27)	6.41(±3.04)	5.53(±3.58)	.661

Data displayed as mean (±standard deviation). Statistical significance calculated using Mann Whitney U tests for non-parametric data ($p\leq.05$). *Abbreviations:* CBS: Charles Bonnet Syndrome; NPI: Neuropsychiatric Inventory; NEVHI: North East Visual Hallucination Interview

No significant relationships between visual acuity or contrast and ratings of any aspect of VH on the NPI or NEVHI was observed in CBS (p>.05). Similarly, no significant difference between people with CBS who experienced predominantly simple or complex VH was observed in terms of visual acuity (U = 31.5, Z = -1.11, p=.269) or contrast sensitivity (U= 14, Z = 1.86, p=.06).

Factors associated with CBS participants' ratings of distress and irritation towards VH are summarised in **Table 4.5**. Overall, higher NPI^{hall} scores were significantly associated with higher ratings of distress and irritation as rated on both the NPI and NEVHI, with the overall hallucination severity being the most strongly associated with both. The length of time participants had experienced CBS was also significantly associated with higher ratings of irritation towards VH, while participants who scored higher on the MMSE also reported more distress towards VH. While not significant, a moderate association between the frequency of VH and both distress and irritation was consistently observed across measures, with more frequent VH associated with greater irritation in particular. Due to sample size and normality distribution of the data, a regression analysis could not be performed on these variables. No significant or consistent associations between overall visual function or duration of VH and irritation and distress were observed.

Table 4.5. *Spearman's rank correlations indicating factors associated with participant ratings of distress and irritation towards visual hallucinations*.

	NPI Distress		NEVHI Distress		NEVHI Irritation	
	r_s	Sig. (*p*)	r_s	Sig. (*p*)	r_s	Sig. (*p*)
NPI^{hall}	**.769**	**.000**	**.604**	**.006**	**.873**	**.000**
Frequency	.392	.097	.306	.203	.447	.055
Severity	**.703**	**.001**	**.567**	**.011**	**.845**	**.000**
NEVHI						
Frequency	.350	.141	.403	.087	.421	.073
Duration	.079	.759	-.163	.506	.339	.155
Years of CBS	.402	.088	.309	.198	**.523**	**.022**
MMSE	.402	.088	**.475**	**.040**	.299	.214
Visual Acuity	-.168	.491	-.064	.793	-.174	.477
Visual Contrast	-.481	.059	-.178	.509	-.125	.646

Significant correlations are highlighted in dark blue; light blue represents rho>.350 but p>.05. *Abbreviations:* NPI^{hall}: Neuropsychiatric Inventory visual hallucination subscale; NEVHI: North East Visual Hallucinations Interview. CBS: Charles Bonnet Syndrome. MMSE: Mini Mental State Exam

4.3.3 Transcranial Magnetic Stimulation

Phosphene thresholds, calculated as the minimum % of stimulation intensity required to elicit phosphenes (CBS: mean = 63.93 ± 27.82; Controls: mean = 80.06 ±15.65) did not differ significantly between groups (U = 78.5, Z = -1.4, p = .162). However, a Levene's test found that the variability between the two groups differed significantly (F(1,28) = 9.31, p = .005), with greater variability observed in the CBS group than Controls. When the CBS group was split by primary VH phenomenology (Simple VH: *mean* = 68.88 ±26.76; Complex VH: *mean* = 57.33 ± 30.3), no significant difference in phosphene thresholds or variability was observed (U = 17.5, Z = -.84, p = .401) *(***Figure 4.3***)*.

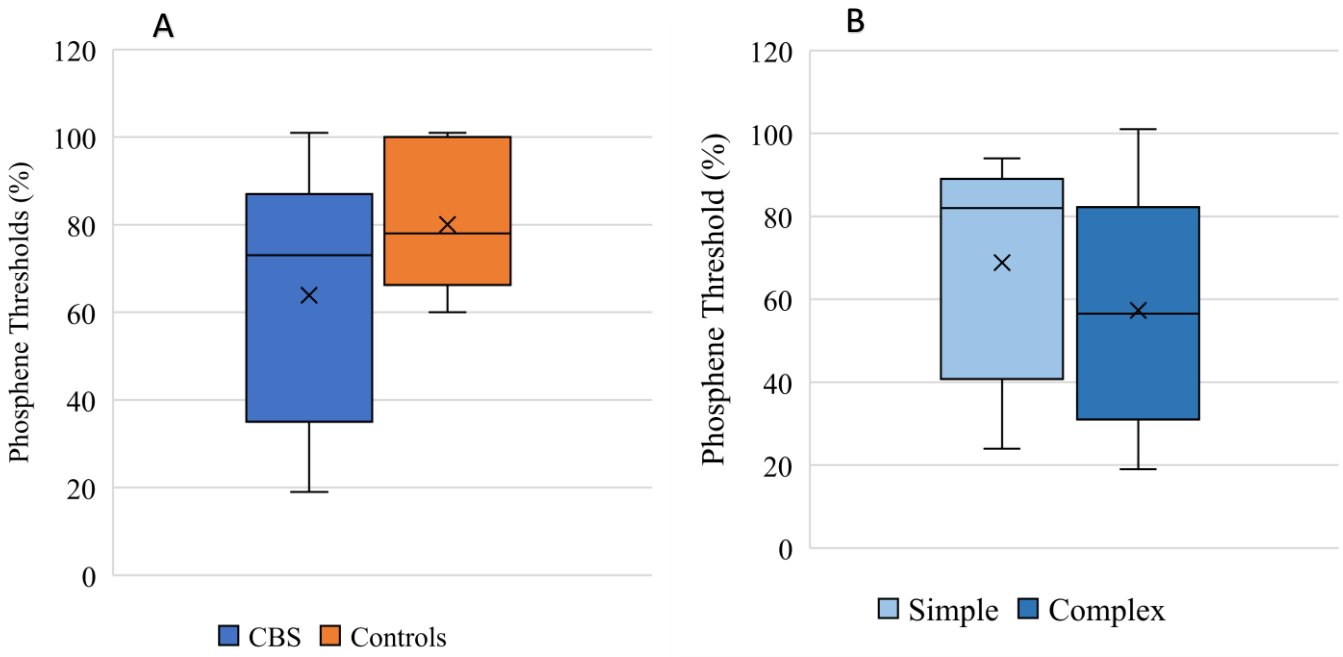

Figure 4.3. *Box Whisker Plots demonstrating the mean (x), median (line) and standard deviation of phosphene thresholds split by group (A) and primary visual hallucination phenomenology (B).*

The percentage of locations tested from which phosphenes could be elicited(CBS: *mean* = 62.47 ±39.24; Controls: *mean* = 41.06 ±39.5) did not differ significantly between groups (U = 78.5, Z = -1.41, p = .160). Similarly, when split by VH type (Simple VH: *mean* = 52.78 ±38.87; Complex VH: *mean* = 75.39 ±39.20) no significant differences were found (U = 16, Z = -1.06, p = .291).

Frequencies of specific phosphene features reported by participants during the TMS protocol are detailed in **Table *4.6***. A chi-square test of the frequencies of these features found no significant differences (p>.05) between groups. Two participants from the CBS group reported 'VH like' phosphenes consisting of piles of wood planks (which was a new VH for the participant) and a garden trellis which the participant had seen previous to TMS assessment. None of the Control group reported defined complex images of this manner during stimulation.

Table 4.6 *Frequency of phosphene features reported by group. Displayed as frequency (Percentage of responders).*

		Phosphene Complexity				
	Frequency of Phosphene Responders	**Simple (%)**	**Defined shape (%)**	**Colourless (%)**	**Coloured (%)**	**VH Like (%)**
Controls	12/16	12 (100)	2 (16.67)	6 (50)	6 (50)	0
CBS	13/14	12 (92.31)	4 (30.77)	4 (30.77)	9 (62.23)	2 (15.38)
Simple VH	8/8	8 (100)	2 (25)	3 (37.5)	5 (62.5)	0
Complex VH	5/6	4 (80)	2 (40)	1 (20)	4 (80)	2 (40)

Associations with VH Severity

The association between phosphene thresholds, the percentage of locations eliciting phosphenes, and measures of VH on the NPI^{hall} and NEVHI were analysed within the CBS group using Spearman's correlations. As a significant correlation was demonstrated between age and phosphene thresholds in the CBS group (r_s = .759, p = .002) but not in the Controls (r_s = -.047, p = .863) and age and % phosphene locations in CBS (r_s = -.587, p =.027) but not controls (r_s = .318, p = .229), Spearman's partial correlations were used to control for the effect of age on further correlations between phosphene and VH measures. No significant correlations (p>.05) were observed between phosphene measures and visual acuity or contrast.

Moderate negative associations between phosphene thresholds and VH ratings on the NPI^{hall} (overall score), VH severity, and irritation were observed, indicating a tentative association between lower phosphene thresholds and more severe/irritating VH (***Table 4.7***). While not significant, a trending positive association between these measures (NPI^{hall}, NPI Severity, NEVHI Irritation) was also observed with the number of sites from which phosphenes were elicited.

Table 4.7. *Spearman's partial correlations between ratings of visual hallucinations on the NPI^{hall} and NEVHI with TMS phosphene measures, controlling for age.*

	Phosphene Thresholds (%)		Phosphene Locations (%)	
	r_s	Sig. (*p*)	r_s	Sig. (*p*)
NPI^{hall} ***(Severity x Frequency)***	**-.650**	**.016**	.519	.069
Severity	**-.618**	**.024**	.531	.062
Frequency	-.179	.559	.120	.695
Distress	-.486	.092	.539	.058
NEVHI				
Frequency	.178	.560	-.097	.752
Duration	-.168	.583	.229	.451
Irritation	**-.559**	**.047**	.534	.060
Distress	-.289	.338	.048	.875

Significant correlations are highlighted in dark blue, light blue represents rho values >.350 but p>.05. *Abbreviations:* NPI^{hall}: Neuropsychiatric Inventory hallucination subscale; NEVHI: North East Visual Hallucination Interview, TMS: Transcranial magnetic stimulation.

4.3.4 Functional MRI activation

No differences in grey matter volume across the whole brain or within specific ROIs, controlling for age, sex and total intracranial volume, were observed between groups (>.05-FWE). Significant cluster activation for the fMRI eye movement task (p <.001 uncorrected.) was evident for both the CBS and Control groups across overlapping visual regions (**Figure *4.4***).

Whole brain anaysis comparing groups did not demonstrate any significant differences in BOLD activation during the eye movement task between the CBS and Control group. On conducting ROI analysis, the CBS group were noted to have reduced overall activation across the occipital regions (t (35)= 1.81, p= .039) compared to controls. Further ROI analysis of lower visual areas (V1/V2) and visual association regions (ventral extrastriate, fusiform area and thalamus) observed significantly reduced activation in the CBS group compared to Controls (**Table *4.8***). However, only the ventral extrastriate cortex demonstrated a significant difference between groups (t (35) = 2.65, p = .03) when corrected for multiple comparisons(**Figure *4.5***). No significant difference was observed in activation in the precuneus between either group. When split by most prominent VH phenomenology

(simple or complex), no differences in BOLD activations were observed in any regions between CBS participants regardless of VH phenomenology.

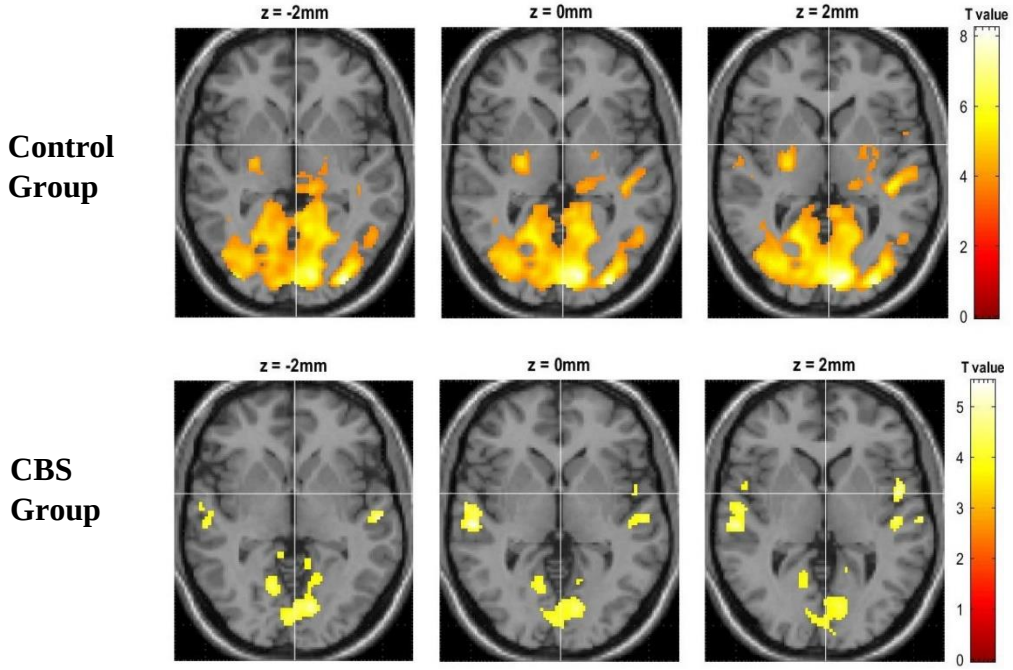

Figure 4.4 *Group fMRI blood oxygen level dependent activation during the eye-movement task compared to rest. Threshold at p<.001 uncorrected and superimposed on a standard T1 weighted brain image.*

Table 4.8. *Independent t-tests comparing activity in regions of interest (ROI) between the CBS and control groups. Significant values (p<.05) highlighted in bold. Corrected p applies a Bonferroni correction for multiple comparisons based on the five ROIs.*

ROI	Contrast Value	t-statistic	Uncorrected *p*	Corrected *p*
V1/V2	.41	1.85	**.036**	.170
Ventral extrastriate	.36	2.65	**.006**	**.030**
Fusiform	.31	2.11	**.021**	.102
Thalamus	.36	1.86	**.036**	.167
Precuneus	.24	1.67	.052	.235

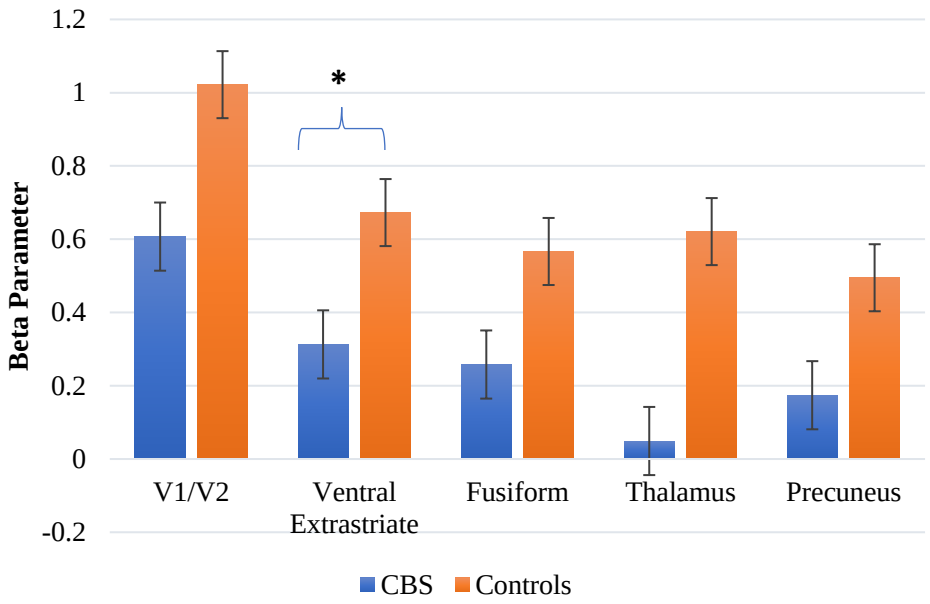

Figure 4.5. *Region of Interest (ROI) analysis comparing functional blood oxygen level dependent activation between Control and Charles Bonnet Syndrome (CBS) groups in response to the eye movement task (mean(+/- SEM.)). *p<.05-FWE.*

When comparing overall hemispheric visual cortical activation, controls were found to have significantly higher activation in both the left (t(35)=2.38, *p*=.023) and right (t(35)=2.05, *p*=.047) hemispheres than the CBS group (FWE-corrected). When comparing differences in left and right hemispheric activation within the specific ROIs, only the left ventral extrastriate was found to be significantly greater in controls than CBS (t(35)= 3.37, *p*=.009-FWE corrected). Comparisons of overall hemispheric activation within each group observed no differences in either controls (t(17)=.43, *p*=.674) or the CBS group (t(17)=-.92, *p*=.37), suggesting no overall hemispheric bias in either group. However, analysis of separate ROIs observed greater right than left ventral extrastriate activation in CBS (t(17)=-2.17, *p*=.04) not observed in Controls (t(17)=-.45, *p*=.658). Similarly, activation in the left thalamus was found to be greater than right in controls (t(17)=2.54, *p*=.02) but not CBS (t(17)=-.59, *p*=.56) (**Figure 4.6**).

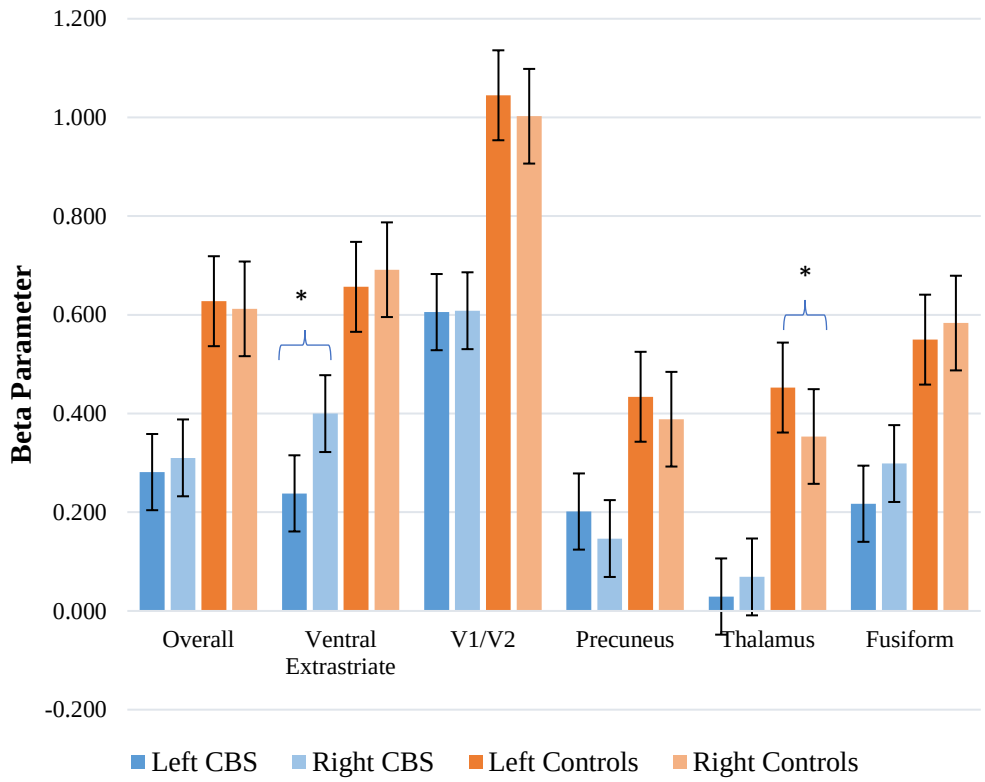

Figure 4.6. *Left and right hemispheric functional activation in visual cortical regions of interest for CBS and control groups. (mean (+/- SEM)). *p<0.05.*

No significant correlations between BOLD activation and measures of visual acuity or contrast were observed in either group (r_s=-.04 to .32, p>.237). Furthermore, no significant correlations between measures of VH on the NPI^{hall} or NEVHI and BOLD activations were observed in the CBS group (r_s=-.001 to -.34, p>.174). While not reaching traditional levels of significance, a trending positive association between activation in the thalamus and frequency of VH measured on the NEVHI was observed (r_s= .42, p=.083).

Associations between functional activation and TMS phosphene measures

Associations between measures of phosphene thresholds and percentage of locations from which phosphenes were elicited with BOLD activation are described in ***Table 4.9***.

Table 4.9 *Partial correlations controlling for age between transcranial magnetic stimulation phosphene measures and functional blood oxygen level dependent activation in each region of interest. Significant associations (p<.05) are highlighted in blue.*

Region of Interest (β)	Phosphene Threshold (%)		Phosphene Locations (%)	
	r_s	Sig. (*p*)	r_s	Sig. (*p*)
Occipital (overall)	.285	.135	-.326	.084
V1/V2	**.378**	**.043**	-.328	.083
Ventral Extrastriate	**.517**	**.004**	**-.378**	**.043**
Fusiform	.310	.102	-.200	.298
Thalamus	.172	.371	-.156	.419
Precuneus	.050	.795	-.156	.418

A moderate relationship between ventral extrastriate activity and phosphene thresholds and percentage of locations that elicited phosphenes was observed across both groups, indicating that lower visual cortical excitability across early visual cortical regions, as targeted and measured by TMS, was associated with greater activation in areas of the later visual association cortex (**Figure *4.7* A**). A weaker association between V1/V2 activation and phosphene thresholds was also observed across both groups. However, separate analysis of each group indicated a stronger significant relationship between V1/V2 activation and phosphene thresholds in the CBS group (r_s= .649, *p*=.016) compared to controls (r_s=.024, *p*= .931), indicating that lower visual cortical excitability was associated with greater BOLD activation of the primary visual cortex in CBS but less so in Controls (**Figure *4.7* B**).

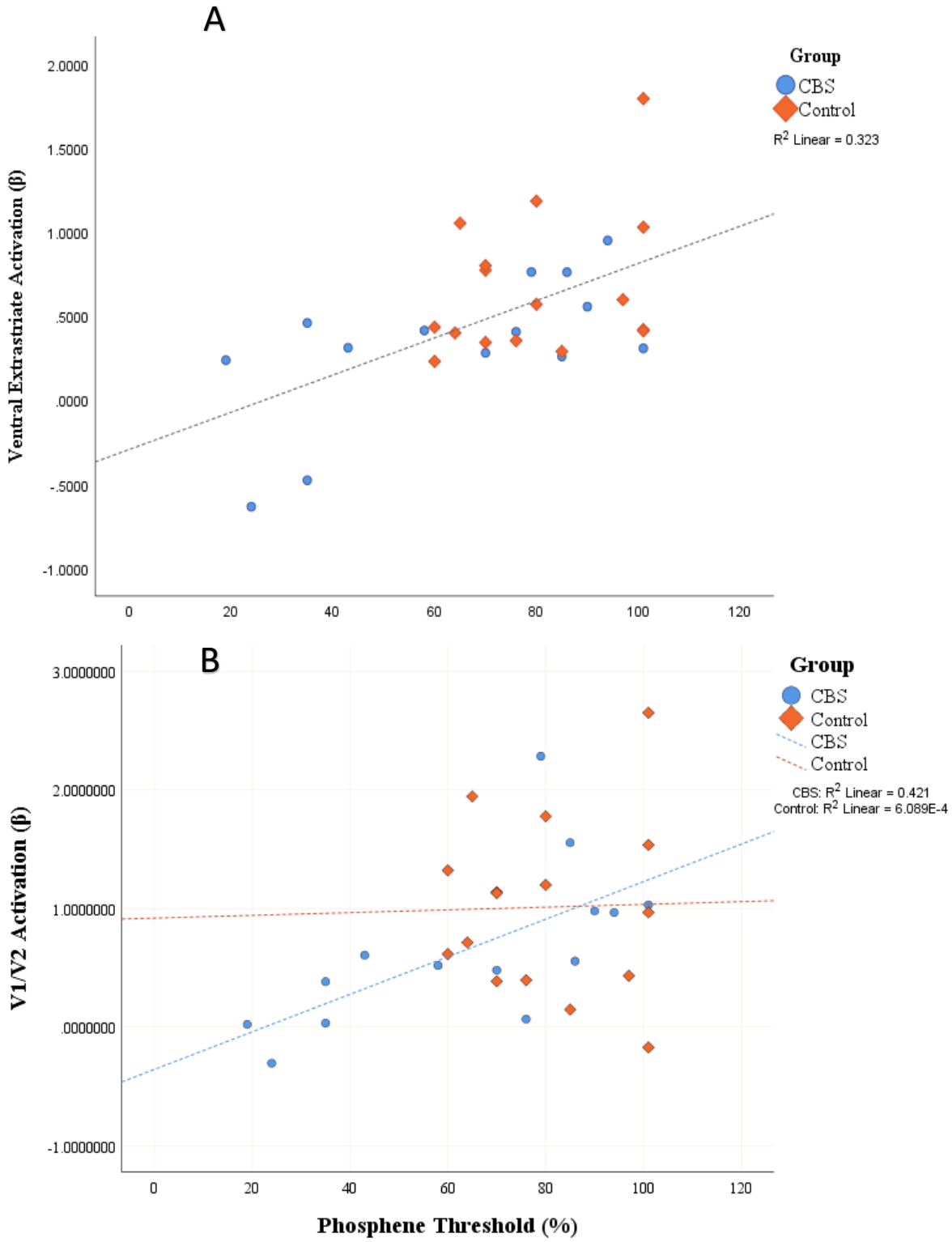

Figure 4.7. *Scatterplots demonstrating the association between ventral extrastriate functional activation and phosphene thresholds across all participants (A), and V1/V2 functional activation with phosphene thresholds split by group (B) with lines of best fit calculated from the mean (R^2).*

4.3.5 Visual Cortical GABA concentrations

Five participants were excluded from analysis due to not meeting MRS fit quality criteria (4 CBS; 1 Control) (see **Chapter 3**). ***Table 4.10*** shows the ratio of GABA+ to creatine for each group, tissue fractions in the voxel being measured and total GABA+ concentration (mm/l) corrected and normalised for voxel CSF, grey and white matter proportions. No significant differences between CBS and controls were observed for GABA+/Cr ratio (***Figure 4.8***). No group differences were observed between grey or white matter proportions within the voxel of interest, CSF volume or corrected GABA+ concentrations (***Table 4.10***).

Table 4.10. *Occipital Spectroscopy results in CBS and controls.*

	CBS	Controls	Sig. (*p*)
N	**15**	**17**	
GABA+/Cr	.105(±.026)	.108(±.014)	.606
GABA + (corrected)	1.27(±.303)	1.35(±.226)	.086
CSF in Voxel	.292(±.056)	.321(±.065)	.131
GM in Voxel	.416(±.089)	.440(±.085)	.417
WM in Voxel	.291(±.085)	.239(±.075)	.073

Results displayed as Mean (± standard deviation). Significance calculated using Mann-Whitney U test.
Abbreviations: CBS: Charles Bonnet Syndrome; GABA: y-aminobutyric acid; Cr: Creatine; CSF: cerebral spinal fluid; GM: grey matter; WM: white matter

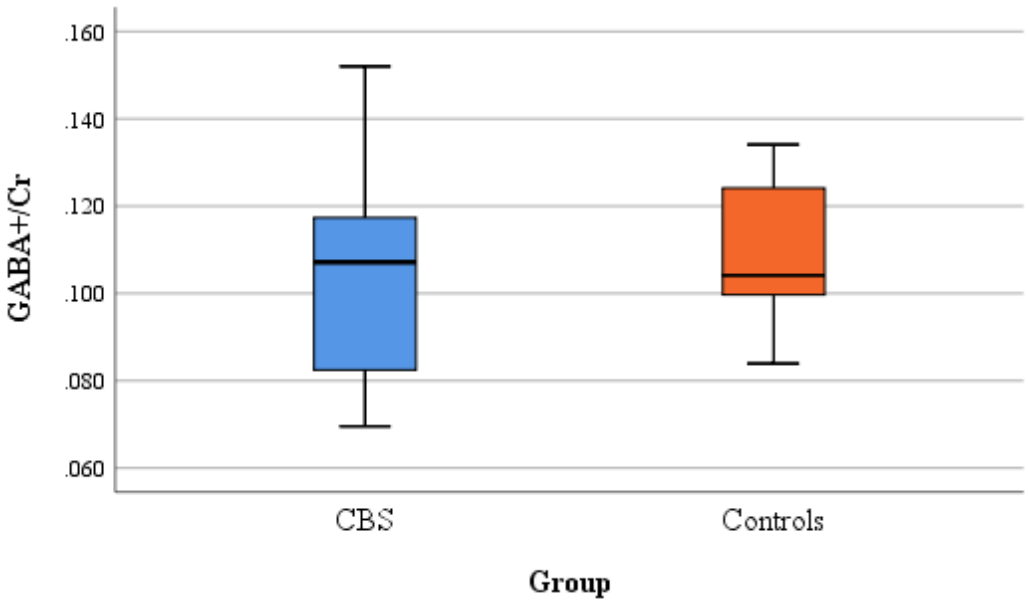

Figure 4.8. *Occipital GABA+ to Creatine ratio in CBS and Controls.*

Spectroscopy results for the CBS group split by most prominent VH phenomenology are displayed in **Table *4.11***. No significant differences in occipital GABA+ to creatine ratio (**Figure *4.9***), grey or white matter proportions, or corrected GABA+ concentrations were observed between participants experiencing predominantly simple or complex VH. However, participants who experienced predominantly complex VH demonstrated a greater proportion of CSF in the voxel of interest than participants endorsing primarily simple VH (**Table *4.11***).

Table 4.11. *Occipital Spectroscopy results for CBS participants split by most prominent visual hallucination phenomenology.*

	Simple	Complex	Sig. (*p*)
GABA+/Cr	.109(±.021)	.099(±.030)	.565
GABA + (corrected)	1.27(±.325)	1.27(±.301)	.908
CSF in Voxel	.256(±.033)	.334(±.049)	**.011**
GM in Voxel	.432(±.070)	.397(±.109)	.563
WM in Voxel	.312(±.082)	.269(±.089)	.355

Results displayed as Mean (± standard deviation). Significance calculated using Mann-Whitney U test.
Abbreviations: GABA: y-aminobutyric acid; Cr: Creatine; CSF: cerebral spinal fluid; GM: grey matter; WM: white matter

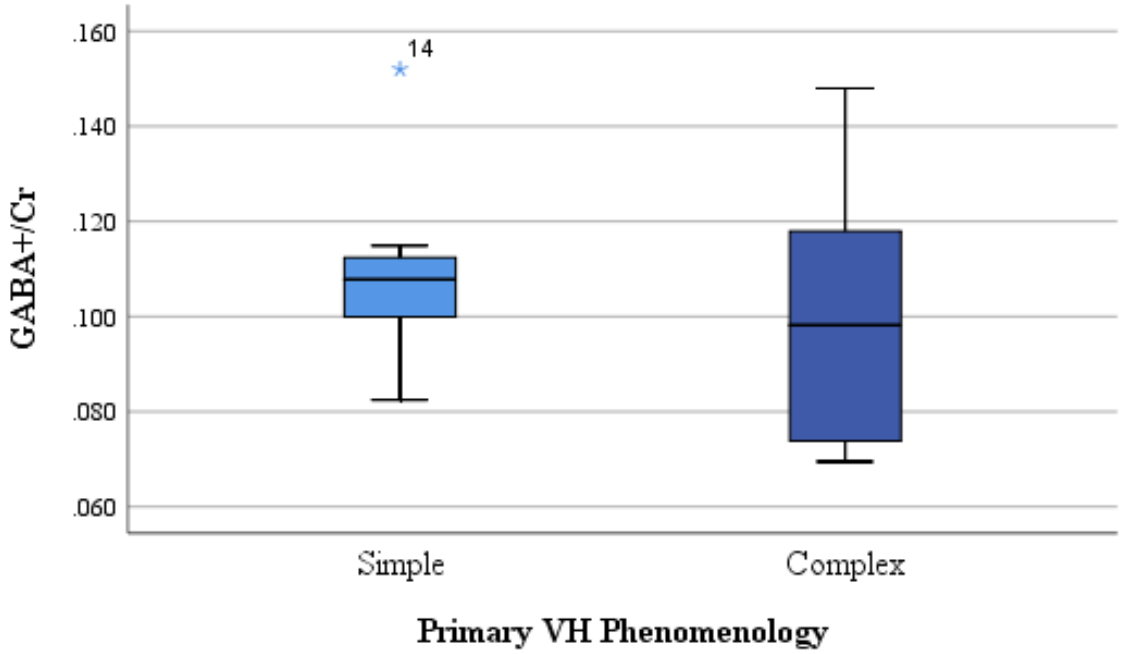

Figure 4.9. *Occipital GABA+ to Creatine ratio in the CBS group split by most prominent visual hallucination (VH) phenomenology.*

There were no significant correlations (p>.05) between GABA+/Cr or GABA+ and age, visual acuity or contrast. No significant correlations between GABA+/Cr or GABA+ were observed between functional activation (fMRI) in any of the regions of interest,

phosphene thresholds or number of locations from which phosphenes could be elicited. In the CBS group, no significant correlations between GABA+/Cr or GABA+ were found between VH ratings on the NPI^{hall} or NEVHI.

4.4 Discussion

The aim of this chapter was to investigate differences in visual-cortical activity between people with eye disease who experience VH (CBS) with those with eye disease who do not (Controls) in an effort to better understand why VH arise in some eye disease patients but not others and the mechanisms involved in the production of VH. The current study represents, to the best of our knowledge, the largest CBS study of its kind. Findings of note include the relationship between increased visual cortical excitability and the severity of VH and reduced visual cortical BOLD response during the fMRI task in CBS when compared to Controls.

4.4.1 Demographic features related to CBS

The current study compared a number of demographic factors between participants with CBS and controls. Whilst not a primary aim of this study, analysis of the demographics of the two samples provides overall context for the following investigations and its representation of the eye disease and CBS population as a whole.

In line with previous prevalence studies of CBS (i.e. Menon et al., 2003), the most common eye disease related with CBS in this sample was age-related macular degeneration (AMD). However, macular degeneration was also found to be the most prominent cause of vision loss in the control group, with no significant differences between groups. This supports the view that the prevalence of CBS in AMD is predominantly reflective of the prevalence of AMD in the general population, with poor visual acuity overall presenting the greatest risk factor for the development of CBS rather than a specific ocular pathology (Khan et al., 2008). Furthermore, while not significant, the CBS group were observed to have overall worse visual acuity and contrast sensitivity than controls in spite of efforts to match the groups as closely as possible in these domains. This corresponds with previous research that has concluded that worse visual function is associated with an increased risk of VH (Gold & Rabins, 1989; Teunisse et al., 1996), with poor bilateral visual acuity presenting the most significant risk factor (Scott et al., 2001). Nevertheless, while it has been suggested that poorer visual acuity is more commonly associated with complex VH phenomenology (Burke,

2002), this was not observed in the present study, with no significant acuity differences observed between participants reporting predominantly simple vs complex VH. However, the suggestion by Burke was based on an anecdotal report of the researcher's own personal experience with vision loss and VH, and subsequent studies of larger CBS samples, similar to the present investigation, have not observed a relationship (Khan et al, 2008).

As the groups were purposefully matched for age and gender in this study, no significant differences between these factors were observed between CBS participants and controls. Previously, the CBS literature has suggested that increased age may confer a greater risk on the development of CBS (Teunisse et al., 1995). However, this has not been replicated in other studies when controlling for associated factors such as visual acuity (i.e. Khan et al., 2008; Menon et al., 2003), and therefore may again be more indicative of the increased prevalence of eye disease in the aging population rather than a direct association between age and CBS. That said, CBS participants recruited to this study ranged between the ages of 53-93 years, to which controls were subsequently matched. Therefore, this sample is not representative of younger people with CBS and would be unable to detect any meaningful direct effect of age on the development of VH.

A significant difference in scores on the IADL was observed between CBS and controls, with CBS participants reporting a greater loss of independence and daily functioning. This corresponds with previous findings in which 46% of people with CBS surveyed reported that VH had an impact on daily activities (Cox & ffytche, 2014). However, poorer visual acuity and contrast were also found to be significantly associated with disruption to daily functioning across groups, reinforcing previous findings that eye disease itself results in a loss of independence and valued activities (Mitchell & Bradley, 2006; Rovner et al., 2002), and when added as a covariate resulted in a non-significant difference in IADL scores between the two groups. As the CBS group reported marginally poorer visual function than the controls, it is possible that this conferred a greater impact on their functioning than the VH themselves, though VH may act as an additive factor in overall disruption to functioning and day-to-day independence. Previously, CBS has also been associated with poorer psychological well-being and emotional distress compared to patients without VH (Mitchell & Bradley, 2006; Scott et al., 2001). However, in the present study, no group differences with regards to depressive symptoms (measured by the GDS) were observed. Nevertheless, this may be more indicative of a recruitment bias, as it is possible that patients reporting greater depressive symptoms would be more reluctant to engage with research participation.

Nevertheless, overall VH severity measured by the NPI^{hall}, which probed the overall disruptiveness of VH perceived by participants, was significantly associated with greater feelings of distress and irritation towards VH in the CBS group. This indicates that negative emotions attached, and in response, to VH were significantly impacted by how disruptive participants found them to be, supporting the similar findings of Cox & ffytche (2014). Similarly, while not statistically reliable, a trending association between the overall frequency of VH and feelings of irritation was also observed, which tentatively supports the association between more frequent hallucination episodes and negative outcomes observed by Cox & ffytche. In contrast, however, the present study observed no effect of the duration of each hallucination episode on feelings of distress or irritation towards VH, but a significant effect of overall duration of CBS on ratings of irritation and a trending association with ratings of distress. The latter findings contradict the observations of Cox & ffytche (2014), who found no association between overall CBS duration and negative outcomes, concluding that habituation to CBS may occur over time. The current study, however, found that this significant association appeared to relate predominantly to the subjective feelings of irritation, and therefore may have probed a more specific emotional response to VH not detected by the negative outcomes measured by Cox & ffytche, which characterised distress, stigma, and reduced quality of life.

Overall, complex hallucinations were the most commonly reported VH phenomena, with even participants who reported predominantly simple VH endorsing sporadic complex imagery at some point during the course of their CBS in the majority of cases. This is in line with previous reports which have found complex VH to be a defining feature of many CBS cases (Collerton et al., 2005; Menon et al., 2003) and suggests that the current sample may offer a good representation of the CBS population in this regard.

Unexpectedly, greater ratings of distress were reported in response to simple rather than complex VH by participants in this study. Previously, negative emotions of distress, fear or anxiety have been most predominantly associated with complex imagery of distorted faces and figures, particularly those that may be associated with threat or dread (Damas-Mora et al., 1982). One potential explanation for this may be the definition of distress as interpreted by the participants themselves. While distress in this context is most commonly used to refer to fear or anxiety induced by the content of the VH (Cox & ffytche, 2014; Damas-Mora et al., 1982; Khan et al., 2008; Menon et al., 2003), it is possible that some people may relate feelings of distress and associated anxiety to the presence of the VH themselves independent of the overall content (Podoll et al., 1989). Distress may also be associated with a perceived

lack of control over VH appearance and qualitative aspects such as its size and intensity which may affect the subsequent disruptiveness or intrusiveness of VH. As the current study noted a significant association between VH severity and ratings of distress (regardless of content) this may indicate the way in which participants interpreted 'distress' in this study. While it is not clear from the present analysis why simple VH may have prompted greater feelings of distress in this group, it is possible that these ratings are the result of a complex interaction between the content of the VH and aspects such as the disruptiveness, intrusiveness, and frequency of that specific imagery.

4.4.2 The role of visual cortical activity in CBS

The primary aim of this study was to investigate differences in cortical activity between people with CBS and those with eye disease who had never experienced VH (controls), in order to better understand the mechanisms involved in the production of VH in these patients.

Transcranial Magnetic Stimulation

Using TMS to assess the excitability of the primary visual cortex, no significant difference in phosphene thresholds or the number of locations from which phosphenes were elicited was observed between the CBS group and controls. These findings suggest that the hallucinating eye disease group (CBS) do not demonstrate overall greater visual cortical hyperexcitability than controls and therefore refutes our primary hypothesis. This is contrary to previous investigations into hallucinating groups, who have observed significantly greater hyperexcitability (in the form of lower phosphene thresholds) in hallucinators than non-hallucinators (Aurora et al., 2003; Brighina et al., 2009; Oliveri & Calvo, 2003). Nevertheless, it is important to note that these observations were made in groups that may not be directly comparable to CBS. While 'aura' is a common visual symptom experienced by migraine patients, it is generally simple in nature (often consisting of dots, lines, or flashing lights) (Aurora et al., 2003). Such imagery has been postulated as arising from early visual regions, such as the primary visual cortex (Collerton et al., 2005; ffytche et al., 1998), and greater excitability in this specific area may result in the production of 'aura' in these patients. As TMS is presumed to assess occipital hyperexcitability in the same region, it may be possible to more easily detect differences in primary visual cortical excitability in these patients (Aurora et al., 2003; Brighina et al., 2009). As the majority of participants in the

current study, and indeed people with CBS as a whole (Collerton et al., 2005; Khan et al., 2008; Menon et al., 2003), report a mix of both simple and complex VH phenomenology, which has been linked to increased excitability arising upstream in the ventral and visual association cortices (ffytche et al., 1998; Jardri et al., 2013), it is likely that a direct comparison with migraine with aura patients is not possible in this regard. Similarly, heavy ecstasy use, which is associated with VH and lower phosphene thresholds (Oliveri & Calvo, 2003), has also been associated with changes to 5HT2A receptor binding increases and decreases in blood flow to the occipital cortex, resulting in hyperexcitability which may lead to the production of VH (Chang et al., 2000; Reneman et al., 2000). Nevertheless, as VH in this group are pharmacologically (and transiently) induced it is difficult to compare to clinical samples such as CBS, in which a long-term change to the functioning of the visual system appears to precipitate VH.

In contrast, studies of short-term visual deprivation have observed decreases in phosphene thresholds, indicating a rise in cortical excitability as a consequence of visual input loss (Boroojerdi, 2000; Fierro et al., 2005) and may provide a further explanation for the findings of this study. As such changes were observed as a consequence of visual deprivation in general, it is possible that vision loss as a result of eye disease may lead to similar excitability changes in both groups regardless of VH, making any differences between groups difficult to detect. Conversely, chronic visual deprivation, as a result of eye disease, may result in adaptive changes to the visual system in which homeostatic mechanisms may attempt to normalise activity in the visual cortex, again making differences between the groups difficult to detect. These mechanisms may subsequently drive enhanced excitability in the visual cortex, independent of overall or absolute levels of excitability, resulting in the manifestation of VH. While collected as part of a different study and therefore not wholly comparable, Taylor et al., (2011) found that healthy, sighted controls of comparable age (mean: 77.6) to the CBS and Controls in this study demonstrated an average phosphene threshold of 55.6% (SD: 8.8%). Although this is lower than the phosphene thresholds reported by both the CBS (63.93%) and control (80.06%) group in this study, the smaller difference between sighted controls and CBS may indicate that increases in excitability may be due to overcompensation of the visual cortex following vision loss, resulting in VH and supporting the deafferentation hypothesis. Comparatively, visually impaired controls may not experience this same degree of compensatory activity, leading to an absence of VH. Perhaps in support of this, the CBS group demonstrated significantly higher variability in their

phosphene thresholds, which could indicate that while vision loss may produce comparable phosphene thresholds in both groups, instability in these levels of excitability may then precipitate the formation of VH and may support models which postulate the dynamic nature of VH (e.g. Tsukada et al., 2015). Such differences in the variability of phosphene thresholds have also been observed in migraineurs and may therefore be similarly important to the susceptibility of some patients to develop visual symptoms compared to others (Aurora et al., 1999). Furthermore, the theory of visual system adaptation following sight loss may also explain why such wide variability in both excitability and the presence of inhibitory neurotransmitters (GABA) in the visual cortex was observed, as adaptation occurs at different rates across individuals and may depend on factors such as degree of sight loss and length of time since onset.

Further supporting the potential role of hyperexcitability in CBS hallucinations, as measured by TMS, is the observed association between phosphene thresholds and VH severity. Significant negative associations between the severity of and irritation felt toward VH and phosphene thresholds indicate that participants with greater cortical excitability were also prone to more severe VH, with a subsequent association with ratings of irritation. This is directly comparable to the findings of Taylor and colleagues (2011) in patients with DLB, who noted that while no differences in phosphene thresholds and overall excitability were observed between patients and controls, increased excitability was strongly correlated with the severity of their VH. It is therefore possible that, while hyperexcitability as a whole may not be directly necessary for the production of VH, it may provide a state-related marker for VH severity in CBS, and that by reducing this spontaneous hyperexcitability a subsequent reduction in VH severity may be observed.

Neuroimaging

With regards to fMRI, participants with CBS demonstrated overall lower functional activity across the visual cortex than controls, with significantly reduced activity within the ventral extrastriate cortex. While this supports our hypothesis that there would be a difference in cortical activity between CBS and controls, the direction of this difference was opposite to that which had been predicted. Although limited, previous investigations of functional activity in CBS have observed increased ventral occipital activity using fMRI (ffytche et al., 1998) and hyperperfusion in areas of the lateral temporal cortex, striatum and thalamus using SPECT imaging (Adachi et al., 2000) representing increases in phasic activity related to VH.

Similar increases to cortical activity and cerebral blood flow have been associated with VH as a result of LSD and in schizophrenia (Carhart-Harris et al., 2016; Oertel et al., 2007). Nevertheless, the present study indicated significantly lower visual cortical activity in people with VH than those without. In contrast to previous studies (e.g. ffytche et al., 1998; Adachi et al., 2000) this study collected fMRI while participants were not actively hallucinating, and thus may indicate trait, rather than state, related changes to cortical activity in people with CBS, thus providing insight into what changes may make some people more susceptible to experiencing VH.

Conversely, no significant differences in concentrations of the inhibitory neurotransmitter GABA were observed between people with CBS and controls, which therefore does not support our hypothesis or prediction that visual cortical GABA would be decreased in CBS when compared to controls. This is in contrast to the findings of Firbank and colleagues (2018) who observed significantly lower GABA+/Cr in PD patients with VH compared to PD without VH. Decreased GABAergic transmission has been linked to a loss of inhibition in the visual cortex, which has subsequently been linked to the presence of VH (Firbank et al., 2018; Khundakar et al., 2016; Su et al., 2016). However, the findings of the present study suggest that altered GABAergic transmission may not be a significant factor underpinning VH in eye disease. Nevertheless, CBS participants, and in particular those with predominantly complex VH, presented overall greater variability in occipital GABA+ to creatine ratios in this study; similar to the greater variability of excitability observed in the form of phosphene thresholds, this may instead indicate that CBS occurs as a result of fluctuating visual cortical excitability and inhibition leading to the formation of VH. As such, future longitudinal investigation of potential fluctuations in comparison to non-hallucinators are required in order to adequately assess their contribution to the formation of VH in this patient group and may help to inform future treatments aimed at decreasing such variability in activity. Furthermore, while not significantly different, lower GABA+/Cr was more frequently observed in complex hallucinators, suggesting that altered resting-state GABAergic transmission within the primary visual cortex may be necessary for subsequent disinhibition, with increases to activity in more ventral visual cortical regions associated with complex VH content. Since PD is most commonly associated with complex VH, this may be tentatively comparable to the findings of Firbank et al (2018). Similar to previous studies, however, this study also observed no significant relationship between GABA and occipital BOLD activations (Firbank et al., 2018; Harris et al., 2015) despite previous suggestions that

these measures are related (Violante et al., 2013) and may indicate that while blood flow and vascular reactivity is significantly altered in CBS, neuronal activity and transmission is less so.

Signal-to-Noise Ratio

One potential explanation for these findings may be found in the episodic nature of VH in most people with CBS. Previous studies which have identified increased functional visual cortical activation in CBS have performed scans while the patients were actively hallucinating (representing hallucinatory state changes i.e. Adachi et al., 2000; ffytche et al., 1998), whereas the present study scanned participants outside of their hallucinatory episodes, potentially providing an indication of their natural baseline or resting-state activity and trait differences associated with VH. In this case, while actively hallucinating may produce a corresponding increase in functional activity in the visual cortex related to VH content (ffytche et al., 1998), the findings of this study may suggest that during hallucination-free periods, functional activity may lie at lower-than-normal levels in order to facilitate the detection of weak sensory signals, effectively allowing for increased signal-to-noise ratio in these patients.

Ordinarily, the brain filters out noise caused both by variability in external stimuli and internal neuronal activity by averaging information it receives (Ermentrout et al., 2008). Alterations to the internal signal-to-noise ratio can produce significant effects on perceptual processing in healthy participants, with lower signal-to-noise ratios in visual cortical areas resulting in disruption to visual perception, such as motion discrimination, while increasing this ratio (i.e. via dopaminergic receptor activation) can enhance perceptual performance (Hayes & Merigan, 2007; Yousif et al., 2016). Correspondingly, altered signal-to-noise ratios have also been observed in schizophrenia, which is often associated with VH, linked to dysfunction of the dopaminergic system and perceptual impairments reported in these patients (Peled & Geva, 2000).

In the case of CBS, an increased signal-to-noise ratio (rather than decreased), in conjunction with a loss of sensory input from the eyes, may lead to a visual cortex which is ‘over-eager’ to perceive stimuli. Bayesian inference has been postulated as a key mechanism in the formation of hallucinations (including VH) in other conditions, including schizophrenia (Collerton et al., 2005; Friston, 2005; Horga & Abi-Dargham, 2019), and may provide further explanation for an increase in incorrect signal detection observed in hallucinators. Bayesian

principles suggest that prior knowledge and expectations are used to determine accurate signal detection, particularly when sensory information is ambiguous (Horga & Abi-Dargham, 2019). In this case, sensory information is filtered based on the prior knowledge of the perceiver, using a sequential framework of expectations to determine what is signal vs noise. While this ordinarily provides an adaptive response to signal-to-noise detection in a 'normal' system, Friston (2005) proposed that, as sensory neurons always exhibit some level of spontaneous activity, there is never a total absence of internal sensory evidence and may therefore provide a point of vulnerability within some pathologies, resulting in more extreme and maladaptive perceptual biases. In particular, the integration of sensory-evoked and spontaneous cortical activity has been shown to be key in the development and overall plasticity of the visual system, with sensory-based learning found to impact the organisation and propagation of subsequent spontaneous activity and network connectivity, and is a key aspect included in several computational models (Ferezou & Deneux, 2017). In the case of CBS, sensory ambiguity due to degraded visual input may create an environment in which erroneous spontaneous bottom-up activity, influenced by previous sensory based-learning and paired with an over-imposing top-down system inappropriately directing attention towards internally generated activity (Collerton et al., 2005), is more likely to produce 'false alarms' in which a signal is detected and attributed meaning, resulting in VH.

Perhaps in support of this, CBS VH have frequently been reported to worsen in low-light environments (Menon et al., 2003), which further increases sensory ambiguity and may lead to a subsequent increase in false alarms. In contrast, total eye-closure has been observed to help dissipate VH in some patients (Cox & ffytche., 2014; Menon et al., 2003) indicating that the presence of some (albeit degraded) bottom-up stimuli may be necessary for VH to occur; further supporting the suggestion that CBS occurs due to over-compensatory activity in the visual cortex.

Overall variability in visual cortical inhibition following sight-loss, potentially demonstrated by greater variation in GABA+/Cr in CBS compared to controls, may further lead to the increased frequency or magnitude of spontaneous spikes of visual cortical activity which are consequently starkly demarcated from low levels of background cortical activity; this may subsequently lead to a chain reaction resulting in an increased activation response in the later visual and association cortices (such as those observed by ffytche et al., 1998), giving rise to the conscious perception of an image (**Figure 4.10**) (Horowitz, 1964; Menon et al, 2003). Conversely, the control group may demonstrate a lower signal-to-noise ratio,

indicated by greater overall visual cortical activity during fMRI, in which case internally generated neuronal activity is more likely to fall below the threshold used to filter out noise, preventing the perception of imagery in the absence of stimuli.

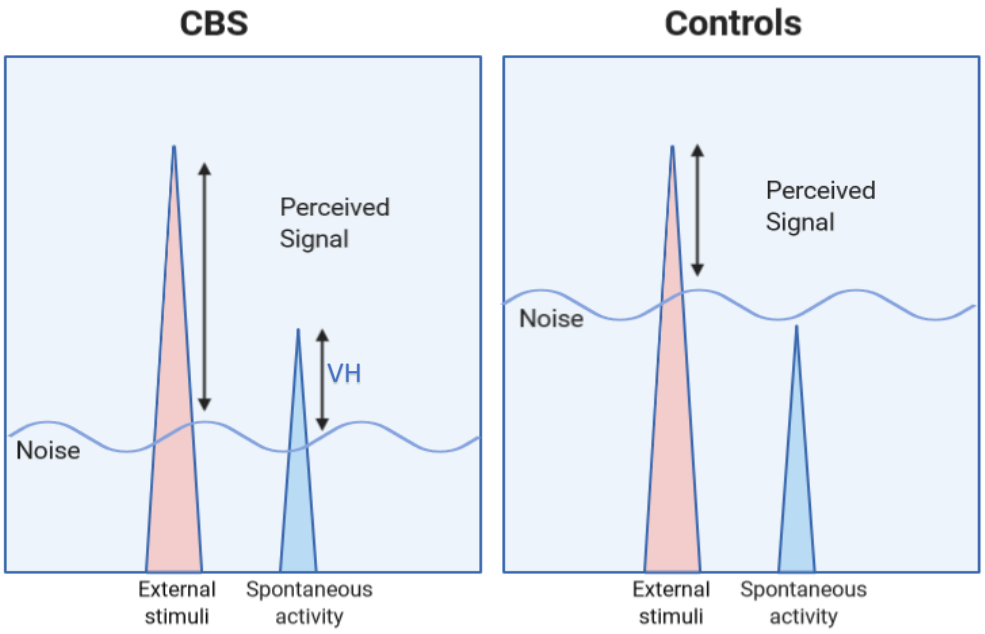

Figure 4.10. *Illustration demonstrating the potential signal-to-noise ratio in people with CBS vs Controls. Activity prompted by external stimuli (from remaining sight) produces a response above the background activity and is perceived in both groups. Spontaneous activity in the visual cortex is able to rise above the lower level of background activity in CBS but not controls, leading to the perception of a visual hallucination (VH).*

Lending further support for this theory is the fact that a significant association between higher phosphene thresholds (indicating lower visual cortical excitability) and increased visual cortical activity during fMRI that was observed in this study. While this finding was initially surprising, as it was expected that greater overall visual cortical activity would be positively associated with increased excitability, greater signal-to-noise ratios in the CBS group may provide an explanation. Participants who demonstrated overall lower levels of visual cortical activity during the fMRI (and therefore a potentially higher signal-to-noise ratio) may have required much lower levels of external stimulation to prompt the perception of visual phenomena (phosphenes). This appears particularly pertinent in the CBS group, in which lower activity in V1/V2 during fMRI corresponded to a much greater response to TMS stimulation targeting the same region. Further supporting this is the incidence of responders vs non-responders to TMS across both groups. Of the 17 control participants tested, 4 did not report any phosphenes even at 100% stimulation intensity (23.5%), whereas in the CBS

group only 1 participant reported no phosphenes (7.1%). While not reaching statistical significance in the current sample, this difference in response rates may be indicative of average differences in signal-to-noise ratios between the two groups, with lower signal-to-noise ratios in controls increasing the likelihood of not perceiving any phosphenes during the assessment. Furthermore, the production of VH-like phosphenes as a result of TMS were exclusively reported by members of the CBS group. While the numbers were low (2/14 participants), this may provide further tentative support for the role of signal-to-noise ratios in the production of complex VH in CBS. These findings provide tentative support for the role of compensatory processing arising in the visual cortex of people with CBS, potentially as an attempt to preserve visual functioning, with VH occurring as an unintended consequence.

Despite this, no differences in cortical activity were observed between CBS participants who predominantly reported simple or complex VH in any of the regions of interest. However, as the majority of the CBS group reported a mix of both simple and complex VH, any differences may have been difficult to delineate. Instead, the phenomenology of any hallucination that arises in each participant may be dependent on the propensity of specific regions to produce spikes of spontaneous activity great enough to surpass background noise, leading to the phasic activity increases previously observed in content specific regions during VH (ffytche et al., 1998). Perhaps in support of this, while the most prominent VH experienced by participants was fairly equally split between simple and complex, the majority of participants endorsed complex hallucinations at some point during their CBS (and commonly within the month preceding study assessments), while the greatest reduction in activity compared to controls was observed in the ventral extrastriate, which has previously been associated with significant increases in activity during complex VH in CBS (ffytche et al., 1998).

Although differing signal-to-noise ratios in people with eye disease may present a potential explanation for why VH occur in some people but not others, this theory is currently speculative and would require further investigation. Nevertheless, the possible involvement of such mechanisms in the production of VH in this patient group may open up new avenues of treatment. The regulation of signal-to-noise ratios and the overall responsiveness of neuronal cells to afferent input are highly dependent on both the serotonergic and dopaminergic systems, and can be influenced by cholinergic mechanisms related to attention (Manford & Andermann, 1998; Peled & Geva, 2000; Yousif et al., 2016). Specifically, the production of VH has been associated with activation of serotonin receptors, in particular $5HT_2$ receptors, which are linked to subsequent changes in cortical excitability, suggesting a

crucial role of the serotonergic system in their formation (ffytche, 2008; Kometer et al., 2013; Kometer et al., 2011; Manford & Andermann, 1998; Roseman et al., 2016). While the investigation of serotonergic function in CBS is currently very limited, a potential beneficial treatment effect of selective serotonin reuptake inhibitors (SSRIs) such as venlafaxine and escitalopram, has been observed in patients with CBS (Bergman & Barak, 2013; Lang et al., 2007) and may provide support for the role of serotonergic pathways in CBS hallucinations. Nonetheless, how this relates to the regulation of potential signal-to-noise ratio differences in hallucinators vs non-hallucinators is not yet clear and may present future prospects for investigation.

Eye-Movement related functional activity

Another possible explanation for the differences in visual cortical activity observed between the CBS group and controls is the means by which functional activity was measured in this study. Simple eye-movements have previously been observed to produce an associated functional response in the occipital cortex during fMRI (Bodis-Wollner et al., 1997) and as such provide a means of measuring the overall activation of the visual cortex compared to rest. Despite this, a limitation of such task-based paradigms in fMRI is that one can only measure the difference between activity during the task vs no task, which can provide little context for the level of an individual's basal 'resting state' activity (Cole et al., 2010). As such, it is not necessarily clear what the starting point of activity is in each individual in this study. Thus, the visual cortical activation observed in the CBS group may not be representative of lower overall activity, but a lower degree of haemodynamic BOLD change between rest and eye-movements. In this case, it is possible that the CBS group may have a starting point of high visual cortical activity, which the eye-movement task did little to affect resulting in little change in activation observed (**Figure *4.11***). Conversely, the control group may have much lower visual cortical activity at rest, followed by a sharper increase during the eye movement task, resulting in a larger pattern of functional activation. In this case, the association between lower fMRI activation and lower phosphene thresholds may be due to an overall more continuously excitable visual cortex which is subsequently likely to respond more sensitively to external stimulation, as opposed to a greater signal-to-noise ratio.

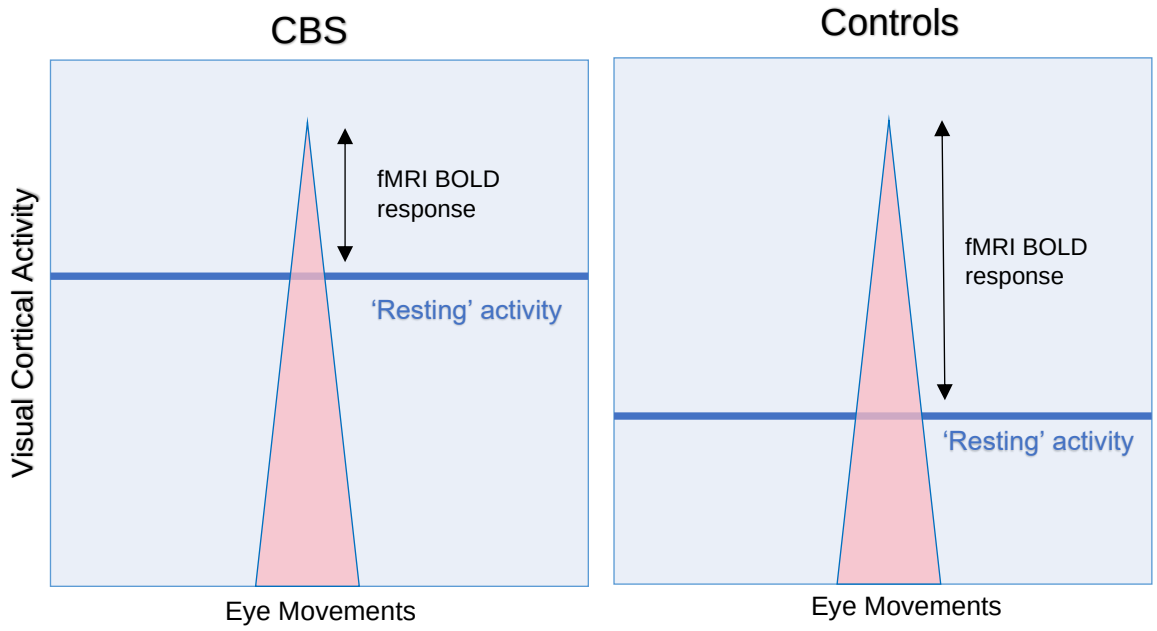

Figure 4.11. *Illustration of how a higher starting point of overall visual cortical activity can impact the size of the blood oxygen level dependent (BOLD) response detected during an fMRI eye-movement task.*

Although this explanation may fit with current hypotheses regarding CBS, with hallucinating patients demonstrating overall greater visual cortical hyperexcitability compared to non-hallucinating controls, it is difficult to verify in the absence of data regarding the 'true resting-state' activity in each group. Similarly, this theory does not provide an adequate explanation for why most people with CBS only experience VH episodically rather than continuously. In addition, it is not clear how this may fit in with findings from the MRS, as one might expect that an overall more basally active visual cortex would demonstrate a lower concentration of inhibitory GABA than one with less resting-state activity – something which was not seen in the present study, as no significant differences in cortical inhibition were observed between hallucinators and non-hallucinators.

One possible consideration for future investigation would be the acquisition of fMRI focused on the spontaneous fluctuations in BOLD signal in the absence of a task, often used for quantifying functional connectivity between regions of interest (Cole et al., 2010), in order to provide an indication of the overall 'resting-state' levels of visual cortical activity between CBS and controls. This information would provide vital context to changes observed during task-based fMRI studies needed to interrogate the underlying mechanisms associated with the presence of VH in one group but not another.

4.4.3 Strengths and Limitations

Although the sample size of the present study is small, and therefore generalisation to the overall CBS population should be made with caution, this study represents the largest neurophysiological comparison study performed in CBS to date and therefore provides important new information regarding the mechanisms underpinning VH following sight loss. Similarly, the demographic features of the groups in this study generally reflect those of larger prevalence and phenomenological studies in CBS (i.e. Cox & ffytche, 2014; Menon et al., 2003; Khan et al., 2008;) suggesting that, while small in number, the participants recruited to this study provide a reasonable representation of CBS as a whole and is an overall strength of the current study. Nevertheless, it is important to take potential methodological weaknesses into account.

Previous studies have suggested that CBS may indicate latent neurodegenerative disease and an increased risk of dementia (Lapid et al., 2012; Pliskin et al., 1996; Terao & Collinson, 2000). While the current study screened for cognitive impairment across all participants and no differences in cognitive ability were detected between CBS and controls, the MMSE has been critiqued in the literature as lacking the sensitivity to adequately detect mild cognitive impairment (Beyermann et al., 2013) and therefore it is possible that participants in this study presenting with more subtly impaired cognition may not have been detected during screening. Similarly, the lack of unified diagnostic criteria and overall awareness of CBS amongst clinical personnel means that very few of the participants involved in this study received a prior clinical diagnosis of CBS. While care was taken to assess participants to exclude potentially confounding variables contributing to the presence of VH, such as a history of psychiatric or neurological conditions or substance abuse, this was predominantly reliant on participant self-report, meaning that it was not possible to comprehensively rule out underlying pathology within the scope of this study.

Similarly, while the control group were screened to ensure that they had never experienced hallucinations in any modality, there may be some debate as to how reliably they can be considered true controls. As VH were observed to start anywhere between immediately to 19 years following sight loss in the CBS group, this suggests that CBS may have a highly variable latency period. The average length of time since initial sight loss in the control group was 5.22 years meaning that, although they were not presently experiencing VH, their status as ‘controls’ may be subject to change further down the line and as their vision changes. Nonetheless, this study still provides important information about visual

cortical differences in people who are currently experiencing VH and those who are not. However, future longitudinal research is needed in order to assess how these differences in cortical activity may evolve over time and which factors precipitate this leading to the emergence of VH, which may provide more avenues for the development of treatments or potential preventative methods.

Related to this, a further limitation of the current study was the focus on VH trait related alterations without contrasting evidence from the VH state in the same participants. However, this limitation is pervasive in hallucination research as a whole, with most studies focussing only on state or trait differences in hallucinating pathologies in isolation (i.e. Adachi et al., 2000; ffytche et al., 1998; Goetz et al., 2014; Meppelink et al., 2009; Stebbins et al., 2004; Taylor et al., 2012). Consequently, there is currently a disconnect between how state vs trait changes are related, and how they interact in order to ultimately form VH in different pathologies. While the investigation of VH state alterations presents many unique challenges to research – such as their occurrence often being unpredictable making data collection difficult – integration of this data in future studies would likely improve interrogation of the aetiological mechanisms involved in VH production while further improving understanding of what increases an individual's susceptibility to VH in the first place.

4.4.4 Future Directions

Future research may wish to investigate the role of functional connectivity in the production of VH in CBS, compared to connectivity in controls, which may provide greater context for the fMRI results observed here. Previous studies investigating VH in other pathologies have indicated a role of changes to overall functional and network connectivity between the visual cortex and further regions throughout the brain in the production of VH (Carhart-Harris et al., 2016; Ffytche, 2008; Hare et al., 2017; Yao et al., 2014). Similarly, a recent case study in CBS observed increased functional connectivity between the precuneus and secondary visual cortex when compared to controls, indicating the potential role of reorganisation of functional activity between regions in the emergence of VH following sight loss (Martial et al., 2019). As VH occur only in a subset of all patients with eye disease, it is unlikely that deafferentation alone can provide an explanation for why CBS occurs, therefore connectivity analysis may help to better interrogate what leads to the differences in cortical activity observed between CBS and controls in this study. Furthermore, integration of both

functional connectivity assessed using fMRI and network connectivity using EEG may provide insight into the dynamic functional mechanisms involved in CBS.

FDG-PET may also be used as a means of assessing glucose metabolism in the occipital cortex of CBS. Reduced FDG uptake, demonstrating reduced glucose metabolism, in the occipital lobe has been observed to be significantly associated with increased severity and frequency of VH in DLB (Firbank et al., 2016). In PD, patients with VH demonstrated significantly higher glucose metabolism in frontal regions than PD patients without VH, suggesting that frontal hypermetabolism may play a role in the formation of VH in this patient group (Nagano-Saito et al., 2004). Similar investigation of cortical metabolism in CBS is currently limited. However, a case study in a patient experiencing VH of colours and movement following sight loss observed a significant bilateral reduction in occipital, parietal and thalamic metabolism (Meppelink et al., 2010) and therefore further investigation may provide important information about the mechanisms underlying VH in these patients.

Similarly, the current study did not analyse differences in structural connectivity between people with CBS and controls. Analysis of grey matter volumes across the whole brain and within ROIs in the primary and visual association cortices indicated no significant differences between the CBS group and controls. However, the primary aim of the structural volumetric analysis reported in the present thesis was to identify potential covariates for analysis of TMS and fMRI data. It would therefore be important to perform further investigation into whether there are more subtle structural changes within the visual system in CBS, and any potential contribution this may have to the development of VH, their frequency or severity. More nuanced structural analyses, such as cortical thickness and structural connectivity, may therefore be helpful in this context.

4.4.5 Conclusions

These study findings indicate that differences in visual cortical activity may underlie the formation of visual hallucinations in some people with eye disease and not others. While visual cortical hyperexcitability appeared comparable between people with VH and those without, greater variability and a potentially lower level of ‘background noise’ activity was observed in CBS compared to controls, with increased excitability providing a marker for VH severity, and may be key in producing a permissive brain state for VH to occur. These findings will consequently help to guide future investigations into CBS, including the development of treatments targeting aberrant visual cortical activity such as by regulating the

variability of spontaneous excitability, and may provide beneficial improvements to aspects of VH such as their frequency or severity in these patients.

Chapter 5 Non-invasive brain stimulation: a novel therapeutic intervention for Charles Bonnet syndrome?

5.1 Introduction

Previous research into the aetiology of CBS supports the theory that visual hallucinations in CBS are, at least in part, the result of increased spontaneous excitability and reduced inhibition of the visual cortex. Comparisons between the CBS and Control group in the previous study (see **Chapter 4**) observed greater BOLD activation in the visual cortex of controls during an eye movement task than CBS participants. This pattern of reduced visual cortical activation in CBS in the absence of VH may indicate resting-state differences in these individuals which produce a more permissive state for spontaneous, internally generated, spikes of visual cortical activity, 'false alarms', to be interpreted as true perceptions, resulting in VH.

Consequently, it is possible that diminishing the likelihood of spontaneous activity arising in the visual cortex may prompt a reduction in VH. Since pharmacological interventions have previously demonstrated limited efficacy in CBS cohorts (Baldessarini, 2009; Hughes, 2013; Menon et al., 2003), directly targeting neurophysiological features, such as increased spontaneous cortical hyperexcitability, may provide an important first step in developing an effective treatment for CBS. One method which may be used to target specific regions demonstrating spontaneous over-activity is non-invasive brain stimulation.

5.1.1 Transcranial Direct Current Stimulation

Using a portable battery powered stimulator, transcranial direct current stimulation (tDCS) delivers a weak electrical current to underlying cortical structures via two or more electrodes placed on the scalp. Current electrophysiological evidence suggests that tDCS is able to modulate the excitability of pyramidal tract neurons and interneurons, utilising a dual-polarity interaction in which anodal stimulation increases neuronal membrane potential and subsequent cortical excitability, while cathodal stimulation decreases membrane potential and inhibits cortical activity (Stagg & Nitsche, 2011)(**Figure *5.1***). Previously, animal studies have indicated that tDCS-induced changes in excitability are reflected both in spontaneous firing and altered responsiveness to afferent synaptic input (Brunoni et al., 2012). Furthermore, tDCS has been observed to alter synaptic and N-methyl-D-Aspartate (NMDA) receptor efficacy along with GABAergic activity (Brunoni et al., 2012; Nitsche et al., 2003; Stagg &

Nitsche, 2011), which may contribute to more long lasting and sustained effects (Liebetanz et al., 2002), with the after-effects of tDCS lasting up to one hour before dissipating (Antal et al., 2004). Consequently, the after effects of tDCS have been found to be influenced by various receptor agonists and antagonists; for example, d-cycloserine (an NMDA receptor agonist) was found to prolong the excitatory effect of anodal stimulation, while amphetamine (a nonspecific noradrenaline and dopamine agonist) enhanced the response (Nitsche, Grundey, et al., 2004; Nitsche, Jaussi, et al., 2004). Conversely, the after-effects of cathodal stimulation have been found to be dependent on the modulation of glutamatergic synapses, with stimulation significantly reducing the concentration of glutamate in the underlying cortex (Stagg et al., 2009). Furthermore, the dopamine agonist pergolide has been found to increase the duration of cathodal inhibition, indicating this system's role in synaptic plasticity and inhibition (Monte-Silva et al., 2009).

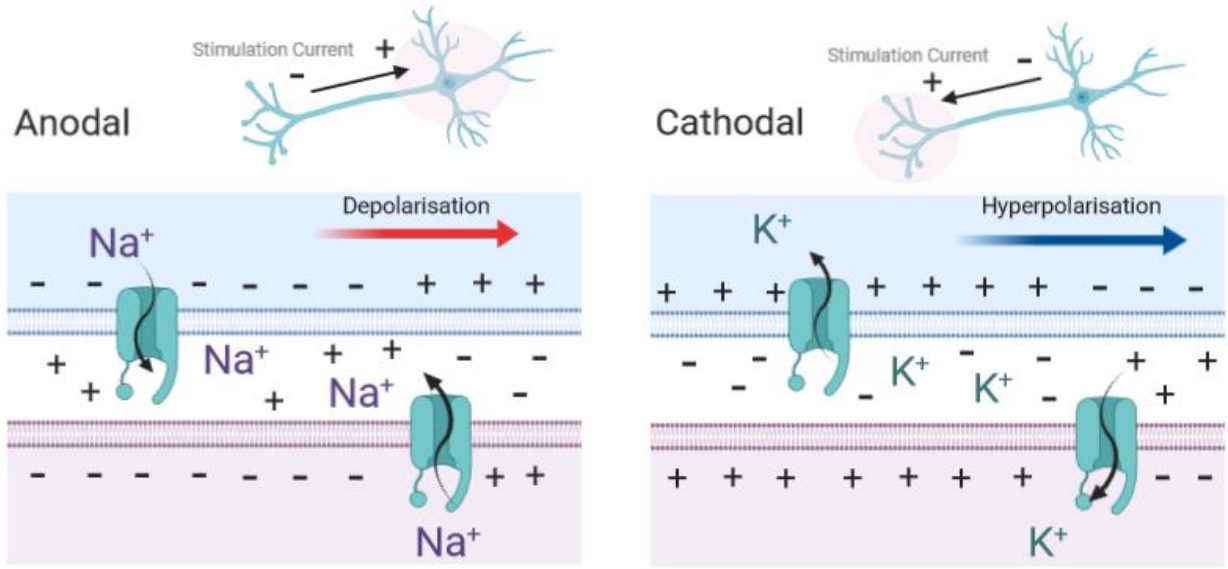

Figure 5.1. *Diagram illustrating membrane depolarisation and hyperpolarisation of pyramidal tract neurons and interneurons by anodal and cathodal transcranial direct current stimulation (tDCS). Diagram created using BioRender.com.*

To date, much of the literature surrounding tDCS has concentrated on investigating modulation of cortical excitability in the motor system (i.e. Ferrucci et al., 2014; Kwon et al., 2008). However, further studies have investigated the effects of tDCS both on the visual cortex and as a modulator for cognitive function and neuropsychiatric symptoms (i.e. Antal et al., 2004; Elder & Taylor, 2014). Anodal tDCS of the occipital cortex has been found to increase visual system responses whilst, conversely, cathodal tDCS attenuates this response

and reduces the amplitude of cortical visual-evoked potentials (VEPs) (Accornero et al., 2007; Antal et al., 2004). Furthermore, evidence from electrophysiology has demonstrated that anodal tDCS of the occipital cortex increases cortical excitability, indicated by reduced TMS-induced phosphene thresholds; while conversely, cathodal stimulation increases phosphene thresholds demonstrating a reduction in visual-cortical excitability (Antal et al., 2003). Since evidence suggests that tDCS is capable of successfully modulating neuronal activity in areas of the brain, including the visual cortex, it is possible that this technique could be utilised in the treatment of various disorders associated with aberrant cortical activity, including CBS.

5.1.2 Treatment applications of tDCS

The investigation of tDCS for the treatment of various neuropsychiatric features has been steadily gaining traction over recent years. Evidence indicating the beneficial effects of tDCS induced neuromodulation have been observed in Alzheimer's disease (AD), depression, PD, tinnitus, and stroke (see **Table *5.1***).

Benefits of tDCS, including the relatively low cost of equipment, its ease of use, and portability means that tDCS may have the potential to be used as a home-based treatment (Elder & Taylor, 2014). In the case of hallucinating CBS patients, this relatively easy to administer technique may allow for use as an immediate treatment for disruptive hallucinations by the patient in their own home, offering an alternative to relatively ineffective pharmacological treatments requiring stricter compliance regimens.

Furthermore, extensive studies into the safety implications of tDCS have reported no significant adverse side effects due to stimulation (Brunoni et al., 2012; Stagg & Nitsche, 2011). Most commonly, participants report experiencing a mild tingling sensation or light itching at the site of stimulation, with moderate fatigue and headaches occurring in fewer cases; mild redness can occur under the electrode site following stimulation sessions, however this is most likely due to localised vasodilation rather than burns or skin damage (Brunoni et al., 2012; Durand et al., 2002). As pharmacotherapy used to treat VH is often associated with significant adverse side effects, the relative lack of such using tDCS makes it an attractive option for treatment interventions, warranting further investigation.

Table 5.1. *Previous studies demonstrating beneficial cognitive and neuropsychiatric applications of tDCS.*

Reference	Pathology	Stimulation Parameters	Main Findings
Boggio et al., 2006	PD	Single 20-minute session of 2mA anodal stimulation of the left DLPFC	Improvements to working memory following single session of stimulation.
Boggio et al., 2009	AD	Three 30-minute sessions of 2mA anodal stimulation of temporal and prefrontal regions	Improvements to visual recognition memory following active stimulation compared to sham.
Doruk et al., 2014	PD	Ten 20-minute sessions of 2mA anodal stimulation to the bilateral DLPFC	Improvements to executive function following active stimulation compared to sham.
Elder et al., 2016	LBD	Single 20-minute session of 2mA anodal stimulation to the left DLPFC.	Improvements to attention following active stimulation (no comparison to sham)
Faber et al., 2012	Tinnitus	Six sessions of 1.5mA anodal stimulation of the left or right DLPFC	Reductions in tinnitus annoyance following stimulation of left or right DLPFC compared to sham. Reduced depressive symptoms following left DLPFC stimulation compared to sham.
Hummel et al., 2005	Chronic Stroke	Single 20-minute session of 1mA anodal stimulation of the primary motor cortex	Hand motor function improved significantly following active, but not sham, stimulation.
Loo et al., 2012	Depression	Fifteen 20-minute sessions of 2mA anodal stimulation of the left DLPFC over 3-weeks.	Significant improvements to mood, attention, and working memory following active but not sham stimulation.

Abbreviations: PD: Parkinson's disease; AD: Alzheimer's disease; DLPFC: Dorsolateral prefrontal cortex; mA: milliamps; LBD: Lewy body dementia.

Investigation into the use of tDCS in hallucinating patients has also revealed promising therapeutic effects. An influential study by Brunelin et al (2012) observed that five consecutive days of active cathodal stimulation of the temporo-parietal cortex successfully reduced the frequency and severity of auditory verbal hallucinations in schizophrenia when compared to placebo stimulation. Furthermore, prolonged therapeutic effects were observed for up to three months following stimulation, suggesting it to be a potentially highly beneficial treatment option in this patient group. In the case of visual hallucinations, little research has yet been conducted utilising tDCS. However, two case reports have found positive indications. Shiozawa et al (2013) noted that multiple sessions of inhibitory cathodal stimulation of the occipital area produced a sustained reduction in the VH of a person with a long-term diagnosis of schizophrenia. Similarly, another case study in a patient with a major depressive disorder observed a significant reduction in the patient's VH, including the complete suppression of their most intrusive and distressing hallucinations, following cathodal occipital tDCS, with effects lasting up to several weeks (Koops & Sommer, 2017). In contrast, a recent trial investigating the use of cathodal occipital tDCS in DLB as an intervention for VH found no significant effect of active stimulation compared to sham (Elder et al., 2019). Evidence of negative findings alongside the fact that there are yet to be any large-scale placebo-controlled studies in VH cohorts using tDCS, means that further investigation is needed before inferences about the potential therapeutic benefits can be made. Nonetheless, studies in these patient groups positively indicate both the feasibility and tolerability of tDCS as a therapeutic intervention and, as such, may also be transferable to CBS.

5.1.3 Challenges and considerations: Stimulation parameters

How effectively stimulation reaches targeted underlying cortical structures to modulate cortical excitability is influenced by several factors. The flow of current produced by both electrical and magnetic stimulation can be impacted by physiological differences, including skin resistance, skull thickness and cortical atrophy. In addition to this, however, the effectiveness of tDCS delivery can depend on a number of specific stimulation parameters, including the current strength (intensity), electrode size and placement on the scalp.

Previous tDCS research has suggested that there is a non-linear relationship between the size and direction of effect (excitation/inhibition) as stimulation intensity increases (Batsikadze et al., 2013). Furthermore, the size of the electrodes used to deliver the current influences the dosage of the stimulation, with the current density, calculated by dividing current intensity (expressed in milli-amperes; mA) by electrode surface area (cm^2), providing an indication of dosage (Brunoni et al., 2012). Accordingly, some studies have observed no effect of stimulation at lower dosages (e.g. 0.03mA/cm^2), but positive effects at higher dosages using higher current intensities (e.g. 0.06 mA/cm^2)(Boggio et al., 2006; Galea et al., 2009), whereas others have found that higher intensity stimulation (above 2mA or 0.06mA/cm^2) can reverse its modulatory effect (i.e. cathodal stimulation becomes excitatory; Batsikadze et al., 2013).

As discussed in **Chapter 1,** previous imaging evidence in CBS has demonstrated that patients experiencing complex hallucinations, such as objects, animals or scenes, generally show greater activation over more anterior regions of the occipito-temporal cortex, whereas those experiencing simple hallucinations, such as coloured lights or flashes, may demonstrate more hyperexcitability in the primary visual cortex (ffytche et al., 1998). In light of this, it is important to consider the location of stimulation in order to best target areas demonstrating aberrant activity.

As no research has previously been performed into the use of tDCS in people with CBS, the optimal stimulation parameters needed to produce a beneficial effect on aspects of VH, such as their frequency, duration and severity, is not yet known. Hence, it is important to consider how changing parameters such as current density and electrode placement may impact its effect on cortical activity and VH.

The following chapter investigates the feasibility of tDCS in a cohort of 6 continuously hallucinating patients with CBS. The use of this specific CBS population offers a unique opportunity to investigate the effects of tDCS on VH as they are occurring in real time, something which is not possible in individuals with more episodic or unpredictable hallucinations. Using participant feedback during stimulation will provide an indication of whether changes to specific stimulation parameters result in a greater impact on VH, informing further treatment studies in CBS. Hence, the aim of this study was to investigate which combination of stimulation parameters, including electrode locations and stimulation intensity, provided the most beneficial therapeutic effects in participant hallucinations.

5.2 Methods

5.2.1 Participants

Six participants (3 Male, 3 Female aged 37-91) took part in the study at the Institute of Psychology, Psychiatry and Neuroscience at King's College London. All participants had been screened previously as part of the Visual Perceptual Disorders clinic by Dr Dominic ffytche and diagnosed with Charles Bonnet syndrome following sight loss in accordance with current CBS diagnostic criteria (i.e. Teunisse., 1996). All participants were cognitively intact and experienced visual hallucinations only (with no hallucinations in other sensory modalities or delusions) continuously throughout their waking hours, which they were able to describe in sufficient detail for investigators to track changes. The specific nature of each participant's visual hallucinations and sight loss is detailed in the case report section.

5.2.2 EEG

Two 5-minute sessions of resting state EEG were performed, once prior to commencing tDCS and once following the last session of tDCS. During recordings participants were asked to open or close their eyes at 30-second intervals. EEG was recorded using a Starstim 8-Channel EEG/tCS data acquisition system (Neuroelectrics, Barcelona, Spain). Eight Ag/Ag/Cl pi-electrodes were placed according to the international 10-20 system within a neoprene cap over occipital and occipital-temporal regions, with a single electrode over the left dorsolateral prefrontal cortex (DLPFC). Reference and ground were taken from the left earlobe and all impedances were kept below 5 kOhms. Data were sampled at 500Hz from DC to 250Hz; artefact rejection and preliminary analysis were performed online. EEG performed in this study was predominantly used for informative purposes in directing the starting location of stimulation, and therefore advanced statistical analysis of this data has not been performed for this thesis.

5.2.3 tDCS

tDCS was performed directly following the first resting-state EEG. Stimulation was administered using a Starstim 8-channel tDCS data acquisition system (Neuroelectrics, Barcelona, Spain) via two-to-three Ag/AgCl Pi-stim electrodes (3.14cm^2) placed on the scalp according to the international 10-20 system within a neoprene cap. Starting stimulation set-up was decided based on preliminary online analysis of individual participant EEGs. Minimum stimulation intensity used started at 0.25mA (current density 0.08mA/cm^2) and maximum

stimulation intensity was 1mA (current density: 0.32mA/cm^2) based on safety recommendations of the manufacturer. During stimulation, the participant was asked to describe any changes to their VH, with experimenters following a semi-systematic approach to prompting and documenting participant descriptions of changes to content, size, intensity, movement, and intrusiveness of VH. Participants were also prompted at regular intervals to report any sensation from stimulation and changes to vision. Each stimulation session lasted five minutes, after which participants were given a five-minute break before the next stimulation session in which stimulation parameters including the intensity and electrode position were adjusted. A total of four different stimulation intensities (0.25mA, 0.5mA, 0.75mA and 1mA) were tested alongside nine separate cathode positions (***Figure 5.2***) and three anode positions (F3, F4, and left deltoid) across participants. Depending on the starting position for stimulation and subsequent reports given by participants, the electrode locations tested differed between participants and individual electrode locations could be repeated. The maximum total stimulation time for any participant was capped at 45 minutes (9 separate stimulations), as the effects of long periods of stimulation above this are currently unknown. A follow-up telephone consultation with their consulting CBS specialist (Df) was arranged with each participant one day after study procedures. Four participants received further contact up to 3 months following study participation as part of their routine clinical assessment in which the effects of stimulation were discussed.

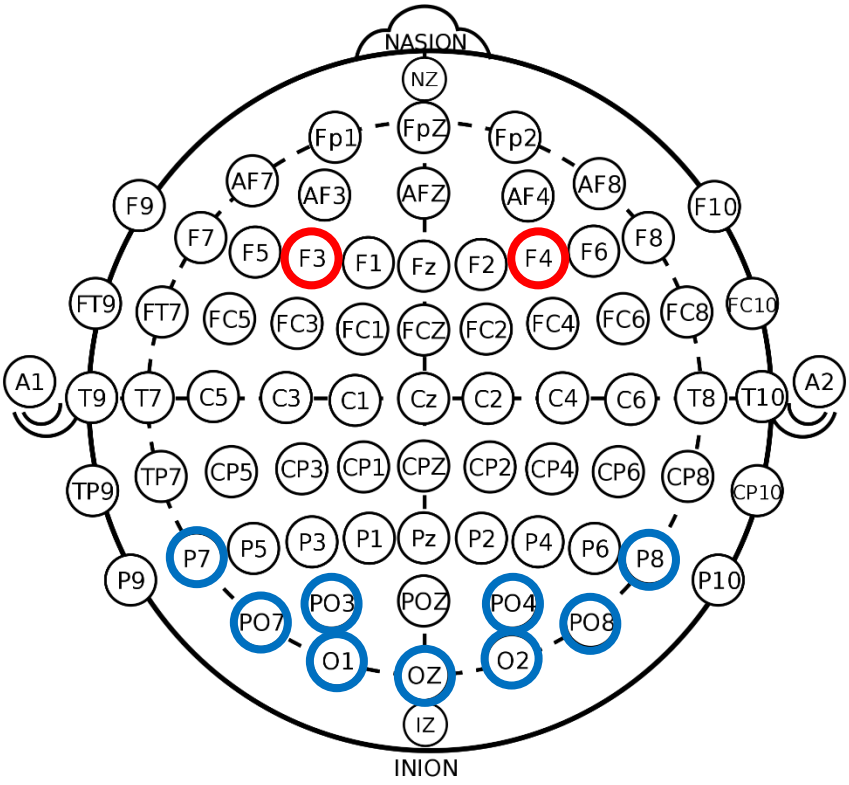

Figure 5.2. *Cephalic cathode (blue) and anode (red) locations tested across the six participants according to the international 10-20 electrode placement system.*

5.2.4 Statistical Analysis

As this study was aimed at exploring the feasibility of tDCS in people with CBS and its effect on the qualitative nature of their VH, no statistical analysis was performed. Instead, data is presented in the form of case reports and group observations of the effect of different stimulation parameters on VH presentation. This study aimed to inform the optimal stimulation parameters to be used in the future investigation of tDCS in CBS, which would employ more stringent experimental design (including randomisation and the use of sham stimulation) and subsequent statistical analysis (see **Chapter 6**) in order to test the overall efficacy of tDCS as a therapeutic intervention in CBS.

5.3 Case reports

Participant 1

Clinical History

The first participant was a 50-year-old man, KC, diagnosed with autosomal recessive retinal dystrophy with a CRB1 mutation which leads to progressive visual loss who retained no usable vision in either eye. The participant first reported photopsia and simple hallucinations consisting of explosions of white light and dynamic colours and shapes at approximately 22-years-old. As visual loss progressed further, KC reported a worsening of the photopsia, in which the visual hallucinations became continuous throughout his waking hours. VH varied in intensity, with periods in which the content appeared 'calmer' and periods in which visual symptoms were more intense. No factors were notably associated with fluctuations in intensity. KC described these visual hallucinatory experiences as highly irritating, consuming much of his attention and impairing his ability to carry out daily activities. A three-month trial of gabapentin was not found to influence the photopsia and impaired his clarity of thought, while he found that meditation was helpful in directing his focus away from the photopsia. At the time of assessment, KC was healthy and was not taking any medications or alternative therapies. While he did not experience migraine, there was a family history.

Study Assessments

On the date of assessment (February 2018) KC described VH in his left visual field as consisting of a vibrant sky blue covering the centre and far left of his vision with pixelated emerald green 'flames' and dots which moved vertically in a continuous manner. In the right visual field, he described bright blue, red and orange 'damask' patterns which similarly moved vertically. While phenomena in the right visual field were described as more complex, KC stated that the visual experience in the left visual field were the most dominant and intrusive.

Online inspection of EEG showed no specific EEG abnormalities. Alpha and theta power were slightly decreased over the left occipital region, which along with VH phenomenology, informed the initial starting position for stimulation.

Stimulation Findings

The participant received bimodal stimulation (one anode, one cathode) testing a combination of three possible cathode positions (P7, P8, Oz) alongside two possible anode positions (F3, Left deltoid). In total, the participant received seven separate stimulation sessions lasting five minutes each. Overall, the participant described no significant changes to VH during or immediately following any of the stimulation sessions. At all intensities tested (0.25mA, 0.5mA, 1mA) in which the cathode was placed over the left occipito-temporal region (P7) and the anode over the DLPFC (F3), KC reported a slight lessening of the intrusiveness of visual phenomena in the left visual field. However, this change was described as being due to the phenomena in the right visual field drawing more attention than usual, rather than a lessening of the overall intensity of phenomena in the left visual field.

During all stimulations in which the anode was placed over the left DLPFC (five stimulations) KC reported positive feelings of 'happiness', 'contentedness' and euphoria. Despite no overall changes to VH content, KC described being less concerned by VH than usual during these trials. While KC was aware when stimulation started (due to being informed by experimenters) and would reliably describe increases in euphoric feelings shortly after stimulation initiation, he was unaware of when they had ended. Feelings of euphoria would consistently dissipate within 30-60 seconds following termination of stimulation and were not reported during stimulations in which the anode was placed on the left deltoid. Physical sensation (tingling) was only reported at the start of three out of seven trials during the initial 30-60 seconds of stimulation.

In a separate session KC received one session of low frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS) over 10 minutes at 100% of phosphene threshold (85% of total stimulator output) over the primary visual cortex. During single pulse TMS, KC reported phosphenes in the form of a momentary 'darkening' of current visual phenomena and abrupt vertical jumps in visual hallucinatory content. Following inhibitory rTMS, KC reported that VH in the left visual field became substantially more intense and subsequently more invasive. Intensity and overall invasiveness remained constant following termination of stimulation. Following stimulation phosphene thresholds were calculated at 90% of total stimulator output.

A follow-up of the participant one day after tDCS treatment reported an overall reduction in the intrusiveness of VH lasting the entire day. KC described this as unusual but

not unprecedented, and due to no treatment effect being observed directly following stimulation on the day, it is unclear whether this improvement was a result of tDCS.

Participant 2

Clinical History

The second participant (EGS) was a 57-year-old woman with a longstanding, progressive visual impairment with no visual function in the left eye and visual functioning in her right eye to the level of hand movements only. EGS first began experiencing instances of VH at the start of 2015, with VH becoming continuous from December 2015. VH content initially consisted of simple hallucinations and shapes but progressed to become more complex (human and animal figures and faces) from early 2017. VH were described as obstructive of her remaining vision, causing disorientation and impacting her confidence when moving around the house. The participant had a long history of migraine involving severe frontal headaches without aura; a white matter lesion in the right parietal lobe with non-specific changes was detected in 2016. Past trials of Topiramate, Sodium Valproate and Sumatriptan have had no beneficial therapeutic effect or have negatively impacted VH.

Study Assessments

On the date of assessment (May 2018) EGS described VH across her visual field consisting of a group of predominantly male figures in black suits and ties against a white background. Figures were highly detailed, stationary and only the head and shoulders were visible; however, the faces were not those she recognised. As was a common experience for the participant, imagery covered her visual field, obscuring the majority of her remaining usable peripheral vision. For technical reasons, EEG was not possible in this participant and therefore a starting position of Oz was used.

Stimulation Findings

A total of four possible cathode positions (PO8, P8, Oz, PO7) alongside three possible anode positions (F3, F4, left deltoid) were tested using bimodal (one anode, one cathode) or multi-array set-ups (2 anodes, 1 cathode or 2 cathodes and 1 anode). In total, the participant received eight separate stimulation sessions lasting five minutes each. During cathodal stimulation of the primary visual cortex (Oz; 0.75mA and 1mA) EGS reported a number of notable changes to VH including changes to their size, intensity and intrusiveness. Imagery was described as fading until faces and clothing were grey and indistinguishable, intermittent

flashing lights usually present over complex imagery became muted and less intense, and the imagery reduced in size allowing the participant to use her intact peripheral vision. Changes to VH became gradually more pronounced following each inhibitory stimulation of Oz suggesting a potential cumulative effect. No effects to VH were observed during cathodal stimulation of more anterior regions (PO8, P8, PO7) and moving anodal stimulation from cephalic regions (F3 & F4) to non-cephalic regions (left deltoid) similarly had no further effect on VH. The participant did not report any affective response to stimulation, reporting no changes in mood or increased feelings of euphoria.

At a follow-up one day after stimulation, EGS reported that her flashing light VH had returned to normal intensity within the hours following the end of stimulation; complex imagery, however, remained markedly faded and reduced in size. Reductions in the size of the imagery remained at follow-ups 4-weeks and 3 months after stimulation, allowing the participant to continue to use a greater portion of her remaining peripheral vision; all other aspects (brightness, detail, and intensity) returned to pre-stimulation levels.

Participant 3

Clinical History

The third participant (GF) was a 71-year-old woman with retinitis choroiditis of unexplained origin with vision consisting only of light perception in the left eye and a region of spared peripheral vision in the right eye. GF began experiencing VH approximately 18 years previously with no specific change to vision or circumstances precipitating their onset. VH most commonly consisted of simple hallucinations of a circle of continuously twinkling white or sliver light present both when her eyes were opened and closed. This twinkling light, likened to a disco ball or search-light, occurred throughout the participant's waking hours, filling a large area which superimposed on whatever she was looking at, thus obstructing her remaining vision. Episodically, GF also experiences complex hallucinations of fragmented photographs of her younger self, "Axminster" carpet, and a sepia map with illegible writing. The participant had a long history of migraine attacks with 'zig-zag' aura not always accompanied by headaches, and coeliac disease; previous brain imaging showed no cerebral calcification or alterations related to these conditions. GF previously attempted distraction techniques and changes in lighting, but these were found to have no effect on VH; she has been reluctant to try pharmacological interventions due to the potential side-effects which could outweigh any therapeutic benefits.

Study Assessments

On the date of assessment (June 2018) GF described her usual VH phenomenology of a continuously twinkling circle of silver/white light covering her visual field and obscuring her remaining vision in the right eye. Online EEG analysis indicated decreased alpha peak frequency over the left occipital hemisphere compared to the right, informing the stimulation starting position.

Stimulation Findings

A total of five separate cathode positions (O1, PO3, Oz, O2, PO8) alongside a consistent bi-frontal anode array (F3 & F4 stimulating in tandem at 50% return of the cathodal electrode each) were tested. In total the participant received 8 separate stimulations lasting 5 minutes and a single stimulation lasting 10 minutes. The participant reported no specific changes to VH during stimulation of the locations O1, PO3, or PO8 at any of the tested stimulation intensities (0.5mA and 1mA). 1mA cathodal stimulation of Oz in combination with bi-frontal anodal stimulation (F3 & F4) resulted in GF reporting a change in the shape of VH (elongating to become 'sausage shaped' rather than circular) along with a reduction in the movement of the VH (twinkling) at the top and bottom of the image, and a reduction in brightness and overall intensity. Further 1mA stimulation of the right adjacent occipital position (O2) resulted in a further and more significant reduction in the size of the imagery, allowing GF to make out an outline of the investigator's face which had previously been obscured by the VH phenomena. GF described the VH as becoming dimmer and less intrusive with successive stimulations, allowing her peripheral vision to become less obscured. Following the end of each stimulation, GF reported that the circle would gradually begin to grow, obscuring her vision once more. In an attempt to increase the longevity of the positive effects, a final stimulation (cathode: Oz; anodes: F3 & F4) was performed for 10 minutes rather than five. While VH appeared to reduce in size again, this was only partially maintained following the end of stimulation (the circle increased in size but did not return to the original size described at the start of the session); intensity and movement remained reduced.

At a follow-up 4 days post-stimulation, GF reported that the circle VH had remained thinner and less intrusive, although it had gradually started to return to pre-stimulation density. A second follow-up was performed one-month post-stimulation, at which point GF reported that VH had returned to pre-stimulation levels, starting with a reoccurrence of VH of

photographs which had been experienced at the onset of her CBS. GF felt that improvements could only be related to tDCS treatments, as this was the only factor that had changed that month.

Participant 4

Clinical History

Participant Four (EN) was a 91-year-old man with end-stage glaucoma in both eyes. The participant had no usable vision in his right eye and a poorly functioning residual crescent remaining in the left. EN gradually began to experience VH coinciding with visual decline over the year prior to assessment. Common hallucinatory content included text, which could either be legible containing information of personal significance, or unreadable, and alternating days of dazzling grey or green fog which remained continuous throughout waking hours. On occasion EN previously reported complex imagery of a face and red meshwork patterns. The participant described these VH as being extremely debilitating, worsening progressively every day and dominating his life. Previous treatment with gabapentin and citalopram had no effect on hallucinations; eye movements and distraction techniques initially yielded positive effects but these were not maintained. The participant had a history of migraine without aura; however, he had not reported an episode in over 25 years.

Study Assessments

On the date of assessment (November 2018) EN described his hallucinations as consisting of a dense, dazzling green fog with illegible text superimposed over the top. The imagery covered his right visual field and moved with his eyes. Online EEG analysis indicated decreased alpha peak frequency over the left hemisphere compared to the right, informing the stimulation starting position.

Stimulation Findings

A total of four cathode locations (O1, Oz, O2, and PO7) were tested alongside a consistent bi-frontal anode array (F3 & F4 stimulating in tandem at 50% return of the cathodal electrode each). In total the participant received nine separate stimulations lasting 5 minutes each, separated by breaks of 3-5 minutes. During the initial stimulation of O1 at 0.75mA EN reported that the text hallucination within his left visual field became paler. Over successive cathodal stimulations at 1mA of O1, Oz, and O2, EN reported that text hallucinations became faded further until barely visible. Following five minutes of 1mA

cathodal stimulation of O1, the participant reported improvements to his peripheral vision in the left visual field: at the start of the assessment the participant was able to decipher fingers in his residual peripheral vision only when they were moving, but following stimulation he stated that he was now able to discern the fingers when they were stationary. Visual function improved further following cathodal stimulation of Oz at 1mA, at which point the participant reported being able to differentiate between index finger, middle finger and thumb in his peripheral vision; this improvement appeared to be sustained throughout the majority of the session, including when the participant stood up to walk around the room. During 1mA cathodal stimulation of PO7, EN reported an abrupt deterioration of peripheral visual function and a worsening of the fog hallucination. Stimulation was immediately aborted and subsequent cathodal stimulation of O1 appeared to restore some of the visual function improvement noted earlier in the session.

Overall, cathodal stimulation of early visual areas O1 and Oz appeared to have the greatest beneficial effect, with text hallucinations becoming less intense and a reported improvement to peripheral visual function. Such improvements occurred predominantly during the first 3-4 stimulations (15-20 minutes of stimulation) before appearing to plateau. The participant tolerated the stimulation well throughout the session, reporting no discomfort or notable side effects.

At follow-up one day and two days after stimulation, EN reported that the positive effects of stimulation had lasted several hours following their visit, but intensity and density of the VH had returned to pre-stimulation levels by day two.

Participant 5

Clinical History

Participant Five (TE) was a 52-year-old man with progressive bilateral retinal dystrophy associated with a DRAM2 genetic variant. The participant reported a gradual loss of central vision spanning over 20 years, accompanied by significant bright-light sensitivity manifesting as lethargy, nausea and light-headedness. TE first reported simple VH 10 years prior to assessment, and had since developed continuous hallucinations throughout his waking hours in both eyes when open and closed. Two types of hallucinations were regularly reported by the participant; these consisted of a grey-white continuously rotating kaleidoscope made up of circles and squares in his central vision, which occasionally broke apart from the centre like a firework, and a band of video static or grey ‘maggots’ which

pulsated in unison across the binocular field at approximately 8Hz. While VH were continuous throughout the participant's waking hours, TE noted that the intensity of the images and frequency of the 'fireworks' increased when he was tired or under stress. The participant has a family history of migraine without aura, but had not reported migraines himself.

Study Assessments

On the date of assessment (May 2019), TE reported a constant binocular band of continuously pulsating static made up of fine grains that looked like maggots. In his central vision, the participant reported a central swirling firework shape which was brighter and more intense than the static. When asked to estimate the size of the visual phenomena, TE stated that the band of static covered approximately two thirds of his vision, while the intense circular section occupied the centre third. Online EEG analysis noted that the participant presented with low bilateral occipital alpha frequencies across primary visual areas (Oz, O1 and O2) indicative of increased occipital excitability in these regions. Consequently, a starting stimulation position of Oz was chosen.

Stimulation Findings

A total of five separate cathode locations (Oz, O2, O1, PO4 and PO8) were tested alongside a consistent bi-frontal anode array (F3 & F4 stimulating in tandem at 50% return of the cathodal electrode each). In total the participant received eight separate stimulations lasting 5 minutes each, separated by breaks of 3-5 minutes. The participant reported no changes to any aspect of his VH during successive stimulation of Oz, O1, and PO4 between 0.75mA and 1mA. Following a total of 30 minutes stimulation at different locations, TE reported the appearance of blurred dark shapes at the bottom of his vision during 1mA cathodal stimulation of O2. The participant noted that these shapes slightly reduced the size of the central band of static, but that it felt 'oppressive' and more unpleasant than normal rather than a beneficial improvement. These areas of dark space remained unchanged throughout further stimulations of PO8 and following the end of assessment. The participant noted that he was unsure of whether these areas of black space were a new phenomenon or whether he had just become more aware of them during the stimulation. While no positive therapeutic effects were experienced by this participant, stimulation was well tolerated throughout, reporting only mild tingling from the frontal electrodes and no discomfort or notable side effects.

At follow-up one day post-stimulation, TE also reported no changes to VH. Two weeks post-stimulation, TE reported that he had continued to see the dark spaces in the lower portion of his visual field, but that these seemed to coincide with periods of stress or over-tiredness and therefore felt that they were unlikely to be a direct result of stimulation.

Participant 6

Clinical History

Participant Six (NC) was a 37-year-old woman with acquired bilateral vision loss as a result of traumatic injury in 2018 which resulted in the removal of her right eye and loss of 95% of the retina in the left eye. On the date of assessment (May 2019), the participant reported a small amount of light perception remaining in the left eye. The participant began experiencing VH 3-4 days following sight loss in both eyes, beginning as simple phenomena consisting of luminous colours and shapes. Over the proceeding days, the VH developed into more complex imagery including faces and animals and since this point NC has reported the presence of images continuously throughout her waking hours, appearing predominantly in her centre and left field of vision. The participant noted that the content of the VH appeared to be influenced by her mood, in that the intensity of the images and colours would become greater and more difficult to ignore when she was stressed. Common phenomena reported by the participant include luminous green mist sometimes accompanied by green bubbles, multi-coloured shapes and stars, and animated/pop-art style images of animals, faces or facial features. The participant had an ongoing history of migraine with aura which had been present since adolescence for which she had been prescribed a combination of paracetamol and codeine. In 2015, NC experienced a transient ischemic attack resulting in a minor white matter lesion which was not linked to any ongoing neurological issues.

Study Assessments

On the date of assessment, NC reported a mosaic of colours over her central vision accompanied by white bubbles and red silhouettes of a cat and duck in her left visual field. The participant described the images as morphing and changing in a ‘constant flow’. Online EEG analysis noted no distinct differences in occipital alpha frequencies between hemispheres. However, based on the participant’s reports that the imagery was predominantly centred over the left visual field, a right hemisphere occipital location was chosen for the starting stimulation position.

Stimulation Findings

In total, six separate cathode locations (PO8, O2, Oz, O1, PO4, PO3) were tested across nine stimulations, alongside a consistent bi-frontal anode array (F3 & F4 stimulating in tandem at 50% return of the cathodal electrode each). The participant noted no changes to any aspect of her VH during stimulations of PO8 at either 0.75mA or 1mA. During 1mA cathodal stimulation of O2, the participant noted a gradual decline in the sharpness and definition of the imagery in her visual field; after 3 minutes of stimulation she noted that the area that the imagery occupied began to shrink and that the flow of the images had slowed down. Additional stimulation of O2 resulted in a darkening of the colours and further loss of definition in the complex images. The participant continued to report a gradual decrease in the size, definition and intensity of the imagery through 1mA cathodal stimulation of early visual areas Oz and O1. These changes were maintained during 1mA stimulation of PO4 and PO3 with the addition of an increase in the lightness of her upper visual field, which the participant reported as more pleasant than usual.

Overall, cathodal stimulation of early visual areas (O2, Oz and O1) appeared to result in the most beneficial effects, with NC reporting significant decreases in the size, intensity and definition of her VH over successive stimulations. In addition, the participant reported that the speed at which the images changed from one item to another was markedly slowed, further helping to decrease the overall intensity of the visual experience. Following the end of stimulation, the participant was able to make out contrast and hand movements utilising her remaining peripheral vision more effectively than she could prior to stimulation. Furthermore, stimulation was well tolerated throughout, with the participant reporting only mild tingling during the first few stimulations and no discomfort.

At follow-up one day after stimulation, NC reported that the darkening of colours and the reduction in the size and intensity of VH had been maintained post-stimulation, although she had experienced a headache which increased the intensity of VH as it progressed.

5.4 Results Summary

5.4.1 Impact on visual hallucinations

Overall, four out of the six participants in this study reported a subjective improvement to several features of their visual hallucinations during and directly following cathodal stimulation of the visual cortex. Beneficial improvements to VH content have been

categorised in the table below (***Table 5.2***). Out of the six participants, two (Participants 1 & 5) reported no improvements to any aspect of their VH, however, Participant 1 reported a beneficial affective response during anodal stimulation of the scalp regions overlying the dorsolateral prefrontal cortex which was not replicated when the anodes were moved to a non-cephalic position. This affective response was not reported by any of the following participants, despite consistent anodal stimulation of the prefrontal regions.

Table 5.2. *Beneficial improvements to visual hallucination content reported by participants across all stimulations.*

Participant	Mood related response (i.e. Euphoria)	Reduced Size	Reduced Definition	Reduced Movement	Reduced Intensity/ Vibrancy	Improved access to remaining vision
1	✓					
2		✓	✓		✓	✓
3		✓	✓	✓	✓	✓
4			✓			✓
5						
6		✓	✓	✓	✓	✓

Follow-up of participants post-stimulation observed that positive therapeutic effects generally lasted 1-4 days following treatment, however some limited lingering positive effects of up to one (Participant 3) and three (Participant 2) months were also reported.

5.4.2 Stimulation Parameters

All participants tolerated the stimulation well, including at the highest intensity of 1mA (current density: 0.32mA/cm^2). However, it was noted that bilateral anodal stimulation, with the 1mA current split equally between the two electrodes (50% each), markedly reduced discomfort from stimulation without negatively impacting therapeutic effects. Using the combination of bilateral frontal anodes plus a single posterior cathode was found to be well tolerated with participants only reporting mild tingling or itching (predominantly from frontal electrodes) during stimulation. Furthermore, any beneficial improvements to VH were consistently reported at 1mA stimulation, compared to lower stimulation intensities such as 0.75mA and 0.5mA, with no positive benefits of 0.25mA noted across participants.

Participants reporting a positive response to stimulation predominantly described improvements following inhibitory stimulation of areas corresponding to the primary visual cortex (***Table 5.3***), whereas stimulation of more anterior or dorsal regions resulted in fewer positive responses. No noticeable effect of anode placement was observed on changes to VH between cephalic and non-cephalic regions.

Table 5.3. *Cathodal electrode locations tested across participants using the international 10-20 electrode placement system. * denotes electrode positions in which a positive effect on visual hallucinations was reported.*

Participant	**Electrode position**								
	P7	**PO7**	**PO3**	**O1**	**Oz**	**O2**	**PO4**	**PO8**	**P8**
1	✓				✓				✓
2		✓			✓*			✓	✓
3			✓	✓	✓*	✓*		✓	
4		✓		✓*	✓*	✓*			
5				✓	✓	✓	✓	✓	
6			✓*	✓*	✓*	✓*	✓*	✓	

While each individual stimulation session lasted 5 minutes, it was observed that the beneficial effects of stimulation across participants were reported most prominently following 3-4 successive stimulations of the primary visual areas (O1, Oz, O2), with multiple stimulations of these regions improving or strengthening these positive effects, indicating a possible positive benefit of longer sessions of stimulation.

5.5 Discussion

The aim of this chapter was to investigate the feasibility and potential of tDCS as a therapeutic intervention for VH in people with CBS, while informing the best stimulation parameters needed to produce a positive effect to be used in future studies of treatment efficacy. To our knowledge, this is the first time that inhibitory tDCS of the occipital cortex has been examined in CBS participants. While this study looked at a very specific subtype of people with CBS (continuous hallucinators) because of the nature of its design, it has provided evidence that tDCS may provide beneficial treatment effects to VH in eye disease and sight loss.

5.5.1 tDCS as a potential intervention for Charles Bonnet visual hallucinations

Observations and participant reports from this case series demonstrate a positive potential effect of inhibitory tDCS of the primary visual cortex on several aspects of VH experienced by these participants. Four of the six study participants reported that cathodal stimulation of primary visual areas at 1mA intensity produced positive changes to VH, including reductions in the size, intensity/brightness, and definition of the VH imagery which, in turn, helped to reduce the overall impact of VH.

These observations tentatively support the results of investigations of tDCS in other pathologies with VH, such as schizophrenia and major depression, in which cathodal stimulation of occipital areas resulted in the suppression and reduction of prominent VH phenomenology lasting from a few weeks to months (Koops & Sommer, 2017; Shiozawa et al., 2013). While a reduction in the frequency of VH in this participant group was not noted (although this may be due to the continuous nature of their VH), a previous survey of people living with CBS has indicated that a complete cessation of VH is not necessary to confer a positive therapeutic benefit, with respondents suggesting that even relatively minor changes to aspects of the VH, including the intensity and intrusiveness of the content, could greatly improve their overall quality of life (Cox & ffytche, 2014). Since four of the six participants in this study reported such changes to the impact of their VH following stimulation, this provides initial support for our hypothesis that inhibitory cathodal tDCS can produce a significant beneficial change to aspects of VH in people with CBS.

An unexpected positive effect of stimulation observed by this study was the reported improvement to aspects of visual function in all four of the participants who reported a positive effect on VH. As tDCS is used to modulate the excitability of the targeted cortical regions, inhibitory stimulation of the visual cortex (while providing potential benefits to VH), might be expected to also inhibit activity relating to any remaining visual function. In support of this, a previous study of cathodal tDCS of the visual cortex has observed subsequent reductions in static and dynamic contrast sensitivities in healthy participants (Antal et al., 2001). Nevertheless, participants in this study reported improvements to their ability to discern contrast, define shapes and detail, and perceive light following stimulation. While cortical stimulation cannot physically reverse the extent of the vision loss, due to it being the consequence of ocular and not cortical pathologies, it is likely that the associated reduction in aspects of VH, such as their size and definition, allowed participants to utilise a greater degree of their remaining vision more effectively since it was no longer being obscured by

the VH imagery. Similarly, all of the participants in this study stated that the continuous nature of their VH commanded a large degree of their visual attention at all times, making them nearly impossible to ignore. In reducing the size, definition or intensity of the VH (and in some cases the degree of activity/movement of the VH), participants may have subsequently been able to reallocate their attention more effectively from the VH to their remaining vision, resulting in a perceived improvement to aspects of visual function.

Furthermore, of the participants who reported improvements, a general consensus regarding the stimulation location and intensity was observed – with the greatest improvements to VH being reported during 1mA stimulation of cortical regions corresponding to the primary visual cortex. Furthermore, most beneficial effects reported by participants were observed following 10-15 minutes of occipital stimulation, providing an indication of the minimum length of stimulation necessary to produce noticeable therapeutic effects. In support of this, multiple 5 minute sessions of stimulation over Oz in Participant 2 may have resulted in the longer period of positive after-effects reported by this participant (3-months) in comparison to other participants who received stimulation dispersed across more locations, although as n=1 in this case, associations between these factors should be made with caution. However, these results provide a good starting point for future, larger, studies investigating the overall efficacy of tDCS as a treatment for VH in this participant group, therefore satisfying the primary aim of this study.

Moreover, stimulation was well tolerated by all the participants, with only mild side effects such as tingling and itching sensations from stimulating electrodes reported consistently across participants. Transient headaches were reported by two of the participants, though both reported that these were not uncommon prior to stimulation. This is in keeping with the findings of similar studies and reviews of the safety implications of tDCS (Brunoni et al., 2012; Elder & Taylor, 2014; Stagg & Nitsche, 2011) which has made tDCS such an attractive prospect for therapeutic interventions.

5.5.2 Implications for our understanding of VH aetiology in CBS

The improvements to VH symptoms following inhibitory cortical stimulation also provide further support for the deafferentation hypothesis as an aetiological explanation for VH in CBS. As the deafferentation hypothesis states that VH are the consequence of spontaneous compensatory hyperexcitability of the visual cortex (Menon et al., 2003), the inhibitory modulation of pyramidal tract neurons and resting membrane potential of

interneurons caused by cathodal tDCS (Stagg & Nitsche, 2011) may have resulted in a subsequent reduction in the overall production of this spontaneous activity. This is supported by previous research into the effects of cathodal stimulation of the visual cortex, which resulted in the reduced amplitude of cortical VEPs, indicating a decrease in visual cortical excitability and the subsequent production of visual cortical activity in response to visual tasks (Accornero et al., 2007). This reduction in the general propensity for spontaneous activity by stimulation in these participants may explain the change to aspects of the VH described. However, due to the continuous nature of the VH in this group, this may have only manifested as reductions in definition, size and intensity of VH reported by participants, as opposed to a reduction or cessation of the VH overall.

Nevertheless, there are still questions regarding the aetiology of certain VH in CBS that are further highlighted by this study. Previous imaging studies of VH in CBS have observed an increase in functional activation in areas related to visual hallucinatory content, with complex phenomena associated with increased activation in ventral occipital regions of the visual association cortex (ffytche et al., 1998). However, in this study, likely inhibitory stimulation of the primary visual cortex was found to elicit a more prominent beneficial response than stimulation of more anterior regions of the visual association cortex, even in participants with complex phenomenology. One possible explanation for this is the key role and overall sensitivity of early visual areas demonstrated during visual perception. During normal visual processing, early visual areas (V1/V2) respond to the general features of a visual image; visual signals are consequently conveyed along the dorsal ('where') pathway toward the posterior parietal cortex to analyse information about the percept's location and motion, and the ventral ('what') pathway towards the inferior temporal areas, which process information about the form, colour and identity of the percept.

Due to the highly tuned nature of neurons in the earliest visual regions (V1) and their projections to later visual areas (Hubel & Wiesel, 1962), significant activation of V1 is seen even during visual tasks related to complex visual processing, such as face perception (Grill-Spector & Malach, 2004) and external stimulation of V1, such as by TMS, can prompt both simple perceptions of light (phosphenes) and featural perceptions of colour, defined lines/edges and even complex shapes (i.e. Taylor et al., 2011; Troyk et al., 2003). Conversely, disruption of V1 activity by external stimulation can correspondingly disrupt the response of later visual areas to visual stimuli (i.e. Beckers & Zeki, 1995; Chung & Fester, 1998).

In the case of this study, hyperpolarisation of these finely tuned neurons and interneurons within V1 may have caused disruption to activation occurring in later ventral regions associated with complex VH (ffytche et al., 1998), causing a subsequent effect on the VH content. Disrupting V1 activity may prevent subsequent upstream transmission of ambiguous or noisy visual input from the eyes and LGN, along with disrupting the production of erroneous spontaneous activity, allowing 'normal' bottom-up activity to provide correction of noise in higher visual areas and subsequently impacting VH (Chen et al., 2007). Furthermore, many of the featural changes to VH reported by the participants, including the definition (contrast), size, brightness and even motion of the imagery, are aspects of visual processing that are intrinsically linked to activation in the early visual cortex during normal visual perception (Grill-Spector & Malach, 2004). Therefore, it is logical that disruption of activity in this region would cause associated effects such as the ones observed.

While unrelated to stimulation, an interesting observation of this study was the high incidence of migraine, or a family history of migraine, within this participant group. Previous studies have indicated that migraineurs in general demonstrate increased visual cortical excitability when compared to healthy controls, regardless of whether they experience 'aura' (Brighina et al., 2009; Khedr et al., 2006). It is therefore possible that a link between CBS and migraine exists in these participants, and that the increased excitability associated with migraine may confer a greater risk of developing VH following sight loss. Furthermore, the high incidence of migraine within the group may also be linked to the unusual presentation of CBS in these participants in the form of continuously occurring VH. However, a link between these phenomena is currently speculative and would require further investigation before any conclusions can be made.

5.5.3 Strengths and Limitations

While the findings of this study indicate a promising application of tDCS in people with CBS, it is important to consider the limitations of the overall study before beginning to draw conclusions.

Although four out of the six participants reported a positive effect of cathodal stimulation, this study was conducted as an open-label treatment in which all participants received active treatment in the absence of any placebo control. Potential placebo effects of this treatment are therefore an important consideration, as a previous investigation into the utility of tDCS for the treatment of VH in DLB observed improvements to VH symptoms

following placebo stimulation (Elder et al., 2019). However, it should be noted that the aforementioned study was performed in dementia participants with variable levels of cognition, in comparison to the present study in which all participants were cognitively intact. Furthermore, most of the participants in this study had tried multiple treatments, previous to stimulation, in the form of both pharmacological and psychological interventions with no positive effects, suggesting that they may have been less amenable to placebo effects.

A strength of the findings of this study, however, is their ability to satisfy a number of the Bradford Hill criteria for causality (Hill, 1965), including a strong effect size (four out of six participants reporting positive effects), reproducibility both within and between participants, specificity of effects (i.e. improvements to similar domains of VH content), temporality of the stimulation effects, a dose-response relationship (with effects improving with stronger stimulation), and a biologically plausible mechanism. Nevertheless, future study would need to include placebo-controlled trials in order to more accurately assess the effect of stimulation on VH in this participant group.

A further consideration must also be the sample used in the present study. While the sample used was small, the exploratory nature of this study was aimed at assessing the feasibility of stimulation in this participant group and so helping to inform stimulation parameters for future study; hence a large sample was not necessary. This is also comparable to previous similarly exploratory studies of tDCS, which have consisted of low sample numbers or single patient case studies (i.e. Elder et al., 2016; Koops & Sommer, 2017; Shiozawa et al., 2013). Although each participant was positively identified as having CBS by an experienced clinician (Df), the participants in this sample represent an unusual subgroup of the overall CBS population. While the aim and consequent design of the study necessitated the recruitment of people experiencing continuous VH, this level of hallucinatory activity is not regularly observed in CBS and its prevalence has consequently not been quantified in the CBS literature (i.e. Khan et al., 2008; Menon et al., 2003; Singh & Sørensen, 2012). Incidences of continuous simple VH have been described in patients following enucleation (Rasmussen et al., 2009). However, unlike the present sample, continuous complex phenomenology was not reported. Nevertheless, while continuous complex VH have been reported in patients with occipital lobe lesions, investigation of functional and electrophysiological correlates within these patients has not provided an explanation for their continuous presentation (Anderson & Rizzo, 1994). Studies of tinnitus, which has been considered analogous to CBS, have theorised that people who experience chronic, or

continuous, tinnitus demonstrate a constant depletion of serotonin leading to hyperexcitability in the auditory system, whereas people experiencing intermittent tinnitus demonstrate fluctuations in this hyperexcitability rather than overall depletion (Koops et al., 2019). However, this has yet to be thoroughly investigated and parallels with CBS in this regard are uncertain. It is therefore not clear whether the underlying mechanisms leading to VH in this particular group are the same as other CBS patients who experience VH more episodically and, therefore, it is possible that the efficacy of tDCS in the wider CBS population may be different.

One important aspect of stimulation which this study was unable to adequately assess was the effect of repeated stimulation over a period of days rather than in a single session. Previous research has suggested that performing stimulation over multiple sessions can lead to prolonged improvements in the targeted domain (i.e. Boggio et al., 2006; Brunelin et al., 2012; Doruk et al., 2014; Shiozawa et al., 2013) by more effectively achieving long term potentiation and synaptic plasticity in the stimulated region (Stagg & Nitsche, 2011). While two participants described some lingering positive effects up to 3 months following stimulation, the most prominent effects of stimulation dissipated in all participants following 1-4 days. Providing stimulation over multiple consecutive days may thus be more appropriate in order to produce a cumulative cortical response. However, the stimulation density used in this study was quite high (0. 32mA/cm^2), due to the smaller focal electrodes (3.14cm^2) used, compared to previous studies which have used current densities of 0.06mA/cm^2 and 0.048mA/cm^2 in hallucinating patients (i.e. Brunelin et al., 2012; Elder et al., 2019). While this stimulation intensity was within manufacturer safety recommendations and was well tolerated across all participants in this study, it is not yet clear whether this will remain tolerable across multiple sessions over consecutive days or how this may affect the overall treatment response.

Finally, the current study did not assess the neurophysiological response to stimulation in these participants. While an EEG was performed prior to and following stimulation, this was mostly used as a means of assessing hemispheric differences in cortical alpha in order to inform stimulation locations, and therefore analysis was mostly performed online. Previous studies of the modulatory effect of tDCS on the visual cortex have observed excitability changes following cathodal tDCS in the form of increased occipital alpha as measured by EEG (Puanhvuan et al., 2013). In order to properly interrogate the effects of stimulation and how these relate to the potential mechanisms involved in VH in CBS, neurophysiological

assessment of neural correlates relating to hyperexcitability in the visual cortex such as this should be considered for future investigations. Similarly, neuroimaging techniques aimed at assessing changes in functional activity (fMRI) and the concentration of excitatory and inhibitory neurotransmitters (MRS) may provide further insight into the effect of stimulation and its interaction with VH.

5.5.4 Conclusions

The observations of this study suggest that 1mA inhibitory transcranial direct current stimulation of the primary visual cortex may produce a beneficial therapeutic effect on visual hallucinations in people with Charles Bonnet syndrome. Repeated stimulations over a single session of the visual cortex were well tolerated and led to qualitative changes in the nature of VH imagery in four out of six participants, constituting a positive change to participant hallucinatory experiences and providing tentative support for the role of deafferentation in the aetiology of CBS. Whether this positive effect can be replicated in non-continuously hallucinating CBS participants remains to be seen. The next chapter employs the use of a placebo-controlled design in order to interrogate the efficacy of stimulation on measures of VH, including their frequency, severity, duration and emotional impact, while considering the effect of repeated sessions over multiple days on the potency of treatment effects. Further investigation into the neurophysiological changes brought about by stimulation and their relationship to VH are performed, which will aid in further understanding of how VH arise in CBS.

Chapter 6 Transcranial direct current stimulation as a treatment for visual hallucinations in Charles Bonnet Syndrome

6.1 Introduction

Evidence from the pilot study detailed in **Chapter 5** indicates that repeated cathodal inhibitory tDCS of the primary visual areas of the occipital cortex may produce beneficial therapeutic effects to VH in people with CBS without significant adverse effects. Nevertheless, while these results are promising, it is important that they are examined more rigorously in order to assess the extent of any meaningful therapeutic benefit before the findings can be generalised. Consequently, further investigation employing a robust clinical study design and considering further clinical factors is necessary to effectively interrogate the efficacy of tDCS in CBS. The therapeutic applications and the neurophysiological mechanisms involved in tDCS were introduced in **Chapter 5**; the following sections will discuss relevant considerations for the investigation of tDCS as a potential therapeutic intervention.

6.1.1 Intervention study design: Placebo stimulation

Often considered the gold-standard in clinical research, the implementation of a placebo-controlled crossover study design allows researchers to examine the direct effects of active treatment in comparison to placebo (sham) treatment on a target symptom (Kessels et al., 2019). In the context of this study, such a design allows the comparison of the effects of active inhibitory tDCS treatment and sham tDCS treatment on measures of VH and cortical excitability within a group of CBS patients.

Placebo effects, in which patients report a clinically significant improvement to symptoms following placebo intervention, are an important consideration in assessing the clinical efficacy of any therapeutic intervention (Kessels et al., 2019), including non-invasive brain stimulation. Using tDCS, sham stimulation involves a short period of stimulation (typically between 20-60 seconds) which mimics the skin sensation of initial active tDCS without delivering any significant neuromodulatory effect. Such protocols have been used successfully in several previous tDCS studies with various patient groups (i.e. Brunelin et al., 2012; Brunoni et al., 2012) with participants generally reporting sham stimulation to be indistinguishable from active stimulation (Gandiga et al., 2006). A study by Elder et al (2019) recently observed a marked placebo effect on the remediation of VH in patients with Lewy

body dementia following 4-consecutive days of placebo stimulation: suggesting that comparable improvements reported by patients receiving the active stimulation were not due to the stimulation itself and may be indicative of high-levels of inter-individual variation in neuropsychiatric symptoms in these patients. This is particularly pertinent when considering the highly subjective nature of VH and patient reports regarding them, thus further highlighting the need for placebo conditions in this type of study.

6.1.2 Intervention study design: Prolonging stimulation after-effects

Previous research into the utility of tDCS as a clinical intervention have found that the after-effects of stimulation can vary in length from a few hours to several months (Boggio et al., 2006, 2009; Brunelin et al., 2012; Doruk et al., 2014; Elder et al., 2016; Koops & Sommer, 2017; Shiozawa et al., 2013). While reasonably sustained therapeutic effects were noted by two participants in our pilot study (see **Chapter 5**) following a single session of tDCS, the general consensus in the literature suggests that repeated spaced tDCS sessions appear to prolong neuromodulatory after-effects and may be more effective at achieving long-term potentiation and synaptic plasticity (Boggio et al., 2006; Nitsche, Jaussi, et al., 2004; Stagg & Nitsche, 2011). Multiple sessions of anodal tDCS over a course of ten consecutive days have been found to prolong improvements to executive functioning in patients with PD (Doruk et al., 2014), while five daily sessions of cathodal tDCS in stroke patients resulted in prolonged motor function improvements compared with less regular weekly sessions (Boggio et al., 2007). As such, the use of multiple tDCS sessions may be more beneficial in the development of longer lasting treatments for neuropsychiatric symptoms.

In the context of hallucinations, prolonged therapeutic effects of up to three months were observed following five consecutive days of active cathodal stimulation in patients with schizophrenia with auditory verbal hallucinations (Brunelin et al., 2012), while Shiozawa et al (2013) observed sustained improvement to VH in a patient with schizophrenia only after multiple sessions of inhibitory cathodal stimulation.

As the pilot study (**Chapter 5**) performed inhibitory tDCS on only one day, it is currently unclear whether repeated sessions over consecutive days may have a cumulative effect in CBS, resulting in either more prominent or prolonged therapeutic benefits similar to those observed in previous studies (i.e. Brunelin et al., 2012; Boggio et al., 2007).

Accordingly, the following study aimed to investigate this further by applying inhibitory tDCS to CBS patients over four consecutive days.

6.1.3 Measuring physiological and functional changes following stimulation

The use of tDCS to modulate cortical activity is the theoretical underpinning of its use as a clinical intervention (as discussed in **Chapter 5**). However, understanding how the neurophysiological changes induced by stimulation relate to the subjective remediation of symptoms reported by patients may also help to elucidate the mechanisms involved in the formation and maintenance of VH. In the case of CBS, objectively measuring activity in the visual cortex before and after stimulation may be necessary to determine how cortical excitability may contribute to the formation of VH in CBS. Furthermore, comparing activity prior to and following stimulation may help us to better understand the functional and physiological effects of stimulation on the brain. Consequently, the following study used the following techniques to provide objective measures of potential physiological alterations following stimulation:

Functional Neuroimaging

Studies utilising fMRI have demonstrated that tDCS of the human visual cortex can produce measurable changes to cortical activity during visual tasks. Anodal tDCS of the occipital cortex has been found to induce an increase in BOLD response evoked by visual stimulus (Alekseichuk et al., 2016), while cathodal tDCS of the right motion area (MT+) has been associated with increases in fMRI signal in response to moving stimuli (Antal et al., 2012). However, to date, no studies have investigated the effect of tDCS on visually hallucinating patients or patients with CBS using fMRI.

Magnetic Resonance Spectroscopy

Research into the neurobiological effects of transcranial stimulation has suggested that non-invasive brain stimulation such as tDCS may directly influence the concentration of excitatory neurotransmitters (i.e. Brunoni et al., 2012; Nitsche et al., 2003; Stagg & Nitsche, 2011). Anodal tDCS of the primary visual cortex has been associated with significant increases in glutamate concentration in healthy participants, while cathodal stimulation was found to reduce it (Siniatchkin et al., 2012; Stagg et al., 2009). However, the effect of tDCS on the concentration of the inhibitory neurotransmitter GABA, which has been linked to the occurrence of VH (Firbank et al., 2018; Khundakar et al., 2016; Su et al., 2016), is less clear.

An overall decrease in GABA concentration in the motor cortex has been observed following cathodal stimulation, though the close biochemical relationship between GABA and glutamate (which is more obviously modulated by stimulation) makes it difficult to tell whether the reduction was due to a decrease in GABA itself, or a reduction in glutamate needed to synthesise it (Stagg et al., 2009). Similarly, overall alterations to GABA concentrations in people with VH and its relationship with their occurrence is still under question, meaning that the comparison of pre and post stimulation GABA concentration may provide insight into its role in their aetiology.

Visual Function

Although not measuring neurophysiological changes, the (potentially negative) effect of the suppression of excitability in the visual cortex on visual function is an important consideration when assessing the viability of tDCS as an intervention for VH. Cathodal tDCS of the visual cortex has previously been observed to successfully inhibit cortical excitability, but has also been associated with a consequent decrease in static and dynamic contrast sensitivities in healthy volunteers (Antal et al., 2001). While evidence of an effect of tDCS on visual function is currently limited, it is important to consider the impact that inhibitory stimulation of the visual cortex may have on the remaining visual ability of people with CBS, who often retain partial sight. As detailed in **Chapter 4**, worse visual function in both participant groups was associated with a greater loss of independence in daily living. Therefore, any deterioration of vision as a result of stimulation may outweigh any perceived improvement to VH and thus is an important consideration.

The following chapter utilised the optimal stimulation parameters determined during the pilot study (see **Chapter 5**) in order to develop an intervention trial aimed at interrogating the efficacy of inhibitory tDCS over multiple sessions as a therapeutic treatment for VH in CBS. Furthermore, this study aimed to investigate the effect of inhibitory tDCS on measures of cortical activity and their association with VH in this patient group.

It was hypothesised, based on previous studies and evidence from the open-label pilot study conducted in **Chapter 5**, that multiple sessions of cathodal tDCS to the primary visual cortex over four consecutive days would result in a beneficial improvement to VH in people with CBS when compared to sham stimulation. Furthermore, it was predicted that active inhibitory tDCS would result in observable changes to visual cortical activity, in the form of changes to fMRI BOLD activation and GABA concentrations.

6.2 Methods

6.2.1 Participants

A total of 16 people with Charles Bonnet syndrome took part in both weeks of the tDCS treatment study (10 Female; M_{age} = 78.63 SD = 9.77). One participant completed the first week of the study but withdrew from further investigation due to fatigue associated with participation, therefore their data was not included in the analysis. All participants met the current diagnostic criteria for CBS (outlined in **Chapter 1**) and were expected to experience VH a minimum of three times per week. Visual hallucination phenomenology, frequency and impact reported by participants prior to commencing the treatment study is described in **Table *6.1***.

Table 6.1. *Visual hallucination (VH) phenomenology, frequency, duration and emotional impact in Charles Bonnet syndrome (CBS) participants taking part in the treatment study. Emotional impact was categorised by average NEVHI irritation and distress scores: 0-3 = low, 4-7=moderate, 8-10 = high. Multiple VH a day/week indicates three or more VH during this time period.*

Participant	Years of CBS	Frequency	Duration	Emotional impact	Simple VH	Complex VH	Example phenomenology
P1	5	Continuous while awake	Continuous while awake	Moderate	✓	✓	Rapidly spinning pinwheel; coloured 'fireworks'; moving black crosses
P2	13	Multiple times a day	Hours	Moderate	✓	✓	Panoramic scene of destroyed buildings; wallpaper patterns; orange lines; Pink 'wash'.
P3	1	Multiple times a day	Seconds - minutes	Moderate	✓		Starbursts of moving lights; spinning cylindrical lights
P4	1	Multiple times a week	Seconds - minutes	Low	✓	✓	Small turtles/zebras running across the floor; circular and square flashing lights
P5	3	Multiple times a day	Hours	Moderate	✓	✓	'Parquet flooring' pattern; houses and fences; bright sparkling lights
P6	4	Multiple times a week	Seconds - minutes	Moderate		✓	Parked and moving vehicles; people standing outside of the window
P7	1	Multiple times a week	Minutes	Low		✓	Blue and pink lace patterns; an 'ape' sitting in the garden.
P8	2	Continuous while awake	Continuous while awake	High	✓	✓	Raindrops hitting a windscreen at high speed; Black and white paisley patterns
P9	4	Multiple times a week	Minutes	Moderate		✓	Chessboard patterns; realistic faces and queues or crowds of figures; houses and fences
P10	2	Multiple times a day	Minutes	Moderate	✓	✓	Moving 'spikey' shapes; vibrant coloured lights; detailed faces (i.e. 'Hindu gods')
P11	1	Multiple times a week	Seconds - minutes	Low	✓	✓	Black amorphous shapes 'like soot'; netting patterns covering everything in vision.
P12	2	Multiple times a week	Minutes	Moderate	✓	✓	Flashing coloured lights; moving/growing black square; mesh patterns
P13	3	Multiple times a day	Seconds - hours	Low	✓	✓	Blue flashing light; yellow spiderwebs
P14	2	Multiple times a day	Minutes	Low		✓	Scenes of towns/countryside; scrap metal piles
P15	1	Multiple times a day	Minutes – hours	High	✓		Circular/oval/rectangle flashing silver lights
P16	10	Multiple times a day	Seconds - minutes	High	✓		White and blue spinning 'boomerangs'.

6.2.2 Procedure

Following completion of participant demographics, visual function assessments, and baseline neuropsychological and neurophysiological measures (outlined in **Chapter 3**), participants began active or sham (placebo) tDCS treatment. Each participant received a session of active or sham tDCS on four consecutive days. Due to the crossover nature of the trial, participants returned following a four week wash-out period, at which point they received the opposite treatment (i.e. if a participant received active stimulation in the first week, they would receive sham stimulation during the second) (**Figure *6.1***). As the therapeutic benefits of multiple sessions of tDCS over consecutive days have been observed to last between a few weeks to a month in other visual hallucinating pathologies (i.e. Koops & Sommer, 2017; Shiozawa et al., 2013), a minimum period of four weeks was deemed necessary to eliminate possible carry over effects. Nevertheless, the longevity of stimulation in this patient group is still unknown, therefore the type of stimulation participants received during each week was randomised and counterbalanced by an independent statistician (SC), with both participants and investigators blinded to the stimulation being used, in order to investigate possible order effects on treatment response.

On day five of both study weeks (active and sham) participants underwent repeat visual function, EEG, neuroimaging and neuropsychological assessments using the same protocols as day one. Additional paper-based questionnaires assessing impressions of change in symptomology and the feasibility and tolerability of the treatment were also performed, detailed in sections: **6.2.3 & 6.2.4**. During each four-day treatment week, participants were further requested to complete a visual hallucinations diary (Appendix G), documenting any VH experienced including phenomenology, time of day, and duration. Furthermore, participants were asked to record anything they viewed as a subjective change to any aspect of their VH throughout the week (i.e. size, colour, intrusiveness).

6.2.3 Transcranial Direct Current Stimulation

Stimulation was delivered using an 8-channel Starstim 8 integrated tCS/EEG neurostimulator system (Neuroelectrics, Barcelona, Spain) using 3.14cm^2 electrodes soaked in conductive gel. Electrodes were placed according to the 10-20 electrode placement system (Jasper, 1958), with the cathodal electrode placed over Oz (10% of naison-inion distance above the inion) and bilateral anodal electrodes placed over F3 and F4 held in place by a neoprene cap (**Figure *6.2***). Stimulation was delivered at an intensity of 1mA (current density:

0.29mA/cm^2) at the cathodal electrode, with 0.5mA (current density: 0.16mA/cm^2) at each anode. On Day One, in order to reduce study intensity and assess initial feasibility and tolerability of stimulation, participants received a shorter stimulation session. Stimulation was delivered in four blocks each lasting five minutes and separated by 2-minute intervals in which no stimulation occurred. This resulted in 20-minutes total of stimulation. On days 2-4, stimulation was given in six 5-minute blocks separated by 2-minute intervals, totalling 30 minutes overall stimulation. Short stimulation blocks, as opposed to a longer single block, were used in order to most closely replicate stimulation performed during the pilot study (**Chapter 5**).

Following each week of stimulation, participants were also asked to rate the overall tolerability of the stimulation and any side effects that they may have experienced. Participants were given a rating scale (0-10) on which to rate the following common side effects that have been reported in previous tDCS studies(i.e. Brunoni et al., 2012; Durand et al., 2002): headaches, tingling sensations, scalp pain, itching, burning/hot sensation, skin redness, sleepiness, nausea, and trouble concentrating. An additional 'other' category was included for participants to report any novel side effects (Appendix H). Furthermore, following the end of each treatment week, both participants and the investigator who performed stimulation were asked to state whether they believed the stimulation on that week to have been the active or sham treatment in order to test the integrity of the study blinding.

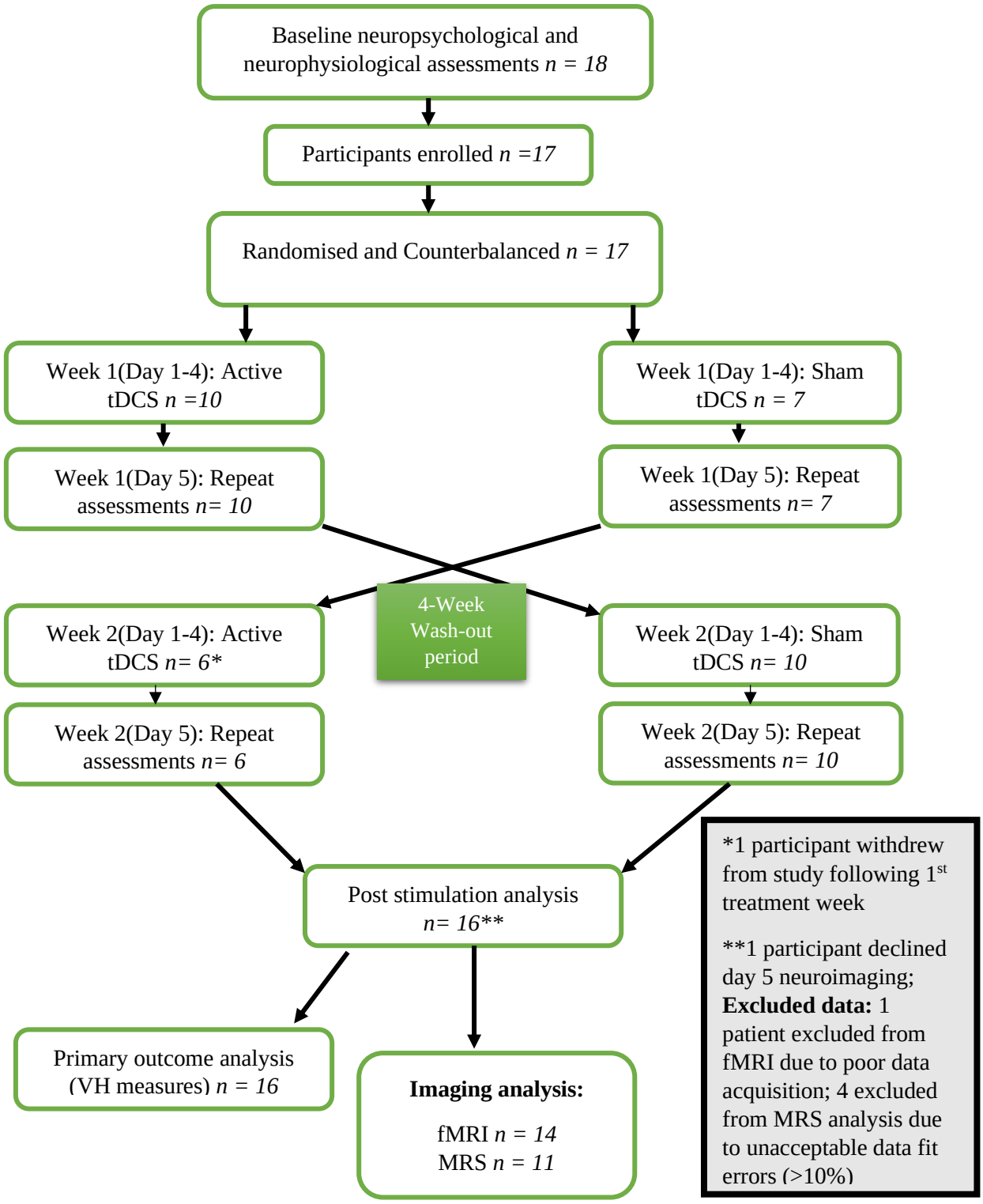

Figure 6.1. *Schematic demonstrating the study's crossover design and procedure. Abbreviations: tDCS: transcranial direct current stimulation; fMRI: functional magnetic resonance imaging, MRS: magnetic resonance spectroscopy.*

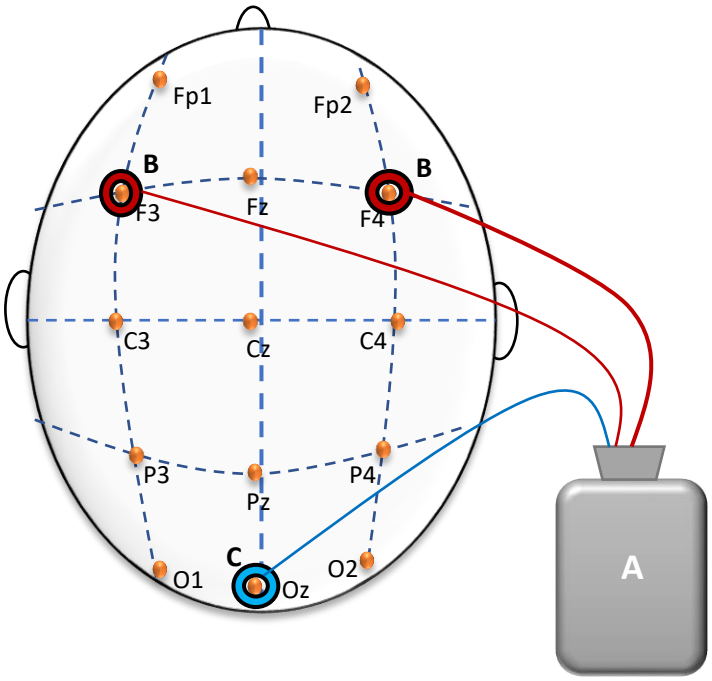

Figure 6.2. *Depiction of electrode set up including battery powered stimulator [A] connected to bilateral anodal electrodes placed over F3 and F4 each stimulating at 0.5mA[B] and cathodal electrode placed over primary visual cortex (Oz) stimulating at 1mA [C].*

During sessions of sham stimulation, direct current was administered for the first and last 20 seconds with the same intensity as the active stimulation (0.32mA/cm^2 Cathode, 0.16mA/cm^2 anodes). This generated sensations similar to those at the start and end of active stimulation without producing a neuromodulatory effect.

6.2.4 Pilot Hallucination Scale

While current visual hallucinatory assessment tools such as the NEVHI achieve a high level of internal consistency when screening for VH (Mosimann et al., 2008) and can be used to quantify behaviours and emotions associated with VH, its use as a tool for assessing the often subtle changes to VH following treatment can be limited. For example, a patient who experiences 7 – 8 separate VH episodes a day may be given the quantifiable score of 5 (Every few hours) on the NEVHI and 4 (Very frequently – once or more per day) on the NPI^{hall}. However, following treatment, the same patient may then report a decrease to 2-3 visual hallucinations a day. While such a reduction may represent a clinically significant difference to the patient, as has been indicated by a patient survey performed for the Macular society (Cox & ffytche, 2014), using the rating systems provided by the NEVHI and NPI would

result in the patient being given an identical score to their pre-treatment rating. For the purpose of research, this means that these scales may lack the sensitivity needed to effectively and meaningfully compare the efficacy of different interventions in these patient groups.

Consequently, as part of this study, a novel assessment tool designed to quantify the participant's perceived change to specific visual hallucinatory domains post-treatment was developed, utilising responses given to the semi-structured NEVHI and patient reports on the visual hallucination diary provided during each treatment week. Using descriptions from the NEVHI, participant VH were classified into primary (most common or intrusive) and secondary (commonly occurring but less frequent or intrusive) phenomenology, including information about the frequency, duration, intrusiveness of VH and patient ratings of irritation and distress. Intrusiveness, while included in the Cardiff Anomalous Perceptions Scale (CAPS; Bell et al., 2006), has not previously been measured on dedicated VH inventories such as the NEVHI and NPI. For the purpose of this study, intrusiveness was defined as how obstructive VH were to a participant's every day functioning and vision, including how easy VH were to ignore. The inclusion of this domain in this scale was informed by participant reports from both the pilot (see **Chapter 5**) and comparison study (**Chapter 4**) in which VH were often described as obstructing vision or impairing daily functioning.

During both treatment weeks, participants were asked to record hallucinations each day as part of the visual hallucination diary, indicating whether they had noticed a change to any aspect of their hallucinations during and at the end of the week. Paired with information collected on Day 5 as part of the NEVHI, the extent of change to each aspect of VH were quantified (Appendix I). For features of VH such as the frequency, duration, and intrusiveness a 6-point Likert scale was used (1= Significant increase, 2= Slight increase, 3= No Change, 4= Slight Decrease, 5= Significant decrease, 6 = Complete cessation). Changes to participant emotional response (irritation and distress) was recorded in a similar manner on a 5-point Likert scale (1= significant increase – 5= significant decrease). As reports from the pilot study (see **Chapter 5**) indicated that tDCS may have a more noticeable effect on certain VH compared to others, these rating scales were repeated for both the participant's primary and secondary VH.

For the purpose of this thesis, the new assessment scale is hereafter referred to as the 'Participant Perceived Change Scale for Visual Hallucinations' (PPC-VH).

6.2.5 Data analysis

Analysis and processing of imaging data collected at all time points (baseline, post-active treatment, post-sham treatment) and general statistical analyses is detailed in **Chapter 3.**

6.2.6 Statistical Analysis

Primary outcome measures

Due to the crossover nature of this trial, all participants completed both an active and sham stimulation treatment week as part of their study participation. Within-subject analysis of the primary outcome measures based on scores on the adapted North East Visual Hallucinations Inventory (NEVHI) and Neuropsychiatric Inventory hallucination sub-scale (NPI^{hall}) between baseline, sham and active tDCS was conducted using the Mann-Whitney U test due to the non-normal distribution of the data. Changes to VH scores following each week of stimulation were calculated by subtracting post-stimulation scores from pre-stimulation scores. While these variables were also found to demonstrate a non-normal distribution, deviation from the mean was mild overall, therefore differences in changes to primary outcome measure scores post-sham and post-active stimulation were analysed using a repeated-measures analysis of variance (ANOVA) due to the robust ability of this test to deal with mild deviations from normality. A non-parametric Friedmann's test was then used post-hoc to confirm any main effects observed. The order in which participants received treatment was included in the repeated-measures ANOVA as the between-subjects factor, allowing for the impact of treatment order to be assessed on changes to scores of VH.

Both the NEVHI and NPI are made up of individual component scores, so for the purpose of this analysis these scores were separated to account for variation across different visual hallucinatory domains. For the NEVHI, separate scores were given for the frequency (1-8) of the VH, VH duration (1-4), participant ratings of irritation (0-10) and distress (0-10). Although the NPI calculates an overall score (maximum 12) by multiplying the frequency (0-4) and severity (0-3) scores of VH, for the purpose of this analysis all three scores were used to increase sensitivity to changes in these domains. In addition, the NPI includes a caregiver-rated distress scale (0-5). However, since all participants retained insight, this scale was instead used by the participant to indicate their level of emotional distress as a result of VH.

Treatment effect size was estimated using Cohen's statistic, calculated as the difference between two means divided by the variance in the sample, and Omega^2, which provides an unbiased estimate of population variances ideal for small samples.

Secondary outcome measures

While currently an unverified scale, responses on the PPC-VH were analysed using a repeated measures ANOVA in order to assess changes to each VH domain following active and sham stimulation. Spearman's correlations were performed between items of the PPC-VH and corresponding/related measures on the NEVHI and NPI^{hall} as a means of assessing concurrent validity of the scale.

As inhibitory tDCS of the visual cortex has been shown to produce changes to aspects of visual function (Antal et al., 2001), within-subject analysis using paired t-tests was used to compare visual acuity and contrast scores pre- and post-treatment, with a repeated measures ANOVA performed in order to assess any effect of stimulation treatment on overall visual function.

Whole brain and region of interest (ROI) fMRI voxelwise data was analysed using a 2x2 flexible factorial model to determine differences in activation patterns between treatment weeks (within-subjects) and interactions with order of treatment (between-subjects) (Altman, 1990). An additional ROI of the bilateral frontal poles, defined using the AAL template for MatLab, was included in the analysis for this study, due to anodal stimulation of the bilateral prefrontal cortex.

Analysis of MRS data compared within-subject changes in GABA+, creatine (Cr), and GABA/Cr ratios between baseline, post-sham and post-active stimulation using non-parametric paired t-tests. GABA+ concentration was calculated controlling for tissue fractions in the voxel of interest, including CSF, grey and white matter. A repeated measures ANOVA was used to look at the interaction between changes to post-treatment GABA/Cr and treatment order.

6.3 Results

6.3.1 Primary Outcomes: The effect of inhibitory tDCS on visual hallucinations

Participant ratings of VH on the NPI^{hall} and NEVHI scales pre- and post- active and sham stimulation are displayed in **Table *6.2***. Overall, participants reported that the severity ($z = -2.0$, $p = .046$) and distress ($z = -2.12$, $p = .034$) of hallucinations as rated on the NPI^{hall} were reduced, with a corresponding reduction in overall NPI^{hall} scores ($z = -2.40$, $p = .016$) following active stimulation. Nevertheless, participants also reported a significant decrease in ratings of VH severity on the NPI following sham stimulation ($z = -2.24$, $p = .025$). On the NEVHI, participants reported a significant reduction to the overall frequency of VH following active stimulation only ($z = -2.71$, $p = .007$). Participants also reported a significant reduction to irritation towards VH following both active ($z = -2.52$, $p = .012$) and sham ($z = -2.38$, $p = .018$) stimulation.

Table 6.2. *Mean (±Standard Deviation) of visual hallucination ratings on the NPI and NEVHI scales before and after each treatment week. Significant differences (Wilcoxon signed rank test, p<.05) are highlighted in bold.*

	Active Stimulation			**Sham Stimulation**		
	Pre	*Post*	*Sig. (p)*	*Pre*	*Post*	*Sig. (p)*
NPI^{hall}	6.69(±2.80)	5.50(±3.37)	**.016**	6.38(±2.92)	5.69(±3.20)	.114
Frequency	3.81(±.40)	3.50(±.82)	.129	3.62(±.81)	3.69(±.60)	.705
Severity	1.75(±.68)	1.50(±.73)	**.046**	1.75(±.683)	1.44(±.629)	**.025**
Distress	1.44(±1.59)	1.00(±1.46)	**.034**	1.38(±1.26)	1.19(±1.42)	.429
NEVHI						
Frequency	5.50(±1.32)	4.94(±1.65)	**.007**	5.06(±1.57)	5.00(±1.63)	.739
Duration	2.25(±1.13)	2.12(±1.20)	.157	2.38(±1.26)	2.06(±1.06)	.102
Distress	2.31(±3.42)	1.88(±3.05)	.221	2.94(3.13)	1.63(±2.75)	.065
Irritation	6.00(±3.43)	3.94(±3.42)	**.012**	5.94(±3.34)	4.38(3.58±)	**.018**

Abbreviations: NPI^{hall}: Neuropsychiatric Inventory hallucination subscale, NEVHI: North East Visual Hallucination Interview.

The degree of change between pre- and post-stimulation ratings of VH were calculated (pre-stimulation rating – post stimulation rating; **Figure *6.3***) and entered into a repeated measures ANOVA to test for any significant differences between active and sham treatment and any subsequent interaction with treatment order. When controlling for

treatment order, participant ratings of VH frequency on the NEVHI were found to be significantly reduced following active stimulation compared to sham (F (1,14) = 9.95, p = .007) with a moderate to large effect size (Cohen's f = .75; partial Omega^2 = .36). While not significant, a similar change trending towards significance was seen with frequency scores on the NPI (F(1,14) = 3.50, p = .082). While significant differences were observed between pre and post stimulation ratings (see **Table *6.2***), no differences between changes following active or sham stimulation, when controlling for treatment order, were found for overall NPI^{hall} scores (F(1,14) = .88, p=.364), NPI severity (F(1,14) = .11, p= .748), or NEVHI irritation (F(1,14) = .23, p= .640).

A significant decrease in scores on the NPI Distress scale was also observed following active compared to sham stimulation (F(1,14)=8.55, p=.013), however this was found to have a significant interaction with both the order in which participants received treatment and their primary VH phenomenology (F(1,14)=6.904, p=.022), with participants experiencing predominantly simple VH reporting greater reductions in distress when they had the active stimulation in the second week (F(1,14)=6.90, p=.022), however no such interaction with NEVHI distress scores was observed. In comparison, reductions in frequency as measured by the NEVHI were independent of both the order of treatment and the primary VH experienced by the participant (F(1,14)=.007, p=.94).

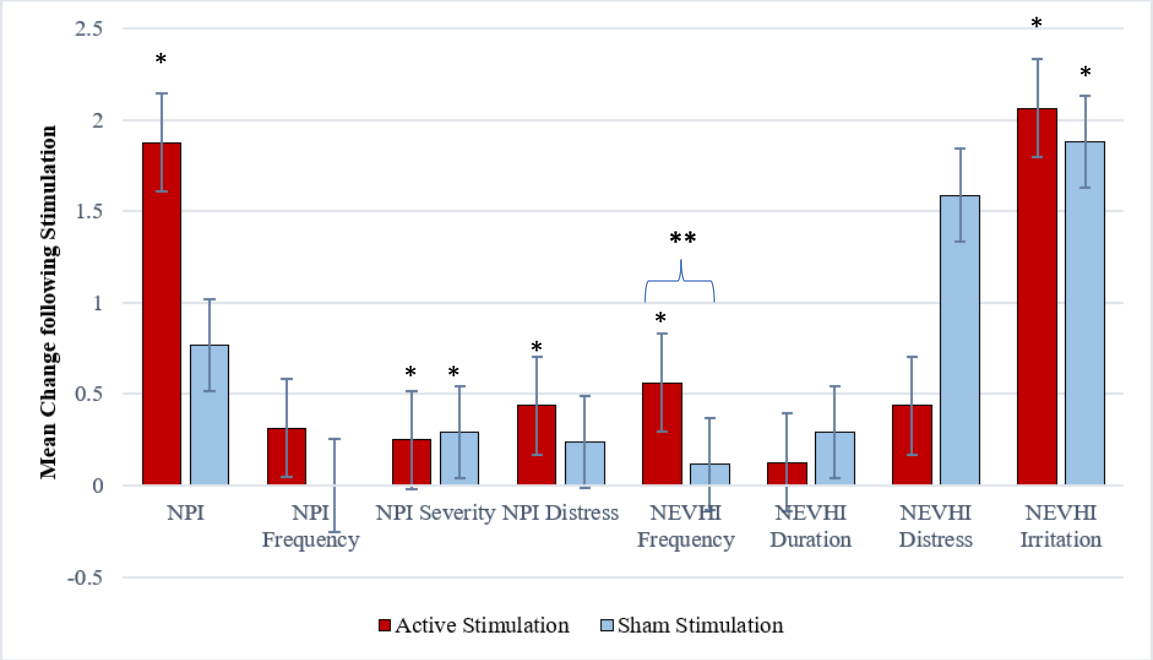

Figure 6.3. *Mean (+/- SEM) change to ratings of visual hallucinations on the Neuropsychiatric Inventory (NPI^{hall}) and North East Visual Hallucination Interview (NEVHI) for active and sham stimulation. *significant change from pre stimulation ratings (p<.05), **significant difference between active and sham stimulation controlling for treatment order and primary VH phenomenology.*

6.3.2 Secondary outcomes: Participant perceived change

No overall treatment effect on participant ratings of perceived change were observed in this study (F(5,7) = 2.29, *p*= .155) and there was no interaction between treatment order (F(5,7) = 1.69, *p*= .254) or most predominant VH type (F(5,7)=2.23, *p*=.162) and VH ratings. However, a significant decrease in the intrusiveness of participant's primary (F(1,11) = 4.10, *p* =.014) and secondary (F(1,11) = 7.34, *p*=.018) VH following active stimulation was observed compared to sham. A significant interaction between ratings of secondary VH intrusiveness and treatment order was observed (F(1,11) = 7.34, *p*=.018), with participants reporting a greater reduction in intrusiveness if they received active stimulation on their second week (F(1,11) = 4.98, *p*=.044). A significant treatment effect on the frequency of primary VH was also observed (F(1,11)= 4.32, *p*=.043), independent of both treatment order (F(1,11)=.01, *p*=.923) and most prominent VH phenomenology (F(1,11)=.49, *p*=.501), with participants perceiving a greater reduction in the frequency of primary VH following active stimulation compared to sham (**Figure 6.4**). A moderate effect size for PPC-VH ratings of frequency was observed (Cohen's *f* = .51, partial Omega^2= .20).

No changes to patient scores on the GDS, regardless of treatment order were observed (p>.05).

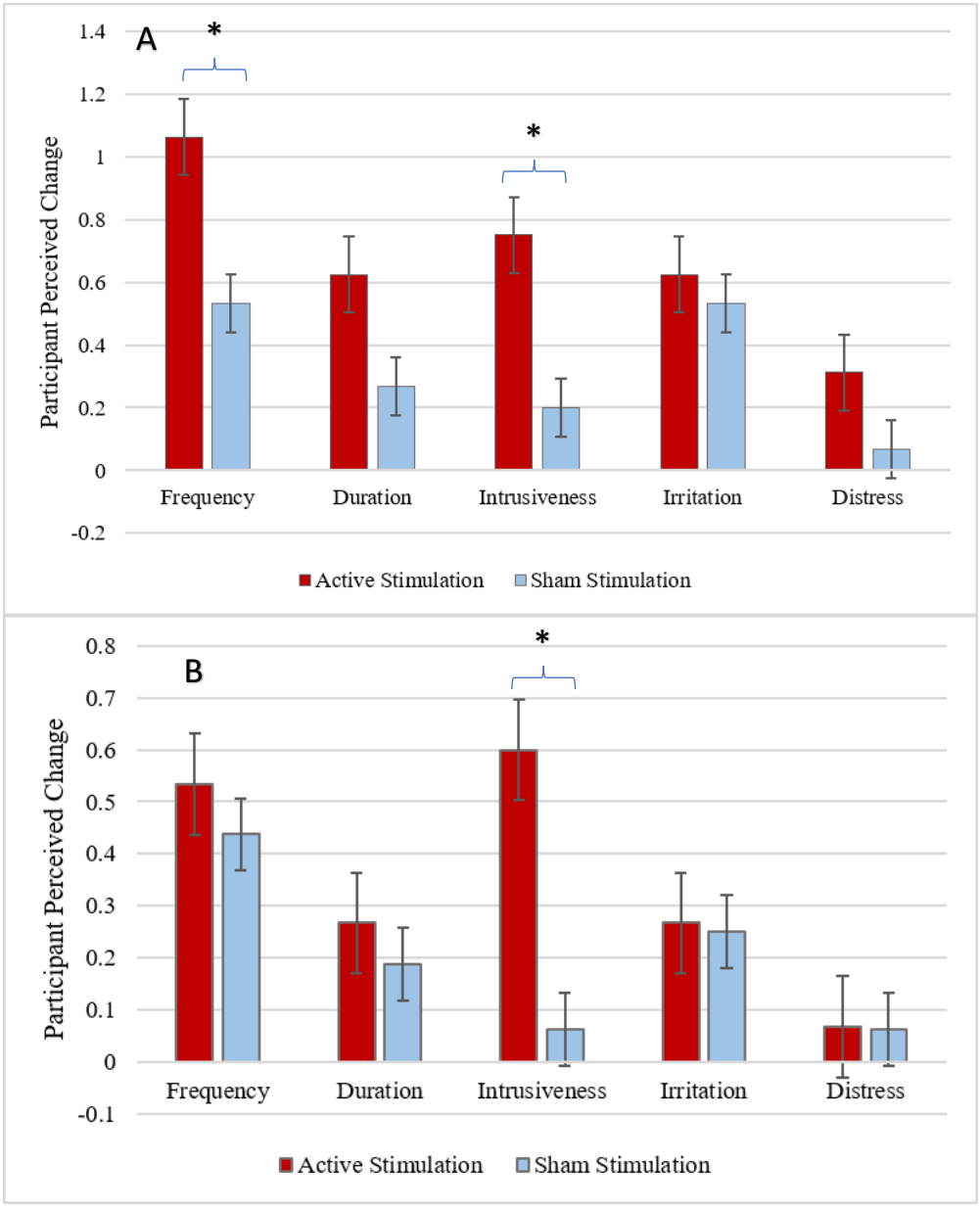

Figure 6.4. *Participant perceived level of change to specific domains of primary (A) and secondary(B) visual hallucinations following active and sham stimulation (mean (+/- SEM)) *p<.05 controlling for treatment order and primary VH phenomenology.*

Concurrent Scale Validation

Correlations between ratings on the PPC-VH for primary and secondary visual hallucinations with corresponding rating changes on the NPI and NEVHI following stimulation were performed in order to assess concurrent validity of the new scale (**Table *6.3***).

Table 6.3. *Spearman's correlations between items on the PPC-VH for primary and secondary visual hallucinations with changes to corresponding ratings on the NPI^{hall} and NEVHI following active and sham stimulation.*

	PPC-VH Primary		PPC-VH Secondary	
	r_s	Sig.(p)	r_s	Sig.(p)
Active:	**Frequency**			
NPI Frequency	**.591**	**.016**	**.568**	**.027**
NEVHI Frequency	**.841**	**.000**	.320	.245
Sham:				
NPI Frequency	**.505**	**.046**	.443	.075
NEVHI Frequency	.320	.226	-.237	.360
Active:	**Duration**			
NEVHI Duration	.150	.580	-.153	.585
Sham:				
NEVHI Duration	**.619**	**.010**	.337	.186
Active:	**Irritation**			
NEVHI Irritation	.373	.155	.038	.893
Sham:				
NEVHI Irritation	**.811**	**.000**	.209	.421
Active:	**Distress**			
NPI Distress	**.730**	**.001**	.336	.221
NEVHI Distress	**.504**	**.046**	-.111	.694
Sham:				
NPI Distress	.346	.190	.422	.092
NEVHI Distress	.382	.144	.146	.577

Abbreviations: NPI^{hall}: Neuropsychiatric Inventory visual hallucination subscale; NEVHI: North East Visual Hallucinations Interview; PPC-VH: Participant Perceived Change Visual hallucination scale. Dark blue represents p<.05, light blue represents rho>.350 but p>.05.

A significant association between decreases in the frequency of VH on the NEVHI and decreases to the overall perceived intrusiveness of VH was observed following active stimulation (r_s=.588, p=.016) but not sham (r_s=.205, p=.446). This also correlated with greater improvements to ratings of distress on both the NPI (r_s=.637, p=.008) and NEVHI (r_s=.535, p=.033). A subsequent linear regression demonstrated that a greater reduction in

VH frequency measured by the NEVHI was a significant predictor of greater reductions in perceived VH intrusiveness ($F(1,15)=7.42$, $p=.016$, $R^2=.346$).

6.3.3 Secondary Outcomes: the impact of stimulation on visual function

While a minor mean reduction in visual acuity was observed following active stimulation (**Figure 6.5**), this was not found to be significant ($z = -.245$, $p=.807$). Similarly, no differences between pre- and post-stimulation measures of visual contrast sensitivity were observed following either the active or sham stimulation weeks ($p>.05$). When comparing active and sham weeks, a repeated measures ANOVA found no significant effect of treatment on visual function ($F(1,16) = .89$, $p=.441$), with no significant interaction with treatment order ($F(1,16) = 1.14$, $p=.359$).

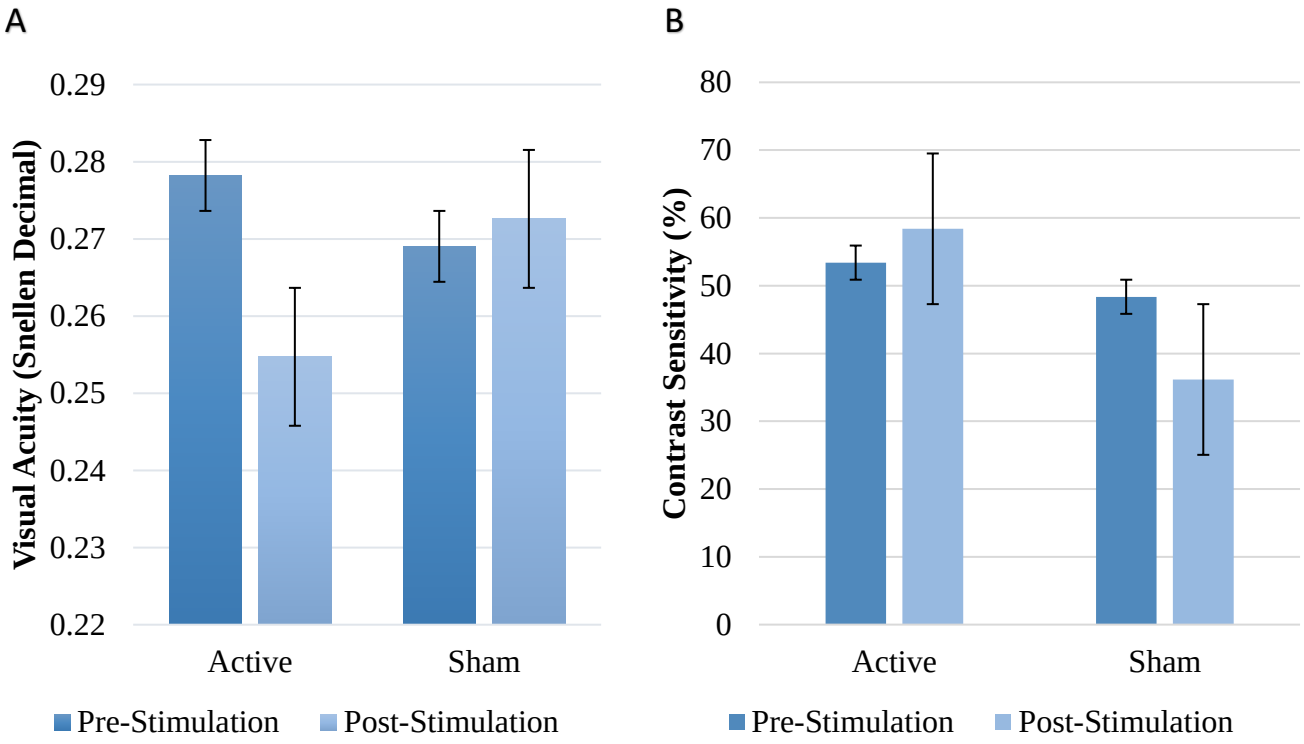

Figure 6.5. *Changes to visual acuity (A) and contrast sensitivity (B) following active and sham inhibitory occipital stimulation (mean (+/- SEM))*

6.3.4 Secondary Outcomes: Functional activity changes following stimulation

Whole brain fMRI analysis showed no significant changes to overall functional activity during the eye-movement task following active or sham stimulation, with no significant interaction with the order in which treatment was given ($p>.05$).

Similarly, ROI analysis of visual cortical regions showed no significant differences in activity during the eye-movement task between active and sham stimulation. Furthermore, no significant differences in functional activity between active and sham were observed in frontal regions that received anodal stimulation. No significant interactions were seen in any ROI with either the order of treatment or the primary VH phenomenology (whether most prominent VH was simple or complex) of the participant (all results $p>.05$).

Nevertheless, significant associations were noted between the degree of change in cortical activity in regions of interest and changes to VH ratings (**Table *6.4***). Following active stimulation, a net increase in V1/V2 BOLD activation was positively associated with greater improvements to overall NPI^{hall} ratings ($r_s=.571$, $p=.033$) and NPI Severity ratings ($r_s=.549$, $p=.042$), conversely decreases in V1/V2 BOLD activation were also correlated with greater improvements to distress ratings on the NEVHI ($r_s=-.629$, $p=.016$). While not reaching statistical significance, changes to VH frequency rated on the NEVHI (which showed a significant effect of treatment) showed a trending association with increases to ventral extrastriate ($r_s=.425$, $p=.130$) and fusiform ($r_s=.457$, $p=.10$) activation. Following sham stimulation, increases in overall thalamic activation were associated with greater improvements to NPI^{hall} ratings of severity ($r_s=.628$, $p=.016$), and NEVHI ratings of distress ($r_s=.570$, $p=.033$) and irritation ($r_s=.652$, $p=.012$). However, these findings should be interpreted with caution due to the small sample size in this study and the variability of the rating scales used to assess change in VH.

Table 6.4. *Spearman's correlations between changes to functional activation and visual hallucination rating changes following active and sham stimulation.*

	Active Stimulation					Sham Stimulation				
	Ventral Extrastriate	V1/V2	Fusiform	Thalamus	Precuneus	Ventral Extrastriate	V1/V2	Fusiform	Thalamus	Precuneus
			r_s					r_s		
NPI^{hall}	.341	**.571***	.341	.309	.191	.090	.141	.105	.252	.396
Frequency	.028	.085	-.143	-.262	.281	-.356	-.223	-.256	-.281	.011
Severity	.353	**.549***	.392	.510	.118	.431	.353	.392	**.628***	.471
Distress	-.101	-.304	-.135	.216	.135	.114	.071	.188	.470	.186
NEVHI										
Frequency	.425	.275	.457	.392	.378	-.147	-.219	-.028	-.095	-.008
Duration	-.447	-.447	-.447	-.378	-.447	.251	.270	.202	.230	.310
Distress	-.380	**-.629***	-.380	-.103	-.146	.161	.086	.174	**.570***	.052
Irritation	.040	.049	.209	.246	-.054	.290	.259	.266	**.652***	.525

Abbreviations: NPI^{hall}: Neuropsychiatric Inventory visual hallucination subscale; NEVHI: North East Visual Hallucinations Interview. Dark blue represents p<.05, light blue represents rho>.350 but p>.05.

6.3.5 Secondary Outcomes: the effect of stimulation on occipital GABA

No significant changes to occipital GABA+ or GABA+/Cr ratios were observed following either active or sham stimulation (p>.05)(**Figure *6.6***). When comparing changes following active and sham stimulation, a significant overall effect of treatment was observed ($F(1,11) = 19.82$, p=.003), with active stimulation resulting in an overall decrease in occipital GABA+/Cr. However, a significant interaction with both treatment order ($F(1,11)=5.66$, p=.049) and most prominent VH phenomenology ($F(1,11)=10.05$, p=.016) was observed, with the greatest decreases to GABA+/Cr occurring in participants with predominantly simple VH when they had active stimulation in the first week. No significant effect of treatment or interactions with treatment order or primary VH phenomenology were observed in changes to GABA+.

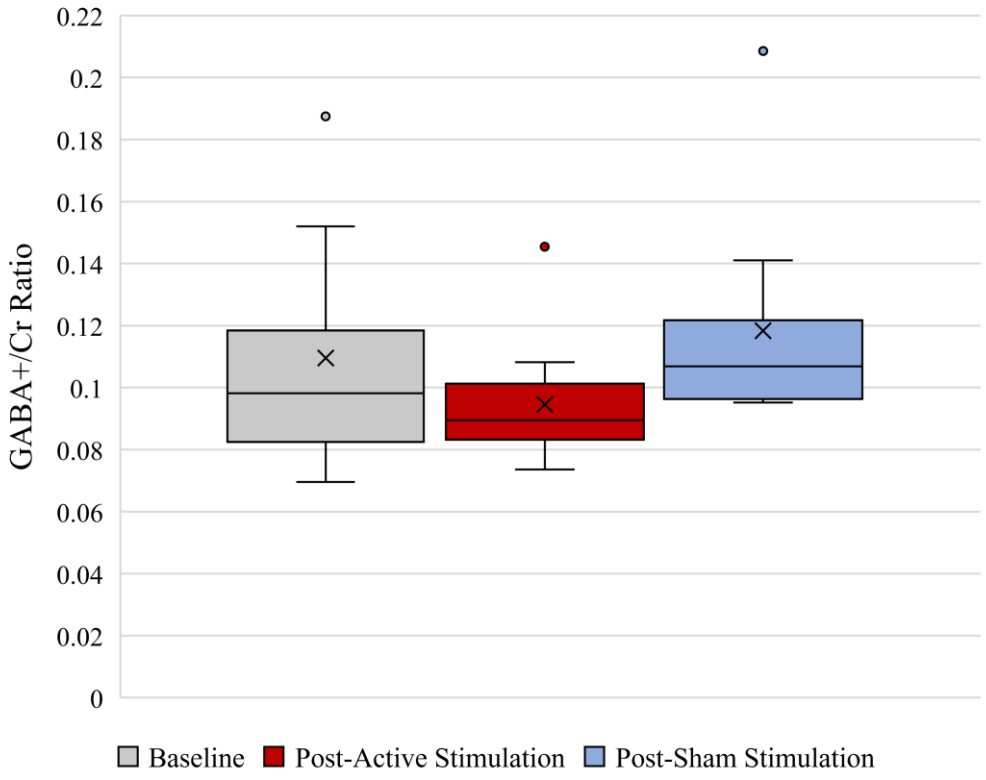

Figure 6.6. *Box Whisker plots demonstrating the mean (x), median (line) and standard deviation of baseline, post-active and post-sham stimulation GABA+/Cr ratios in CBS participants, including outlying data (dots).*

No significant correlations between changes to fMRI activation and GABA+ or GABA+/Cr following active or sham stimulation were observed. Similarly, no significant correlations were observed between changes to VH ratings on the NPI^{hall} or NEVHI and GABA+ or GABA+/Cr following active or sham stimulation. A significant association

between phosphene thresholds and increases to occipital GABA+ following both active and sham stimulation (r_s=-.786, p=.036) and phosphene locations and occipital GABA+ (r_s=.811, p=.027) increases following active stimulation were observed. Nonetheless, neither phosphene thresholds nor number of locations from which phosphenes were elicited had any impact on the response to treatment, and when entered into a backwards regression, neither were found to be significant predictors of change to GABA+ following stimulation (F(2,8)= .320, p = .738, R^2=.096).

6.3.6 Feasibility and Tolerability of tDCS

Overall, tDCS was well tolerated by the participants in this study, with no significant lasting side effects reported. One participant requested that stimulation be terminated prematurely due to discomfort during one session of tDCS, though this participant tolerated all previous and further sessions of stimulation well and discomfort ceased immediately once the stimulation was ended. One further participant declined the last day of stimulation during the sham treatment week due to headaches and fatigue, although it was not clear whether this was directly related to stimulation.

Side effects reported by participants following each treatment week are described in **Table *6.5***. The most frequently reported side effect during both weeks of stimulation was a tingling sensation from one or more of the electrodes, with a smaller proportion of participants reporting an itching or a 'hot/burning' skin sensation during stimulation, regardless of whether it was active or sham. Headaches were the only side effect found to be significantly associated with active compared to sham stimulation (z = -2.45, p=.014) occurring in 43.8% of participants following active stimulation, compare to only one participant (6.3%) following sham.

Table 6.5. *Frequency (Percentage) of side effects reported by participants following active and sham stimulation (n=16). Significant differences calculated using Wilcoxon signed ranks test are highlighted in bold (p<.05).*

	Active Stimulation	**Sham Stimulation**	**Sig. (*p*) (df = 15)**
Headaches	7 (43.8%)	1 (6.3%)	**.014**
Tingling	12 (75%)	11 (68.8%)	.564
Scalp Pain	0	0	
Itching	7 (43.8%)	9 (56.3%)	.157
Hot/Burning Sensation	5 (31.3%)	6 (37.5%)	.564
Skin Redness	0	0	
Sleepiness	4 (25%)	3 (18.8%)	.705
Nausea	0	0	
Trouble Concentrating	0	0	
Other	0	2 (12.5%)	.157

The overall severity of the side effects reported by participants following active and sham stimulation is shown in **Figure *6.7.*** Overall, side effects experienced by participants were reported as moderate to low in severity (≤ 7/10). Of the participants who reported headaches following stimulation, three participants rated these as severe (>7), which were only following active stimulation, although two of the three stated that they had a history of regular, intense, headaches prior to participation. One participant reported a severe (9/10) burning sensation on both active and sham stimulation weeks, but described this as transient and only occurring for the first 10-20 seconds of stimulation and was therefore tolerable and not necessitating termination of stimulation. Severe fatigue/sleepiness (9/10) was reported by one participant, and only following active stimulation. 'Other' side effects endorsed by participants included 'blurred vision/tired eyes' and insomnia, but were only reported following sham treatment. No participants reported scalp pain, skin redness, nausea, or trouble concentrating following either treatment week.

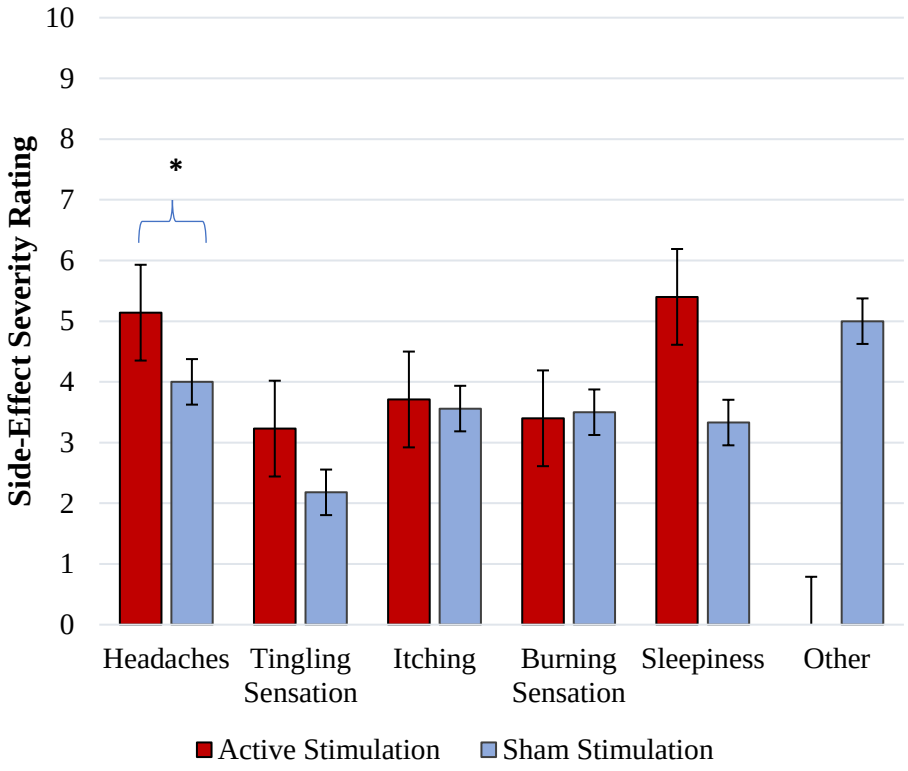

Figure 6.7. *Mean (+/- SEM.) severity ratings of side effects reported by participants following active and sham stimulation (0-10). *p<.05.*

Inspection of blinding integrity of the treatment found that neither participants nor investigators were significantly more likely to guess the correct order of the stimulation (p>.05) (**Figure *6.8***).

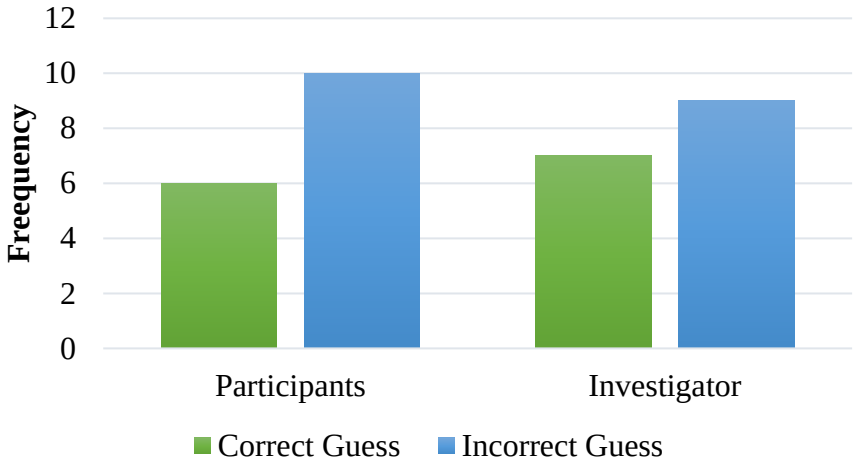

Figure 6.8. *Frequency of correct and incorrect guesses of treatment order by participants receiving stimulation and the investigator administering it. Correct guesses were needed for both treatment weeks to avoid false positives caused by participants giving the same answer for both weeks.*

6.4 Discussion

The primary aim of this chapter was to investigate the feasibility and utility of repeated inhibitory occipital tDCS for the treatment of VH in CBS. This study represents, to the best of our knowledge, the largest intervention study performed in CBS to date, and will therefore provide a vital starting point for the development of future treatments.

6.4.1 tDCS as a therapeutic intervention in CBS

Active 1mA inhibitory stimulation of the primary visual cortex over four-consecutive days was found to produce a significant reduction in the frequency of VH in people with CBS, independent of treatment order and whether participants experienced simple or complex VH. In real terms, as the majority of participants involved in the study reported VH occurring multiple times a day, reductions to frequency translated to VH only being reported 1-2 times a day or every few days as rated on the NEVHI following active stimulation. Consequently, as VH frequency was one of the primary outcome measures of this study, this finding supports our hypothesis that inhibitory stimulation would produce a beneficial therapeutic effect on VH in CBS. Furthermore, this finding is comparable to previous investigations into the use of tDCS for the remediation of VH, which found that repeated sessions of inhibitory tDCS of the primary visual cortex resulted in a reduction to or complete cessation of VH in patients with schizophrenia and major depression (Koops & Sommer, 2017; Shiozawa et al., 2013).

While a positive effect of active stimulation was observed on ratings of distress on the NPI, this was highly dependent on both the order in which treatment was received and the most prominent VH phenomenology reported by the participant. As such, participants with predominantly simple VH reported the greatest reduction in distress, but only when active stimulation was received during their second week. As identified in **Chapter 4**, CBS participants with predominantly simple VH reported overall greater distress towards VH, therefore it is possible that reductions noted following stimulation were likely to be comparatively greater in these participants than those with complex VH who already reported relatively low ratings of distress. Furthermore, as participants received both active and sham stimulation during the study, a tendency for participants to rate improvements due to active stimulation on the second week as higher may be due to their ability to compare it to their subjective experiences during the first week. As participants were aware that they would receive placebo stimulation during the study, participants may have subsequently provided

more cautious ratings of their VH following their first week of stimulation, particularly with regards to highly subjective measures of emotional impact, which may have affected the ability to accurately assess relative changes following active stimulation. Nonetheless, no significant changes to ratings of distress on the NEVHI (which provides a less restrictive rating scale than the repurposed caregiver rating scale on the NPI) were observed and therefore these findings should be interpreted with caution.

In addition to changes to VH detected on the primary NPI^{hall} and NEVHI outcome measures, a significant improvement to patient perceptions of VH intrusiveness was observed on the PPC-VH following active stimulation compared to sham. Ratings of changes to intrusiveness on this scale were based on patient reports throughout each stimulation week of qualitative aspects of VH phenomenology, such as their size and intensity, and subsequently how easy they were to ignore. Intrusiveness is an aspect of VH which receives limited representation on existing scales of VH. However, qualitative reductions to intrusiveness were reported to represent a clinically significant change to participants during the pilot study (see **Chapter 5**). Consistent with the findings of the pilot study, active stimulation appeared to result in a significant reduction in the intrusiveness of VH, with participants reporting that VH were easier to ignore and dominated less of their attention, therefore indicating that this aspect of VH should be considered in future treatment investigations. Furthermore, a significant reduction in perceived frequency of VH following active compared to sham stimulation was detected using the PPC-VH, which was directly associated with reductions in intrusiveness, and may suggest that this represents not only a statistically significant change to VH but also a clinically significant improvement to participants.

The improvements to VH observed in this study are in contrast to those of Elder et al (2019), who noted that active inhibitory occipital stimulation over four consecutive days did not lead to any significant beneficial effect on VH when compared to sham in patients with DLB. Despite this, caregiver-based ratings of VH severity improved following both active and sham stimulation, indicating that study participation may have been beneficial to these patients. Comparatively, the current study noted an improvement to both participant ratings of VH severity on the NPI and ratings of distress and irritation towards VH on the NEVHI following both active and sham stimulation. Similar to Elder et al (2019) this may indicate a positive benefit of study participation, particularly on the emotional impact of VH, in people with CBS.

Previously, social isolation has been implicated in both the formation of CBS hallucinations, predisposing a state of overall sensory deprivation and mental vulnerability (Cole, 1992; Menon et al., 2003), and their exacerbation, with social interaction and support groups suggested as effective methods of attenuating VH (Eperjesi & Akbarali, 2004; Rovner et al., 2002). In the present study, participants received two weeks of daily study contact, including home visits, in which they were actively encouraged to describe and discuss the impact of their VH. While the impacts of social isolation on participants in this study were not actively investigated, it is possible that improvements to emotional aspects of their VH experience observed following both stimulation weeks may have been the result of increased social interaction. Furthermore, study participation allowed many participants access to further information about CBS as a whole, including reassurance regarding common concerns such as links to psychiatric illness and dementia. As overall knowledge of CBS and quality of information has previously been associated with a decreased likelihood of negative outcomes in CBS (Cox & ffytche, 2014) this may indicate the value of increased social interaction and, potentially, the utility of support groups and talking therapies in attenuating the impact of VH.

In line with previous studies, tDCS was also found to be well tolerated by all participants, with no significant or severe adverse effects reported (Brunoni et al., 2012). Comparable to previous literature reviews of common side effects, participants were most likely to report mild tingling or itching sensations, headaches, and moderate fatigue during both active and sham stimulation (Brunoni et al., 2012; Poreisz et al., 2007). In the case of this study, headaches were the only symptom significantly related to active over sham stimulation. However, the severity of these was generally moderate-to-low and all participants reported that they were transient and responsive to over-the-counter analgesics. Furthermore, repeated sessions over consecutive days were not found to increase the likelihood of severe adverse effects, and provides support for the tolerability of the current density used in this study. Overall, both active and sham stimulation were observed to produce comparable sensations with only minimal discomfort in line with previous studies (Brunoni et al., 2012; Gandiga et al., 2006). Reflective of this, participants were unable to reliably differentiate active from sham stimulation, supporting the integrity of blinding in this study and is a strength of the overall design.

Furthermore, investigation of visual function including visual acuity and contrast before and after stimulation found no significant changes to vision following either active or

sham stimulation. While this is in contrast to a previous study which observed a reduction in static contrast sensitivity following cathodal occipital stimulation (Antal et al., 2001), that study was performed in healthy volunteers with normal or corrected-to-normal vision, and therefore is unlikely to be comparable to the visually impaired participants in this study. As worsening visual function has been associated both with the onset or worsening of VH (Gold & Rabins, 1989; Scott et al., 2001; Teunisse et al., 1996) and poorer independence and quality of life (Mitchell & Bradley, 2006; Rovner et al., 2002), any intervention designed to treat CBS should be mindful of any effect it may have on a patient's remaining vision. In the case of tDCS, however, the lack of significant difference between active and sham stimulation suggests that this may not be a problem for this treatment. Nevertheless, as a marginal although not significant decrease in visual acuity was noted following active stimulation in this study, future larger studies must consider this in case the lack of significant findings in this domain were a result of small sample sizes.

As such, this study indicates that future investigation of the clinical utility of tDCS as a means of treating VH in CBS is both feasible and valuable, as this may present a relatively low-cost, low-intensity alternative to pharmacological interventions.

6.4.2 Neurophysiological response to tDCS

The secondary aim of this study was to investigate the effect of inhibitory stimulation of the occipital cortex on visual cortical activity, in order to better understand both the mechanisms underlying VH and the physiological effects of stimulation.

Visual cortical BOLD activation

Based on previous research, this study predicted that inhibitory stimulation of the primary visual cortex would result in changes to visual cortical fMRI BOLD activation observed during an eye-movement task (i.e. Alekseichuk et al., 2016; Antal et al., 2012). Despite this, no significant differences in visual cortical BOLD activation were observed following active or sham stimulation.

As noted in **Chapter 4**, people with CBS demonstrate altered functional BOLD activation in response to an eye-movement task when compared to non-hallucinating controls, therefore demonstrating a different baseline physiological state on which tDCS must work, compared to previous studies performed in healthy volunteers (Aleksheiuk et al., 2016; Antal et al., 2012). As cathodal tDCS has been observed to work by reducing overall membrane potentials

in the targeted region, this may be reflected in an overall reduction in the likelihood of spontaneous activity arising in the cortex (Brunoni et al., 2012; Stagg & Nitsche, 2011). Consequently, this reduction in spontaneous cortical activity may lead to a reduction in the frequency of VH, as observed in this study. As fMRI in this study was performed when participants were not hallucinating (thus evaluating trait rather than state changes), using a task-based paradigm, it is likely that this protocol would not be able to adequately detect subtle changes to the propensity of the cortex to produce this spontaneous activity. In addition, as scans were not performed during active VH, it is not possible to detect whether tDCS resulted in changes to VH state activity, which may provide further indication of any physiological relationship between tDCS and changes to VH observed in this study.

An additional consideration is that the BOLD signal collected from fMRI is an indirect measure of neuronal activity, which is dependent on blood flow and vascular reactivity (Ho et al., 2008; Logothetis, 2008), and therefore may not be an accurate representation of changes to excitability. Furthermore, even minor sensory stimulation (such as that resulting from the eye-movement task used in this study) detected via BOLD activation may mask spontaneous cortical activity related to VH (Ringach, 2009). Further research may wish to utilise more temporally sensitive measures of dynamic activity, such as EEG, in order to interrogate the effect of tDCS on spontaneous cortical activity. Utilising electrophysiology in conjunction with fMRI may also provide a means of investigating the role of cortical network connectivity in both the production of spontaneous activity linked to VH (Ringach, 2009) and its response to stimulation.

Visual Cortical GABA concentrations

The current study predicted that inhibitory stimulation of the primary visual cortex would result in a significant increase in relative concentrations of the inhibitory neurotransmitter GABA within the stimulated region. However, while no significant differences were noted as a consequence of active stimulation, GABA+/Cr appeared to be marginally reduced when compared to sham. As decreased GABA is a marker of decreased inhibitory activity this appears contradictory to both the positive treatment effects reported by participants and the current understandings of how cathodal stimulation works. Despite this, similar decreases in cortical GABA concentration were observed in a previous study following cathodal stimulation, in which the authors proposed that this may have been the result of the close biochemical relationship between GABA and glutamate (Stagg et al., 2009). Significant

decreases to glutamate, an excitatory neurotransmitter, have been observed in the stimulated cortex following cathodal tDCS (Stagg et al., 2009), with aftereffects significantly dependent on the modulation of glutamatergic synapses (Nitsche et al., 2003). However, glutamate provides the only synthetic pathway for the production of GABA in the human cortex, via the glutamic acid decarboxylase enzyme, and therefore a significant reduction in the availability of this enzyme may therefore lead to a subsequent decrease in GABA (Stagg & Nitsche., 2011). As glutamate was not quantified in this study, due to limitations of the available equipment and procedures, it is possible that cathodal tDCS may have led to a significant decrease in excitatory glutamatergic transmission (resulting in a related decrease to GABA), which may have had a subsequent effect on the frequency of VH in these participants. As altered glutamatergic transmission has been previously implicated in the production of VH across pathologies such as DLB, schizophrenia, and drug induced hallucinosis (Brawley & Duffield, 1972; Friston, 1998; Khundakar et al., 2016), this may provide a better indication of changes to excitability within the visual cortex and how this is affected by neuromodulatory stimulation.

6.4.3 Associations between VH and cortical activity changes following stimulation

No correlations were observed between changes to VH frequency and changes to BOLD activation or GABA+/Cr in any region, therefore it is currently unclear whether these aspects are related. However, participants who reported greater changes to aspects of their VH as measures by the NPI^{hall} and NPI severity scales also demonstrated greater increases to V1/V2 BOLD activity following active stimulation. Referring back to the discussion in **Chapter 4** this may support the postulate that people with CBS have higher resting state visual cortical activity (resulting in a lower change in BOLD activation during eye movements), in which a reduction to this baseline via inhibitory stimulation may be reflected in BOLD activation approaching a level more similar to that of non-hallucinating controls. Alternatively, this may also support the signal-to-noise ratio hypothesis discussed in **Chapter 4**, as an increase in V1/V2 activity following stimulation would reduce the overall signal-to-noise ratio resulting in spontaneous activity being more likely to be filtered out as background noise and reducing both the frequency and overall impact of VH. One potential problem with this explanation, however, is that an increase in cortical activity following active inhibitory stimulation appears to be counterintuitive. However, it should be noted that a drawback of fMRI is its relative inability to accurately distinguish between excitatory and inhibitory activity, with an

increase in inhibitory activity resulting in a similar increase in BOLD magnitude to excitatory activity (Logothetis, 2008). As such, an increase in V1/V2 activity following cathodal tDCS may represent an increase in regional inhibitory activity, which is then associated with a corresponding reduction in VH severity reported by participants.

Nevertheless, the polarity of stimulation, and in particular cathodal stimulation, has sometimes been observed to reverse at higher current densities (above 0.057mA/cm^2), producing an excitatory rather than inhibitory effect (Batsikadze et al., 2013) and may provide an alternative explanation for the functional activity changes observed. As the current density in this study (0.29mA/cm^2) was much higher than that tested by Batsikadze and colleagues, it is possible that the stimulation provided to the primary visual cortex was high enough that it inverted the current's polarity resulting in an excitatory effect and a consequent increase to V1/V2 activity. Despite this, the previous study was performed on the motor cortex and assessed using measures of excitability via TMS (Batsikadze et al., 2013) and therefore may not be comparable to changes detected in the visual cortex using fMRI. In addition, as changes to V1/V2 activity following stimulation were not found to be significant either in isolation or when compared to sham stimulation, this explanation is highly speculative.

A correlation between improvements to measures of VH severity and emotional impact and increases in thalamic BOLD activity was also noted exclusively following sham stimulation. As sham stimulation does not produce a current able to induce neuromodulation it is unlikely that these changes were as a direct consequence of the stimulation. Furthermore, while tDCS is able to modulate activity in surface structures of the brain, current flow becomes more dispersed as it travels through the cortex, making the modulation of deeper cortical structures like the thalamus difficult (Brunoni et al., 2012). Nevertheless, one potential explanation for this may be the role of the thalamus in providing a gating function for sensory stimulus, which has been found to be altered under hypnosis (Müller et al., 2013). This suggests that thalamic activity may be susceptible to alteration via suggestion and may provide evidence of a physiological response to the placebo condition corresponding with perceived improvements to emotional aspects of VH.

Conversely, this finding may also be indicative of connectivity changes across the visual system associated with VH presentation and severity in general. Previously, increased thalamic hyperperfusion and preserved connectivity has been noted in people with CBS

compared to non-hallucinators (Adachi et al., 2000; Martial et al., 2019), with the pulvinar of the thalamus suggested to regulate visual attention and excitation of this region linked to the release of dopamine and the production of VH. Functional connectivity changes between the thalamus and the primary visual cortex have also been indicated in the production of VH, in both integrative and attentional models (Adachi et al., 2000; Collerton et al., 2005; Diederich et al., 2005), therefore variability in the activity of these regions as indicated by fMRI activation in this study may play an intrinsic role in the modulation and variability of VH intensity and severity (and its subsequent emotional impact) within people with CBS. However, as noted in **Chapter 4**, further study into functional connectivity in CBS, and how tDCS may affect this, is necessary.

6.4.4 Strengths and Limitations

A strength of the current study is in the robust placebo-controlled crossover design, which offers the opportunity to better interrogate the effect of stimulation on specific surrogate outcomes while eliminating much of the variation between participants.

While small, the sample size of this study constitutes the largest intervention study of its type performed to-date in CBS. Furthermore, a positive effect of tDCS treatment was observed and was found to have a medium-to-large effect size, indicating that this may represent a reasonably robust and clinically significant finding translatable to larger samples.

Nevertheless, while no specific differences in visual-cortical activity were observed between participants with predominantly simple or complex VH (see **Chapter 4**) heterogeneity in the presentation of VH symptoms (and the high incidence of participants reporting variability in the types of VH they experienced on a regular basis) within this sample may produce a confounding effect on treatment outcomes and may explain why no significant changes were observed in certain domains, both with regards to visual cortical activity and ratings of VH. Consequently, future research studies may need to explore ways to more robustly delineate CBS groups depending on their symptom presentation, including continuous, episodic, simple, and complex hallucinators, in order to assess any differential effect of stimulation on each subtype.

Limitations to Outcome Measures

Limitations of the primary outcome measures used in this study must also be taken into consideration. Currently, no dedicated assessment tool has been developed for VH aimed

at assessing clinically significant or relevant changes to VH symptoms following treatment. The statistically significant change in frequency noted following active stimulation is likely due to a large difference in the occurrence of VH (i.e. from multiple times a day to once every few days). However, smaller changes, such as to VH duration, may have been more difficult to detect due to lack of sensitivity by the respective scales. Similarly, as previously discussed, current VH scales do not have an adequate provision for assessing factors such as the intrusiveness of the hallucinations, including how much space or attention they take up or how difficult they are to ignore. Due to the retained insight, lack of cognitive impairment, and overall reduced vision in individuals with CBS, intrusiveness is likely to play an important role in how disruptive VH are to everyday life and to their emotional impact. While this study attempted to quantify this by assessing the participant's perceived level of change in this domain, this scale has not been fully validated and therefore no robust conclusions can be made. Nonetheless, preliminary validation, using relationships between the novel scale measures and related NEVHI and NPI^{hall} subscale items collected in these participants, indicates promising construct and concurrent validity. Furthermore, use of the new scale indicates that intrusiveness may represent an important and clinically significant domain that should be investigated further with regards to VH, with this study observing it to be significantly associated with both VH frequency and feelings of distress towards VH. However, future scale development must be performed to effectively interrogate the reliability of the scale, including assuring inter-rater reliability, and to ensure that it has enough sensitivity to detect clinically meaningful changes to symptoms.

A further consideration regarding the primary outcome measures is the reliability of self-report for a symptom as subjective as VH. Despite retaining insight and absent of cognitive decline, which often presents problems for the accurate representation of VH in conditions such as DLB, PDD and schizophrenia (i.e. Brunelin et al., 2012; Elder et al., 2019), participants may still have been unable to accurately report all aspects of their VH. For instance, the study asked participants to make a judgement of aspects such as the frequency, duration, and severity of VH over the month preceding participation in order to produce a baseline score against which to compare treatment. It is possible that participants may have been prone to over-estimating or misremembering these factors, particularly if VH had been worse or better than normal in the days directly before assessment. While a strength of the present study was the detailed VH diaries completed by participants during each treatment week, future treatment studies should endeavour to have participants complete detailed VH

diaries in the weeks preceding treatment as well, in order to collect a more accurate representation of their baseline symptom presentation, including any fluctuations in their severity and impact. As initial inspection of questionnaire data showed particular variability in the emotional impact of VH at different time points independent of treatment, this may require extra consideration when assessing treatment outcomes.

Limitations to Stimulation

Cortical atrophy and structural lesions have previously been observed to distort the current flow of tDCS and may consequently affect the distribution of current through the targeted structures and the overall treatment effectiveness (Brunoni et al., 2012; Minjoli et al., 2017). Visual cortical atrophy has been observed in the form of bilateral reductions to both grey and white matter following sight loss due to eye disease such as AMD (Boucard et al., 2009; Hernowo et al., 2014), while volumetric reductions in the visual cortex of hallucinating patients with DLB and PDD have also been reported (Goldman et al., 2014; Ibarretxe-Bilbao et al., 2011; Sanchez-Castaneda et al., 2010).While investigation into patterns of structural atrophy have not been specifically performed in CBS, the findings from other hallucinating groups and patients with eye disease implies that patients with CBS are likely to demonstrate some level of volumetric reduction in the visual cortex. As a consequence, it is possible that the effect of tDCS may have been impacted by these changes and may explain why no significant change in neurophysiological activity was detected in the current study. Similarly, this may also have implications for who tDCS may be an appropriate and effective treatment for, and may further explain why some participants report no change to symptoms on either week. In this way, while the present study estimates the location of the primary visual cortex using cranial measurements (10% above inion), it is possible that inaccuracies in electrode placement may occur due to individual anatomical differences, resulting in the application of current to slightly differing regions. Due to the focal nature of the stimulation performed in this study, which used smaller electrodes than previous similar studies (i.e. Elder et al., 2019; Koops & Sommer, 2017; Shiozawa et al., 2013) who used larger electrodes which permitted stimulation of a greater area (albeit resulting in a more diffuse current), this may have had a greater impact on the effectiveness of stimulation. Therefore, future research should integrate structural analysis into both the localisation of stimulation targets in the individual, and in order to control for confounding variables such as cortical atrophy.

Finally, the current study did not assess the longitudinal effects of stimulation, meaning that it is still unclear as to how long any beneficial after-effects may remain. As repeated tDCS reportedly causes changes to long-term potentiation and plasticity within interneurons in the targeted region (Stagg & Nitsche, 2011) this may also mean that changes in cortical activity, such as those measured by GABA concentrations, may be more gradual over time and may explain why no change was detected immediately following stimulation in this study. Furthermore, a limitation of crossover studies is the potential of carry over effects impacting treatment responses during the second week. While the current study analysed the impact of treatment order on changes to VH ratings and found no significant effect, it is possible that lingering effects of stimulation may have still impacted participant responses. As such, future treatment studies will need to employ longitudinal follow-up of participants following treatment, in order to assess both the extent of any beneficial treatment effects and any long-term neurophysiological effects of stimulation.

6.4.5 Future Directions

Neurophysiological investigation of changes to visual cortical activity were assessed using neuroimaging in the present study. However, analysis of electrophysiological data collected before and after stimulation may present another means of assessing the temporal effects of stimulation in relation to VH in CBS. Cathodal tDCS has been observed to impact spontaneous neuronal oscillations in healthy participants, in the form of theta and delta band increases (Ardolino et al., 2005) and increased occipital alpha (indicative of decreased cortical excitability) (Puanhvuan et al., 2013). As generalised decreased alpha-power, altered theta activity and generalised cortical slowing has previously been observed in CBS (Hanoglu et al., 2016; Lorberboym et al., 2002; Pliskin et al., 1996), tDCS may have an observable effect on cortical oscillations in these participants, providing further indication of the interaction between cortical activity and VH. Advances in the development of concurrent tDCS-EEG devices also presents an opportunity for detailed modelling of current flow and activity modulation during stimulation, which may further elucidate the mechanisms involved in CBS by offering a more nuanced insight into dynamic cortical functioning than more spatially focussed imaging (Brunoni et al., 2012; daSilva Morgan et al., 2018).

6.4.6 Conclusions

The findings of this study indicate that 1mA active cathodal tDCS of the primary visual cortex over four consecutive days results in a significant decrease in the frequency and

overall perceived intrusiveness of VH in people with CBS when compared to sham stimulation. This supports the findings of the pilot study (**Chapter 5**) and suggests that tDCS may present a feasible beneficial treatment option for CBS hallucinations with few significant side effects. However, measures of visual cortical activity, including BOLD activation and GABA concentrations, were not found to be significantly affected by stimulation, which may suggest the presence of other underlying mechanisms on which tDCS acts in order to produce the treatment effect observed. Larger, multi-centre trials should be performed in future in order to assess the efficacy of tDCS as a treatment for CBS further, including investigation of longitudinal after-effects and the impact of tDCS on aspects of cortical functioning such as connectivity, glutamatergic transmission and cortical oscillations.

Chapter 7 Overview and Conclusions

The primary purpose of this thesis was to investigate the role of altered visual cortical activity in Charles Bonnet syndrome, in order to further understand the mechanisms involved in the production of VH in eye disease. From this, we aimed to investigate a novel treatment in the form of non-invasive brain stimulation as a means of targeting altered cortical activity in CBS, in order to determine whether this may produce beneficial effects on aspects of VH such as their frequency, duration, severity, and emotional impact.

Previous research into CBS is currently limited, with past studies predominantly consisting of case reports and small sample sizes (see **Chapter 1**). Consequently, this has hindered both the understanding of why CBS occurs in some patients and not others, and the development of effective treatments and interventions. As such, the studies described in this thesis constitute some of the largest of their kind and the findings will provide a solid basis for future research into both the mechanisms underpinning CBS and the development of clinically effective treatments.

7.1 Summary of Main Findings

The investigations described in this thesis provide evidence for altered cortical activity in people with CBS when compared to individuals with eye disease without VH, which may contribute to the occurrence of VH. For detailed interpretations and critique of the individual findings please refer to the discussion sections of **Chapter 4** (Demographics and group comparisons), **Chapter 5** (tDCS pilot study), and **Chapter 6** (tDCS treatment crossover trial).

7.1.1 Visual Cortical Activity in CBS

In **Chapter 4**, the group comparison study observed evidence of lower visual cortical BOLD activation in people with CBS outside of hallucinatory periods. However, this reduced activation was noted across key regions previously associated with activity increases during hallucinations (ffytche et al., 1998). While in isolation this finding somewhat contradicts the deafferentation hypothesis, which suggests that VH arise following sight loss due to hyperexcitability in the visual cortex, this decreased fMRI activation was also associated with greater hyperexcitability in the form of lower phosphene thresholds. One explanation for this finding may be that people with CBS demonstrate a higher signal-to-noise ratio during hallucination-free periods, meaning that internally generated spontaneous activity is more

likely to be allocated inappropriate attention, allowing activity to be perceived as a 'false alarm' and enter conscious perception as VH. Conversely, lower BOLD activation during the eye movement task in CBS participants may indicate higher overall visual cortical activity, resulting in a reduced overall change in cortical response to eye-movements, and supporting traditional models of deafferentation. In both cases, the cortex of individuals with CBS may be primed to respond to even minimal amounts of external stimulation, and may explain the positive relationship between BOLD activation and phosphene thresholds during TMS in this group. In addition, while no significant differences were observed between CBS and Controls, both hyperexcitability (as measured by TMS) and GABA+/Cr ratios were found to be more variable in people with CBS. Furthermore, increased hyperexcitability in the form of lower phosphene thresholds were significantly associated with more severe VH, replicating similar findings observed in DLB (Taylor et al., 2011).

7.1.2 Using tDCS as a treatment for CBS

In the treatment pilot study (**Chapter 5**), 1mA cathodal tDCS over the early visual cortex was observed to result in qualitative changes to VH content as described by CBS participants with continuous hallucinations. These changes, including reductions in the size, movement, intensity and intrusiveness of VH, were described by 4 out of the 6 participants tested as representing significant improvements to their VH, therefore indicating that these tDCS parameters may produce a beneficial therapeutic effect on VH in CBS.

A placebo-controlled crossover study (**Chapter 6**) confirmed that active 1mA cathodal tDCS of the primary visual cortex resulted in a significant reduction in the frequency of VH compared to sham stimulation, with participants also reporting a significant decrease to their perceived level of intrusiveness of VH. However, neurophysiological investigation of post-stimulation cortical activity observed no significant changes to fMRI BOLD activation or GABA+/Cr concentrations in the visual cortex, suggesting that tDCS may work on different mechanisms associated with VH in the visual cortex.

7.2 Clinical Implications

The findings of these studies provide both novel and valuable insight into the mechanisms involved in the production of VH following sight loss, and subsequently the potential methods of treating them.

Differential cortical activity, as observed using fMRI, and the relationship between hyperexcitability and the severity of VH (assessed using TMS), further supports the role of bottom-up mechanisms in CBS as has been previously postulated (Collerton et al., 2005; ffytche et al., 1998; Menon et al., 2003). Nevertheless, the seemingly reduced level of visual cortical activity observed in CBS and the lack of evidence for altered inhibitory transmission (in the form of GABA concentrations) suggests that deafferentation and bottom-up explanations alone may be insufficient. Alterations to how the brain filters out or interprets internally generated spontaneous activity may be an important factor in the production of VH in CBS, and such alterations have been previously linked to changes in the serotonergic, dopaminergic, and cholinergic systems in other hallucinating pathologies (Galvin et al., 1999; Manford & Andermann, 1998; Peled & Geva, 2000; Yousif et al., 2016). As such, future investigations may need to look at specific alterations within these systems in CBS, and may have implications for the development of pharmacological interventions aimed at targeting their dysfunction which may prove beneficial to people with CBS.

Notably, the tDCS treatment study detailed in this thesis provides a strong justification for the future investigation of non-invasive inhibitory brain stimulation as a beneficial intervention for people with CBS. While the neurophysiological mechanisms that tDCS acts on in relation to VH are still unclear, the observation of a significant improvement in the frequency and perceived intrusiveness of VH following active treatment compared to placebo is an important finding. Treatment studies in CBS are currently sparse, and therefore therapeutic options for patients are limited, providing little aid for the estimated one-third of people with CBS who find VH to be distressing or disruptive to their daily lives (Cox & ffytche, 2014). Consequently, the positive findings of this trial may provide a promising therapeutic alternative for people with CBS with relatively few side effects, with the stimulation parameters tested here providing a realistic starting point for future multi-centre clinical trials.

Furthermore, while this thesis focuses on VH in eye disease and following sight loss, the findings of this research will help to provide further insight into the aetiology of VH as a whole, potentially aiding research into VH in other pathologies such as PD and DLB, in which sight loss and visual perceptual dysfunction are either co-existing conditions or pervasive symptoms (Holroyd & Wooten, 2006; Mosimann et al., 2004; Onofrj et al., 2006; Weil et al., 2016).

7.3 Critique and Future Directions

The studies detailed in this thesis provide novel information regarding VH using previously unused techniques in the study of CBS, however there are still notable gaps in our understanding of the mechanisms involved in VH following sight loss which should be addressed in future investigations.

As discussed in **Chapter 4**, assessing the role of aspects of functional, structural and network connectivity in CBS may help to provide greater elucidation of the cortical activity alterations observed in this study. Tentative evidence of connectivity changes has come from a case study of CBS, with evidence of greater functional activity between the precuneus and secondary visual cortex when compared to eye-disease controls (Martial et al., 2019). Changes in long-range and short-range connectivity and coherence between visual cortical and further regions has also been associated with VH in other hallucination studies (Carhart-Harris et al., 2016; ffytche, 2008; Hare et al., 2017; Yao et al., 2014). Nevertheless, this area is still lacking investigation in CBS.

Relevant to this, VH models, such as the General Perception and Attention Deficit (PAD; Collerton et al., 2005), integrative (Diederich et al., 2005), and Attentional Control (Shine et al., 2011) models, propose that the interaction between visual and attentional systems may be key in the formation of VH, with the suggestion that a combination of impaired attentional and perceptual processing may be necessary for VH to occur. As such, several VH-prone pathologies, such as PD and LBD, demonstrate significant dysfunction to visuo-perceptual and attentional processing (Meppelink et al., 2009; Mosimann et al., 2004; Onofrj et al., 2006; Taylor et al., 2011), indicating that the role of these cortical networks may be more pertinent in development of VH in these patients. Nevertheless, the role of visuo-perceptual and attentional networks in CBS have yet to be investigated, thus it is currently unclear what contribution these may have to VH in these patients.

The current studies have also further highlighted the need for unified diagnostic criteria for the assessment of CBS. Inconsistent and contradictory diagnostic criteria (detailed in **Chapter 1**) along with an overall lack of clinical awareness surrounding CBS (Cox & ffytche, 2014) has impeded previous investigation of both the causes of and potential treatments for this condition. While the current studies have attempted to mitigate this by ruling out potentially confounding conditions which may underpin or contribute to VH, along with independent assessment of cases by a clinical specialist (Df), the overall lack of clarity

in this area makes it difficult to determine how ‘pure’ any sample is in CBS research. As such, the future of CBS research is likely to require greater scrutiny of how CBS is diagnosed and the extent to which certain criteria, such as level of visual acuity or the presence of formed or complex VH, are necessary for a positive diagnosis. Inherent in this may also be a need for the distinct classification of potential subtypes of CBS, such as patients experiencing continuous hallucinations versus episodic, bilateral vs unilateral, or those with complex vs simple phenomenology, with such stratification potentially aiding investigation of the mechanisms involved in their production and the development of more effective treatments. Furthermore, improving awareness of CBS within both clinical and public settings, by providing clear information to medical personnel and patients alike, will help to improve both patient outcomes and strengthen future research (Cox & ffytche, 2014).

Similarly, as highlighted in **Chapter 6**, this thesis has emphasised a distinct need for the development of more sensitive methods for detecting changes to VH in treatment studies. Future research into the development of clinical assessment tools is needed to ensure that they provide the sensitivity to detect not only statistically significant changes to VH, but that these also translate to clinically significant changes to the patient. The development of these tools will likely improve the overall efficacy of treatments for this highly subjective symptom, not only in CBS populations but VH pathologies as a whole.

Appendices

Appendix A. MMSE-Blind

Participant number_____ Date tested_____/____/____

MMSE Total_____

Orientation

Time

1. What day of the week is it? ☐
2. What is the date today? ☐
3. Month ☐
4. Year ☐
5. What is the season? ☐

Allow flexibility when season changes, e.g. for northern hemisphere March = winter/spring: June = spring/summer, September = summer/autumn: December = autumn/winter

Place

6. Can you tell me where we are now? For instance, what county are we in? ☐
7. What is the name of this town (city)? ☐
8. What are two main streets nearby (or near your home)? ☐
9. What floor of the building are we on? ☐
10. What is the name of this place? (*or* What is this address? *If the subject is tested at home*) ☐

If tested at home, the subject must include enough information for post to arrive

Registration

I am going to name three objects. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

11. Name the following three objects taking one second to say each:
Apple, Table, Penny.
Tick which are correct on the <u>first</u> attempt and enter number correct under total

Apple ____
Table ____
Penny ____

	Total	____
If any errors or omissions are made on the first attempt, repeat all the names until the subject learns all three (maximum of five repeats). Record number of repeats (record 0 if all correct on first attempt)	Number of repeats	____
<u>Attention/concentration</u>		
12a) Now I would like you to take 7 away from 100.	93	____
Now take 7 away from the number you get.	86	____
Now keep subtracting 7 until I tell you to stop.	79	____
	72	____
	65	____
Record answers. Score 1 point each time the difference is 7, even if a previous answer was incorrect. Maximum score = 5	**Total**	____
<u>OR</u>	D	____
	L	____
12b)Can you spell the word "WORLD" backwards?	R	____
	O	____
	W	____
	Total	____
The score is the number of letters in the correct order (e.g. dlrow=5, dlorw=3)		
Ask participant both 12a) and b). Only score highest.		

Memory: Recall

13. What were the three objects I asked you to repeat a little while ago?

Apple	____
Table	____
Penny	____
Total	____

Tick each item answered correctly and enter number correct under Total

Expression: Naming

Descriptions of function or approximate answers are not acceptable. Acceptable answers may depend on local usage. Errors include description of function (e.g.' used for telling the time' for watch) and approximate answers.

In the case of approximate answers you should say 'Can you think of another word for it?'

14. **Show pencil**	Pencil	_____
What is this called?		
Show wristwatch	Wristwatch	_____
What is this called?		
	Total	_____

Expression: Repetition

Only one presentation is allowed so it is essential that you read the phrase clearly and slowly, enunciating all the S's.

15. I am going to say something and I would like you to repeat it after me: 'No ifs, ands or buts'. ☐

Code 1 only if entire phrase is correct

Praxis: Ideational

Read the following statement and then hand a sheet of paper to the subject. Make a point of handing to the subject's midline. No repetition of this question is allowed. Speak clearly and slowly having first made sure that you have the subject's full attention.

16. I am going to give you a piece of paper. When I do, take the paper in your *right* hand. Fold the paper in half with both hands, and put the paper down on the floor.

Right hand ____

Folds ____

On floor ____

Total ____

Do not repeat instructions or coach

Score a move as correct only if it takes place in the correct sequence.

Tick each correct move and enter number correct under Total

The following sections are removed from the original MMSE as they rely on visual elements.

Language: Reading comprehension

Show sentence 'Close your eyes' and say to participant.

I would like you to read this and do what it says

It is not necessary for the subject to read aloud. If the subject reads the instruction but fails to carry out action, say 'now do what it says'

If failure appears to be due to illiteracy, enquire whether the subject learned to read.

17. Close your eyes ☐

Writing: Spontaneous

☐

18. Write a complete sentence on this sheet of paper.

Spelling and grammar are not important, but the sentence must have a subject (real or implied) and a verb. 'Help!' or 'Go away' are acceptable.

Copying

19. Copy this design (pentagon). ☐

Each pentagon should have 5 sides and 5 clear corners and the overlap should form a diamond

Appendix B. Geriatric Depression Scale (GDS)

Geriatric Depression Scale

Sheik & Yesavage. Clin Gerontol 1986; 5: 156

Participant ID:_____

Date of Assessment:_____

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life?	Yes/NO
2. Have you dropped many of your activities and interests?	YES/No
3. Do you feel that your life is empty?	YES/No
4. Do you often get bored?	YES/No
5. Are you in good spirits most of the time?	Yes/NO
6. Are you afraid that something bad is going to happen to you?	YES/No
7. Do you feel happy most of the time?	Yes/NO
8. Do you often feel helpless?	YES/No
9. Do you prefer to stay at home rather than going out and doing new things?	YES/No
10. Do you feel you have more problems with your memory than most?	YES/No
11. Do you think it is wonderful to be alive now?	Yes/NO
12. Do you feel pretty worthless the way you are now?	YES/No
13. Do you feel full of energy?	Yes/NO
14. Do you feel that your situation is hopeless?	YES/No
15. Do you think that most people are better off than you are?	YES/No

Appendix C. Instrumental Activities of Daily Living scale (IADL)

INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (IADL)

M.P. Lawton & E.M. Brody

A. Ability to use telephone

1. Operates telephone on own initiative; looks up and dials numbers, etc.	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone at all.	0

B. Shopping

1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip.	0
4. Completely unable to shop.	0

C. Food Preparation

1. Plans, prepares and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats, serves and prepares meals or prepares meals but does not maintain adequate diet.	0
4. Needs to have meals prepared and served.	0

D. Housekeeping

1. Maintains house alone or with occasional assistance (e.g. "heavy work domestic help")	1
2. Performs light daily tasks such as dish-washing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness.	1
4. Needs help with all home maintenance tasks.	1
5. Does not participate in any housekeeping tasks.	0

E. Laundry

1. Does personal laundry completely	1
2. Launders small items; rinses stockings, etc.	1
3. All laundry must be done by others.	0

F. Mode of Transportation

1. Travels independently on public transportation or drives own car.	1
2. Arranges own travel via taxi, but does not otherwise use public transportation.	1
3. Travels on public transportation when accompanied by another.	1
4. Travel limited to taxi or automobile with assistance of another.	0
5. Does not travel at all.	0

G. Responsibility for own medications

1. Is responsible for taking medication in correct dosages at correct time.	1
2. Takes responsibility if medication is prepared in advance in separate dosage.	0
3. Is not capable of dispensing own medication.	0

H. Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent, bills goes to bank), collects and keeps track of income.	1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
3. Incapable if handling money.	0

Source: Lawton, M.P., and Brody, E.M. "Assessment of older people: Self-maintaining and instrumental activities of daily living." Gerontologist 9:179-186, (1969).

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Appendix D. Neuropsychiatric Inventory hallucinations subscale (NPI^{hall})

Neuropsychiatric Inventory with Caregiver Distress Scale cont'd **NPI-D**

Subject's initials [ ] [ ] [ ] (1 2 fam.) Date of this examination [ ] [ ] [ ] (day month year)

B. Hallucinations

Does the patient have hallucinations such as false visions or voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive, rather we are asking if the patient actually has abnormal experiences of sounds, or visions.

☐ not applicable ☐ no (→ proceed to next screening question) ☐ yes (→ proceed to subquestions)

☐ 1. does the patient describe hearing voices or act as if he/she hears voices?

☐ 2. does the patient talk to people who are not there?

☐ 3. does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)?

☐ 4. does the patient report smelling odours not smelled by others?

☐ 5. does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her?

☐ 6. does the patient describe tastes that are without any known cause?

☐ 7. does the patient describe any other unusual sensory experience?

A-Frequency:

[1] occasionally – less than once per week
[2] often – about once per week
[3] frequently – several times per week but less than every day
[4] very frequently – once or more per day

B-Severity:

[1] mild – hallucinations present but seem harmless and cause little distress for the patient
[2] moderate – hallucinations are distressing and are disruptive to the patient
[3] marked – hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them.

C-Distress: How emotionally distressing do you find this behaviour?

[0] not at all
[1] minimally
[2] mildly
[3] moderately
[4] severely
[5] very severely or extremely

Total Hallucinations (AxB) [ ] [ ]

Appendix E. Adapted North East Visual Hallucinations Interview (NEVHI)

DIRECTIONS FOR ADMINISTRATION:

- Do not use the term 'hallucination', unless term is first used by the participant. Instead, use the term 'experience'.
- There is a series of screening questions which refer to the presence/absence of visual hallucinations and other experiences. Whenever the answer 'Yes' is given, record in as much detail as possible in the box below what they have seen. Prompt participant to report if what they saw moved, its colour, its size, its contour, its shape and where in the field of view it was seen. After description, ask the specific sub-questions for further details about the experience.
- If no screening question is endorsed, miss the following section asking the participant to choose their most distressing visual experience, and ask the final screening question about auditory hallucinations.
- The opening question is for the participant to get comfortable talking about their experience (so write description in relevant screening section). Even if they say no, go through remaining screening items.

1. DO YOU FEEL LIKE YOUR EYES EVER PLAY TRICKS ON YOU? HAVE YOU EVER SEEN SOMETHING (OR THINGS) THAT OTHER PEOPLE COULD NOT SEE?

No ☐ (0) → **GO TO Q.3**

Yes ☐ (1)

2. IF YES, PLEASE DESCRIBE WHAT YOU HAVE SEEN:

ILLUSION

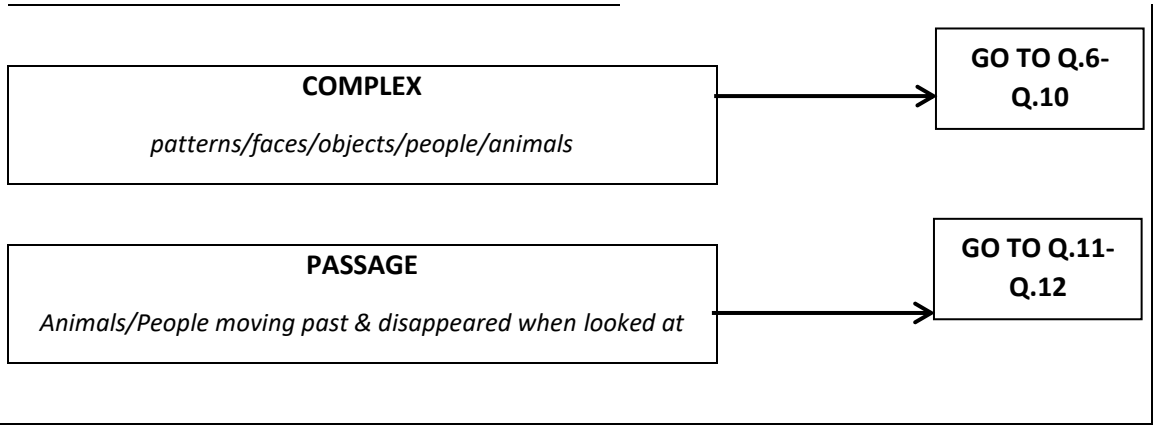
Faces/objects in patterns/surfaces/textures → **GO TO Q.3**

PRESENCE

Presence of somebody/something next to you → **GO TO Q.4**

SIMPLE

dots/flashes of light → **GO TO Q.5**



3. HAVE YOU SEEN FACES OR OBJECTS IN PATTERNS, SURFACES, OR TEXTURES?

No ☐ (0) → **GO TO Q.4**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

A. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

B. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds	☐	(1) ***specify*** → ☐
Minutes	☐	(2) ***specify*** → ☐
Hours	☐	(3) ***specify*** → ☐
Continuous while awake	☐	(4)

D. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months	☐	(1)
Every few months	☐	(2)
Every few weeks	☐	(3)
Every few days	☐	(4)
Every few hours	☐	(5)
Every few minutes	☐	(6)
Every few seconds	☐	(7)
Continuously- present throughout the day	☐	(8)

E. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

☐☐☐☐☐

F. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

G. IN THE <u>LAST 3 MONTHS</u> HOW MANY EXPERIENCES HAVE YOU HAD?

☐☐☐☐☐

H. AND IN THE <u>LAST 3 MONTHS</u>, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

I. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

J. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night ☐ (0) Day time ☐ (1) Any time ☐ (2)

K. DOES THE EXPERIENCE EVER SPEAK OR MAKE NOISES?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

L. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

P. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

4. HAVE YOU EVER HAD THE FEELING OF THE PRESENCE OF SOMEBODY, OR SOMETHING, NEXT TO YOU?

No ☐ (0) → **GO TO Q.5**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

A. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

B. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds ☐ (1) ***specify*** →

Minutes ☐ (2) ***specify*** →

Hours ☐ (3) ***specify*** →

Continuous while awake ☐ (4)

D. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months	☐	(1)
Every few months	☐	(2)
Every few weeks	☐	(3)
Every few days	☐	(4)
Every few hours	☐	(5)
Every few minutes	☐	(6)
Every few seconds	☐	(7)
Continuously- present throughout the day	☐	(8)

E. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

☐☐☐☐☐

F. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

G. IN THE LAST 3 MONTHS HOW MANY EXPERIENCES HAVE YOU HAD?

☐☐☐☐☐

H. AND IN THE LAST 3 MONTHS, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

I. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

J. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night ☐ (0) Day time ☐ (1) Any time ☐ (2)

K. DOES THE EXPERIENCE EVER SPEAK OR MAKE NOISES?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

L. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

P. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

5. HAVE YOU SEEN DOTS, FLASHES OF LIGHT, OR SIMILAR THAT WERE NOT THERE?

No ☐ (0) → **GO TO Q.6**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

A. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

B. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds		(1) ***specify*** →
Minutes		(2) ***specify*** →
Hours		(3) ***specify*** →
Continuous while awake		(4)

D. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months		(1)
Every few months		(2)
Every few weeks		(3)
Every few days		(4)
Every few hours		(5)
Every few minutes		(6)

Every few seconds ☐ (7)

Continuously- present throughout the day ☐ (8)

E. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

☐☐☐☐☐

F. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

G. IN THE LAST 3 MONTHS HOW MANY EXPERIENCES HAVE YOU HAD?

☐☐☐☐☐

H. AND IN THE LAST 3 MONTHS, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

I. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

J. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night ☐ (0) Day time ☐ (1) Any time ☐ (2)

K. DOES THE EXPERIENCE EVER SPEAK OR MAKE NOISES?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

L. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

P. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

If participant says 'Yes' to any of the following 5 experiences (complex hallucinations- patterns, faces, objects, people or animals), ask them to complete the relevant sub-questions on the most prevalent experience.

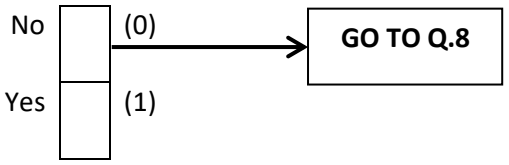
6. HAVE YOU SEEN PATTERNS, LATTICES, BRICKWORK, CHEQUER-BOARDS OR SIMILAR THAT WERE NOT THERE?

No ☐ (0) → **GO TO Q.7**

Yes ☐ (1)

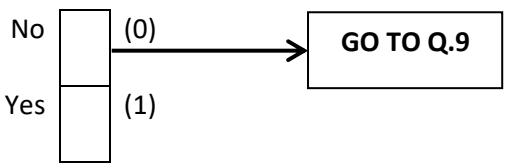
PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

7. HAVE YOU EVER SEEN FACES WITHOUT A BODY?



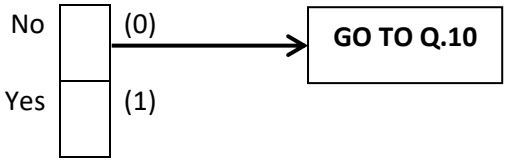
PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

8. HAVE YOU SEEN OBJECTS THAT WERE NOT THERE?



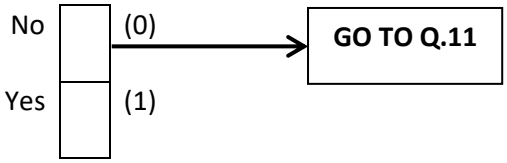
PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

9. HAVE YOU EVER SEEN PEOPLE THAT WERE NOT THERE? (make sure that this is not a passage hallucination (see people moving past and when looked at disappeared, Q. 11))



PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

10. HAVE YOU EVER SEEN ANIMALS THAT WERE NOT THERE (make sure that this is not a passage hallucination (see animals moving past and when looked at disappeared, Q. 12))



PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

If participant has said 'Yes' to any of the past 5 experiences (complex hallucinations- patterns, faces, objects, people or animals), ask them to complete the next sub-questions on the most prevalent experience.

A. OUT OF THE LAST EXPERIENCES YOU JUST DESCRIBED (specify: PATTERNS, FACES, OBJECTS, PEOPLE, ANIMALS) **WHICH DID YOU HAVE MOST OFTEN?**

Patterns	☐	(0)
Faces	☐	(1)
Objects	☐	(2)
People	☐	(3)
Animals	☐	(4)

B. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

D. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds	☐	(1) ***specify*** →
Minutes	☐	(2) ***specify*** →
Hours	☐	(3) ***specify*** →
Continuous while awake	☐	(4)

E. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months	☐	(1)
Every few months	☐	(2)

Every few weeks	☐	(3)
Every few days	☐	(4)
Every few hours	☐	(5)
Every few minutes	☐	(6)
Every few seconds	☐	(7)
Continuously- present throughout the day	☐	(8)

F. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

☐☐☐☐☐

G. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

H. IN THE LAST 3 MONTHS, HOW MANY EXPERIENCES HAVE YOU HAD?

☐☐☐☐☐

I. AND IN THE LAST 3 MONTHS, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

J. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

K. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night ☐ (0) Day time ☐ (1) Any time ☐ (2)

L. DOES THE EXPERIENCE EVER SPEAK OR MAKE NOISES?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

P. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

Q. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

11. HAVE YOU EVER SEEN PEOPLE <u>MOVING PAST YOU</u> AND THAT <u>DISAPPEARED WHEN YOU LOOKED</u> AT THEM?

No ☐ (0) → **GO TO Q.12**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

12. HAVE YOU EVER SEEN ANIMALS <u>MOVING PAST YOU</u> AND THAT <u>DISAPPEARED WHEN YOU LOOKED</u> AT THEM?

No ☐ (0) → **GO TO Q.13**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

If participant has said 'Yes' to any of the past 2 experiences (passage hallucinations) ask them to complete the next sub-questions on the most prevalent experience.

A. OUT OF THE LAST EXPERIENCES YOU JUST DESCRIBED (specify: seeing people or animals moving), **WHICH DID YOU HAVE MOST OFTEN?**

People ☐ (0)

Animals ☐ (1)

B. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

D. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds ☐ (1) ***specify*** →

Minutes ☐ (2) ***specify*** →

Hours ☐ (3) ***specify*** →

Continuous while awake ☐ (4)

E. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months	(1)
Every few months	(2)
Every few weeks	(3)
Every few days	(4)
Every few hours	(5)
Every few minutes	(6)
Every few seconds	(7)
Continuously- present throughout the day	(8)

F. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

G. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

H. IN THE LAST 3 MONTHS, HOW MANY EXPERIENCES HAVE YOU HAD?

I. AND IN THE LAST 3 MONTHS, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

J. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never (0) Sometimes (1) Always (2)

K. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night (0) Day time (1) Any time (2)

L. DOES THE EXPERIENCE EVER SPEAK OR MAKE NOISES?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

P. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

Q. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

13. HAVE YOU EVER HAD ANY OTHER VISUAL EXPERIENCE?

No ☐ (0) → **GO TO Q.14**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE SEEN: does it move, colour, size, contour, shape, field of view

A. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

B. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds ☐ (1) ***specify*** →

Minutes ☐ (2) ***specify*** →

Hours ☐ (3) ***specify*** →

Continuous while awake	☐	(4)

D. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months	☐	(1)
Every few months	☐	(2)
Every few weeks	☐	(3)
Every few days	☐	(4)
Every few hours	☐	(5)
Every few minutes	☐	(6)
Every few seconds	☐	(7)
Continuously- present throughout the day	☐	(8)

E. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

☐☐☐☐☐

F. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

G. IN THE LAST 3 MONTHS, HOW MANY EXPERIENCES HAVE YOU HAD?

☐☐☐☐☐

H. AND IN THE LAST 3 MONTHS, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

I. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

J. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night ☐ (0) Day time ☐ (1) Any time ☐ (2)

K. DOES THE EXPERIENCE EVER SPEAK OR MAKE NOISES?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

L. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

P. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

If participant has said 'Yes' to any of the past visual experiences ask them to complete the next sub-questions on the most distressing experience.

If participant has not said 'Yes' to any of the past experiences, go to Q. 15.

14. OUT OF ALL THE EXPERIENCES YOU JUST DESCRIBED (specify: INSERT RELEVANT DESCRIPTION), **WHICH DID YOU FIND MOST DISTRESSING?**

Illusions	☐	(0)
Presence	☐	(1)
Simple	☐	(2)
Complex	☐	(3)
Passage	☐	(4)
Other	☐	(5)

A. FROM 0 TO 10, HOW FRIGHTENING OR DISTRESSING WAS THIS EXPERIENCE? WITH 0 BEING NOT AT ALL FRIGHTENING/DISTRESSING, AND 10 BEING VERY FRIGHTENING/DISTRESSING?

☐☐

B. FROM 0 TO 10, HOW IRRITATING OR FRUSTRATING WAS THIS EXPERIENCE? WITH 0 BEING NOT AT ALL IRRITATING/FRUSTRATING, AND 10 BEING VERY IRRITATING/FRUSTRATING?

☐☐

C. DID THIS EXPERIENCE MAKE YOU WORRY THAT YOU WERE LOSING YOUR MIND?

Not at all ☐ (0) Somewhat ☐ (1) A lot ☐ (2)

D. DO YOU FIND YOUR CLOSE RELATIONSHIPS (E.G. WITH FAMILY) DIFFICULT BECAUSE OF THESE EXPERIENCES?

Not at all ☐ (0) Somewhat ☐ (1) A lot ☐ (2)

E. ARE YOU ABLE TO IGNORE THESE EXPERIENCES?

Not at all ☐ (2) Somewhat ☐ (1) A lot ☐ (0)

F. HAVE YOU STOPPED DOING THINGS YOU USED TO BECAUSE OF THESE EXPERIENCES?

Not at all ☐ (0) Somewhat ☐ (1) A lot ☐ (2)

15. HAVE YOU EVER HEARD A VOICE OR SOUND WHEN NO ONE WAS THERE?

No ☐ (0) → **GO TO NEXT SECTION (STUDY PARTNER)**

Yes ☐ (1)

PLEASE DESCRIBE WHAT YOU HAVE HEARD:

A. WHEN DID THIS FIRST START?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

B. WHEN DID THIS LAST HAPPEN?

If date unknown: 01/1900

M	M	/	Y	Y	Y	Y

C. APPROXIMATELY HOW LONG DO THESE EXPERIENCES USUALLY LAST?

Seconds ☐ (1) ***specify*** →

Minutes ☐ (2) ***specify*** →

Hours ☐ (3) ***specify*** →

Continuous while awake ☐ (4)

D. HOW OFTEN DO THEY USUALLY OCCUR?

Less than every few months ☐ (1)

Every few months ☐ (2)

Every few weeks ☐ (3)

Every few days ☐ (4)

Every few hours ☐ (5)

Every few minutes ☐ (6)

Every few seconds ☐ (7)

Continuously- present throughout the day ☐ (8)

E. IN A TYPICAL MONTH, HOW MANY EXPERIENCES WOULD YOU HAVE?

☐☐☐☐☐

F. AND IN THIS TYPICAL MONTH, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

G. IN THE LAST 3 MONTHS, HOW MANY EXPERIENCES HAVE YOU HAD?

☐☐☐☐☐

H. AND IN THE LAST 3 MONTHS, HOW MANY DAYS WOULD YOU HAVE THESE EXPERIENCES?

☐☐

I. IS THIS EXPERIENCE ASSOCIATED WITH FALLING ASLEEP OR WAKING UP?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

J. AT WHAT TIME OF THE DAY DOES THIS EXPERIENCE USUALLY OCCUR?

Night ☐ (0) Day time ☐ (1) Any time ☐ (2)

K. IS THIS EXPERIENCE ASSOCIATED WITH AN ODD SMELL OR TASTE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

L. DOES IT EVER FEEL LIKE IT IS TOUCHING YOU?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

M. WHILST YOU ARE HAVING THE EXPERIENCE DO YOU EVER BELIEVE IT IS REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

N. DO YOU EVER ACT ON THE EXPERIENCE?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

O. DO YOU HAVE AN EXPLANATION OF THESE EXPERIENCES THAT OTHERS SAY ARE NOT TRUE OR REAL?

Never ☐ (0) Sometimes ☐ (1) Always ☐ (2)

Appendix F. TMS Phosphene reporting sheet

Location	Intensity	Stim 1	2	3	4	Notes
i.e. 6F	60%	✓	✓	X	✓	Moving blue circles in lower left visual field

Appendix G. Visual Hallucination Diary

MONDAY		TUESDAY	
TIME	**DESCRIPTION**	**TIME**	**DESCRIPTION**
CHANGES		**CHANGES**	

WEDNESDAY		THURSDAY	
TIME	**DESCRIPTION**	**TIME**	**DESCRIPTION**
CHANGES		**CHANGES**	

Appendix H. Feasibility and Tolerability questionnaire

Study ID: ……..
Date:……

Treating Visual Hallucinations in people with Macular Degeneration: a non-invasive stimulation study

VISMAC

INTERVIEWER-ADMINISTERED QUESTIONNAIRE FOR PATIENTS

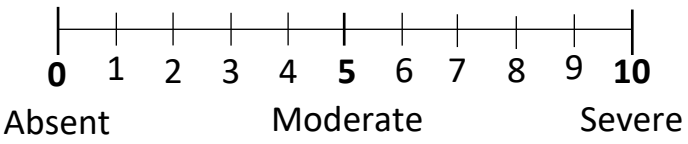
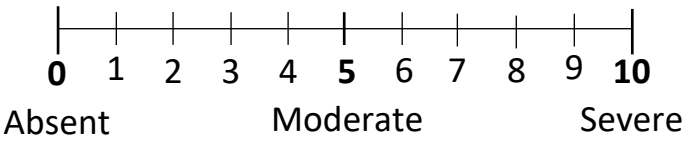
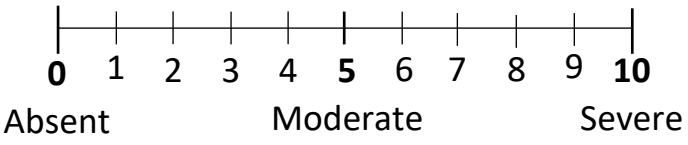
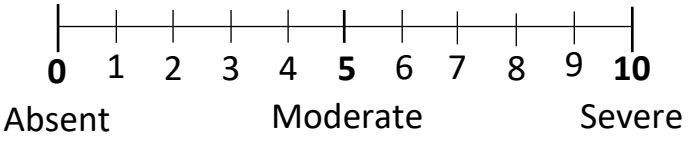
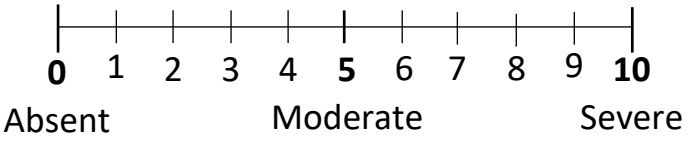
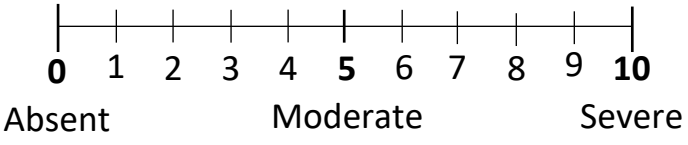
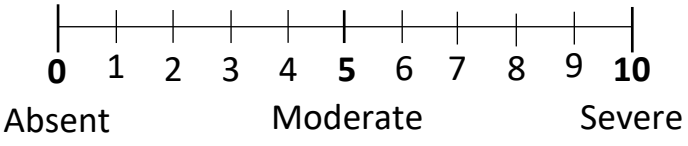
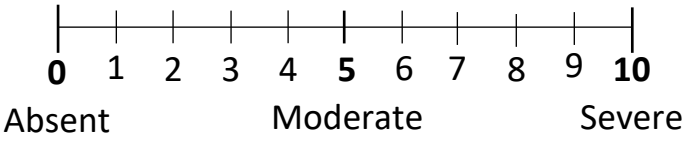
Thank you for agreeing to take part in this study. I would like to ask you a few questions regarding your experience of direct current stimulation.

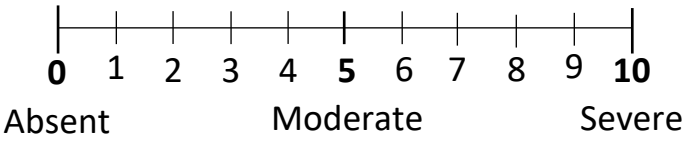
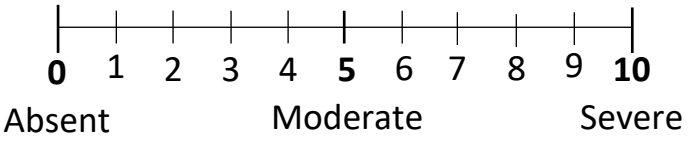
1.	How did you feel about receiving direct current stimulation before the study began?	Very positive…… 5 Fairly positive…….. 4 Not sure, mixed…….. 3 Fairly negative…… 2 Very negative…….. 1
2.	How do you feel about receiving direct current stimulation now that the trial is finished?	Very positive…… 5 Fairly positive…….. 4 Not sure, mixed…….. 3 Fairly negative…… 2 Very negative…….. 1
3.	How satisfied are you with the overall time it took to set up and administer direct current stimulation?	Very satisfied…….. 5 Fairly satisfied…….. 4 Not sure…….. 3 Fairly dissatisfied…….. 2 Very dissatisfied…… 1
4.	How physically comfortable were you during direct current stimulation?	Very comfortable…….. 5 Fairly comfortable…… 4 Not sure…….. 3 Fairly uncomfortable…….. 2 Very uncomfortable…… 1
5.	Do you feel that your symptoms were improved following direct current stimulation?	Much improved…….. 5 Slightly improved…….. 4 Not sure/no change…… 3 Slightly worse…….. 2 Much worse…….. 1

6.	Do you believe that you received the real direct current treatment or placebo (pretend) treatment in this trial? Why is this?	
	REAL PLACEBO Why: …… ……	
7.	How satisfied are you with the explanation of what was going to happen and any potential effects of stimulation by staff?	Very satisfied…….. 5 Fairly satisfied…….. 4 Not sure…….. 3 Fairly dissatisfied…….. 2 Very dissatisfied…….. 1
8.	Did staff put you at ease?	Always…….. 5 Most of the time…….. 4 Some of the time…….. 3 Not at all…….. 2 Not sure…….. 1
9.	How would you rate your overall experience of direct current stimulation?	Extremely good…….. 7 Very good…….. 6 Fairly good…….. 5 Not sure…….. 4 Fairly poor…….. 3 Very poor…….. 2 Extremely poor…….. 1
10.	How could your experience of having direct current stimulation have been improved?	

ADVERSE SIDE-EFFECTS PATIENT QUESTIONNAIRE

During or following direct current stimulation treatment, did you experience any of the following symptoms or side effects? If so, please rate these on the scale provided to indicate how severe they were.

1.	Headache	
2.	Tingling	
3.	Scalp pain	
4.	Itching	
5.	Burning sensation	
6.	Skin redness	
7.	Sleepiness	
8.	Nausea	

9.	Trouble concentrating	
10.	Other (Please specify):	

Appendix I. Participant Perceived Change – Visual Hallucination scale (Unvalidated scale)

WEEK __

Primary Visual Hallucination (most common/intrusive)

Frequency:	
Duration:	
Intrusiveness (i.e. size)	
Irritation:	
Distress:	

Secondary Visual Hallucinations (other common phenomenology, but not main VH)

Frequency:	
Duration:	
Intrusiveness (i.e. size)	
Irritation:	
Distress:	

Day 5

Notable changes:

Primary VH

VH Features

Frequency

1) Significant increase (occurring markedly more often)	
2) Slight increase (slightly more occurrences than normal, but noticeable)	
3) No Change	
4) Slight Decrease (slightly fewer occurrences than normal, but noticeable)	
5) Significant decrease (markedly fewer occurrences)	
6) Complete cessation (no occurrences all week)	

Notes:

Duration

1) Significant increase (last substantially longer i.e. mins become hours)	
2) Slight increase (slightly longer, enough to be noticeable)	
3) No Change	
4) Slight Decrease (slightly shorter, enough to be noticeable)	
5) Significant decrease (substantially shorter, i.e. secs instead of mins/hours)	
6) Complete cessation	

Notes:

Intrusiveness (Can describe the size/opaqueness of the VH – how much it intrudes on patient's vision and functioning and subsequently how difficult it is to ignore)

1) Significant increase (substantially more intrusive/difficult to ignore)	
2) Slight increase (slightly more intrusive i.e. slightly larger/more distracting)	
3) No Change	
4) Slight Decrease (slightly less intrusive i.e. slightly smaller/less distracting)	
5) Significant decrease (substantially less intrusive/easier to ignore)	
6) Complete cessation	

Notes:

Emotional Response:

Irritation

1) Significant increase (substantially more irritating/frustrating)	
2) Slight increase (slightly more irritating/frustrating)	
3) No Change	
4) Slight Decrease (slightly less irritating/frustrating)	
5) Significant decrease (substantially less irritating/frustrating)	

Notes:

Distress

1) Significant increase	
2) Slight increase	
3) No Change	
4) Slight Decrease	
5) Significant decrease	

Notes:

Secondary VH

VH Features

Frequency

1) Significant increase (occurring markedly more often)	
2) Slight increase (slightly more occurrences than normal, but noticeable)	
3) No Change	
4) Slight Decrease (slightly fewer occurrences than normal, but noticeable)	
5) Significant decrease (markedly fewer occurrences)	
6) Complete cessation (no occurrences all week)	

Notes:

Duration

1) Significant increase (last substantially longer i.e. mins become hours)	
2) Slight increase (slightly longer, enough to be noticeable)	
3) No Change	
4) Slight Decrease (slightly shorter, enough to be noticeable)	

5) Significant decrease (substantially shorter, i.e. secs instead of mins/hours)	
6) Complete cessation	

Notes:

Intrusiveness (Can describe the size/opaqueness of the VH – how much it intrudes on patient's vision and functioning and subsequently how difficult it is to ignore)

1) Significant increase (substantially more intrusive/difficult to ignore)	
2) Slight increase (slightly more intrusive i.e. slightly larger/more distracting)	
3) No Change	
4) Slight Decrease (slightly less intrusive i.e. slightly smaller/less distracting)	
5) Significant decrease (substantially less intrusive/easier to ignore)	
6) Complete cessation	

Notes:

Emotional Response:

Irritation

1) Significant increase (substantially more irritating/frustrating)	
2) Slight increase (slightly more irritating/frustrating)	
3) No Change	
4) Slight Decrease (slightly less irritating/frustrating)	
5) Significant decrease (substantially less irritating/frustrating)	

Notes:

Distress

1) Significant increase	
2) Slight increase	
3) No Change	
4) Slight Decrease	
5) Significant decrease	

Notes:

Total no. of VH phenomenology affected:

Patient perceived improvement (Feasibility and tolerability scale):

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